Highlights of the congress:
HFpEF: heart failure with preserved ejection fraction 2012

C. Tschöpe
Charite – Campus Benjamin Franklin
Berlin

www.escardio.org/HFA
Outcome

HFREF vs. HFpEF

Heart Failure with Preserved Ejection Fraction – is it really Heart Failure?

Prof. Burkert Pieske

Department of Cardiology

Med.University of Graz

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### Differences in the causes of death between HPpEF and HFREF

<table>
<thead>
<tr>
<th>Cause</th>
<th>Noncardiovascular, n (% of TM)</th>
<th>Renal, n (% of non-CV)</th>
<th>Respiratory, n (% of non-CV)</th>
<th>Cancer, n (% of non-CV)</th>
<th>Trauma, n (% of non-CV)</th>
<th>Infection/sepsis, n (% of non-CV)</th>
<th>Suicide, n (% of non-CV)</th>
<th>Other, n (% of non-CV)</th>
<th>Unknown, n (% of TM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>268 (30)</td>
<td>9 (3)</td>
<td>19 (7)</td>
<td>104 (39)</td>
<td>6 (2)</td>
<td>72 (27)</td>
<td>3 (1)</td>
<td>51 (19)</td>
<td>81 (9)</td>
</tr>
</tbody>
</table>

**Devices†**


Zile et al. Circulation 2010
Heart failure with preserved EF

- Ventricular Dysfunction
  - Impaired relaxation
  - Impaired filling
  - Systolic Dysfunction

- Atrial dysfunction

- Autonomic dysfunction
  - Chronotropic incompetence

- Vascular dysfunction
  - Vascular stiffening
  - Ventriculo-arterial coupling

- Elevated blood pressure
  - Inadequate BP response to exercise
  - Pulmonary hypertension

- Valvular disease
  - Dynamic mitral regurgitation

- Lung Disease
  - COPD

- Iron deficiency and anemia

- Renal dysfunction
  - Volume overload

- Aging & Deconditioning

- Obesity & Sarcopenia

- Psychic Disorders
  - Depression

- Valvular disease
  - Dynamic mitral regurgitation

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DEPRESSION IN DIASTOLIC HEART FAILURE

M.C. Tomescu, A.M. Mavrea, I.M. Citu, A. Pogorevici, I. Korpos-Gyalai

University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania
DEPRESSION IN DIASTOLIC HEART FAILURE

- M.C. Tomescu, A.M. Mavrea, I.M. Citu, A. Pogorevici, I. Korpos-Gyalai
- University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania

Correlation between depression and life quality
## Comorbidities & Incident HF

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)*</th>
<th>P value*</th>
<th>Cut-off percentile</th>
<th>Cut-off value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1.21 (1.01–1.45)</td>
<td>0.036</td>
<td>&gt;75th percentile</td>
<td>&gt; 92.8 μmol/l</td>
<td>1</td>
</tr>
<tr>
<td>FEV1:FVC</td>
<td>1.21 (1.02–1.43)</td>
<td>0.029</td>
<td>&lt;25th percentile</td>
<td>&lt; 91 % predicted</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.24 (1.09–1.40)</td>
<td>&lt;0.001</td>
<td>&lt;25th percentile</td>
<td>&lt; 13 g/dl</td>
<td>1</td>
</tr>
</tbody>
</table>

*Hazards ratio are for 1SD increase in serum creatinine, 1SD decrease in FEC1:FVC ratio and 1 unit decrease in hemoglobin concentration, adjusting for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, valvular heart disease, and left ventricular systolic and diastolic function.

Lam C.S. et al Circulation 2011
Summary

• „HFPEF“ is a heterogeneous syndrome
• Patients need to be classified according to the underlying pathophysiology and CV phenotypes
• Co-morbidities have to be taken into account
• Specific etiologies need to be excluded
• In clinical practice, we often deal with a mixed picture of cardiac and extracardiac abnormalities that sum up to „HFPEF“
All-cause mortality

Rate per 1000 patient years

- ACCORD: 11.4
- ANBP-2: 15.7
- ACTION: 16.4
- LIFE: 17.3
- VALUE: 25.6
- ALLHAT: 28.7
- I-PRESERVE: 52.5
- CHARM-Preserved: 54.0

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Heart failure hospitalization rates

Rate per 1000 patient years

- ACTION*: 4.6
- ANBP-2: 5.5
- LIFE: 7.1
- ACCORD*: 7.5
- VALUE*: 11.0
- ALLHAT*: 11.5
- I-PRESERVE: 43
- CHARM-Preserved: 69

* fatal or non-fatal HF
Mechanismes
Endomyocardial biopsies

Westermann et al – Charite - Berlin
ECM remodeling favour dilation in some patients?
Differences in ECM remodeling between patients with DCM and HFNEF

- Relative mRNA level to CDKN1b
- DCM
- **ns**
- x6

- MMP1
- TIMP1

- Relative change to control after TGF beta
Diagnosis

Stress test
New Echo
New Guidelines
Heart Failure with Preserved Ejection Fraction: Biomarkers and imaging – Can they “assure” the diagnosis?

Scott D. Solomon, MD
Professor of Medicine
Harvard University
Director, Noninvasive Cardiology
Brigham and Women’s Hospital
Associate Editor, Circulation
Boston, MA
What is the Appropriate Cutoff in HFpEF?

Low Ejection Fraction

10%  20%  30%  40%  50%  60%  70%  80%

Preserved Ejection Fraction

CHARM, TOPCAT, I-Preserve

ASE "normal"
Influence of Therapy on Primary Outcome by Ejection Fraction in CHARM-Preserved

Hazard Ratio for Primary Outcome (CV Death or HF Hospitalization)

CHARM Investigators. Lancet 2004
Current criteria use resting measures of diastolic function

How to diagnose HFNEF

Symptoms or signs of heart failure

Normal or mildly reduced left ventricular systolic function
LVEF > 50%
LVEDVI < 97 mL/m²

Evidence of abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness

Invasive Haemodynamic measurements
mPcSW > 12 mmHg
or
LVEDP > 16 mmHg
or
t > 48 ms
or
b > 0.27

Biostatistics
NT-proBNP > 220 pg/mL
or
BNP > 200 pg/mL

Echo - Bloodflow Doppler
E/Ar < 0.5 and DT < 50 ms
or
Ard-Ad > 30 ms
or
LAVI > 40 mL/m²
or
LVM > 122 g/m² (♂); >149 g/m² (♀)
or
Atrial fibrillation

TD

Biomarkers
NT-proBNP > 220 pg/mL
or
BNP > 200 pg/mL

TD

E/E' > 8

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E/é and LVEDP

LV Filling Pressure (mmHg)

E/E' < 8    E/E' 8-15    E/E' > 15

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Little et al.; Circulation 2009; 120: 802-809
New imaging modalities in HFpEF

Elisabeth Kraigher-Krainer, MD
Cardiovascular Research Fellow
Brigham and Women’s Hospital

May 21st 2012

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Echo Imaging Modalities

1. 2D Speckle Tracking
   a) LV
   b) LA

2. 3D Echocardiography and Principal Strain
## Strain in HFpEF: Literature

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>n</th>
<th>EF %</th>
<th>Longitudinal</th>
<th>Circumferential</th>
<th>Radial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yip GW et al. Heart 2011</td>
<td>112</td>
<td>61±6</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Carluccio E et al. Eur J Heart Fail 2011</td>
<td>47</td>
<td>62±7</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu YW et al. J Card Fail 2009</td>
<td>26</td>
<td>63±8</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heart Failure with Normal Ejection Fraction (HFnEF):

Is Global Longitudinal Strain Helpful?

Pierpaolo Pellicori, Valentina Carubelli, Anna Bennett, Pierluigi Costanzo, Teresa Castiello, Olga Khaleva, Kenneth Wong, Jufen Zhang, Andrew L Clark, John GF Cleland

Department of Cardiology, Hull York Medical School, Castle Hill Hospital, Kingston-upon-Hull, UK
Pts with symptoms & signs suggesting HF but LVEF > 50% (and 20 controls)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>LA ≤ 4 cm &amp; NTproBNP &lt;400 ng/L</th>
<th>LA &gt; 4 cm OR NTproBNP &gt; 400 ng/L</th>
<th>LA &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: No HFpEF</td>
<td>No symptoms or signs of HF, left atrium &lt; 4 cm &amp; NTproBNP &lt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm OR NTproBNP &gt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td></td>
</tr>
<tr>
<td>Group B: Possible HFpEF</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm OR NTproBNP &gt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td></td>
</tr>
<tr>
<td>Group C: Definite HFpEF</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td>No symptoms or signs of HF, left atrium &gt; 4 cm &amp; NTproBNP &gt; 400 ng/L</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control (20)</th>
<th>Group A (76)</th>
<th>Group B (99)</th>
<th>Group C (138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65</td>
<td>67</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>107 (46-147)</td>
<td>164 (59-288)</td>
<td>414 (143-887)</td>
<td>1627 (868-2837)</td>
</tr>
<tr>
<td>Atrial Fib (%)</td>
<td>0%</td>
<td>1%</td>
<td>25%</td>
<td>73%</td>
</tr>
<tr>
<td>LVEF – %</td>
<td>60 (5)</td>
<td>59 (6)</td>
<td>59 (6)</td>
<td>58 (6)</td>
</tr>
<tr>
<td>GLS - %</td>
<td>-19.1 (2.1)</td>
<td>-15.9 (2.4)</td>
<td>-15.2 (3.1)</td>
<td>-13.6 (3.0)</td>
</tr>
<tr>
<td>LAVI - ml/m²</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TAPSE - mm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TR grad - mmHg</td>
<td>20 (4)</td>
<td>19 (5)</td>
<td>25 (12)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>IVC - mm</td>
<td>15 (2)</td>
<td>15 (2)</td>
<td>17 (3)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>MR: Mild – Mod.</td>
<td>5 (25) - 0</td>
<td>7 (9) - 2 (3)</td>
<td>18 (16) - 4 (4)</td>
<td>41 (36) - 34 (24)</td>
</tr>
<tr>
<td>TR: Mild – Mod.</td>
<td>0 - 0</td>
<td>2 (3) - 0 (0)</td>
<td>12 (12) - 7 (7)</td>
<td>34 (25) - 25 (18)</td>
</tr>
</tbody>
</table>

GLS is impaired in patients with LVEF >50% who have symptoms or signs of HF, even if left atrium is undilated & NTproBNP <400ng/L. Impaired GLS suggests subtle systolic dysfunction.

High prevalence of AF in Group C, which may confound Diagnosis both by Echo and NT-proBNP.
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable analysis</th>
<th>MV Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF hospitalisation or CV death, 62 events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>χ²</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.03-1.09)</td>
<td>15.60</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>6.70 (2.05-21.90)</td>
<td>6.70</td>
</tr>
<tr>
<td>Definite HFnEF</td>
<td>4.32 (2.44-7.64)</td>
<td>25.31</td>
</tr>
<tr>
<td>IHD</td>
<td>1.14 (0.68-1.89)</td>
<td>0.26</td>
</tr>
<tr>
<td>DM</td>
<td>0.75 (0.44-1.27)</td>
<td>1.13</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.54 (1.52-4.25)</td>
<td>12.73</td>
</tr>
<tr>
<td>Congestion score ≥3</td>
<td>3.87 (2.31-6.50)</td>
<td>26.37</td>
</tr>
<tr>
<td>Creatinine – umol/l</td>
<td>1.01 (1.00-1.01)</td>
<td>20.26</td>
</tr>
<tr>
<td>Urea – mmol/l</td>
<td>1.10 (1.07-1.14)</td>
<td>36.85</td>
</tr>
<tr>
<td>Log (NT-proBNP)</td>
<td>6.09 (3.73-9.96)</td>
<td>51.93</td>
</tr>
<tr>
<td>IVC - mm</td>
<td>1.21 (1.15-1.26)</td>
<td>72.94</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>1.09 (1.00-1.18)</td>
<td>3.976</td>
</tr>
<tr>
<td>LA VI - ml/m²</td>
<td>1.02 (1.01-1.02)</td>
<td>30.23</td>
</tr>
<tr>
<td>TAPSE – mm</td>
<td>0.87 (0.82-0.93)</td>
<td>19.65</td>
</tr>
<tr>
<td>TR gradient - mmHg</td>
<td>1.04 (1.030-1.06)</td>
<td>33.55</td>
</tr>
</tbody>
</table>

*But GLS is a weak predictor of prognosis on univariable analysis and adds no prognostic information in a MV model.*

*Serum Urea, Inferior Vena Cava diameter and NT-proBNP carry powerful prognostic information in this population.*
Understanding HFpEF: lots of news!

Atrial dysfunction

Vojtech Melenovsky

Institute for Clinical and Experimental Medicine - IKEM
Prague
Czech Republic
LA dysfunction in HFpEF by strain analysis

HFpEF

LA expansion

LA contraction

Asymptomatic diastolic dysfuntion

LA expansion

LA contraction

<table>
<thead>
<tr>
<th></th>
<th>HFpEF (n=119)</th>
<th>Asymptomatic DD (n=301)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial enlargement (LAVI&gt; 24 ml/m²)</td>
<td>78%</td>
<td>20%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>↓ LA strain rate in LA systole</td>
<td>65%</td>
<td>30%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA „systolic“ dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ LA strain rate in LA expansion</td>
<td>28%</td>
<td>1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA diastolic dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LA in HFpEF ↓ contraction - LA systolic dysfunction

↓ expansion - increased LA stiffness

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Morris DA, JASE 2011; 24: 651-62
Atrial dysfunction by speckle tracking

PALS
peak atrial longitudinal strain

312 older adults with SR
f-u 3.1 years

Graded relation **between** PALS and CV events (death, AF, stroke, HF)

PALS predicted CV events better than LA EF or LAVI

Cameli M et al. Am J Cardiol 2012, in press
Conclusions

• The relevance of deformation measures to incident HFpEF and outcome in prevalent HFpEF need to be further evaluated.
Exercise testing in HFnEF

Michael Frenneaux
Regius Professor of Medicine
University of Aberdeen

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Exercise haemodynamics in HFnEF

Maeder et al J Am Coll Cardiol 2010
ESC criteria perform badly but passive leg raising PCWP or PASP perform well against max exercise haemodynamics

Borlaug et al Circ Heart Failure 2010
Multivariate logistic regression analysis: predictors of DD

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VCO2 slope</td>
<td>0.001</td>
<td>1.68</td>
<td>1.24 - 2.24</td>
</tr>
</tbody>
</table>

- CPET correlates with stress induced ECHO changes
- VE/VCO2 slope - independant predictor of stress induced DD, with cutoff value of 33.5
- Combined test is useful for early detection of DD in pts normal resting LV function

Cutoff for VE/VCO2 slope: 33.5
Sn 90.9%, Sp 95.7%
Treatments
## Therapy of HFpEF: New options

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Therapy Name</th>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-Inhibitor</td>
<td></td>
<td></td>
<td>neutral</td>
</tr>
<tr>
<td>AT1-Blocker</td>
<td></td>
<td></td>
<td>neutral</td>
</tr>
<tr>
<td>AT1-Blocker</td>
<td></td>
<td></td>
<td>neutral</td>
</tr>
<tr>
<td>Digitalis</td>
<td></td>
<td></td>
<td>negative</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>Nebivolol</td>
<td></td>
<td>neutral</td>
</tr>
<tr>
<td>Aldo-Antagonists</td>
<td>Eplerenone</td>
<td></td>
<td>promising</td>
</tr>
<tr>
<td>late Na- Inhibitoren</td>
<td>Ranolazine</td>
<td></td>
<td>!</td>
</tr>
<tr>
<td>PDE-Inhibitor</td>
<td>Sildenafil</td>
<td></td>
<td>!</td>
</tr>
<tr>
<td>Exercise training</td>
<td></td>
<td></td>
<td>!</td>
</tr>
<tr>
<td>Ivabradine</td>
<td></td>
<td></td>
<td>!</td>
</tr>
</tbody>
</table>
Characterization of heart failure patients with preserved ejection fraction in the I-PRESERVE trial who have improved outcomes with irbesartan therapy

David P Kao MD, James K Lewsey PhD, Barry M Massie MD, John McMurray MD, Peter E Carson MD, Inder S Anand MD, Michael Zile MD, Robert McKelvie MD, Michel Komjada MD, JoAnn Lindenfeld MD
### Extra/ancillary information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
<th>Class 5</th>
<th>Class 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 yrs</td>
<td>100%</td>
<td>18.5%</td>
<td>8.1%</td>
<td>30.2%</td>
<td>14.4%</td>
<td>16.9%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Female</td>
<td>60.4%</td>
<td>0.0%</td>
<td>60.1%</td>
<td>100.0%</td>
<td>0.0%</td>
<td>95.8%</td>
<td>77.1%</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td>40.9%</td>
<td>23.8%</td>
<td>75.1%</td>
<td>45.8%</td>
<td>43.2%</td>
<td>44.0%</td>
<td>24.0%</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>29.8%</td>
<td>44.0%</td>
<td>32.4%</td>
<td>31.7%</td>
<td>17.6%</td>
<td>5.0%</td>
<td>51.1%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>51.8%</td>
<td>61.6%</td>
<td>66.5%</td>
<td>42.2%</td>
<td>56.5%</td>
<td>51.8%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.8%</td>
<td>17.5%</td>
<td>99.7%</td>
<td>22.5%</td>
<td>26.9%</td>
<td>23.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>47.0%</td>
<td>39.3%</td>
<td>86.6%</td>
<td>45.7%</td>
<td>51.4%</td>
<td>47.1%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>11.0%</td>
<td>12.5%</td>
<td>20.8%</td>
<td>10.2%</td>
<td>2.5%</td>
<td>1.5%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>10.8%</td>
<td>20.1%</td>
<td>13.4%</td>
<td>5.2%</td>
<td>20.2%</td>
<td>2.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Creat. clear. &lt; 60 ml/min</td>
<td>35.3%</td>
<td>39.5%</td>
<td>66.2%</td>
<td>36.4%</td>
<td>11.1%</td>
<td>3.0%</td>
<td>80.5%</td>
</tr>
<tr>
<td>Hematocrit &lt; 40%</td>
<td>33.2%</td>
<td>20.5%</td>
<td>73.0%</td>
<td>29.6%</td>
<td>0.0%</td>
<td>43.2%</td>
<td>61.2%</td>
</tr>
</tbody>
</table>

#### Effect of irbesartan

- **Primary outcome**
  - All: 0.95 (0.86-1.05)
  - Class 1: 1.12 (0.89-1.42)
  - Class 2: 1.10 (0.78-1.54)
  - Class 3: 0.82 (0.68-0.99)
  - Class 4: 0.93 (0.71-1.21)
  - Class 5: 0.89 (0.77-1.28)
  - Class 6: 0.95 (0.72-1.27)

- **All-cause mortality**
  - All: 1.00 (0.88-1.14)
  - Class 1: 1.23 (0.90-1.67)
  - Class 2: 1.19 (0.77-1.86)
  - Class 3: 0.77 (0.60-0.99)
  - Class 4: 1.03 (0.73-1.47)
  - Class 5: 0.91 (0.65-1.26)
  - Class 6: 1.23 (0.86-1.76)
Results

Primary endpoint

<table>
<thead>
<tr>
<th>Class</th>
<th>Irbesartan (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>35.9%</td>
<td>37.0%</td>
</tr>
<tr>
<td>Class 1</td>
<td>38.0%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Class 2</td>
<td>43.3%</td>
<td>39.7%</td>
</tr>
<tr>
<td>Class 3</td>
<td>32.6%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Class 4</td>
<td>35.1%</td>
<td>36.4%</td>
</tr>
<tr>
<td>Class 5</td>
<td>34.6%</td>
<td>34.6%</td>
</tr>
<tr>
<td>Class 6</td>
<td>38.3%</td>
<td>38.7%</td>
</tr>
</tbody>
</table>

Hazard ratio

All-cause mortality

<table>
<thead>
<tr>
<th>Class</th>
<th>Irbesartan (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>21.5%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Class 1</td>
<td>23.4%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Class 2</td>
<td>26.4%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Class 3</td>
<td>17.8%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Class 4</td>
<td>21.3%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Class 5</td>
<td>19.6%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Class 6</td>
<td>27.3%</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

Hazard ratio
Renin-Angiotensin System Antagonists are Associated with Reduced Mortality in Heart Failure with Preserved EF – a Prospective Propensity Score-Matched Cohort Study

Lars H Lund, Lina Benson, Ulf Dahlström, Magnus Edner on behalf of the Swedish Heart Failure Registry

Conflicts of interest: Research funding, speaker’s fees, consultancies: AstraZeneca Inc.
4. Methods

The Swedish Heart Failure Registry

64,140 Registrations
2000 – 2011
64 of 77 hospitals
84 of 1,011 primary care clinics
→ validity / generalizability
43 relevant co-variates
→ reliability

22,349 Re-registrations

41,791 Unique patients

25,575 EF < 40%
EF unknown
ACEi or ARB unknown

16,216 EF ≥ 40%

- Propensity score
- Matching 1:1 based on propensity score and age

6,658 Matched population

RAS No: 3,329
RAS Yes: 3,329

RAS No: 3,673
RAS Yes: 12,543

www.escardio.org/HFA
RAS-antagonists are associated with reduced mortality in HFpEF

Un-adjusted HR: 0.48, p < 0.001

1-year survival
- Un-adjusted HR: 0.48, p < 0.001
  - 86%
- Matched HR: 0.91, p = 0.008
  - 77%
  - 72%
  - 69%

Survival proportion

Year

No. at risk
- Overall
  - No RAS: 3673, 2156, 1425, 884, 467, 234
  - RAS: 12543, 9177, 6580, 4193, 2340, 1216
- Matched
  - No RAS: 3329, 2028, 1349, 846, 453, 229
  - RAS: 3329, 2181, 1447, 880, 475, 238
### Why different from randomized trials?

The Swedish Heart Failure Registry: older, sicker, more "real-life"

<table>
<thead>
<tr>
<th></th>
<th>CHARM-Preserved Candesartan</th>
<th>PEP-CHF Perindopril</th>
<th>I-PRESERVE Irbesartan</th>
<th>Owan / Bhatia</th>
<th>Matched cohort ACEi / ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>67</td>
<td>75</td>
<td>72</td>
<td>74 / 75</td>
<td>79</td>
</tr>
<tr>
<td><strong>Creatinine, µmol/L , mL/min</strong></td>
<td>-</td>
<td>95-97</td>
<td>88</td>
<td>141 / -</td>
<td>Clearance 52-53</td>
</tr>
<tr>
<td><strong>NT-proBNP, ng/L</strong></td>
<td>-</td>
<td>335-453</td>
<td>320-360</td>
<td>-</td>
<td>4,577-5,192</td>
</tr>
<tr>
<td><strong>Treatment change</strong></td>
<td>-</td>
<td>26% cross-over</td>
<td>34% stopped 40% hade ACEi</td>
<td>NA</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Primary end-point</strong></td>
<td>CV death or HF hospitalization</td>
<td>Death or HF hospitalization</td>
<td>Death or CV hospitalization</td>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td><strong>Endpoint at 1 yr</strong></td>
<td>~8%</td>
<td>~10%</td>
<td>~12%</td>
<td>29% / 22%</td>
<td>23% vs. 28%</td>
</tr>
<tr>
<td><strong>Significant benefit</strong></td>
<td>↓ HF hospitalization</td>
<td>↓ HF hospitalization at 1 year</td>
<td>None</td>
<td>NA</td>
<td>↓ Mortality</td>
</tr>
</tbody>
</table>
Summary:

Implication:

• Adequately powered randomized trial needed until then: consider RAS-antagonists for likely but not proven benefit in HFpEF
A sample of therapies being tested
Therapy of HFpEF: New options - role of devices
Limitation: Not randomized → residual confounding despite propensity score

4 consistency analyses suggest representative data:
Main analysis: matched cohort: HR 0.91

1. Overall cohort with adjustment for propensity score: HR 0.90
   Similar to matched

2. Introduce hypothetical un-measured confounder: Would have to be large

3. Target dose ≥ 50% vs. < 50% vs. none: HR 0.85 vs. 0.94 vs 1.00
   Expected dose effect

4. Same registry: 20,111 patients with HFrEF: HR 0.80
   Expected Larger effect than HFpEF
   Expected similar to RCTs in HFrEF

www.escardio.org/HFA
Renale denervation in hypertension and HFpEF

- Systolic blood pressure (mmHg)
  - Baseline: RD vs. Control
  - 1 Month: RD vs. Control
  - 6 Months: RD vs. Control
  - P-values: 0.530, <0.001, <0.001

- LVMI (g/m²)
  - Baseline: RD vs. Control
  - 1 Month: RD vs. Control
  - 6 Months: RD vs. Control
  - P-values: 0.01, <0.001, 0.007

- Mitr valve lateral EE
  - Baseline: RD vs. Control
  - 1 Month: RD vs. Control
  - 6 Months: RD vs. Control
  - P-values: 0.006, <0.001, <0.001

- Lateral EE delta
  - 1 Month: SBP decrease
  - 6 Months: SBP decrease
  - Categories: 0 mmHg to 16.6 mmHg, 16.7 mmHg to 47.2 mmHg, 47.3 mmHg to 78.0 mmHg
  - P-values: not provided

Brandt et al. JACC 2012
Role of dyssynchrony in HFpEF

CRT

www.escardio.org/HFA
Speckle tracking:
Delay of contraction leads to a high energy lost.
Shunt induction between LA and RA in patients with HFpEF

Patients admitted had an average LAP of 23 mm Hg

Rule of thumb:
- LAP < 18 = good
- LAP 18-24 = b’line
- LAP > 24 = trouble
Shunt induction between LA and RA in patients with HFpEF

Before Implant

After Implant

Bulging Septal Wall
Shunt induction between LA and RA in patients with HFpEF

DCD barrel size is 4mm radius
Ivabradine in Diastolic heart failure

13 patients
Mean age 78 ± 9.2 years

Oral Ivabradine
Mean doses 12.5 mg/day

follow-up 4 months

Echocardiogram 2D
Doppler
Radiostopic (rest/effort)
ventrculography

Diastolic and right heart failure

Before

After

Castillo-ML, Orea-TA, et al.,
Mexico City, Mexico
Ivabradine in Diastolic heart failure

Improved functional class
45.5 % from II → I
66.7 % from III → II

P = 0.08

Pulmonary arterial Pressure 8.3 %
(59.6±8.4 vs 54.9±20.2)

p = 0.05

Right ventricle diastolic diameter (40.5 ±7.8 vs 36.4±5.3)

p = 0.08

Improve functional class and pulmonary arterial pressure

Castillo-ML, Orea-TA, et al., Mexico City, Mexico

www.escardio.org/HFA

HEART FAILURE 2012 – BELGRADE SERBIA
Effect of ivabradine on endothelial function in diastolic and right heart failure patients

15 patients (mean age of 78.1 ± 9.2 years) with diastolic and right heart failure on optimal treatment.

Mean dose: 12.5 mg/day, during 6 months of follow up.

They underwent to photoplethysmography, before an after ischemic period to evaluate the blood flow wave of the finger, through the Maximum Amplitude Time /Total Time (MAT/TT) Index.

Orea-Tejeda A, Balderas-Muñoz K, et al, Mexico City, Mexico
Ivabradine improves endothelial function in diastolic and right heart failure patients

<table>
<thead>
<tr>
<th></th>
<th>BASAL</th>
<th>Pre-ischemic period</th>
<th>Post-ischemic period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>29.1 ± 2.2</td>
<td>30.4 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>24.3 ± 3.2</td>
<td>23.3 ± 2.9</td>
</tr>
</tbody>
</table>

p=0.05  
p=0.002

Orea A, Balderas-MK, et al, Mexico City, Mexico

HEART FAILURE 2012 – BELGRADE SERBIA
Methods

• 4128 HFPEF patients with symptomatic HF and EF ≥ 45% were randomized to receive irbesartan vs. placebo
• Patients characterized according to age, gender, BMI, atrial fibrillation/flutter, coronary artery disease, diabetes mellitus, hyperlipidemia, valvular disease, alcohol use, creatinine clearance, and hematocrit
• Most prevalent patient subtypes derived using latent class analysis (LCA), and most likely subtype determined for each patient
• Outcomes were all-cause mortality or CV hospitalization and all-cause mortality
• Effect of irbesartan on outcomes for each subtype determined using Cox proportional hazards analysis
Renin-Angiotensin System Antagonists are Associated with Reduced Mortality in Heart Failure with Preserved EF – a Prospective Propensity Score-Matched Cohort Study

Lars H Lund, Lina Benson, Ulf Dahlström, Magnus Edner
on behalf of the Swedish Heart Failure Registry

Conflicts of interest:
Research funding, speaker’s fees, consultancies: AstraZeneca Inc.
Heart Failure with Preserved Ejection Fraction – HFpEF:

- As common and possibly as lethal as HF reduced EF
- Renin-angiotensin system (RAS) activation
  → fibrosis, hypertrophy, diastolic dysfunction
- But RAS-antagonists in randomized controlled trials: no reduction in primary endpoints:

CHARM-Preserved:
CV death or HF hospitalization
Yusuf, Lancet 2003

PEP-CHF:
Death or HF hospitalization
Cleland, EHJ 2006

I-PRESERVE:
Death or CV hospitalization
Massie, NEJM 2008

But signals toward benefits
And were trials under-powered?
Myocardial deformation in the heart

Systolic Strain

Diastolic Strain

Animation courtesy of BE Bulwer
Resting cardiac function is usually (but not universally) abnormal

- Increased passive LV stiffness
- Impaired LV relaxation
- Impaired long axis systolic function
- Reduced and delayed LV untwist
- Abnormal atrial function and/or atrial fibrillation
Exercise Pathophysiology of HFnEF-exercise induced diastolic and systolic dysfunction and chronotropic incompetence

<table>
<thead>
<tr>
<th></th>
<th>HFnEF</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise HR</td>
<td>97± 14</td>
<td>114± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative SV on ex</td>
<td>0.99± 0.34</td>
<td>1.25± 0.47</td>
<td>0.04</td>
</tr>
<tr>
<td>Relative arterial elastance on exercise</td>
<td>1.52± 0.48</td>
<td>1.28± 0.44</td>
<td>0.17</td>
</tr>
<tr>
<td>Relative ventricular systolic elastance on exercise</td>
<td>1.35± 0.5</td>
<td>1.85± 0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Change vasculo-ventricular coupling ratio</td>
<td>-0.01± 0.15</td>
<td>-0.25± 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting nTTPF</td>
<td>0.18± 0.08</td>
<td>0.18± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Change nTTPF on exercise</td>
<td>+0.07± 0.11</td>
<td>-0.03± 0.12</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Phan et al JACC 2009
New diastolic stress testing: cardiopulmonary testing with echocardiographic monitoring

110 Patients with hypertension and exertional dyspnea

LV EF > 50%; E/E' at rest <8

Combined CPET stress ECHO

Max Exercise E/E' < 8

Normal

Max Exercise E/E' > 8

Diastolic dysfunction
Is there distinctive echocardiographic predictor of severity of diastolic dysfunction in patients with diabetes mellitus?

Georgievska-Ismail Lj, Zafirovska P, Andova V, Bosevski M.

University Clinic of cardiology, Medical school, University “St. Cyril&Methodius”, Skopje, Republic of Macedonia
Method and results

- 197 pts with LA enlargement (44.7 ± 2.9 mm), enlarged LA volume index (42.1±13.ml/m2) and preserved EF% (64.8 ±15.6) were selected for participation in this study.
- All pts were divided according to the presence of DM. LV systolic and diastolic function were evaluated by traditional, TDI and color Doppler M-mode echocardiographic methods.
- There was no difference between pts with and without DM regarding gender, BMI, presence of hypertension, dislipidemia, presence of CAD, LA dimension and volume and its normalization for BSA, only pts with DM were significantly older (p=0.045) and had lower EF, since steel within normal range.
Results

• Pts with DM showed significantly worse septal, lateral and average early diastolic velocity (Ea) (p=0.031; p=0.033; p=0.018, respectively) as well as significantly worse peak septal and average E/Ea ratio (p=0.012; p=0.017, respectively) in comparison with those without DM.

• The results of stepwise logistic regression analysis of significant parameters of diastolic dysfunction assessed by TDI as independent variables and DM presence as dependent variable showed that the risk of having DM cardiomyopathy is 1.1 times higher if there is higher septal E/Ea ratio (OR=1.059; 95%CI 1.010-1.110; p=0.018). The model showed that lack of prominent septal E/Ea ratio could predict lack of DM cardiomyopathy presence in around 90% of subjects.
The test result variable(s): Es cm/s, El cm/s, Eaverage, Ees, Eeaverage has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

- Under the nonparametric assumption
- Null hypothesis: true area = 0.5
Conclusion

• Our study revealed that in pts with DM and preserved LVEF with already affected diastolic function manifested by enlarged LA volume index, septal E/Ea ratio and its average value appears as a distinctive markers of diabetic cardiomyopathy presence and severity. Their assessment should be part of standard procedure in pts with DM in order to preserve development of LV systolic dysfunction.
Results

- 6 latent clinical classes identified
- Irbesartan associated with significant decreases in both ACM/CVH (HR 0.82, p = 0.035) and ACM (HR 0.77, p = 0.041) in Class 3
- Class 3 was female, generally < 80 years old (98%), mostly overweight or obese (85.6%), with mild-moderate renal insufficiency (98.9% Stage 2 or 3 CKD) and ~ 30% anemic
- This method may have identified a group of patients more likely to respond to RAAS inhibition
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2035, Route des Colles
Les Templiers - BP 179
06903 Sophia Antipolis CEDEX - France
Phone: +33 (0)4 92 94 76 00
Fax: +33 (0)4 92 94 76 01
E-mail: guidelines@escardio.org

ESC Guidelines
Committee for Practice Guidelines
To improve the quality of clinical practice and patient care in Europe

Heart Failure
Guidelines for the diagnosis and treatment of acute and chronic heart failure

For more information
www.escardio.org/guidelines

For more information
www.escardio.org/guidelines
### ESC 2012: Diagnosis of HF

The diagnosis of HF-PEF requires four conditions to be satisfied:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Symptoms typical of HF</strong></td>
<td></td>
</tr>
<tr>
<td><strong>2. Signs typical of HF</strong></td>
<td>†</td>
</tr>
<tr>
<td><strong>3. Normal or only mildly reduced LVEF and LV not dilated</strong></td>
<td></td>
</tr>
<tr>
<td><strong>4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Symptoms and Signs of HF

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical</strong></td>
<td><strong>More specific</strong></td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Elevated jugular venous pressure</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>Hepatojugular reflux</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnoea</td>
<td>Third heart sound (gallop rhythm)</td>
</tr>
<tr>
<td>Reduced exercise tolerance</td>
<td>Laterally displaced apical impulse</td>
</tr>
<tr>
<td>Fatigue, tiredness, increased time to recover after exercise</td>
<td>Cardiac murmur</td>
</tr>
<tr>
<td>Ankle swelling</td>
<td></td>
</tr>
</tbody>
</table>
Objective evidence of cardiac dysfunction

<table>
<thead>
<tr>
<th>Parameters related to diastolic function</th>
<th>Abnormalities of the mitral inflow pattern, tissue velocities (e') or the E/e' ratio</th>
<th>Indicate LV diastolic dysfunction degree and suggest level of filling pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic dysfunction parameters</td>
<td>Abnormalities of the mitral inflow pattern, tissue velocities (e') or the E/e' ratio</td>
<td>Indicate LV diastolic dysfunction degree and suggest level of filling pressure</td>
</tr>
<tr>
<td>Left atrial volume index</td>
<td>Increased (volume &gt;34 mL/m²)</td>
<td>Increased LV filling pressure (past or present) Mitral valve disease</td>
</tr>
<tr>
<td>LV mass index</td>
<td>Increased: &gt;95 g/m² in women and &gt;115 g/m² in men</td>
<td>Hypertension, aortic stenosis, hypertrophic cardiomyopathy</td>
</tr>
</tbody>
</table>
## Echo parameters of diastolic dysfunction

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Abnormality</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>e’</td>
<td>Decreased (&lt;8 cm/s septal, &lt;10 cm/s lateral, or &lt;9 cm/s average)</td>
<td>Delayed LV relaxation</td>
</tr>
<tr>
<td>E/e’ ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High (&gt;15)</td>
<td>High LV filling pressure</td>
</tr>
<tr>
<td></td>
<td>Low (&lt;8)</td>
<td>Normal LV filling pressure</td>
</tr>
<tr>
<td></td>
<td>Intermediate (8–15)</td>
<td>Grey zone (additional parameters necessary)</td>
</tr>
<tr>
<td>Mitral inflow E/A ratio&lt;sup&gt;b&lt;/sup&gt;</td>
<td>‘Restrictive’ (&gt;2)</td>
<td>High LV filling pressure</td>
</tr>
<tr>
<td></td>
<td>‘Impaired relaxation’ (&lt;1)</td>
<td>Delayed LV relaxation</td>
</tr>
<tr>
<td></td>
<td>Normal (1–2)</td>
<td>Normal LV filling pressure</td>
</tr>
<tr>
<td></td>
<td>Inconclusive (may be ‘pseudonormal’)</td>
<td></td>
</tr>
<tr>
<td>Mitral inflow during Valsalva manoeuvre</td>
<td>Change of the ‘pseudonormal’ to the ‘impaired relaxation’ pattern (with a decrease in E/A ratio ≥0.5)</td>
<td>High LV filling pressure (unmasked through Valsalva)</td>
</tr>
<tr>
<td>(A pulm–A mitral) duration</td>
<td>&gt;30 ms</td>
<td>High LV filling pressure</td>
</tr>
</tbody>
</table>

ESC Guidelines 2012
Distribution of Ejection Fraction
CHARM

Ejection Fraction by Echo is a ± 7 Point Measurement

Solomon et al. CHARM Investigators, Circulation 2005
Prognostic Value of Ejection Fraction in HFpEF: CHARM

Event Rate (per 100 patient-years)

Ejection Fraction

<= 40
40-45
45-50
50-55
> 55

Adapted from Solomon et al. CHARM Investigators. Circulation 2005
Study Design

Patients with HFNEF and HFREF

Endomyocardial biopsies and primary human cardiac fibroblast cell culture

Gene expression changes for genes involved in cardiac dilation?
**Left Atrial Function Predicts Heart Failure Hospitalization in Subjects With Preserved Ejection Fraction and Coronary Heart Disease**

Longitudinal Data From the Heart and Soul Study

855 subjects with CAD and LV EF >50%, f-u 7.9 years

Log-rank test p < 0.001

Left atrial functional index (LAFI) =

LA emptying fraction x LVOT VTI / LA end-systolic volume/BSA

Welles CC, JACC 1012; 59: 673-680
I-Preserve: Analysis of baseline cardiac structure/function on outcome

echo substudy of I-preserve trial, n=745
LVH or concentric remodelling present in 59%, LA enlargement in 66%

increased LV mass, mass/volume ratio and LA size independently predicted morbidity and mortality in multivariate analysis

Zile et al., Circulation 2011; 124: 2491-2501
Left Atrial Function Predicts Heart Failure Hospitalization in Subjects With Preserved Ejection Fraction and Coronary Heart Disease

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Left atrial functional index (LAFI) =

\[
\text{LAFI} = \frac{\text{LA emptying fraction} \times \text{LVOT VTI}}{\text{LA end-systolic volume}/\text{BSA}}
\]

log-rank test $p < 0.001$

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increased LV mass, mass/volume ratio and LA size independently predicted morbidity and mortality in multivariate analysis

Zile et al., Circulation 2011; 124: 2491-2501
But is this the hallmark of the disease?

• Cardiac dysfunction is a dynamic phenomenon during exercise in HFnEF and may not be predicted by resting diastolic parameters

• Diastolic abnormalities are common in the elderly and patients may have an alternate cause for their breathlessness
Summary

• Current criteria for the diagnosis of HFnEF are based on resting parameters

• When E/E’ is markedly raised in the appropriate clinical scenario the diagnosis of HFnEf is reasonable (but still not certain based on exercise criteria)

• However exercise testing may add substantially to diagnostic accuracy in other cases
5. Results

Baseline characteristics:

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAS- No n=3,673</th>
<th>RAS- Yes n=12,543</th>
<th>Standard difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAS-agent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>0%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>ARB alone</td>
<td>0%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>ACEi + ARB</td>
<td>0%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>80±10</td>
<td>74±11</td>
<td>46***</td>
</tr>
<tr>
<td><strong>Gender, female</strong></td>
<td>54%</td>
<td>44%</td>
<td>19***</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15%</td>
<td>16%</td>
<td>4***</td>
</tr>
<tr>
<td>II</td>
<td>41%</td>
<td>51%</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>38%</td>
<td>30%</td>
<td>16</td>
</tr>
<tr>
<td>IV</td>
<td>7%</td>
<td>2%</td>
<td>27</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49%</td>
<td>36%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td>64%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine clearance, mL/min</strong></td>
<td>51±30</td>
<td>67±34</td>
<td>49***</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>5,758±8,505</td>
<td>3,529±5,101</td>
<td>38***</td>
</tr>
</tbody>
</table>

*** p<0.001; * p<0.05

Overall cohort: Treated patients: younger and healthier
Baseline characteristics:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort</th>
<th>Matched cohort</th>
<th>Standard difference</th>
<th>RAS- No n=3,329</th>
<th>RAS- Yes n=3,329</th>
<th>Standard difference</th>
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</thead>
<tbody>
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<td>RAS- No n=3,673</td>
<td>RAS- Yes n=12,543</td>
<td>Standard difference</td>
<td>RAS- No n=3,329</td>
<td>RAS- Yes n=3,329</td>
<td>Standard difference</td>
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<td>ACEi</td>
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<td>73%</td>
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<td>73%</td>
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</tr>
<tr>
<td>ARB alone</td>
<td>0%</td>
<td>25%</td>
<td></td>
<td>0%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>ACEi + ARB</td>
<td>0%</td>
<td>2%</td>
<td></td>
<td>0%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>80±10</td>
<td>74±11</td>
<td>46***</td>
<td>79±10</td>
<td>79±10</td>
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</tr>
<tr>
<td>Gender, female</td>
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<tr>
<td>NYHA class</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15%</td>
<td>16%</td>
<td>4***</td>
<td>15%</td>
<td>17%</td>
<td>6*</td>
</tr>
<tr>
<td>II</td>
<td>41%</td>
<td>51%</td>
<td>21</td>
<td>42%</td>
<td>44%</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>38%</td>
<td>30%</td>
<td>16</td>
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</tr>
<tr>
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<td>7%</td>
<td>2%</td>
<td>27</td>
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<td></td>
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<td>39%</td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td>64%</td>
<td>47%</td>
<td></td>
<td>63%</td>
<td>61%</td>
<td></td>
</tr>
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<td>49***</td>
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<td>52±29</td>
<td>2</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>5,758±8,505</td>
<td>3,529±5,101</td>
<td>38***</td>
<td>5,192±7,573</td>
<td>4,577±6,070</td>
<td>9</td>
</tr>
</tbody>
</table>

*** p<0.001; * p<0.05

Overall cohort: Treated patients: younger and healthier
Matched cohort: No difference
7. Results

Propensity score for RAS-antagonist

Propensity scores

Different

Similar
Heart Failure with Preserved Ejection Fraction – HFpEF:

- As common and possibly as lethal as HF reduced EF
- Renin-angiotensin system (RAS) activation → fibrosis, hypertrophy, diastolic dysfunction
- But RAS-antagonists in randomized controlled trials: no reduction in primary endpoints:

CHARM-Preserved:
CV death or HF hospitalization
Yusuf, Lancet 2003

PEP-CHF:
Death or HF hospitalization
Cleland, EHJ 2006

I-PRESERVE:
Death or CV hospitalization
Massie, NEJM 2008

But signals toward benefits
And were trials under-powered?
3. Background

Hypothesis:

RAS-antagonists are associated with reduced all-cause mortality in a broad un-selected HFpEF population