Treatment of HFPEF: evidence (or lack of it) and clinical approach

Adriaan Voors, MD, PhD, Cardiologist
Professor of Cardiology, UMC Groningen, Netherlands
Prevalence of Diastolic Heart Failure

Consecutive patients hospitalised for HF in Olmsted county 1987-2001; 6076 CHF patients, EF >50% vs. EF <50%

Increasing prevalence of DHF patients

Number of hospitalizations for SHF decreasing but DHF increasing

Owan et al. NEJM 2006
Treatment of HFPEF: ESC Guidelines

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFPEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF.
Treatment of HFPEF: options

- Diuretics
- ACE-inhibitors/ARBs
- Beta-blockers
- Calcium-channel blockers
- Digoxin
- Statins
Treatment of HFPEF: diuretics

ALLHAT: n=42418 high risk hypertension patients

Figure 1. Validated hospitalized HF. Validated HF by PEF, REF, and no EF data categories by treatment group (A through D, chlorthalidone [solid line]/amlodipine [dashed and dotted line]/lisinopril [dotted line]; E through H, chlorthalidone [solid line]/doxazosin [dashed and dotted line]).
Treatment of HFPEF: diuretics

The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction

G W K Yip, M Wang, T Wang, S Chan, J W H Fung, L Yeung, T Yip, S-T Lau, C-P Lau, M-O Tang, C-M Yu, J E Sanderson

Heart 2008
Hong Kong DHF trial

150 HFPEF patients; LVEF >45%; mean age 74 years; 60% female; Primary endpoints QOL and echo: NO DIFFERENCE IN QOL

**Figure 1** Quality of life scores (QoL) in the three treatment groups over 1 year. *p<0.01, significant differences between baseline and follow-up at 12 weeks, 24 weeks or 1 year.
Hong Kong DHF trial

150 HFPEF patients; LVEF >45%; mean age 74 years; 60% female; Primary endpoints QOL and echo; NO DIFFERENCE IN ECHO
Treating diastolic heart failure

Adriaan A Voors, Richard M de Jong

Unfortunately, the Hong Kong diastolic heart failure study does not provide solid evidence that an ACE inhibitor or an ARB has additional effects to those of diuretics on improvement of symptoms and measures of diastolic function in patients with diastolic heart failure.
Treatment of HFPEF: options

• Diuretics
• ACE-inhibitors/ARBs
• Beta-blockers
• Calcium-channel blockers
• Digoxin
• Statins
Treatment of HFPEF: ACEi/ARBs

VALIDDD: 384 pts with hypertension and evidence of diastolic dysfunction, randomized to valsartan (320 mg) or placebo. NO EFFECT ON DIASTOLIC FUNCTION

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>38 weeks</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valsartan (n=186)</td>
<td>Placebo (n=198)</td>
<td>Valsartan (n=166)</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>7.5 (1.3)</td>
<td>7.5 (1.2)</td>
<td>8.1 (1.8)</td>
</tr>
<tr>
<td>A' (cm/s)</td>
<td>9.3 (2.4)</td>
<td>9.2 (2.4)</td>
<td>9.1 (2.4)</td>
</tr>
<tr>
<td>S' (cm/s)</td>
<td>6.2 (1.3)</td>
<td>6.4 (1.4)</td>
<td>6.5 (1.5)</td>
</tr>
<tr>
<td>E/E'</td>
<td>10.0 (2.7)</td>
<td>9.7 (2.6)</td>
<td>9.8 (3.1)</td>
</tr>
</tbody>
</table>

Lancet 2008
Treatment of HFPEF: ACEi/ARBs

VALIDD: 384 pts with hypertension and evidence of diastolic dysfunction, randomized to valsartan (320 mg) or placebo. BP ↓ = Diastolic Function ↑
Effects of Eprosartan on Diastolic Function and Neurohormones in Patients with Hypertension and Diastolic Dysfunction

Adriaan A. Voors • Ruud M. van de Wal • Jasper W. L. Hartog • Richard G. Vijn • Yoran M. Hummel • Thijs W. M. Plokker • Dirk J. van Veldhuisen • Wybren Jaarsma

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Treatment of HFPEF: ACEi/ARBs

EEND: 97 patients with hypertension, LVEF>0.50, and evidence of diastolic dysfunction, randomized to eprosartan or other anti-hypertensives
Treatment of HFPEF: ACEi/ARBs

EEND: 97 patients with hypertension, LVEF>0.50, and evidence of diastolic dysfunction, randomized to eprosartan or other anti-hypertensives.

Cardiovasc Drugs Ther 2010
## Treatment of HFPEF: ACEi/ARBs

<table>
<thead>
<tr>
<th></th>
<th>Charm-Preserved</th>
<th>PEP-CHF</th>
<th>I-PRESERVE</th>
</tr>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Candesartan 32 mg vs. Placebo</td>
<td>Perindopril 4 mg vs. Placebo</td>
<td>Irbesartan 300 mg vs. Placebo</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>3023</td>
<td>850</td>
<td>4128</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>67 years</td>
<td>75 years</td>
<td>72 years</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>40</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td>&gt;40% (54)</td>
<td>&gt;40% (64)</td>
<td>&gt;45% (60)</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>CV-death or HF-hosp</td>
<td>Death or HF-hosp</td>
<td>Death or CV-hosp</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>37 months</td>
<td>25 months</td>
<td>50 months</td>
</tr>
</tbody>
</table>
Effect of ACEi in DHF: PEP-CHF

850 DHF patients, mean age 75 years, 55% female; mean LVEF 64%
Primary endpoint: Death or HF-hospitalization after 3 years.
Effects of ARB in DHF: CHARM-preserved

Hazard ratio 0.89
(95% CI 0.77–1.03), p=0.118
Adjusted hazard ratio 0.86, p=0.051

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

Time (years)

Number at risk

Candesartan 1514 1458 1377 833 182
Placebo 1509 1441 1359 824 195

Yusuf et al. Lancet 2003
Effects of ARB in DHF: I-PRESERVE

Massie et al. NEJM 2008
Treatment of HFPEF: options

- Diuretics
- ACE-inhibitors/ARBs
- Beta-blockers
- Calcium-channel blockers
- Digoxin
- Statins
## Treatment of HFPEF: Betablockers

### Table 3: Overview of trials using a β-blocker in post-myocardial infarction patients with normal left ventricular ejection fraction (LVEF) or in patients with diastolic heart failure (DHF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compound</th>
<th>Duration</th>
<th>Ref</th>
<th>Patient population</th>
<th>Systolic LV function</th>
<th>Diastolic LV dysfunction</th>
<th>Positive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow</td>
<td>Propranolol</td>
<td>32 months</td>
<td>w21</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td>Mortality –30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prior MI</td>
<td></td>
<td></td>
<td>LVEF, LV mass</td>
</tr>
<tr>
<td>Dobre</td>
<td>β-blockers</td>
<td>25 months</td>
<td>w22</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td>Mortality –43%</td>
</tr>
<tr>
<td>COHERE</td>
<td>Carvedilol</td>
<td>1 year</td>
<td>w23</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td>Mortality –6% hospital</td>
</tr>
<tr>
<td>SWEDIC</td>
<td>Carvedilol</td>
<td>6 months</td>
<td>w24</td>
<td>HF</td>
<td>LVEF &gt;45%</td>
<td>E/A &lt;1.0</td>
<td>E/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wall motion score</td>
<td></td>
<td>IVRT &gt;85 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ard-Ad &gt;20 ms</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>Nebivolol</td>
<td>12 months</td>
<td>16</td>
<td>HF</td>
<td>LVEF &gt; 35%</td>
<td></td>
<td>Mortality + hospital. –14%</td>
</tr>
<tr>
<td></td>
<td>Nebivolol or atenol</td>
<td>6 months</td>
<td>w26</td>
<td>HF V̇O₂ max ↓</td>
<td>LVEF &gt; 50%</td>
<td>PCW-R &gt; 12 mm Hg</td>
<td>LV mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVEDD &lt; 60 mm</td>
<td></td>
<td>PCW-Ex &gt; 20 mm Hg</td>
<td>E/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Only nebivolol V̇O₂, PCW</td>
</tr>
</tbody>
</table>

Ard, duration of reverse pulmonary vein atrial systole flow; Ad, duration of mitral valve atrial wave flow; E/A, ratio of early (E) to late (A) mitral valve flow velocity; hospital., hospitalisation; HF, heart failure; IVRT, isovolumetric relaxation time; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; MI, myocardial infarction; PCW-Ex, pulmonary capillary wedge pressure during exercise; PCW-R, pulmonary capillary wedge pressure at rest.

Heart 2010; 96:1147–1153. doi:10.1136/hrt.2009.169052

1151
Treatment of HFPEF: Betablockers

SWEDIC-Trial: Double-blind, randomised 70 vs.70
Carvedilol 2x 25-50 mg/d vs. Placebo

Improved diastolic function and QoL only in those with high heart rate at inclusion

![Graphs showing E/A ratio improvement with carvedilol compared to placebo in high and low heart rate groups](image)

Bergström et al. Eur J Heart Fail 2004
Beta-Blockade With Nebivolol in Elderly Heart Failure Patients With Impaired and Preserved Left Ventricular Ejection Fraction

Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)

Dirk J. van Veldhuisen, MD,* Alain Cohen-Solal, MD,† Michael Böhm, MD,‡ Stefan D. Anker, MD,§ Daphne Babalis, MSc,|| Michael Roughton, PhD,|| Andrew J. S. Coats, MD,¶ Philip A. Poole-Wilson, MD,|| Marcus D. Flather, MBBS,|| on behalf of the SENIORS Investigators

Groningen, the Netherlands; Paris, France; Homburg/Saar and Berlin, Germany; London, United Kingdom; and Sydney, Australia
Treatment of HFPEF: Betablockers

Figure 1: Kaplan-Meier Curve of Primary Outcome

Kaplan-Meier curve of primary outcome (all-cause mortality or cardiovascular hospitalization) for impaired (≤35%) and preserved (>35%) ejection fraction (EF) group for nebivolol (dotted line) versus placebo (solid line).
Treatment of HFPEF: options

- Diuretics
- ACE-inhibitors/ARBs
- Beta-blockers
- Calcium-channel blockers
- Digoxin
- Statins
Usefulness of Verapamil for Congestive Heart Failure Associated with Abnormal Left Ventricular Diastolic Filling and Normal Left Ventricular Systolic Performance

John F. Setaro, MD, Barry L. Zaret, MD, Douglas S. Schulman, MD, Henry R. Black, MD, and Robert Soufer, MD

**FIGURE 1.** Protocol for crossover study of verapamil, congestive heart failure and abnormal diastolic function. Groups I and II received verapamil and placebo, respectively, and then crossed over to the alternate treatment. Evaluations (*) by congestive heart failure (CHF) score, exercise treadmill test, left ventricular ejection fraction, peak filling rate and dosage adjustment (**) were conducted at the time points shown.
Main Findings

In 20 men with CHF; age 68; LVEF>45%; and evidence of abnormal filling rates:

• Verapamil significantly increased exercise capacity by 33%
• Verapamil significantly increased ventricular filling rate by 30%
• Significantly more improvement in heart failure score compared to placebo
Treatment of HFPEF: options

- Diuretics
- ACE-inhibitors/ARBs
- Beta-blockers
- Calcium-channel blockers
- Digoxin
- Statins
Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure
The Ancillary Digitalis Investigation Group Trial

Ali Ahmed, MD, MPH; Michael W. Rich, MD; Jerome L. Fleg, MD; Michael R. Zile, MD; James B. Young, MD; Dalane W. Kitzman, MD; Thomas E. Love, PhD; Wilbert S. Aronow, MD; Kirkwood F. Adams, Jr, MD; Mihai Gheorghiade, MD

988 pts with SR and LVEF>45%
Age 67 mean EF 55%; 40% female
Follow-up: 37 months
Primary outcome: HF-hosp or HF death
Treatment of HFPEF: options

- Diuretics
- ACE-inhibitors/ARBs
- Beta-blockers
- Calcium-channel blockers
- Digoxin
- Statins
137 patients with HF and LVEF≥50%. Aim: Effect of baseline treatment on survival Follow-up 21 months; Age 65; 57% female; 80% Hypertension

<table>
<thead>
<tr>
<th>TABLE 3. Univariate and Adjusted RR of Medications for All-Cause Death by Cox Proportional Hazards Regression Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Calcium blocker</td>
</tr>
</tbody>
</table>
Conclusions

• HFPEF Patients with hypertension and AMI should be treated according to these guidelines
• no evidence-based recommendations for “pure” HFPEF
• Diuretics in case of fluid retention
• In clinical practice, most patients receive RAS-inhibitor: many studies, conflicting evidence
• Differential effects of drugs in HFREF and HFPEF indicate two different disease entities