Optimal treatment of heart failure with preserved LV systolic function (HF-PSF)

Jun Kwan
Dept. of Cardiology
Inha University Hospital
What is HF-PSF?

- Definition of HF-PSF:
  HF with EF > 45 -50%

- But, still controversial in both pathology & terminology
Is LV systolic function really preserved in HF-PSF?
EF is imperfect to assess LV systolic function

- Outcome data of volume reduction
- Load dependent
  - preload: high EF ≠ good contractility in severe MR
  - afterload: low EF ≠ poor contractility in severe AS
- Not reflect intrinsic muscle function
Technical Pitfalls of EF

- Identification of endocardial border
- Rhythm
  - beat to beat variation in AF or VPC
- Load dependent
- Geometry of LV
  - reduced midwall shortening in LVH
If LV systolic function is preserved, HF-PSF = Diastolic HF?

Causes of HF-PSF

• Diastolic HF: pure DHF + DHF with subtle SHF
• Valvular HD
• Pericardial disease
• HF due to circulatory cause
• Cor pulmonale
HF-PSF as a hybrid within the spectrum of HF phenotype
General course of HF

EF: 55-60%  
Systolic activation

EF: 45-55%  
Mild systolic dysfunction  
But, preserved pump function

EF < 45%  
Pump failure

LVH  
Adverse LV remodeling

Time

Brutsaert DL ACC 2005
Preserved left ventricular systolic function

Reduced left ventricular systolic function
Spectrum of HF phenotype

Cardiac dysfunction

Minor change

Major change

NYHA class

I

II

III

IV

Subtle systolic abnormality

Diastolic Pump failure

Global systolic Pump failure

HF-PSF

HF-RSF

Spectrum of HF phenotype

Brutsaert DL ACC 2005
**Stages of HF from ACC/AHA Guideline**

**Stage A:** identifies the patient who is at high risk for developing HF

**Stage B:** refers to a patient with structural disorder of the heart but who has never developed symptoms of HF

**Stage C:** denotes the patient with past or current symptoms of HF

**Stage D:** designates the patient with end stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care
• Pure DHF or advanced SHF is the extreme of either side of HF

• HF-PSF is one of the hybrids within the spectrum of HF phenotype
Clinical significance of HF-PSF

- Not a minor clinical SD any more
  30-60% of HF

- Lower mortality than HF-RSF, but still 30-45% mortality during 4-5 year

- Comparable degree of morbidity
Euroheart Failure: Distribution of left ventricular ejection fraction

11,322 patients from 115 hospitals in 24 countries

% Patients

% Left ventricular ejection fraction

M > F

M < F

Women

Men

Cleland et al, EHJ 2003
Kaplan-Meier survival plots of CHF patients with normal and reduced LVEF

Vasan et al. JACC 1999
<table>
<thead>
<tr>
<th>Study—Year of Publication</th>
<th>No. of Patients (% DHP)</th>
<th>Mean Age (yrs)</th>
<th>CHF Diagnosis</th>
<th>Mortality—SHF</th>
<th>Mortality—DHP</th>
<th>p Value SHF vs. DHP Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies where mean age &lt; 65 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnowicz—1983 (22)</td>
<td>39 (41%)</td>
<td>DHF 63 ± 9 SHF 66 ± 11</td>
<td>Acute pulmonary edema</td>
<td>30% (9 mo)</td>
<td>25% (9 mo)</td>
<td>NS</td>
</tr>
<tr>
<td>Kinney—1989 (11)</td>
<td>91 (48%)</td>
<td>All 64 ± 10</td>
<td>2 major or 1 major + 1 minor§ VO₂max &lt; 25 ml/kg/min</td>
<td>Median SURVIVAL = 11 mo</td>
<td>Median SURVIVAL = 26 mo</td>
<td>0.01</td>
</tr>
<tr>
<td>Cohn—1990 (12)</td>
<td>623 (13%)</td>
<td>DHF 60 ± 7 SHF 58 ± 8</td>
<td>19% (annualized)</td>
<td>8% (annualized)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Ghalili—1992 (13)</td>
<td>78 (28%)</td>
<td>DHF 60 ± 9</td>
<td>24% (1 yr)</td>
<td>22% (1 yr)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>SHF 59 ± 14</td>
<td>46% (2 yr)</td>
<td>26% (2 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies where mean age &gt; 65 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aronow—1990 (14)</td>
<td>166 (40%)</td>
<td>DHF 84 ± 6</td>
<td>Rales + CXR vascular congestion</td>
<td>47% (1 yr)</td>
<td>22% (1 yr)</td>
<td>0.001</td>
</tr>
<tr>
<td>SHF 81 ± 8</td>
<td>71% (2 yr)</td>
<td>38% (2 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taffet—1992 (15)</td>
<td>94 (43%)</td>
<td>DHF 82 ± na SHF 83 ± na</td>
<td>Framingham</td>
<td>≈ 24% (1 yr)</td>
<td>≈ 24% (1 yr)</td>
<td>NS</td>
</tr>
<tr>
<td>≈ 42% (2 yr)</td>
<td>≈ 30% (2 yr)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDermott—1997 (16)</td>
<td>192 (46%)</td>
<td>DHF 73 ± na SHF 72 ± na</td>
<td>Framingham</td>
<td>35% (27 mo)</td>
<td>35% (27 mo)</td>
<td>NS (0.78)</td>
</tr>
<tr>
<td>Kupari—1997 (17)</td>
<td>41 (51%)</td>
<td>ALL ≥ 80</td>
<td>Other†</td>
<td>54% (4 yr)</td>
<td>43% (4 yr)</td>
<td>NS</td>
</tr>
<tr>
<td>Perimaskil—1997 (19)</td>
<td>501 (34%)</td>
<td>DHF 81 ± 6</td>
<td>Other‡</td>
<td>38% (1 yr)</td>
<td>28% (1 yr)</td>
<td>p = 0.045</td>
</tr>
<tr>
<td>SHF 78 ± 6</td>
<td>19% (3–12 mo)</td>
<td>17% (3–12 mo)</td>
<td>p = NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semn—1998 (5)</td>
<td>137 (43%)</td>
<td>DHF 78 ± 12 SHF 74 ± 13</td>
<td>Framingham</td>
<td>24% (1 yr)</td>
<td>24% (1 yr)</td>
<td>NS (0.569)</td>
</tr>
<tr>
<td>McAlister—1999 (18)</td>
<td>566 (21%)</td>
<td>DHF 69 ± 14 SHF 65 ± 14</td>
<td>Framingham</td>
<td>42% (3 yr)</td>
<td>42% (3 yr)</td>
<td>NS (0.25)</td>
</tr>
<tr>
<td>Vasan—1999 (4)</td>
<td>73 (51%)</td>
<td>DHF 72 ± 9 SHF 74 ± 7</td>
<td>Framingham</td>
<td>64% (3 yr)</td>
<td>32% (5 yr)</td>
<td>p = 0.023</td>
</tr>
<tr>
<td>Ansari—2001 (abstr) (23)</td>
<td>376 (27%)</td>
<td>ALL 72 ± na</td>
<td>Framingham</td>
<td>20% (20 mo)</td>
<td>20% (20 mo)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Treatment of “HF-PSF”

The theory: Hundreds of papers

The evidence: Virtually none!!
Theoretical treatment of HF-PSF

- Sx targeted Tx
  Consider pathophysiology
- Disease targeted Tx
- Mechanism targeted Tx
Sx targeted Tx

Decrease diastolic pressure

- Reduce LV volume with diuretics or nitrate
- Enhance LV relaxation
- Maintain atrial contraction: keep sinus rhythm
- Prevent tachycardia or rate control in A fib. with HR limiting Ca antagonist or beta blocker:
- Use inotropic agents with caution (prevent excess contractility)
Consider Pathophysiology

(Pressure-Volume Loop in HF-PSF)

Even small volume reduction may be quite effective for Sx improvement.

- DHF
- Increase contractility & myocardial mass
- Increase afterload
- Diastolic dysfunction

ESPVR
EDPVR
EDPVR'
LV pressure (mmHg)
LV volume (ml)
Consider Pathophysiology
(Frank-Starling LV Function Curve)

Even small volume reduction may result in significant BP decrease
Disease targeted Tx

Resolve causative and aggravating factor

- **HiBP**: JNC targeted BP control with ACE I or ARB
- **AS or LVOT obstruction**: Surgical resolution
  - prevent or regress LVH
  - reduce mortality and morbidity
- **CAOD**: prevent / treat myocardial ischemia
Mechanism Targeted Treatment

- Modify myocardial and extramyocardial mechanism
- Modify intracellular and extracellular mechanism

Blunt neurohormonal activation
Prevent / regress LVH
Angiotensin II
Direct and indirect effects in organ damage

Angiotensin II → AT₁ receptor

↓ Glomerular filtration rate
Proteinuria / albuminuria
Glomerulosclerosis
↑ Aldosterone release

Renal failure

Heart failure
Myocardial infarction
Arrhythmia

Death

Left ventricular hypertrophy
Fibrosis
Remodelling
Apoptosis

Myocardial infarction
Arrhythmia

Stroke
Hypertension

Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction
Atherosclerosis

Inhibition of the Renin Angiotensin System

Angiotensinogen

Renin

Ang I

ACE

Ang II

ACE-Inhibitor

AT₁-Receptor Blocker

AT₁

AT₂

ACE-independent ANG II-Formation

ANG II

Bradykinin

Frag ments
Differences between pharmacological treatment of HF-RSF and HF-PSF

<table>
<thead>
<tr>
<th></th>
<th>HF-RSF</th>
<th>HF-PSF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td>high dose</td>
<td>smaller dose</td>
</tr>
<tr>
<td><strong>ACE, ARB</strong></td>
<td>increase CO</td>
<td>BP control</td>
</tr>
<tr>
<td></td>
<td>prevent LV dilatation</td>
<td>prevent, regress LVH</td>
</tr>
<tr>
<td></td>
<td>need titration</td>
<td>yes or no titration</td>
</tr>
<tr>
<td><strong>B blocker</strong></td>
<td>B receptor ↑</td>
<td>slow HR, LV filling ↑</td>
</tr>
<tr>
<td></td>
<td>need titration</td>
<td>no titration</td>
</tr>
<tr>
<td><strong>Ca antagonist</strong></td>
<td>contra-Ix</td>
<td>slow HR, improve relaxation</td>
</tr>
</tbody>
</table>
Treatment of “HF-PSF”

The theory: Hundreds of papers

The evidence: Virtually none!!
Lack of Clinical Evidence

All evidence based therapy is for patients with low LVEF CHF

How should CHF with “preserved LV systolic function” (or “diastolic dysfunction”) be treated?
Randomised trials in HF-PSF

Symptoms/functional capacity as endpoints
Published randomised trials of treatment of “diastolic heart failure”

- Calcium channel blocker
  - 2 placebo-controlled trials with Verapamil (n ~20)
    - Improve Sx, exercise tolerance
      - Philbin et al. Am Heart J 1997
      - Serato et al. Am J Cardiol 1990

- ACE inhibitor
  - Philbin et al. Am Heart J 1997
    - 350 pts of EF ≥ 40% but non-randomised
  - Aronow et al. Am J Cardiol 1993 (Enalapril)
    - 21 pts of >80 yrs, EF ≥ 50%
    - Improve CT ratio, EF, NYHA class and exercise tol.
    - too small No, uncontrolled, not double-blind
Randomised trials in HF-PSF

Morbidity/mortality outcomes as endpoints
Randomised trials of treatment of HF-PSF

**Completed**
- Beta-blocker (propranolol)
- Digitalis glycoside (digoxin)
- ARB (candesartan)

**Ongoing**
- ACE inhibitor (perindopril)
- Beta-blocker (nebivolol)
- ARB (irbesartan)

**Proposed**
- Aldosterone-blocker (spironolactone/eplerenone?)
Beta-blocker - propranolol

- Randomised trial: *lack of placebo (control) group*

- 158 patients ≥62 (mean 81 yrs) with NYHA II/III CHF, ≥ 2 months diuretic therapy, prior Q-wave (≥ 6months) MI and LVEF ≥ 0.40

- Excluded valve disease, COPD

- Propranolol 30mg tid or no propranolol for 32 months

Aronow et al, Am J Cardiol 1997;2:207-9
Effects of propranolol in HF-PSF

Incidence (%)

- Mortality: 76 (Placebo), 56* (Propranolol)
- Risk of death or non-fatal MI: 82 (Placebo), 59+ (Propranolol)

* p=0.007
† p=0.002
Digoxin in HF-PSF

**GOOD?**
- Reduces HR and favorable autonomic actions
  - sympatho-inhibitory
  - pro-parasympathetic
  - suppress RAAS

**BAD?**
- Increases intracellular calcium and impairs myocardial relaxation?
Digitalis investigation group

- 7,788 patients with CFH
- NYHA Class I-IV
- Sinus rhythm
- LVEF ≤0.45 main trial (n=6800)
  LVEF ≥0.45 ancillary trial (n=988)
- Qualitatively similar effects on mortality/morbidity in the LVEF ≥ 0.45 subgroup
  No further information
CHARM Program

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

Primary outcome for each trial: CV death or CHF hospitalisation

The first major outcome study in this type of CHF to complete
CHARM-Preserved: Primary outcome

CV death or CHF hospitalisation

placebo

relative RR: 11%

Candesartan

HR 0.89 (95% CI 0.77 - 1.03), p=0.118
Adjusted HR 0.86, p=0.051

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>1514</td>
<td>1458</td>
<td>1377</td>
<td>833</td>
<td>182</td>
</tr>
<tr>
<td>Placebo</td>
<td>1509</td>
<td>1441</td>
<td>1359</td>
<td>824</td>
<td>195</td>
</tr>
</tbody>
</table>

Candesartan

366 (24.3%)

Placebo

333 (22.0%)
### CHARM-Preserved: Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Candesartan</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>p-value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death CHF hosp.</td>
<td>333</td>
<td>366</td>
<td>0.89</td>
<td>0.118</td>
</tr>
<tr>
<td>CV death</td>
<td>170</td>
<td>170</td>
<td>0.99</td>
<td>0.918</td>
</tr>
<tr>
<td>CHF hosp.</td>
<td>241</td>
<td>276</td>
<td>0.85</td>
<td>0.072</td>
</tr>
<tr>
<td>CV death, CHF hosp, MI</td>
<td>365</td>
<td>399</td>
<td>0.90</td>
<td>0.078</td>
</tr>
<tr>
<td>CV death, CHF hosp, MI, stroke</td>
<td>388</td>
<td>429</td>
<td>0.88</td>
<td>0.123</td>
</tr>
<tr>
<td>CV death, CHF hosp, MI, stroke, revasc</td>
<td>460</td>
<td>497</td>
<td>0.91</td>
<td>0.126</td>
</tr>
</tbody>
</table>

Candesartan better than placebo.
CHARM-Preserved:
Investigator reported CHF hospitalisations

- Proportion of patients (%): HR 0.85, p=0.017
- Number of episodes: RRR 29%, p=0.014

**Patients hospitalised**

**Hospitalisations**

- Placebo
- Candesartan
CHARM-Preserved:
Patients with single or multiple CHF hosps.

Number of hospitalisations

<table>
<thead>
<tr>
<th>Number of Hospitalisations</th>
<th>Placebo</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.4</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>3.9</td>
<td>3.6</td>
</tr>
<tr>
<td>≥3</td>
<td>4.2</td>
<td>2.9</td>
</tr>
</tbody>
</table>

p=0.014 test for difference in distribution
CHARM-Preserved, the largest trial of HF-PSF, provided a direct information on Tx of HF-PSF, despite a moderate benefit, that candesartan reduces the number of hospital admission for CHF.
ARBs in HF-PSF: why should they work?

- Angiotensin II seems to play a causal role in LVH
- Angiotensin II reduces LV relaxation/increases LV stiffness
- ARBs regress LVH, fibrosis and improve diastolic function
More to Evaluate

- In comparison with ACE-I?
- Same target dose as HF-RSF?
  - Not need to reduce afterload as much as HF-RSF to increase CO & prevent LV remodeling
  - Not need to suppress N-H as much as HF-RSF
  - More prominent BP lowering effect in HF-PSF with no association with clinical improvement (CHARM)
- More effective in combination with ACE-I?
Randomised trials of treatment of HF-PSF

**Completed**
- Beta-blocker (propranolol)
- Digitalis glycoside (digoxin)
- ARB (candesartan)

**Ongoing**
- ACE inhibitor
  - PEP-CHF (perindopril)
  - 1000 pts of >70yrs, EF ≥ 40%
- Beta-blocker
  - SENIORS (nebivolol)
  - 2000/3 pts of >70yrs, EF ≥ 40%
- ARB
  - I-PRESERVE (irbesartan)
  - pts of >60yrs, EF ≥ 45%

**Proposed**
- Aldosterone-blocker
  - (spironolactone/eplerenone?)
Conclusion

• Current recommendations for treatment of HF-PSF are based not only on the pathophysiological theory but also sparse data or extrapolations from trials involving related disorders (HF-RSF).

• For evidence based therapy for HF-PSF, further large randomized clinical trials, including several ongoing trials, should be initiated and completed in the future.