Heart Failure preserved Ejection Fraction

Therapeutic Targets and Interventions

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Disclosures:

1. Novartis: Speaker Honorarium
2. St. Jude / Abbott Medical: Speaker Honorarium
HFpEF is a clinical syndrome in which patients have symptoms and signs of heart failure (HF), normal or near normal left ventricular (LV) systolic function.

Diastolic heart failure (DHF) is a major cause of heart failure with preserved ejection fraction (HF-PEF).

Definitions:
HFpEF : EF > 50%
HFrEF: EF < 40%
HFpEF, borderline: : EF 40-50%
Diastolic CHF?

Understanding nondiastolic mechanisms of Heart Failure with Normal Ejection Fraction may provide further answers and, more importantly, lead to more therapeutic advances.

Prevalence

<table>
<thead>
<tr>
<th>Location</th>
<th>EF ≥ 50%</th>
<th>EF ≥ 50%</th>
<th>EF ≥ 50%</th>
<th>EF ≥ 45%</th>
<th>EF ≥ 45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham</td>
<td>N=73</td>
<td>51%</td>
<td>51%</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Olmstead</td>
<td>N=137</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
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<tr>
<td>CHS</td>
<td>N=269</td>
<td>78%</td>
<td>78%</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>CA HMO</td>
<td>N=338</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
</tr>
<tr>
<td>CA Medicare</td>
<td>N=782</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Prevalence

**Prevalence (%)**

- <50
- 50-70
- >70

**Annual Mortality (%)**

- <50
- 50-70
- >70

*Zile, Brutsaert, Circulation 2002*
Survival

Mayo Observational Study 1987-2001
Post HF Hospitalization

Survival

Years

EF ≥50%

EF <50%

No. at risk

EF <50%

EF ≥50%

2,424

1,637

1,350

1,049

813

604

2,166

1,539

1,270

1,001

758

574

Owan T et al: NEJM, 2006
Readmission

Readmissions in HFpEF

Patients readmitted for HF (%)

Studies (S) comparing HF readmission rates

Bhatia RS et al, NEJM, 2006; Hogg et al, JACC, 2004, Owan et al, Prog Cardiovas Dis, 2005
HFpEF Risk Factors

• Age: DHF > SHF
• Females: DHF > SHF
• Hypertension: DHF ≥ SHF
• Coronary Disease: DHF < SHF
• Diabetes: DHF = SHF
• Obesity: DHF ≥ SHF

Reviewed by Hogg K et al, 2004 and Owan T et al, 2005
Acute Decompensated HFpEF Precipitating Factors

• **Hypertensive Episode (50%)**
  Labile HTN
  Med non-compliance
  Diet non-compliance
  Renal artery stenosis
  Iatrogenic (NSAID, Fluids)

• **Atrial fibrillation (30%)**

• **Ischemia (?)%**

• **Comorbidities** (infection, GI bleed, post-op, etc)

Chen et al, JCF, 2002
The choice of medications in patients with DHF is determined by two factors:

1. Treatment of concomitant underlying processes: CAD, DM, HTN

2. The possible beneficial effect of the drug on the pathophysiology of DHF:
   - Regression of LVH
   - Reducing Tachycardia
   - Reducing Congestion
Regression of left ventricular hypertrophy with antihypertensive therapy

Change in left ventricular mass index, percent

Angiotensin II receptor blockers
Calcium channel blockers
ACE inhibitors
Diuretics
Beta blockers
ACEi / ARB

RAAS inhibition:
Important role in the treatment of hypertension, coronary artery disease and diabetes.
Can lead to regression of left ventricular hypertrophy
improve survival in Systolic HF, HFrEF.

No clear evidence from randomized clinical studies that ACEi/ARB therapy directly improves overall morbidity or mortality in patients with DHF.
PEP Study

- N = 850 patients ≥70 yo
- 2006
- Diastolic heart failure
- Perindopril or placebo
- Composite HF / Death

Results:
- Non-significant trend toward reduction in the primary end point (8.0 vs 12.4 percent, HR 0.69; 95% CI 0.47-1.01)
- Entirely due to fewer unexpected hospitalizations for HF.
- Also had significant improvements in functional class and six minute walk distance.

CHARM-Preserved: Results

- N = 3023 pts, symptomatic HF, LVEF > 40 percent
- (NYHA class II - III) 2003
- HFpEF, mean LVEF: 54%
- Primary endpoint: CV death or hospitalization

- Results:
  - Nonsignificant reduction in primary and secondary outcomes
  - Total number of hospital admissions for CHF significantly reduced in candesartan group
  - All-cause mortality similar in both groups (244 vs. 237 patients)

I-Preserve Trial: Irbesartan vs. placebo

Figure 1. Kaplan–Meier Curves for the Primary Outcome.

The primary outcome of death from any cause or hospitalization for prespecified cardiovascular causes (worsening heart failure, myocardial infarction, stroke, atrial or ventricular arrhythmia, and myocardial infarction or stroke occurring during hospitalization for any cause) is shown for patients receiving irbesartan and those receiving placebo. The Kaplan–Meier curves illustrate the time to the first event (hazard ratio in the irbesartan group, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P=0.35 by the log-rank test). The vertical lines represent 95% confidence intervals.

N = 4129 pts EF > 45%
mean LVEF: 59 percent

No difference in primary or secondary outcome

Barry M. Massie, M.D., et al. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction
Beta Blockers

Beta blockers: potential beneficial effects in patients with DHF:

- slowing the heart rate (which increases the time available for both LV filling and coronary flow, particularly during exercise)
- reducing myocardial oxygen demand
- lowering the blood pressure
- regression of LVH
- treating symptomatic arrhythmias (atrial fibrillation).
- Improving calcium exit from myocytes, thereby reversing the cellular calcium overload characteristic of diastolic dysfunction.
HR = 60 bpm: RR = 1000 ms

HR = 120 bpm: RR = 500 ms

Hay et al: AJP, 2005
Swedic: Carvedilol Trial

- N=113 patients, 2004
- HfPef and abnormal diastolic function
- Carvedilol or placebo
- Echocardiographic assessment.

Results:
- Significant improvement in E/A ratio

### OPTIMIZE – HF: Betablockers

<table>
<thead>
<tr>
<th>Population and Outcome</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td><strong>Left ventricular systolic dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>(n = 3,001)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.65 (0.57–0.73)</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.82 (0.75–0.90)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.79 (0.72–0.86)</td>
</tr>
<tr>
<td><strong>Preserved systolic dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>(n = 4,153)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.87 (0.77–0.97)</td>
</tr>
<tr>
<td>Readmission</td>
<td>0.96 (0.88–1.03)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.95 (0.88–1.02)</td>
</tr>
</tbody>
</table>

Seniors: Nebivolol

- Nebivolol (β1 + VD)
- Age ≥70 yrs
- HF History +
  - Hsp within 12 mo or
  - EF ≤35%
- PEP = All cause mortality + CV hospitalization
- P<0.04 for PEP (favor drug)
- No interaction between EF group (≤35% vs >35%) and drug effect
Seniors : Nebivolol Trial

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).

Mean EF : 49%

Event free survival %

Hazard Ratio 0.86 [0.74;0.99]

p = 0.039

No. of events: Nebivolol 332 (31.1%); Placebo 375 (35.3%)
Chronotropic Incompetence is common in HFpEF

Control

HFpEF

Associated with worse Aerobic capacity

\[ r = 0.7, \ p < 0.0001 \]

\[ p = 0.02 \]
### Hong Kong Diastolic Heart Failure Study

- 2008, N=150 pts HFpEF

#### Randomised:
1. diuretics alone
2. diuretics + irbesartan
3. diuretics + ramipril.

#### Results:
- QoL score improved similarly in all three groups
- 6MWT increased (average +3-6) all 3 groups.
- HTN improved in all 3 groups
- No change in LV dimensions or LVEF

#### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Diuretic alone</th>
<th>Diuretic + Irbesartan</th>
<th>Diuretic + Ramipril</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission for HF (%)</td>
<td>6 (12.2)</td>
<td>6 (11.1)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death (weeks)</td>
<td>1 (38)</td>
<td>1 (51)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other cause of death</td>
<td>2 (liver and lung cancer)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Withdrawn (%)</td>
<td>3 (6.0)</td>
<td>3 (5.3)</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>QoL score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20 (1.8)</td>
<td>19 (2.1)</td>
<td>23 (2.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>12 weeks</td>
<td>12.9 (1.5)**</td>
<td>10.8 (1.6)**</td>
<td>12.7 (1.4)**</td>
<td>0.9</td>
</tr>
<tr>
<td>24 weeks</td>
<td>10.9 (1.3)**</td>
<td>9.6 (1.2)**</td>
<td>12.9 (1.7)**</td>
<td>0.8</td>
</tr>
<tr>
<td>52 weeks</td>
<td>10.9 (1.3)**</td>
<td>9.4 (1.3)**</td>
<td>11.4 (1.4)**</td>
<td>0.7</td>
</tr>
<tr>
<td>6MWT (feet/6 mins)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1011 (37)</td>
<td>950 (37)</td>
<td>962 (42)</td>
<td>0.4</td>
</tr>
<tr>
<td>12 weeks</td>
<td>1055 (38)</td>
<td>988 (37)</td>
<td>1011 (43)</td>
<td>0.2</td>
</tr>
<tr>
<td>24 weeks</td>
<td>1048 (43)</td>
<td>1007 (33)</td>
<td>1028 (37)</td>
<td>0.8</td>
</tr>
<tr>
<td>Blood pressure (mean (SD)) (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>145 (23)/80 (12)</td>
<td>144 (19)/82 (10)</td>
<td>143 (22)/82 (10)</td>
<td>0.9</td>
</tr>
<tr>
<td>4 weeks</td>
<td>139 (21)/77 (10)**</td>
<td>134 (16)/76 (11)**</td>
<td>138 (21)/77 (12)***</td>
<td>0.3</td>
</tr>
<tr>
<td>8 weeks</td>
<td>134 (18)/76 (13)**</td>
<td>135 (18)/76 (11)**</td>
<td>139 (20)/76 (11)**</td>
<td>0.6</td>
</tr>
<tr>
<td>12 weeks</td>
<td>134 (21)/75 (12)**</td>
<td>136 (20)/76 (10)**</td>
<td>136 (18)/77 (10)***</td>
<td>0.9</td>
</tr>
<tr>
<td>24 weeks</td>
<td>138 (17)/80 (9)**</td>
<td>136 (20)/76 (12)**</td>
<td>137 (21)/76 (11)</td>
<td>0.5</td>
</tr>
<tr>
<td>52 weeks</td>
<td>138 (24)/78 (10)</td>
<td>137 (21)/73 (10)</td>
<td>141 (23)/76 (13)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Aldosterone Antagonism

Aldosterone contributes to cardiac hypertrophy and fibrosis

These processes may be preventable or even reversible by aldosterone blockade
A large NIH sponsored study, TOPCAT, is evaluating the hypothesis that *spironolactone* is beneficial in patients with a normal ejection fraction and heart failure.

**Enrollment:** 3445
*Study Start Date:* August 2006
*Estimated Study Completion Date:* June 2013
*Estimated Primary Completion Date:* June 2013 (Final data collection date for primary outcome measure)

**DESIGN NARRATIVE:**
Randomized, double-blinded, placebo-controlled trial of aldosterone antagonist therapy
15 mg dose spironolactone or placebo; titrated up to 30 or 45 mg/day)
Heart failure and preserved systolic function.
Patients were recruited from August 2006 thru 2012, followed through June 2013.
Multicenter trial
Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

N = 3445 pts
Randomized, double-blinded, placebo-controlled trial of aldosterone antagonist therapy
15 mg dose spironolactone or placebo; titrated up to 30 or 45 mg/day
Heart failure and preserved systolic function.

At a mean of 3.3 years, there was no significant difference in death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.

TOPCAT: possible benefits?

Hospitalization for HF was less frequent: \(12.0\%\) vs. \(14.2\%, \text{HR 0.83}\)

Subgroup analysis showed a significant reduction in the primary outcome among patients with high BNP or N-terminal pro-BNP criteria.

Although the test for interaction between region and study group was not significant, a lower rate of primary outcome was seen with spironolactone in the Americas (27.3 versus 31.8 percent with placebo) but not in patients enrolled in Russia and Georgia, where event rates were much lower (9.3 versus 8.4 percent with placebo).
Pfeffer et al. *Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial*. Circulation. 2014
Implantable Hemodynamic Monitor

Implantable hemodynamic monitor:

• Ability to decongest patients often difficult
• Concomitant CKD very common
• Identifying filling pressures by physical exam often difficult in our overweight population.
Champion Trial

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

Table 1. Baseline demographic characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=270)</th>
<th>Control group (n=280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>61 (13)</td>
<td>62 (13)</td>
</tr>
<tr>
<td>Male sex</td>
<td>194 (72%)</td>
<td>205 (73%)</td>
</tr>
<tr>
<td>White</td>
<td>196 (73%)</td>
<td>205 (73%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>31 (7)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (≥40%)</td>
<td>62 (23%)</td>
<td>57 (20%)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>158 (59%)</td>
<td>174 (62%)</td>
</tr>
<tr>
<td>CRT or CRT-D device</td>
<td>91 (34%)</td>
<td>99 (35%)</td>
</tr>
<tr>
<td>ICD device</td>
<td>88 (33%)</td>
<td>98 (35%)</td>
</tr>
<tr>
<td>Time from CRT, CRT-D, or ICD to CM implant (days)</td>
<td>868 (831)</td>
<td>844 (733)</td>
</tr>
</tbody>
</table>
CHAMPION CLINICAL TRIAL: PA PRESSURE-GUIDED THERAPY IMPROVES OUTCOMES IN PATIENTS WITH PRESERVED EJECTION FRACTION

- Preserved Ejection Fraction Heart Failure (HFpEF) or diastolic HF patients represent ~50% of all HF patients
- Pulmonary artery pressure-guided therapy significantly reduced HF hospitalizations in HFpEF patients in the treatment group by 46% at 6 months (p<0.0001) and by 50% at 18 months (p<0.0001)
- The effect in HFpEF patients is even more dramatic than HFrEF or systolic patients with an estimated NNT = 2

50% RRR
NNT = 2

What about Exercise?

It's not that diabetes, heart disease and obesity runs in your family. It's that no one runs in your family.
Metanalysis of Exercise trials in HFpEF
Completed Trials for HFpEF
HFpEF Trials?
Targeting Responders for Specific Interventions
Need Multifactorial Approach

% Deaths Due to Non-CV Causes
Olmsted County MN 1979-2002
1,063 Pts: 5-Year Mortality 55%; HPpEF=HFrEF

HPpEF
- CAD 29%
- Non-CAD CV 22%
- Non-CV 49%

HFrEF
- CAD 43%
- Non-CAD CV 21%
- Non-CV 36%

Henkle DM: Circ-HF 2008
Subgroup analysis of the I-preserve trial

Kao et al. EJHF 2015
HFpEF treatment pearls

1. “Garden-variety”-HFpEF: Rx BP, DM, obesity, refer for clinical trial; If AF -> trial of cardioversion
2. CAD-HFpEF: Rx like HF w/reduced EF (BB, ACE-I/ARB, revasc)
3. Right heart failure-HFpEF: diuresis / ultrafiltration, digoxin, sildenafil??
4. HCM-HFpEF: verapamil, diltiazem, long-acting metoprolol
5. High-output HFpEF: Rx underlying cause; diuretics/UF
6. Valvular HFpEF: Rx valve disease if possible
7. Rare causes of HFpEF: clinical trial, Rx underlying cause
Summary

• The treatment of HFpEF remains empiric since trial data are limited.

• General principles for treatment of DHF:
  - control of systolic and diastolic hypertension
  - control of ventricular rate
  - control of pulmonary congestion
  - coronary revascularization

• Direct evidence to support a specific drug regimen to treat HFpEF is lacking.