Heart Failure
preserved Ejection Fraction

Therapeutic Targets and Interventions

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Advocate Medical Group
Disclosures:

1. *Novartis: Speaker Honorarium*
Diastolic Heart Failure

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

- DHF is a clinical syndrome in which patients have symptoms and signs of heart failure (HF), normal or near normal left ventricular (LV) systolic function, and evidence of diastolic dysfunction (eg, abnormal LV filling and elevated filling pressures).
### HFpEF

**Heart failure with preserved ejection fraction (HFpEF)**

HFpEF (contributing factors include hypertension, aging, coronary heart disease, diabetes mellitus, sleep-disordered breathing, chronic kidney disease, and obesity)

**Cardiomyopathies with preserved ejection fraction**

- **Restrictive cardiomyopathy**
  - Familial causes include sarcomeric gene mutations, familial amyloidosis (TTR or apolipoprotein mutation), unknown gene mutation, familial causes of iron overload (hereditary hemochromatosis, hereditary anemias), Fabry disease, glycogen storage disease, desminopathy, and pseudoxanthoma elasticum
  - Non-familial causes include amyloid (AL or wild-type TTR), systemic sclerosis, endomyocardial fibrosis (idiopathic, caused by hypereosinophilic syndrome, or drugs), carcinoid heart disease, metastatic cancer, radiation, non-familial iron overload (eg, acquired iron-loading anemia, high-dietary intake) and drug toxicity (anthracycline)

- **Hypertrophic cardiomyopathy**
  - Familial causes in addition to sarcomere gene mutations include unknown mutations, glycogen storage disease, lysosomal storage disease (including Fabry disease), syndromic hypertrophic cardiomyopathy (eg, Noonan's syndrome, LEOPARD syndrome, Friedrich's ataxia), and familial amyloidosis (TTR or apolipoprotein mutation)
  - Non-familial causes include non-familial amyloidosis (AL or wild-type TTR)

- **Noncompaction cardiomyopathy**

**Valvular heart disease**

- Valvular stenosis
- Valvular regurgitation

**Right heart failure**

- Pulmonary hypertension
- Right ventricular infarction
- Arrhythmogenic right ventricular cardiomyopathy

**Pericardial disease**

- Cardiac tamponade
- Constrictive pericarditis
- Effusive-constrictive pericardial disease

**Obstructive lesion in heart or great vessel**

- Atrial myxoma
- Pulmonary vein stenosis
Prevalence

- Framingham: EF≥50% (N=73)
- Olmstead: EF≥50% (N=137)
- CHS: EF≥45% (N=269)
- CA HMO: EF≥45% (N=338)
- CA Medicare: EF≥40% (N=782)
Prevalence

Prevalence (%)

Annual Mortality (%)

Zile, Brutsaert, Circulation 2002
Heart Failure with Preserved EF

- ↑ Prevalence
  - Aging of population
  - ↑ Recognition
  - ? True ↑ prevalence

- Prevalence and pt profile varies
  - Region / Socioeconomic profile
  - Ethnicity
  - Practice type
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 left ventricular (LV) diastolic pressure versus volume relationship is significantly different in patients with diastolic heart failure (DHF) compared with systolic heart failure (SHF) patients. In this graph, the LV diastolic pressure versus volume relationship (from mitral valve opening to mitral valve closure) is plotted for normal individuals in green, patients with DHF in red, and patients with SHF in blue. In DHF, the LV diastolic pressure-volume relationship is shifted upwards, indicating a decreased distensibility. By contrast, in patients with SHF, the LV diastolic pressure versus volume relationship is shifted to rightwards, indicating an increased distensibility. It should be clear from this graph that all patients with heart failure, whether diastolic heart failure or systolic heart failure, have a significant increase in LV diastolic pressure. However, the mechanisms responsible for these increased pressures are different between these two different patient groups.
Effects of exercise on left ventricular filling dynamics

Changes in left ventricular (LV) pressure (LVP), left atrial pressure changes (LAP), and the rate of change of LVP (dV/dt) at rest and during exercise.

(Top panel) During exercise in normals, minimal LVP decreases without any change in LAP, leading to an increase in the peak mitral valve gradient and producing a higher peak filling rate (E).

(Bottom panel) In heart failure, the peak LV filling rate (E) increases during exercise due to an increase in the early transmitral valve pressure gradient. However, the gradient is produced by an increase in left atrial pressure instead of a reduction in LVP as occurs in normals.
Pathophysiology

- Reduced ventricular compliance (myocardial stiffness) and fluid retention
- Abnormal renal sodium handling and arterial stiffness, in addition to myocardial stiffness
- The majority of patients have a history of hypertension
- Most of the patients have evidence of LVH on echocardiography.
- More frequent in elderly women

Pathophysiology

Systolic HF

Normal heart

Diastolic HF

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

Non-diastolic mechanisms

• Volume overload
• Venoconstriction/volume redistribution
• Ventricular vascular coupling abnormalities
• Chronotropic incompetence
• Endothelial dysfunction
Survival

Mayo Observational Study 1987-2001
Post HF Hospitalization

No. at risk
EF <50% 2,424 1,637 1,350 1,049 813 604
EF ≥50% 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, Owne et al, Prog Cardiovas Dis, 2005
Current Treatment Options

• 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
ACE inhibitors

- ACE inhibitors —
- ACE inhibitors play an important role in the treatment of hypertension, coronary artery disease and diabetes.
- Can lead to regression of left ventricular hypertrophy
- ACE inhibitors are beneficial and improve survival in Systolic HF, HFrEF.

- No clear evidence from randomized clinical studies that ACE inhibitor therapy directly improves overall morbidity or mortality in patients with DHF.
Diastolic Indices Improve with ACEi

**TABLE 1. Hemodynamics at Baseline and in Response to Administration of Intracoronary Enalaprilat and Vehicle**

<table>
<thead>
<tr>
<th></th>
<th>Aortic Stenosis (n=20)</th>
<th>Dilated Cardiomyopathy (n=8)</th>
<th>Aortic Stenosis (n=8)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Enalaprilat</td>
<td>Baseline</td>
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<tr>
<td>Heart rate, bpm</td>
<td>73±3</td>
<td>73±3</td>
<td>77±6</td>
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<td>Right atrial pressure, mm Hg</td>
<td>7±1</td>
<td>7±1</td>
<td>9±1</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96±3</td>
<td>90±3†</td>
<td>105±5</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes · s · cm⁻⁵</td>
<td>1626±128</td>
<td>1458±102‡</td>
<td>1611±163</td>
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<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>23±3</td>
<td>22±3</td>
<td>22±1</td>
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<tr>
<td>LV systolic pressure, mm Hg</td>
<td>212±7</td>
<td>205±7§</td>
<td>148±4</td>
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<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>24±2</td>
<td>19±2‖</td>
<td>22±2</td>
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<tr>
<td>Arteriovenous oxygen difference, mL/L</td>
<td>45±2</td>
<td>46±2</td>
<td>44±2</td>
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<tr>
<td>Cardiac output, L/min</td>
<td>4.8±0.4</td>
<td>4.9±0.3</td>
<td>5.0±0.4</td>
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<tr>
<td>Peak +dP/dt, mm Hg/s</td>
<td>1761±104</td>
<td>1740±89</td>
<td>1034±64</td>
</tr>
<tr>
<td>Peak −dP/dt, mm Hg/s</td>
<td>1811±95</td>
<td>1760±85</td>
<td>1100±72</td>
</tr>
<tr>
<td>Isovolumic relaxation constant, ms</td>
<td>58±4</td>
<td>53±3</td>
<td>101±7</td>
</tr>
</tbody>
</table>

Advocate Heart Institute
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.

Angiotensin Receptor Blockers

- Angiotensin II receptor blockers (ARBs) may be beneficial in patients with left ventricular diastolic dysfunction:
  - Regression of LVH associated with an improvement in LV diastolic filling.
  - Improved exercise tolerance and quality of life
  - Reduced myocardial fibrosis and stiffness.

- Angiotensin II receptor blockers — There is no clear evidence from randomized clinical studies that ARB therapy directly improves overall morbidity or mortality in patients with DHF.
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

No difference in primary or secondary outcome

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.
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>
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<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
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<tr>
<td><strong>Left ventricular systolic dysfunction</strong> (n = 3,001)</td>
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<tr>
<td>Mortality</td>
<td>0.65 (0.57–0.73)</td>
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<tr>
<td>Readmission</td>
<td>0.82 (0.75–0.90)</td>
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<tr>
<td>Combined</td>
<td>0.79 (0.72–0.86)</td>
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<tr>
<td><strong>Preserved systolic dysfunction</strong> (n = 4,153)</td>
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<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>

OPTIMIZE – HF: Betablockers

Seniors: Nebivolol

2005
2128 pts

- 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

Advocate Heart Institute
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%

No. of events: Nebivolol 332 (31.1%); Placebo 375 (35.3%)
Hong Kong Diastolic Heart Failure Study

- 2008, N=150 pts HFP EF
- 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
Main clinical outcomes

<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>
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<tr>
<td>Cardiovascular death (weeks)</td>
<td>1 (38)</td>
<td>1 (51)</td>
<td>0</td>
<td></td>
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<tr>
<td>Other cause of death</td>
<td>2 (liver and lung cancer)</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Withdrawn (%)</td>
<td>3 (6.0)</td>
<td>3 (5.3)</td>
<td>6 (13.3)</td>
<td></td>
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<tr>
<td>QoL score</td>
<td></td>
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<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>
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<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>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1011 (37)</td>
<td>950 (37)</td>
<td>962 (42)</td>
<td>0.4</td>
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<tr>
<td>12 weeks</td>
<td>1055 (38)</td>
<td>988 (37)</td>
<td>1011 (43)</td>
<td>0.2</td>
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<tr>
<td>24 weeks</td>
<td>1048 (43)</td>
<td>1007 (33)</td>
<td>1028 (37)</td>
<td>0.8</td>
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<tr>
<td>Blood pressure (mean (SD) (mm Hg))</td>
<td></td>
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<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>
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<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>
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<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>
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<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
Improvement in left ventricular long-axis function with intervention.

• N=30 pts w/ HTN, EF >50%

• Diastolic dysfunction (E/A<1, E deceleration time>250 m/sec)

• Randomized to spironolactone 25 mg/d or placebo for 6 months

• Improvement in Strain and Strain rate at 6 months

Original Article

Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., Sonja M. McKinlay, Ph.D., for the TOPCAT Investigators

TOPCAT trial:
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

Primary Outcome:
Composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization

N Engl J Med
Volume 370(15):1383-1392
April 10, 2014
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%, HR 0.83)*

• Subgroup analysis showed a significant reduction in the primary outcome with 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).
PDE5 inhibition

- Pulmonary venous hypertension now more prevalent (>65%)
- HFPEF: freq of PHTN is very high (83%)
- Affecting 2.5 million individuals in the United States alone.
PDE5-Inhibition

44 pts, DHF with PA > 40mmHg

Baseline Hemodynamics:
RA: 23
PA: 52/29, m: 37
WP: 22
TPG: 14
PVR: 3.3 WU
LV diastolic parameters improved

<table>
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<tr>
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<th>Baseline</th>
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<tr>
<td></td>
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<td>6 mo</td>
<td>12 mo</td>
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<td>6 mo</td>
<td>12 mo</td>
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<td>Systolic arterial pressure,</td>
<td>147±17</td>
<td>149±16</td>
<td>150±14</td>
<td>150±15</td>
<td>152±13</td>
<td>154±12</td>
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<td>mm Hg,</td>
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<td>Diastolic arterial</td>
<td>84±11</td>
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<td>Mean arterial pressure,</td>
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<td>106±11</td>
<td>107±10</td>
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<td>mm Hg</td>
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<tr>
<td>Mean wedge pulmonary</td>
<td>21.9±2.0</td>
<td>22.4±1.8</td>
<td>22.2±1.6</td>
<td>22.0±2.5</td>
<td>18.7±2.3††</td>
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<tr>
<td>Cardiac index, L · min⁻¹·</td>
<td>2.33±0.64</td>
<td>2.28±0.60</td>
<td>2.32±0.56</td>
<td>2.39±0.59</td>
<td>2.49±0.62‡‡</td>
<td>2.51±0.51††</td>
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<td>m²</td>
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<td>Systemic vascular</td>
<td>2694±688</td>
<td>2809±625</td>
<td>2859±710</td>
<td>2717±721</td>
<td>3157±686††</td>
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<td>resistance index, dyne·s·</td>
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<td>cm⁻¹·m²</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>60±6</td>
<td>56±8</td>
<td>58±7</td>
<td>60±4</td>
<td>59±5</td>
<td>63±3</td>
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<td>Velocity of</td>
<td>0.79±0.1</td>
<td>0.77±0.08</td>
<td>0.78±0.09</td>
<td>0.81±0.1</td>
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<td>fiber shortening,</td>
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<tr>
<td>LV relative wall</td>
<td>0.48±0.06</td>
<td>0.50±0.04</td>
<td>0.50±0.05</td>
<td>0.49±0.07</td>
<td>0.45±0.06††</td>
<td>0.41±0.05††</td>
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<td>thickness, index</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV internal dimension, cm</td>
<td>5.0±0.3</td>
<td>5.0±0.2</td>
<td>5.1±0.2</td>
<td>5.0±0.3</td>
<td>5.3±0.2††</td>
<td>5.5±0.2††</td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>1.35±0.08</td>
<td>1.37±0.09</td>
<td>1.39±0.1</td>
<td>1.34±0.1</td>
<td>1.28±0.08††</td>
<td>1.22±0.07††</td>
</tr>
<tr>
<td>thickness, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV posterior wall</td>
<td>1.27±0.09</td>
<td>1.27±0.12</td>
<td>1.29±0.11</td>
<td>1.26±0.10</td>
<td>1.21±0.08††</td>
<td>1.15±0.08††</td>
</tr>
<tr>
<td>thickness, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>168.2±10.5</td>
<td>165.1±11.6</td>
<td>174.8±10.4</td>
<td>166.4±12.1</td>
<td>167.2±9.9</td>
<td>163.9±11.2</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>243±47</td>
<td>248±32</td>
<td>249±41</td>
<td>254±53</td>
<td>219±37††</td>
<td>218±54††</td>
</tr>
<tr>
<td>Isovolumetric relaxation</td>
<td>92±21</td>
<td>94±20</td>
<td>94±23</td>
<td>97±18</td>
<td>83±18 ††</td>
<td>80±20 ††</td>
</tr>
<tr>
<td>time, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.88±0.21</td>
<td>0.85±0.22</td>
<td>0.85±0.24</td>
<td>0.91±0.26</td>
<td>0.97±0.29††</td>
<td>0.99±0.25††</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.89±0.23</td>
<td>0.98±0.20†</td>
<td>1.10±0.13†</td>
<td>0.93±0.19</td>
<td>0.88±0.15††</td>
<td>0.86±0.10††</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.93±0.42</td>
<td>0.89±0.36</td>
<td>0.78±0.32†</td>
<td>0.95±0.36</td>
<td>1.09±0.31††</td>
<td>1.13±0.34††</td>
</tr>
<tr>
<td>E' septal, m/s*</td>
<td>0.048±0.022</td>
<td>0.046±0.026</td>
<td>0.044±0.030</td>
<td>0.051±0.029</td>
<td>0.09±0.023††</td>
<td>0.09±0.029††</td>
</tr>
<tr>
<td>E/E' ratio*</td>
<td>18.33±6.71</td>
<td>18.45±5.85</td>
<td>19.31±6.12</td>
<td>17.80±7.52</td>
<td>10.65±3.67††</td>
<td>10.64±3.73††</td>
</tr>
<tr>
<td>TE'-E, ms*</td>
<td>24±5</td>
<td>22±8</td>
<td>23±5</td>
<td>26±6</td>
<td>72±14 ††</td>
<td>3±7 ††</td>
</tr>
</tbody>
</table>
Primary Outcome Measures:

- Change in exercise capacity, as determined by peak oxygen uptake
### Table 3. Primary, Secondary, and Safety End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo</th>
<th>Variable</th>
<th>Sildenafil</th>
<th>Variable</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min</td>
<td>94</td>
<td>0.20 (-0.70 to 1.00)</td>
<td>91</td>
<td>-0.2 (-1.70 to 1.11)</td>
<td>.90</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical rank score, mean(^a)</td>
<td>94</td>
<td>95.8</td>
<td>95</td>
<td>94.2</td>
<td>.85</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>95</td>
<td>15.0 (-26.0 to 45.0)</td>
<td>90</td>
<td>5.0 (-37.0 to 55.0)</td>
<td>.92</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
<td>96</td>
<td>0.03 (-1.10 to 0.67)</td>
<td>97</td>
<td>0.01 (-1.35 to 1.25)</td>
<td>.98</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>96</td>
<td>18.0 (-14.5 to 48.0)</td>
<td>99</td>
<td>10.0 (-25.0 to 36.0)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Components of clinical rank score at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%){(^b)}</td>
<td>103</td>
<td>0</td>
<td>113</td>
<td>3 (3)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
<td>103</td>
<td>13 (13)</td>
<td>113</td>
<td>15 (13)</td>
<td>.89</td>
</tr>
<tr>
<td>Change in MLHFQ, median (IQR)</td>
<td>91</td>
<td>-8 (-21 to 5)</td>
<td>91</td>
<td>-8 (-19 to 0)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Safety end points, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103</td>
<td>78 (76)</td>
<td>113</td>
<td>90 (80)</td>
<td>.49</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>103</td>
<td>16 (16)</td>
<td>113</td>
<td>25 (22)</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire.
\(^a\)A mean value of 95 in each group is expected under the null hypothesis of no treatment effect.
\(^b\)Site investigator identified causes of death were sudden death (n = 1), progressive cardiorenal failure (n = 1), and noncardiovascular (n = 1).
## Completed trials for HF with preserved EF

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug</th>
<th>Subjects</th>
<th>Follow-up</th>
<th>Results for primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG-PEF&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Digoxin</td>
<td>n = 988, EF &gt;45%, sinus rhythm, current or past clinical symptoms, signs or radiological evidence of HF</td>
<td>37 months</td>
<td>No effect on hospitalisation or mortality; trend towards decreased HF hospitalisations ($P = 0.094$) negated by trend towards increased hospitalisations for unstable angina ($P = 0.061$).</td>
</tr>
<tr>
<td>CHARM-Preserved&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Candesartan</td>
<td>n = 3023, EF &gt;40%, NYHA II-IV, prior cardiac hospitalisation</td>
<td>36.6 months</td>
<td>No effect on cardiovascular mortality; trend towards decreased HF hospitalisations with candesartan (RRR 15%; $P = 0.072$) which only reached statistical significance after adjusting for baseline characteristics (RRR 16%; $P = 0.047$).</td>
</tr>
<tr>
<td>PEP-CHF&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Perindopril</td>
<td>n = 846, EF ≥40%, age ≥70 years, diuretics, specific clinical and echo criteria, cardiovascular hospitalisation in prior 6 months</td>
<td>26.2 months</td>
<td>No effect on mortality or HF re-hospitalisation over the entire duration of the study; at one year a reduction in HF re-hospitalisation with perindopril was observed (RRR 37%; $P = 0.033$).</td>
</tr>
<tr>
<td>I-PRESERVE&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Irbesartan</td>
<td>n = 4128, EF ≥45%, age &gt;60 years, NYHA II-IV</td>
<td>49.5 months</td>
<td>No effect on all-cause mortality or cardiovascular hospitalisation.</td>
</tr>
</tbody>
</table>
Need Multifactorial Approach

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

Advocate Heart Institute
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
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

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

William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, ...

P.E.: 46% reduction in HF hospitalization (incidence rate ratio, 0.54; 95% confidence interval, 0.38–0.70; $P<0.0001$).

Figure. Cumulative heart failure hospitalizations in patients with preserved ejection fraction (EF, A) with treatment patients shown in red and control patients in blue. B. The cumulative heart failure hospitalizations in patients with reduced EF.
Interatrial shunt devices: A new method to reduce LAP?

Figure 1

(A) Diagram of interatrial shunt device allowing communication between the left and right atria. (B) Echocardiographic image showing Doppler colour flow from the left to right atrium.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Physicians should control ventricular rate in patients with atrial fibrillation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Physicians should use diuretics to control pulmonary congestion and peripheral edema.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Physicians might recommend coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>The use of digitals to minimize symptoms of heart failure might be considered.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Summary

• The treatment of DHF 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 DHF is lacking.