What’s New in the Treatment of Heart Failure with Preserved Ejection Fraction?

Dalane W. Kitzman, M.D.

Professor of Internal Medicine: Sections on Cardiology and Geriatrics
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Potential Conflicts of Interest

- Have received research grant support, served as consultant or member of advisory board, or hold stock or stock options for:
  - Bristol Meyers Squibb
  - Novartis
  - Synvista
  - Boston Scientific
  - Relypsa
  - Gilead
CASE PRESENTATION

- CC 81 y.o. woman with severe, progressive DOE

- HPI
  - 35 year h/o HTN
  - 25 years ago: onset of exertional fatigue and dyspnea, orthopnea; felt due to ‘aging’; family MD concurred
  - 15 years ago: worsened DOE, began sleeping upright in recliner, pedal edema, rx: furosemide
  - 2 years ago: chest pain, +stress test; cath showed no CAD, EF 76%
  - Past 18 months: 3 admissions for pulmonary edema

- Exam
  - Frail appearing woman no acute distress; BP 135/85; HR 74/min
  - Lungs: clear
  - Heart: prominent apical impulse and S4, no murmur
  - Extremities: 1+ bilateral pedal edema
CASE PRESENTATION

- Labs
  - Normal TSH and Hgb
  - Normal PFTs
  - Electrocardiogram
    - Normal sinus rhythm
    - Left anterior fascicular block
  - Echocardiogram
    - Concentric LVH
    - No wall motion abnormalities
    - EF 75%
    - Mildly dilated left atrium
    - Normal valves
    - E/A 0.9; Ea 8.2; E/Ea 10.8
Heart Failure with Preserved EF (HFPEF): The Most Common Form of HF in Community-Dwelling Elderly
The Cardiovascular Health Study

Women >> Men

Exclusion of MI, COPD, valve disease, anemia—still 29%

Kitzman et al, Am. J. Cardiol 2001
HFPEF Prevalence is Increasing Out of Proportion to HFREF

Mortality in HFPEF vs HFREF

Update July 2006 *NEJM*: mortality in DHF unchanged despite significant improvement in mortality in SHF
Morbidity of HFPEF is Equal to HFREF

- Frequent rehospitalizations
- Acute exacerbations with pulmonary edema
- Chronic symptoms of exercise intolerance: DOE, fatigue
- Poor quality of life
- High health care costs

Multicenter Randomized Treatment Trials of HFPEF 2011

HFREF
VHeFT-I*
VHeFT-II*
PROFILE
EMT
MDPT
PRAISE I & II
Dig-Captopril
CONSENSUS
SOLVD-T
SOLVD-P
SAVE
AIRE
Milrinone-Dig
RADIENCE

HFPEF
ELITE
ELITE II
MERIT-HF
RALES
PROVED
DIG
Xamoterol
PRIME
PROMISE
VEST
PICO
MDC
CIBIS-I
Carvedilol
ANZ
CIVIS-II
Many others

> 75 clinical trials, 100,000 patients

ACC/AHA HF Treatment Recommendations

HFREF: 21 pages
HFPEF: 4 paragraphs
SHEP: Treatment of systolic hypertension in the elderly prevents heart failure (HFPEF?)

JAMA 1997;278:212

New CHF

Placebo

Therapy

P<0.05

years of follow-up
Processes Underlying Diastolic Dysfunction

Hypertension*
Aging
Atherosclerosis*
Diabetes*

Arteries
Hypertrophy*
Altered elastin & collagen*
Calcification
Endothelial dysfunction*
Loss of compliance*

Myocardium
Hypertrophy*
Fibrosis*
Cellular dysfunction*
Ischemia*
Loss of compliance*
Impaired relaxation*

Heart Failure*

* potential benefit of A-II antagonism

Modified from B. Massie
Effect of ARB on Exercise Performance in Patients with Diastolic Dysfunction  

JACC 1999;33:1567

+ 15% improvement in Quality of Life (MLHF)

J Cardiovascular Pharm 2004;43:288: ARB and CCB (verapamil) both reduced peak SBP, but only ARB significantly improved exercise time and quality of life.
Drug Trials Targeting Exercise Intolerance in HFPEF

- **Verapamil (Setaro et al, 1992)**
  - Small number (20 patients); cross-over design
  - Mild improvements in exercise time, associated with lower BP

- **Spironolactone aldosterone inhibitor**
  - No improvement in exercise function, quality-of-life, or diastolic function, despite promising pilot study results (Daniel et al, 2009), and small previously published study of patients with Doppler diastolic dysfunction

- **Alagebrium cross-link breaker (DIAMOND, Little et al 2006)**
  - No improvement in exercise function or aortic stiffness, despite improved diastolic function

- **Sixtaseptan endothelin antagonist (Zile et al, 2009)**
  - Ongoing analysis; possible improvement in exercise time

- **Aliskiren direct renin inhibitor**
  - Currently enrolling

- **Enalapril ACE-Inhibitor (PIE-I, Kitzman et al, 2010)**
  - No improvement in exercise function, quality-of-life, aortic stiffness, despite modest improvement in diastolic function
No Effect of 12 Months of Enalapril on Peak Exercise Oxygen Consumption in Patients with HFPFEF

Kitzman et al, Circulation Heart Failure 2010
CHARM-Preserved: Candesartan ARB
Primary outcome: death or HF hospitalization

EF > 40%; n = 3025

CV deaths identical: 170 pts each

Yusuf, Lancet 2003; 362: 777
DIG Ancillary Trial: Digoxin
988 Pts, Ambulatory HF, EF > 0.45, Normal sinus rhythm

All-cause mortality

- 2-year HR (95% CI) = 0.88 (0.62 – 1.25); p = 0.480
- Overall HR (95% CI) = 0.99 (0.76 – 1.28); p = 0.925

All-cause hospitalization

- 2-year HR (95% CI) = 1.06 (0.89 – 1.25); p = 0.533
- Overall HR (95% CI) = 1.03 (0.89 – 1.20); p = 0.683

Ahmed, Circ 2006; 114: 397
I-PRESERVE
Irbesartan (ARB) for Heart Failure with Preserved Ejection Fraction

- Multicenter, randomized, controlled, placebo-controlled trial
- International study: 400 sites in 26 countries
- 4,133 elderly patients with HFPEF
  - Age ≥ 60, (mean age 72; 60% women); EF ≥ 45% (mean 59%)
  - Heart failure admission within the past 6 months, or class III HF symptoms plus CXR, EKG, echo findings
- Irbesartan ARB vs placebo
I-PRESERVE: Primary Endpoint
Death or CV hospitalization in 4,128 pts with HFPEF

Cumulative Incidence of Primary Events (%)

HR (95% CI) = 0.95 (0.86-1.05)
Log-rank p = 0.35

(Mean follow-up 49.5 months)
I-PRESERVE
Conclusions

- Irbesartan ARB was safe but did not improve outcomes in patients with HFPEF.

- Results are consistent with other ACEI/ARB trials: Charm-Preserved and PEP-CHF.

- Need better understanding of pathophysiology.

- Focus on treatment and prevention of co-morbidities.
Non-Cardiac Co-Morbidities
In Elderly (>65 yrs) Patients with HF
\[ N = 122,630, \text{ Age } = 80, \text{ 60\% Women} \]

- Hypertension (76\%)
- Diabetes (31\%)
- COPD / Asthma (31\%)
- High Cholesterol (21\%)
- PVD/CVD (19\%)
- Renal Disease (11\%)

Braunstein, JACC 2003;42:1226
Slide courtesy of W. Little
SENIORS
Beta-Blockade with Nebivolol in Elderly Patients with Reduced vs “Preserved” EF

J Am Coll Cardiol 2009;53:2150

- Multicenter, randomized, controlled, placebo-controlled trial
- 2,111 patients
  - Age > 70
  - Acute heart failure hospital admission < 12 months, or EF ≤ 35 < 6 months
  - 2/3 had EF < 35%, 1/3 had EF > 35%
- Primary outcome: death or CV hospitalization, p = 0.04
- Effect on outcomes not different by EF
- However:
  - EF > 35% not really ‘preserved’
  - Confidence limits of hazard ratio of individual EF groups exceeded 1.0
  - Nebivolol indication for HF not approved by recent FDA
TOPCAT
Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

- Multicenter, randomized, controlled, placebo-controlled trial
- 200 sites in 12 countries
- 4,500 patients
  - Age ≥ 55, EF ≥ 45%
  - Heart failure admission within the past 3 months or BNP > 100
- Spironolactone 30 mg
- Primary outcome: mortality during up to 3 year follow-up
- Recruitment ongoing
Contribution of Chronotropic Incompetence to Exercise Intolerance in Elderly Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>NO</th>
<th>HFREF</th>
<th>HFPEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Heart rate (bpm)</td>
<td>143 ± 4.5</td>
<td>127 ± 3.3 †</td>
<td>129 ± 3.5 †</td>
</tr>
<tr>
<td>% Chron Incomp</td>
<td>7</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>

Peak VO₂

- Without CI
- With CI

Independent of medications
RESET Trial

- Symptomatic HFPEF with documented CI
- Physiologic atrial pacing
- Primary outcome exercise capacity
- Launched 2008; ongoing study
- Sponsor- Boston Scientific; David Kass PI
- Equipoise: pacing in HFPEF could decrease LV filling or induce ischemia
Non-Pharmacological Intervention

- Nurse case manager
- Education
- Restricted sodium diet
- Daily weights
- Moderate physical activity
Efficacy of Multi-Disciplinary Intervention in Elderly CHF Patients: HFPEF + HFREF
Rich et al, NEJM 1995

Cost savings per patient: $460
45% of patients in the study had preserved EF
Effect of Exercise Training on Exercise Capacity in Elderly Patients with HFPEF

Kitzman et al, Circulation HF, 2010

p < 0.0001
CASE PRESENTATION, follow-up

- **Exercise test**
  - Peak RER 1.16 (good effort)
  - VE/VO2 not indicative of pulmonary limitation; finger O2 sat 94% at peak exercise
  - Peak heart rate 121 bpm (87% predicted max)
  - Peak workload 25 watts (expected = 50)
  - Peak VO\textsubscript{2} 10.8 ml/kg/min (expected = 15.5)

- **Supervised exercise training, 3X/week for 16 wks**
  - Peak workload increased to 50 watts
  - Peak VO\textsubscript{2} increase to 13.8 ml/kg/min
  - QOL score improved from 35 (moderate) to 25 (mild)
  - Resumed shopping, visiting friends independently
Summary: Treatment of HFPEF

- Control of HTN may be a key to prevention
- Look for other contributors and correct if possible: ischemia, chronotropic incompetence, uncontrolled atrial fib, thyroid dysfunction, anemia, pneumonia/COPD, severe obesity
- Large drug treatment trials have had neutral results
- TOPCAT trial of spironolactone ongoing
- Diuretic for volume overload, sodium restriction
- BP control
- Disease management reduces readmissions
- Management of co-morbidities may be key to improving long-term outcomes
- Exercise training improves exercise capacity and quality of life
- More studies needed
Perioperative Management of Elderly Patients with Heart Failure with Preserved EF

- Few data in this specific population
- If well compensated, likely to do well
- Reduced cardiovascular reserve: advanced age, comorbidities, physical deconditioning, stiff heart & arteries
- Consider possibility of subtle volume overload; S3 rare, JVD less common, pedal edema often mild, BNP lower compared to HF with reduced EF
- Beware of underfilled, hypercontractile LV with cavity obstruction leading to hypotension, tachycardia and high wedge pressure—gentle fluids, reduce catechols
- May be prone to hypertensive spikes
- May have underlying CAD, ischemia, espec. men