Heart Failure with Preserved Ejection Fraction

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December 8, 2019
DISCLOSURES

• Speaker: Boehringer Ingelheim
• Speaker: Care Dx
Types of Heart Failure

- **Systolic Heart Failure**
  - Less blood pumped out of ventricles
  - Weakened heart muscle can’t squeeze as well

- **Normal Heart**

- **Diastolic Heart Failure**
  - Less blood fills the ventricles
  - Stiff heart muscle can’t relax normally
2013 ACCF/AHA Guidelines for the Management of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>≤ 40</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date</td>
</tr>
<tr>
<td>HFpEF</td>
<td>≥ 50</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified</td>
</tr>
<tr>
<td>a. HFpEF Borderline</td>
<td>41 to 49</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF</td>
</tr>
<tr>
<td>b. HFpEF Improved</td>
<td>&gt; 40</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients</td>
</tr>
</tbody>
</table>

Congestive Heart Failure with Normal Systolic Function

ANNE HAMILTON DOUGHERTY, MD, GERALD V. NACCARELLI, MD, ELAYNE L. GRAY, BSN, CHARLES H. HICKS, MD, and RICHARD A. GOLDSTEIN, MD

Although there have been isolated reports of congestive heart failure (CHF) with normal systolic function, the prevalence and characteristics of this condition have not previously been described. Accordingly, 188 patients with CHF undergoing radionuclide ventriculography were prospectively evaluated. Sixty-seven (36%) had a normal ejection fraction (EF) of 0.45 or greater, and 121, an abnormal EF of less than 0.45. Of these, 72 (55 with an abnormal EF [group I] and 17 with a normal EF [group II]) were also reviewed for clinical characteristics. There was no demographic difference between groups, except that systemic hypertension appeared to be a contributing factor in 65% of the patients in group II, compared with 23% of the patients in group I (p <0.002). Echocardiographic left atrial emptying index, reflecting left ventricular compliance, was determined in 72 patients and 14 normal subjects. Left atrial emptying index in normal control subjects was 0.93 ± 0.11 (± standard deviation), compared with 0.41 ± 0.18 in group I and 0.44 ± 0.19 in group II patients (p <0.001 vs control in both groups). Thus, normal systolic function is common among patients with CHF. Diastolic dysfunction, consistent with a noncompliant left ventricle, was found in both CHF groups.

(Am J Cardiol 1984;54:778–782)
Incidence of HFpEF is Increasing

N=15,217 (FHS, CHS); 60% women; 2,524 incident HF cases; 115,703 person-years of follow-up

Tsao et al. JACC: HF 2018
Causes and Temporal Patterns of 30-Day Readmission Among Older Adults Hospitalized With Heart Failure With Preserved or Reduced Ejection Fraction
Causes and Temporal Patterns of 30-Day Readmission Among Older Adults Hospitalized With Heart Failure With Preserved or Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Cause</th>
<th>HFP EF Readmissions (n=3075)</th>
<th>HFrEF Readmissions (n=3367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>743 (24.2)</td>
<td>1105 (32.8)</td>
</tr>
<tr>
<td>Non-HF cardiovascular-related</td>
<td>517 (16.8)</td>
<td>673 (20.0)</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>139 (4.5)</td>
<td>142 (4.2)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>54 (1.8)</td>
<td>108 (3.2)</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>60 (2.0)</td>
<td>97 (2.9)</td>
</tr>
<tr>
<td>Hypertension with complications</td>
<td>77 (2.5)</td>
<td>89 (2.6)</td>
</tr>
<tr>
<td>Non-cardiovascular-related</td>
<td>1815 (59.0)</td>
<td>1589 (47.2)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>168 (5.5)</td>
<td>167 (5.0)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>160 (5.2)</td>
<td>155 (4.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>150 (4.9)</td>
<td>106 (3.1)</td>
</tr>
<tr>
<td>Adult respiratory failure</td>
<td>141 (4.6)</td>
<td>104 (3.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>99 (3.2)</td>
<td>84 (2.5)</td>
</tr>
<tr>
<td>Fluid/electrolyte diagnosis</td>
<td>82 (2.7)</td>
<td>81 (2.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>73 (2.4)</td>
<td>60 (1.8)</td>
</tr>
</tbody>
</table>
What is HFpEF

• Signs and Symptoms of Heart Failure

• LVEF ≥ 50%

• Evidence of elevated left ventricular filling pressures (rest or exercise)

• Evidence of a cardiac predominate problem
Pathophysiology of HFpEF

• LV diastolic and systolic dysfunction

• Vascular stiffening and abnormal ventricular-arterial coupling
  – Cardiac Output reduction during exercise
  – Markedly elevated filling pressures during exercise

• Chronotropic incompetence
The abnormalities in left ventricular diastolic function limited patients' ability to augment stroke volume by means of the Frank-Starling mechanism, resulting in severe exercise intolerance.
Diastolic Dysfunction

Pressure

Left Ventricular Volume
HFpEF & CoMorbidities

• Advanced age, hypertension, obesity, female gender, anemia, diabetes, renal dysfunction, and impaired LV compliance have been either associated with the prevalence of HFpEF or the ventricular-vascular dysfunction seen in patients with HFpEF

• These comorbidities do not fully account for the poor outcomes seen in the HPeEF population


Lungs:
- Primary lung co-morbidities
  - Secondary PVH
    - Increased pulsatile load on RV
      - Impaired respiratory muscle metabolism

Abdominal Compartment:
- Cardiac preload
- Chronic venoconstriction
  - Long-standing congestion
    - Spleen third spaces fluid
      - Non-occlusive bowel ischemia
        - Gut flora translocation
          - Endotoxin-mediated inflammatory response

Ventricular-Vascular Stiffening:
- Labile and stress-induced hypertension
  - Limits systolic reserve

Skeletal Muscle:
- Exercise intolerance
  - Endothelial dysfunction
    - Impaired metabolism, decreased mitochondrial volume and enzymes
      - Impaired peripheral vasodilation

Kidneys:
- Passive venous congestion
  - Renal impairment
    - Fluid imbalance
      - Oliguria, hypertension, Diuretic resistance
Phosphokinase G (PKG) & HFpEF

• PKG is found in cardiac myocytes, vascular smooth muscle cells, renal cells, zona glomerulosa, adrenal cortex, intestinal mucosa, fibroblast, leukocytes
PKG Pathway as Treatment Targets for HFpEF

NOS → NO → sGC → cGMP → PKG

Nitrites stimulators

PDE5 inhibitors

Natriuretic Peptides

Neprilysin inhibitors

NPRA/B → pGC → cGMP → PKG

ANP, BNP

PDE9 inhibitors
Benefits of Phosphokininase G (PKG)

• Promotes Smooth muscle relaxation
• ↓ Cardiac Hypertrophy
• ↓ Cardiac fibrosis
• ↓ Cardiac dysfunction
• ↓ Endothelial dysfunction
• ↑ Lipolysis
• ↑ Metabolism
• ↑ Skeletal muscle performance
• ↑ Renal function
HFpEF Remodeling Pathway

Comorbidities
- Metabolic syndrome
  - Obesity
  - Type 2 DM
  - Hypertension
- Renal insufficiency
  - CRP
  - IL1RL1
  - GDF15

Systemic inflammation
- CRP
- IL1RL1
- GDF15

Multiorgan involvement
- PH
- Na+ retention
- \( \Delta(A-VO_2)_{EX} \)

Endothelium-cardiomyocyte signaling
- ONOO-
- ROS
- NO
- VCAM
- E-selectin
- Leukocytes
- TGF-\( \beta \)
- Collagen
- Fibroblasts
- Myofibroblasts
- Cardiomyocytes

Endothelium
- sGC
- cGMP
- PKG
- Hypertrophy

Circulation 2016
Shah S...Paulus W
Medical Therapy for HFpEF
TOPCAT
Spironolactone vs. Placebo
1º endpoint: composite of CV death, aborted cardiac arrest, or HF hospitalization

Pitt et al. NEJM 2014
Regional Variation in Outcomes in TOPCAT

**A** Primary Outcome

- **Placebo**: HR = 0.82 (0.69-0.98)
- **Spironolactone**: HR = 1.1 (0.79-1.51)

**B** CV Death

- **Americas**: HR = 0.74 (0.57-0.97)
- **Russia/Georgia**: HR = 1.31 (0.91-1.90)

**C** Heart Failure Hospitalization

- **Americas**: HR = 0.82 (0.67-0.99)
- **Russia/Georgia**: HR = 0.76 (0.44-1.32)
Regional Variation in Outcomes in TOPCAT

A. Participants Who Reported Taking Assigned Spironolactone or Placebo
- Placebo: 82/90, 91/105
- Spironolactone: 66/70, 76/101

B. Participants Who Reported Taking Spironolactone but Had No Detectable Canrenone Concentration
- Russia (N=66): 30
- United States and Canada (N=76): 3

P values: 0.45, 0.04, <0.001

de Denus et al. NEJM 2017
## Lack of Benefit for Medical Therapy in HFP EF

### TABLE 1 Summary of Major Published HFP EF Randomized Clinical Trials (Phase 2-3)

<table>
<thead>
<tr>
<th>Drug/Intervention (Ref. #)</th>
<th>Phase</th>
<th>Study Size</th>
<th>Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan (31)</td>
<td>3</td>
<td>3,023</td>
<td>Composite of cardiovascular mortality or HF hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Irbesartan (30)</td>
<td>3</td>
<td>4,128</td>
<td>Composite of all-cause mortality or cardiovascular hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Perindopril (29)</td>
<td>3</td>
<td>850</td>
<td>Composite of all-cause mortality and HF hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Nebivolol (60)</td>
<td>3</td>
<td>752</td>
<td>Composite of all-cause mortality or cardiovascular hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Carvedilol (61)</td>
<td>2</td>
<td>245</td>
<td>Composite of cardiovascular mortality or HF hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Digoxin (62)</td>
<td>3</td>
<td>988</td>
<td>Composite of HF mortality or HF hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Spironolactone (63)</td>
<td>2</td>
<td>422</td>
<td>E/e’ on echocardiography; peak oxygen consumption</td>
<td>Positive; neutral</td>
</tr>
<tr>
<td>Spironolactone (64)</td>
<td>3</td>
<td>3,445</td>
<td>Composite of death from cardiovascular cause, aborted cardiac arrest, or HF hospitalization</td>
<td>Neutral</td>
</tr>
<tr>
<td>Eplerenone (65)</td>
<td>2</td>
<td>44</td>
<td>6-min-walk distance</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sildenafil (66)</td>
<td>2</td>
<td>216</td>
<td>Peak oxygen consumption</td>
<td>Neutral</td>
</tr>
<tr>
<td>Ivabradine (67)</td>
<td>2</td>
<td>61</td>
<td>Exercise capacity/peak oxygen consumption</td>
<td>Positive</td>
</tr>
<tr>
<td>Ivabradine (68)</td>
<td>2</td>
<td>44</td>
<td>Peak oxygen consumption</td>
<td>Negative</td>
</tr>
<tr>
<td>Ivabradine (69)</td>
<td>2</td>
<td>179</td>
<td>E/e’ on echocardiography; 6-min-walk distance; NT-proBNP</td>
<td>Neutral; neutral; neutral</td>
</tr>
<tr>
<td>Exercise training (70)</td>
<td>N/A</td>
<td>64</td>
<td>Peak oxygen consumption</td>
<td>Positive</td>
</tr>
<tr>
<td>Sacubitril/valsartan (71)</td>
<td>2</td>
<td>301</td>
<td>NT-proBNP</td>
<td>Positive</td>
</tr>
<tr>
<td>Vericiguat (72)</td>
<td>2</td>
<td>477</td>
<td>NT-proBNP; left atrial volume</td>
<td>Neutral; neutral</td>
</tr>
<tr>
<td>Isosorbide mononitrate (57)</td>
<td>2</td>
<td>110</td>
<td>Daily activity level</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Parikh et al. JACC: HF 2018
Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction


N=4822
NYHA II-IV
EF ≥45%
Evidence of structural heart disease
Elevated levels of natriuretic peptides
Requiring chronic treatment with diuretics
A Total Hospitalizations for Heart Failure and Death from Cardiovascular Causes

HR 0.87
(95% CI 0.87 – 1.01)

B Total Hospitalizations for Heart Failure

HR 0.85
(95% CI 0.72 – 1.00)

C Death from Cardiovascular Causes

HR 0.95
(95% CI 0.79 – 1.16)
**SGLT-2 Inhibitors and CVD**

**EMPA-REG**
- Empagliflozin lowered composite outcome and all-cause death
- Reduction in HF hospitalization
- BP reduced ≈4/2 mmHg; weight loss ≈2 kg

**CANVAS**
- In two trials involving patients with T2DM and CVD risk, canagliflozin reduced risk for CV events
- Reduction in HF hospitalization

**CVD-REAL**
- A real world comparative effectiveness study of SGLT-2i compared to other glucose lowering drugs
- 39% lower risk of HF hospitalization, 51% lower risk of death, and 46% lower risk of composite (HF hospitalization and death)
EMPA-REG

- Primary Outcome
  - Hazard ratio: 0.86 (95% CI: 0.74–0.99)
  - P=0.04 for superiority

- Death from Cardiovascular Causes
  - Hazard ratio: 0.62 (95% CI: 0.49–0.77)
  - P<0.001

- Death from Any Cause
  - Hazard ratio: 0.68 (95% CI: 0.57–0.82)
  - P<0.001

- Hospitalization for Heart Failure
  - Hazard ratio: 0.65 (95% CI: 0.50–0.85)
  - P=0.002

No. at Risk:
- Empagliflozin: 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
- Placebo: 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

No. at Risk:
- Empagliflozin: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
- Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168
Mechanisms of Preservation of CV and Renal Function in SGLT2-inhibition that May Benefit HFpEF

SGLT-2 inhibition\[^{[a,b]}\]  Mechanism\[^{[a-d]}\]  Cardio-renal effects\[^{[e,f]}\]  Clinical outcomes\[^{[g,h]}\]

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### ACC/AHA 2017 Guidelines for Treatment of HFpEF

<table>
<thead>
<tr>
<th><strong>Recommendations</strong></th>
<th><strong>COR</strong></th>
<th><strong>LOE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In appropriately selected patients with HFpEF, aldosterone receptor antagonists might be considered to decrease hospitalizations</td>
<td>IIb</td>
<td>B-R</td>
</tr>
</tbody>
</table>
Device Therapy
CHAMPION TRIAL
CardioMEMS
CHAMPION Trial
HF Hospitalization

N=550 NYHA III, 22% HFpEF

## CHAMPION – Results

<table>
<thead>
<tr>
<th></th>
<th>Not enrolled (n=25)</th>
<th>Treatment group (n=270)</th>
<th>Control group (n=280)</th>
<th>All patients (n=575)</th>
<th>Risk (95% CI)</th>
<th>p value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart-failure-related hospitalisations up to 6 months (number; events per patient per 6 months)</td>
<td>NA</td>
<td>84 (0.32)</td>
<td>120 (0.44)</td>
<td>NA</td>
<td>0.72† (0.60-0.85)</td>
<td>0.0002</td>
<td>8</td>
</tr>
<tr>
<td><strong>Primary safety endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related or system-related complications</td>
<td>2 (8%)</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>8 (1%)</td>
<td>§</td>
<td>&lt;0.0001</td>
<td>NA</td>
</tr>
<tr>
<td>Pressure-sensor failures</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>§</td>
<td>&lt;0.0001</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Prespecified supplementary efficacy endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart-failure-related hospitalisations during entire randomised follow-up</td>
<td>NA</td>
<td>158</td>
<td>254</td>
<td>NA</td>
<td>0.63† (0.52-0.77)</td>
<td>&lt;0.0001</td>
<td>4</td>
</tr>
<tr>
<td><strong>Secondary efficacy endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in pulmonary artery mean pressure at 6 months (mm Hg x days; mean area under the curve)</td>
<td>NA</td>
<td>-156</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>0.008</td>
<td>NA</td>
</tr>
<tr>
<td>Patients admitted to hospital for heart failure at 6 months</td>
<td>NA</td>
<td>55 (20%)</td>
<td>80 (29%)</td>
<td>NA</td>
<td>0.71</td>
<td></td>
<td>(0.53-0.96)</td>
</tr>
<tr>
<td>Days alive outside hospital at 6 months (mean, SD)</td>
<td>NA</td>
<td>174.4 (31.1)</td>
<td>172.1 (37.8)</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
<td>NA</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure Questionnaire at 6 months (mean, SD)</td>
<td>NA</td>
<td>45 (26)</td>
<td>51 (25)</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
<td>NA</td>
</tr>
</tbody>
</table>

FDA approved for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III HF (HFrEF or HFpEF) patients who have been hospitalized for HF in the previous year

Wireless PA monitoring: Real World Experience

**A**

HR 0.55, 95% CI (0.49-0.61)
p<0.001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Pre-implant</th>
<th>Post-implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1114</td>
<td>1114</td>
</tr>
<tr>
<td>1mo</td>
<td>1114</td>
<td>1080</td>
</tr>
<tr>
<td>2mo</td>
<td>1114</td>
<td>1049</td>
</tr>
<tr>
<td>3mo</td>
<td>1114</td>
<td>1019</td>
</tr>
<tr>
<td>4mo</td>
<td>1114</td>
<td>1002</td>
</tr>
<tr>
<td>5mo</td>
<td>1114</td>
<td>976</td>
</tr>
<tr>
<td>6mo</td>
<td>1114</td>
<td>955</td>
</tr>
</tbody>
</table>

**B**

HR 0.66, 95% CI (0.57-0.76)
p<0.001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Pre-implant</th>
<th>Post-implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>480</td>
<td>480</td>
</tr>
<tr>
<td>1mo</td>
<td>480</td>
<td>450</td>
</tr>
<tr>
<td>2mo</td>
<td>480</td>
<td>435</td>
</tr>
<tr>
<td>3mo</td>
<td>480</td>
<td>409</td>
</tr>
<tr>
<td>4mo</td>
<td>480</td>
<td>394</td>
</tr>
<tr>
<td>5mo</td>
<td>480</td>
<td>373</td>
</tr>
<tr>
<td>6mo</td>
<td>480</td>
<td>357</td>
</tr>
</tbody>
</table>

Exercise Training
## HFpEF Exercise Training Trials Summary

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Mo</th>
<th>Diast Fx</th>
<th>ET Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitzman et al 2010</td>
<td>53</td>
<td>4</td>
<td>N/A</td>
<td>Aerobic</td>
<td>Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HR peak, HRR, O2 pulse. Improved physical score of MLHFQ</td>
</tr>
<tr>
<td>Edelman et al 2011</td>
<td>64</td>
<td>3</td>
<td>Grade ≥1</td>
<td>Both</td>
<td>Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Improved E/e'. Decreased LAVI. Improved SF-36 and MLHFQ scores. Reduced procollagen type 1 blood levels</td>
</tr>
<tr>
<td>Smart et al 2012</td>
<td>30</td>
<td>4</td>
<td>Delayed relax or Psnl</td>
<td>Aerobic</td>
<td>Increased exercise capacity (VO2peak, workload). Increased CO. Improved strain rate, SV, and CO, in patients with &gt;10% increase in VO2peak</td>
</tr>
<tr>
<td>Haykowsky et al 2012</td>
<td>40</td>
<td>4</td>
<td>N/A</td>
<td>Aerobic</td>
<td>Improved exercise capacity (VO2peak). Increased HRpeak, HRR. Increased estimated peak and reserve A-VO2 Diff and peak and reserve circulatory power</td>
</tr>
<tr>
<td>Fujimoto et al 2012</td>
<td>20</td>
<td>12</td>
<td>N/A</td>
<td>Aerobic</td>
<td>Improved E/A ratio</td>
</tr>
<tr>
<td>Kitzman et al 2013</td>
<td>63</td>
<td>4</td>
<td>N/A</td>
<td>Aerobic</td>
<td>Improved exercise capacity (VO2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HRpeak, Improved SF-36 score</td>
</tr>
</tbody>
</table>
Higher Cardiorespiratory Fitness Predicts Long-term Survival in Patients with Heart Failure & Preserved Ejection Fraction

The Henry Ford Exercise Testing (FIT) Project

Results:

• Mean age was 64 ±13 years, with 55% women, and 46% Black

• Over a median follow-up of 9.7 (5.2–18.9) years, there were 103 deaths

• In fully adjusted models, **moderate-high CRF was associated with 63% lower mortality risk (HR = 0.37, 95% CI: 0.18–0.73)** compared to the poor-CRF group

• In the propensity-matched cohort, HFpEF was associated with a HR of 2.3 (95% CI: 1.7–3.2) for mortality compared to non-HFpEF patients, which was attenuated to 1.8 (95% CI: 1.3–2.5) after adjusting for CRF

Orimoloye o, Kambhampati S, Hicks A et.al Arch Med Sci 2019
Higher Cardiorespiratory Fitness Predicts Long-term Survival in Patients with Heart Failure & Preserved Ejection Fraction
The Henry Ford Exercise Testing (FIT) Project

Mortality Rates of the Study Population with HFpEF Stratified by METs Category

<table>
<thead>
<tr>
<th>Death</th>
<th>Total, n, %</th>
<th>1–4 METs, n, %</th>
<th>5–6 METs, n, %</th>
<th>≥ 7 METs, n, %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 year</td>
<td>10, 6.0</td>
<td>7, 7.8</td>
<td>3, 9.1</td>
<td>0, 0</td>
<td>0.14</td>
</tr>
<tr>
<td>At 2 years</td>
<td>17, 10.2</td>
<td>13, 14.4</td>
<td>4, 12.1</td>
<td>0, 0</td>
<td>0.03</td>
</tr>
<tr>
<td>At 3 years</td>
<td>26, 15.6</td>
<td>20, 22.22</td>
<td>5, 15.2</td>
<td>1, 2.3</td>
<td>0.01</td>
</tr>
<tr>
<td>At 4 years</td>
<td>31, 18.6</td>
<td>25, 27.8</td>
<td>5, 15.2</td>
<td>1, 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>At 5 years</td>
<td>40, 24.0</td>
<td>32, 35.6</td>
<td>6, 18.2</td>
<td>2, 4.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 7 years</td>
<td>59, 35.3</td>
<td>41, 45.6</td>
<td>13, 39.4</td>
<td>5, 11.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 10 years</td>
<td>78, 46.7</td>
<td>50, 55.6</td>
<td>16, 48.5</td>
<td>12, 27.3</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Orimoloye o, Kambhampati S, Hicks A et.al Arch Med Sci 2019
Amyloid Cardiomyopathy
Left Ventricular Amyloid Deposition in Patients with HFpEF

Mohammed et al. JACC HF 2014
# Tafamadis for TTR amyloid Cardiomyopathy

Maurer et al. NEJM 2018

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>P Value from Finkelstein-Schoenfeld Method</th>
<th>Survival Analysis Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>Cardiovascular Hospitalization Relative Risk Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall — pooled tafamadis vs. placebo</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>TTR genotype</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ATTRm</td>
<td>0.30</td>
<td></td>
<td>0.79</td>
<td></td>
<td>0.11</td>
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<tr>
<td>ATTRwt</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
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<tr>
<td>NYHA baseline</td>
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<td></td>
</tr>
<tr>
<td>Class I or II</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class III</td>
<td>0.78</td>
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<tr>
<td>Dose</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>80 mg vs. placebo</td>
<td>0.003</td>
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<tr>
<td>20 mg vs. placebo</td>
<td>0.005</td>
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</tbody>
</table>
Final Thoughts

• US adults 65 years and older increased 22.9% from 41.4 million to 50.9 million between 1/1/2011 – 12/31/2017
  – Population of adults younger than 65 years increased by only 1.7%

• Age-adjusted Mortality rates
  – Decreased 5.0% for Heart Disease (HD)
  – Decreased 14.9% for Coronary Heart Disease (CHD) while increasing
  – INCREASED 20.7% for HEART FAILURE

• The number of Heart Failure Deaths INCREASED by 38 %
  – A total of 80% of HD deaths occurred in the group of adults aged 65 years and older

Final Thoughts

• “With the number of adults aged 65 years and older projected to increase an additional 44% from 2017 to 2030, innovative and effective approaches to prevent and treat HD, particularly the substantially increasing rates of heart failure, are needed” (Sidney et al JAMA Cardiol 2019)

Questions