Therapeutic Concepts in HF With Preserved EF
(What Disease(s) are we Talking About? Can it be treated?)

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CARDIOMYOPATHIES

ISCHEMATIC

IDIOPATHIC
DILATED

HYPERTENSIVE

Konstam MA. J Card Failure, 2003
Figure 11.1. Differential Diagnosis of Heart Failure with Preserved LVEF

Heart Failure with Preserved LVEF

- Dilated LV
  - Valvular disease
    - AR; MR
  - No valvular disease
    - High output HF
  - Normal or Increased QRS voltage
    - Hypertrophic disease
  - Low QRS voltage
    - Infiltrative myopathy

- Non-dilated LV
  - Increased thickness
  - Normal thickness
  - Mitral obstruction
    - MS; Atrial myxoma
  - No mitral obstruction

Aortic/Mitral Valve Disease

- No Aortic valve disease
- Aortic valve disease
  - Aortic stenosis

Constrictive/Restrictive Disease

- Pericardial disease
  - Tamponade /Constriction

Hypertensive Disease

- No Hypertensive Hx or PE
- Hypertensive Hx or PE
  - Hypertensive-hypertrophic cardiomyopathy

RV Dysfunction

- Right Ventricular Dysfunction*
  - Pulmonary Hypertension
  - Isolated or predominant RVMI

* Some patients with right ventricular dysfunction have LV dysfunction due to ventricular interaction.

LVEF=left ventricular ejection fraction; HF=heart failure; QRS=electrocardiographic ventricular depolarization; AR=aortic regurgitation; MR=mitral regurgitation; MS=mitral stenosis; RVM=right ventricular myocardial infarction; Hx=history; PE=physical examination.

Figure courtesy Marvin Konstam MD and Marvin Kronenberg MD

HFSA
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Case 1

53 yo man with progressive dyspnea on exertion
Tc99m-pyrophosphate
Case 1

Transthyretin (TTR) Amyloid Cardiomyopathy
Tafamidis Binds to TTR Free Tetramer and Prevents Dissociation

Note: patients with restrictive CMP are HR-dependent to maintain / augment CO
## Risk Factors for Incident Heat Failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson et al</td>
<td>Goteborg, Sweden</td>
<td>Hypertension, smoking, weight, heart size, T wave abnormality, heart rate variability, peak expiratory flow rate, and psychological stress</td>
</tr>
<tr>
<td>Chen et al</td>
<td>EPESE</td>
<td>Gender, age, diabetes, pulse pressure, and body mass index</td>
</tr>
<tr>
<td>Kannel et al</td>
<td>Framingham Heart Study</td>
<td>Age, blood pressure, LVH, vital capacity, heart rate, CHD, murmurs, diabetes, cardiomegaly, and body mass index</td>
</tr>
<tr>
<td>Gottdiener et al</td>
<td>Cardiovascular Health Study</td>
<td>Age, gender, cerebrovascular disease, diabetes, blood pressure, FEV\textsubscript{1}, creatinine, C-reactive protein, ankle-arm index, atrial fibrillation, LVH, abnormal ejection fraction, electrocardiographic ST-T abnormality</td>
</tr>
<tr>
<td>He et al</td>
<td>NHANES I</td>
<td>Gender, education, physical activity, smoking, weight, hypertension, diabetes, valvular disease, and CHD</td>
</tr>
<tr>
<td>Wilhelmsen et al</td>
<td>Goteborg, Sweden</td>
<td>Age, family history of infarction, diabetes, history of chest pain, smoking, coffee consumption, alcohol abuse, blood pressure, and body mass index</td>
</tr>
<tr>
<td>Bibbins-Domingo et al</td>
<td>Heart and Estrogen/Progestin Replacement Study</td>
<td>Diabetes, atrial fibrillation, myocardial infarction, creatinine clearance, blood pressure, smoking, body mass index, left bundle branch block, and LVH</td>
</tr>
<tr>
<td>Carr et al</td>
<td>RENAAL and LIFE studies</td>
<td>Age, history of myocardial infarction, vascular disease, atrial fibrillation, urinary albumin/creatinine ratio, alcohol abuse, Cornell product, and body mass index</td>
</tr>
<tr>
<td>Butler et al</td>
<td>Health ABC</td>
<td>Age, CHD, smoking, blood pressure, heart rate, serum creatinine, fasting glucose, albumin level, and LVH on electrocardiogram</td>
</tr>
</tbody>
</table>

Phenotype Map for HFpEF

<table>
<thead>
<tr>
<th>HFpEF Clinical Presentation Phenotypes</th>
<th>Lung Congestion</th>
<th>+Chronotropic Incompetence</th>
<th>+Pulmonary Hypertension (CpcPH)</th>
<th>+Skeletal muscle weakness</th>
<th>+Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/obesity/metabolic syndrome/type 2 DM</td>
<td>Diuretics (loop diuretics)</td>
<td>+Pulmonary vasodilators (e.g., PDE5I)</td>
<td>+Exercise training program</td>
<td>+Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>+Arterial hypertension</td>
<td>ACEI/ARB +Rate adaptive atrial pacing</td>
<td>ACEI/ARB +Pulmonary vasodilators (e.g., PDE5I)</td>
<td>ACEI/ARB +Exercise training program</td>
<td>ACEI/ARB +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>+Renal dysfunction</td>
<td>Ultrafiltration if needed</td>
<td>Ultrafiltration if needed +Pulmonary vasodilators (e.g., PDE5I)</td>
<td>Ultrafiltration if needed +Exercise training program</td>
<td>Ultrafiltration if needed +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>+CAD</td>
<td>ACEI +Revascularization</td>
<td>ACEI +Revascularization +Pulmonary vasodilators (e.g., PDE5I)</td>
<td>ACEI +Revascularization +Exercise training program</td>
<td>ACEI +Revascularization +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
</tbody>
</table>

A phenotype of HFpEF? Or Metabolic CVD

Myocardial Remodeling in HFPEF
Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

Endothelium

- ONOO-
- NO
- ROS
- VCAM
- E-selectin
- Leukocytes
- TGF-β
- Fibroblasts
- Myofibroblasts
- Collagen

Cardiomyocytes

- sGC
- cGMP
- F_passive
- PKG
- Hypertrophy

EF Distribution by Diagnosis

Ischemic CMP

MET-CVD

LV Ejection Fraction (%)

Konstam M. European Journal of Heart Failure (2018) 20, 1240–1242
Echocardiogram: Key Questions
If LV is Non-Dilated / If EF is Preserved

• Is there diastolic dysfunction?
• Are LV walls thick?
• Is the left atrium enlarged?
• Is there pulmonary hypertension?
Left Atrial Enlargement

Primary Endpoint

- Increased LA Area (66%)
- Normal LA Area (34%)

* = p = 0.0001

LVH

Heart Failure Endpoint

- LVH (29%)
- Concentric Remodeling (30%)
- No LVH, No Concentric Remodeling (41%)

Case 2

- **History**
  - 79 year old woman admitted with pulmonary edema.
  - Long-standing HTN
  - Type 2 diabetes
  - 2-flight DOE
- **Meds**
  - Atenolol, amlodipine, HCTZ
- **Px:**
  - BP 180/80; HR 100 regular
  - JVP “mildly elevated”
  - Bilateral rales
  - Prominent apical impulse. Summation gallop.
  - No edema / ascites
Case 2

• Lab:
  – BUN 38; Cr 1.4; 1+proteinuria; BNP 380; Hgb A1c 8.5

• ECG:
  – SR, LAE, LVH; NSSTTWA

• Echo:
  – Non-dilated LV
  – EF 60%
  – “mild” concentric LVH; septal thickness 11 mm
  – E-A ratio normal (“? Pseudo-normal”); prolonged e-wave decleration time.
Diagnosis: “HFpEF”?

Metabolic / Senescent CardioVascular Disease

MetS-CVD

CVD
Treatment
Clinical Trials in HF with Preserved EF

CHARM-Preserved

- Hazard ratio 0.89 (95% CI 0.77–1.03), p=0.118
- Adjusted hazard ratio 0.86, p=0.051

I-PRESERVE

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

Massie BM et al. NEJM 2008;359:2456-67
Treatment Of Preserved Cardiac Function
Heart Failure with an Aldosterone antagonist (TOPCAT)

• Objective
  ❖ To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.

• Inclusions:
  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  ❖ Hospitalization within the past year for management of heart failure, or
  ❖ Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)

• Major Exclusions:
  eGFR<30 mL/min/1.7m², serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)
1° Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

HR = 0.89 (0.77 – 1.04)
p=0.138

Spironolactone
Placebo

351/1723 (20.4%)
320/1722 (18.6%)

Number at risk
Spironolactone: 1722, 1502, 1168, 870, 614, 330, 53
Placebo: 1723, 1462, 1145, 834, 581, 331, 53
Exploratory (post-hoc): Placebo vs. Spiro by region

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Interaction p=0.122

Placebo: 280/881 (31.8%)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)

Placebo: 71/842 (8.4%)
Vascular MR in Cardovascular Disease

- Angiotensin I → Angiotensin II
  - Lungs
  - Angiotensin converting Enzyme (ACE)
  - Adrenals
- Aldosterone → Sodium & Water Retention → Increased BP
- Vasoconstriction → Arteries → MR
- Vascular Aging

- Liver → Angiotensinogen → Renin
- Acts on Kidney

- McGraw AP, JAHA 2013
- Jaffe IZ, ATVB 2014
- Jaffe IZ, JCI 2010
- Ehsan A, JTCVS, 2013
- Preston, Am J Phys, 2013
- McCurley, Nat Med 2012

Vascular Inflammation and Atherosclerosis

- Vascular Remodeling

McGraw AP, JAHA 2013
Jaffe IZ, ATVB 2014
Jaffe IZ, JCI 2010
Ehsan A, JTCVS, 2013
Preston, Am J Phys, 2013
## RENAAAL
### Secondary Composite Endpoint and Components

<table>
<thead>
<tr>
<th>Composite and Components</th>
<th>Losartan (+CT) n (%)</th>
<th>Placebo (+CT) n (%)</th>
<th>p-value</th>
<th>% Risk Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV morbidity/mortality</td>
<td>247 (32.9)</td>
<td>268 (35.2)</td>
<td>0.255</td>
<td>10</td>
<td>(-8, 24)</td>
</tr>
<tr>
<td>CV Death</td>
<td>90 (12.0)</td>
<td>79 (10.4)</td>
<td>0.455</td>
<td>-12</td>
<td>(-52, 17)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>89 (11.9)</td>
<td>127 (16.7)</td>
<td>0.005</td>
<td>32</td>
<td>(11, 48)</td>
</tr>
<tr>
<td>MI</td>
<td>50 (6.7)</td>
<td>68 (8.9)</td>
<td>0.079</td>
<td>28</td>
<td>(-4, 50)</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>42 (5.6)</td>
<td>41 (5.4)</td>
<td>0.881</td>
<td>-3</td>
<td>(-59, 33)</td>
</tr>
<tr>
<td>Stroke</td>
<td>47 (6.3)</td>
<td>50 (6.6)</td>
<td>0.787</td>
<td>5</td>
<td>(-41, 36)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>69 (9.2)</td>
<td>60 (7.9)</td>
<td>0.332</td>
<td>-19</td>
<td>(-68, 16)</td>
</tr>
</tbody>
</table>

## RENAAL Baseline Characteristics (II)

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Losartan (+CT) (n=751)</th>
<th>Placebo (+CT) (n=762)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for Hypertension</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Lipid Disorders</td>
<td>31%</td>
<td>36%</td>
</tr>
<tr>
<td>Anemia</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Amputation</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>66%</td>
<td>62%</td>
</tr>
<tr>
<td>Laser therapy/photocoagulation</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>20%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Myocardial Remodeling in HFPEF
Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

IL-6
TNF-α
sST2
Pentraxin 3

Endothelium

ROS
ONOO-
NO↓

VCAM
E-selectin

Leukocytes

TGF-β

Fibroblasts
Myofibroblasts

Collagen

Cardiomyocytes

Soluble Guanylate Cyclase Stimulators

sGC↓
cGMP↓

PKG↓
Hypertrophy

F_{passive}↑
CAPACITY

Soluble Guanylate Cyclase Stimulator in Patients with “HFpEF” and Metabolic Cardiovascular Disease

• Primary efficacy endpoint: Peak exercise capacity @ 12 weeks

• Inclusion criteria (partial list)
  • EF ≥ 45%
  • Max VO$_2$ < 80% predicted
  • One of:
    a) Hospitalization or ER visit for HF within 12 mos;
    b) Elevated natriuretic peptide level;
    c) Echo with LVH, LAE, or diastolic dysfunction;
    d) Hemodynamic evidence for HF
  • Two of:
    a) T2D or A1c ≥5.6;
    b) Hypertension;
    c) BMI >30 kg/m$^2$;
    d) Age ≥70 years
## Recommendations for Stage C HFP EF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>Systolic and diastolic blood pressure should be controlled in patients with HFP EF in accordance with published clinical practice guidelines to prevent morbidity.(^{164,165})</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>Diuretics should be used for relief of symptoms due to volume overload in patients with HFP EF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>IIA</td>
<td>C</td>
<td>Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HFP EF despite GDMT.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>IIA</td>
<td>C</td>
<td>Management of AF according to published clinical practice guidelines in patients with HFP EF is reasonable to improve symptomatic HF.</td>
<td>2013 recommendation remains current (Section 9.1 in the 2013 HF guideline).</td>
</tr>
<tr>
<td>IIA</td>
<td>C</td>
<td>The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFP EF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>IIB</td>
<td>B-R</td>
<td>In appropriately selected patients with HFP EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate &gt;30 mL/min, creatinine &lt;2.5 mg/dL, potassium &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.(^{83,166,167})</td>
<td><strong>NEW:</strong> Current recommendation reflects new RCT data.</td>
</tr>
<tr>
<td>IIB</td>
<td>B</td>
<td>The use of ARBs might be considered to decrease hospitalizations for patients with HFP EF.(^{169})</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFP EF is ineffective.(^{171,172})</td>
<td><strong>NEW:</strong> Current recommendation reflects new data from RCTs.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C</td>
<td>Routine use of nutritional supplements is not recommended for patients with HFP EF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>

Case 3

• History:
  – 63 year old man with progressive DOE.
  – Hx of CABG
  – No recurrence of characteristic angina
  – Hx of HTN, smoking, +FHx.

• Meds:
  – Metoprolol, lisinopril, aspirin, atorvastatin

• Physical Exam:
  – HR 88; BP 105/80;
  – JVP estimated at 12 cm H$_2$O
  – Lungs clear
  – Heart: diminished heart sounds; no murmurs; soft third heart sound
  – Ext: 2+ edema
Case 3

• ECG:
  – Sinus rhythm; old ASMI; low voltage

• Echocardiogram:
  – Non-dilated LV; EF 55%; No LVH
  – Antero-septal hypokinesis
  – RV not dilated; “normal function”
  – Enlarged LA
  – Prominent e-wave (“Restrictive filling pattern”); respiratory flow variation

• Right heart cath
  – Elevated and equal RAP & PCWP

• Chest CT scan
  – Patchy pericardial thickening throughout with “spotty” calcification.
Diagnosis: Pericardial constriction (post-cardiotomy)
Conclusions (1)

- The most common cause of HFpEF (HF with a non-dilated LV) is “metabolic-senescent cardio-vascular disease”.
- Other categories / diseases often presenting with “HFpEF”:
  - RV dysfunction / PHT
  - Mitral / aortic valve disease
  - Constrictive / restrictive / infiltrative disease
  - Hypertrophic cardiomyopathy
- New Therapies are emerging for amyloid cardiomyopathy (ATTR)
Conclusions (2)

• Clinical trials in heart failure with preserved LVEF have not demonstrated clear outcome benefit. (?mixture of diagnoses)

• Nevertheless, the following recommendations may be made:
  • Treat hypertension; manage obesity and diabetes
  • Manage fluid status meticulously
  • Control heart rate? (Not in restrictive disease)
  • Diminish / prevent ischemia; consider revascularization
  • ACE inhibitors, ARBs, and/or MRAs are reasonable to consider in patients with MetS-CVD.

• Future trials should focus on the continuum of the metabolic syndrome and senile CV changes, seeking to modify the underlying patho-biology.
Let’s reconsider how we think about and interpret EF (What’s the disease?)