Update in Management of Heart Failure with Preserved Ejection Fraction

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Outcome Trials in HF-PEF

CHARM-Preserved

**I-PRESERVE**

I-PEF (95% CI) = 0.95 (0.86-1.05)
Log-rank p=0.35
N=4,128
(Mean follow-up 49.5 months)

PEP-CHF

Treatment Group
- Perindopril
- Placebo

HR = 0.92; 95% CI 0.70 to 1.21; P=0.545

TOPCAT

Placebo
Spironolactone

HR = 0.89 (0.77 – 1.04), p=0.138

No treatment has been proven to reduce morbidity and mortality in patients with HF-PEF.
HF with Preserved EF: ACC/AHA Guidelines

Class I

• Control hypertension
• Chronotropic control
• Judicious use of diuretics

Class II

• Revascularization
• Management of AF
• Beta blockers, ACEi, ARBs for HTN
• Consider ARBs to reduce hospitalization

TOPCAT Primary Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

HR = 0.89 (0.77 – 1.04)
p=0.138

Primary Outcome, by region, in Placebo-Assigned Patients

- Americas:
  - 280/881 (31.8%)
  - 12.6 per 100 pt-yr

- Russia/Georgia:
  - 71/842 (8.4%)
  - 2.3 per 100 pt-yr

## Potassium

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Americas</th>
<th>Russia/Georgia</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N = 1767</td>
<td>N = 1678</td>
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<tr>
<td></td>
<td>(18,727 samples)</td>
<td>(20,344 samples)</td>
</tr>
<tr>
<td>Spiro (N = 886)</td>
<td></td>
<td></td>
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<tr>
<td>Placebo (N = 881)</td>
<td></td>
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</tr>
<tr>
<td>Hyperkalemia¹ (K≥5.5)</td>
<td>223 (25%)</td>
<td>99 (12%)</td>
</tr>
<tr>
<td></td>
<td>78 (9%)</td>
<td>79 (9%)</td>
</tr>
<tr>
<td>OR=3.46; 95% CI: (2.62 – 4.56)</td>
<td>OR=1.30; 95% CI: (0.95-1.77)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia¹ (K&lt;3.5)</td>
<td>135 (15%)</td>
<td>144 (17%)</td>
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<tr>
<td></td>
<td>231 (26%)</td>
<td>163 (19%)</td>
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<tr>
<td>OR=0.51; 95% CI: (0.40 – 0.64)</td>
<td>OR=0.87; 95% CI: (0.68 – 1.11)</td>
<td></td>
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</tbody>
</table>

¹Any report during study;

SBP Change, by Region

**Average SBP Change (Spiro-Placebo)**

- **Americas**
  - N = 1767
  - -4.2 mmHg (p<0.001)

- **Russia/Georgia**
  - N = 1678
  - -0.6 mmHg (NS)

*Interaction p<0.001

Treatment effect, by Region

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

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

Interaction $p=0.122$

Placebo:
US, Canada, Argentina, Brazil: 280/881 (31.8%)
Russia, Rep Georgia: 71/842 (8.4%)

Spiro:
US, Canada, Argentina, Brazil: 242/886 (27.3%)
Russia, Rep Georgia: 78/836 (9.3%)

Post Hoc Analysis By Region

- Differences between the Americas and Russia/Georgia:
  - Prognosis
  - Patient populations
  - Responses to Spironolactone
    (In Americas, relative to Russia/Georgia):
      • Greater:
      • Potassium Increase
      • Creatinine Increase
      • Blood Pressure Decrease
      • Differential in reported doses of Spiro and Placebo
      • Reduction in Primary Endpoint

Patients assigned to and reported taking spironolactone:

% without detectable canrenone at 12 months

Despite higher reported doses of spironolactone, less detectable spironolactone metabolites in Russian patients.

P<0.001

30%

3%

US/Canada (n = 76) Russia (n = 66)
TOPCAT-Americas: Placebo vs. Spiro (exploratory, post-hoc)

US, Canada, Argentina, Brazil

Placebo: 280/881 (31.8%)
Spiro: 242/886 (27.3%)

Primary HR 0.82 (0.69 to 0.98)
CV Death HR 0.74 (0.57 to 0.97)
HHF HR 0.82 (0.67 to 0.99)

A Clinical Approach to HF-PEF

- Is the diagnosis correct?
- Is the volume status optimized?
- Are there modifiable cardiovascular factors?
- Are there relevant comorbidities?
Just HFpEF?
Is the Diagnosis Correct?

**Restrictive CMP**
- Amyloidosis
- Hemochromatosis
- Endomyocardial Fibrosis
- Radiation-Induced
- Chemotherapy-induced
- Idiopathic

**Pericardial Disease**
- Constrictive Pericarditis
- Constrictive-Effusive Disease
- Post-Pericardiotomy Syndrome

**RV Failure**
- PAH
- ARVC
- Sarcoidosis
- TR

**HF Signs and Symptoms Normal LVEF**

**Hypertrophic CMP**

**Storage Disease**
- Fabry
- LAMP2
- PRKAG2

**HF-PEF**
- PAH
- ARVC
- Sarcoidosis
- TR
Incidental Diagnosis of TTR Amyloid
More Common than we Think

99mTc-DPD Scintigraphy

Disease Heterogeneity

- Hypertension
  - Diabetes
  - Renal dysfunction
  - Deconditioning
- Coronary disease
- Obesity
- COPD

<table>
<thead>
<tr>
<th>Disease Heterogeneity</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>31%</td>
</tr>
<tr>
<td>Concentric remodeling</td>
<td>27%</td>
</tr>
<tr>
<td>Concentric hypertrophy</td>
<td>26%</td>
</tr>
<tr>
<td>Eccentric hypertrophy</td>
<td>16%</td>
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CV Targets for Therapy

• Hypertension
  – Treat to guideline-recommended targets

• Coronary Artery Disease
  – Revascularize patients with symptoms or large ischemic burden

• Atrial Fibrillation
  – Restoration/Maintenance of SR key
  – Aggressive Efforts Likely worthwhile (AAD, AVJ ablation)

• Pulmonary Arterial Hypertension?

• Chronotropic Incompetence?
BP reduction and Diastolic Function
VALIDD and EXCEED trials (N=527)

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<tr>
<th>Decrease in SBP (mmHg)</th>
<th>Change in lateral $E'$ (cm/sec)</th>
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<tbody>
<tr>
<td>&lt;3 mmHg (n=127)</td>
<td>0.4±0.12</td>
</tr>
<tr>
<td>3-15 mmHg (n=128)</td>
<td>0.6±0.13</td>
</tr>
<tr>
<td>16-28 mmHg (n=138)</td>
<td>1.1±0.11</td>
</tr>
<tr>
<td>≥29 mmHg (n=134)</td>
<td>1.3±0.14</td>
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$P < 0.0002^{†}$

*Mean ± SEM

†After adjustment for age, gender, race, smoking, diabetes, baseline SBP, DBP, HR, and $E'$, and treatment assignment

Congestion Drives HF Events in HFpEF, as in HFrEF

Cumulative HF Hospitalization in HF-PEF, CHAMPION trial

Study Duration
50% RRR, p < 0.0001

HFpEF Pathophysiology, c. 2010

- Pulmonary hypertension
- ↓LV diastolic dysfunction
- ↑LV filling pressures
- Pulmonary hypertension
- Arterial stiffening
- Endothelial dysfunction
- ↓LV systolic reserve
- ↓HR reserve
- Exertional dyspnea and fatigue

Borlaug, Nature Rev Cardiol 2014
HFpEF Pathophysiology, 2015

Exercise Training in HFPeF

Improvements in Cardio-respiratory Fitness and Quality of Life

No impact on systolic/diastolic function

High burden of Non-CV Hospitalization in HF-PEF (CHARM)

![Bar chart showing incidence rates of Non-CV and CV hospitalizations by ejection fraction categories.]

- **< 22% (N=1013)**: Non-CV 15.1, CV 16.9
- **23-32% (N=1887)**: Non-CV 14.4, CV 19.7
- **33-42% (N=1904)**: Non-CV 13.8, CV 19.2
- **43-52% (N=1295)**: Non-CV 13.5, CV 17.5
- **> 52% (N=1500)**: Non-CV 15.0, CV 21.1

Aggressive Management of non-CV comorbidities may be important to sustained improvement in clinical outcomes in HF-PEF.
HFpEF pathophysiology
Comorbidity driven microvascular inflammation

Paulus W, JACC, 2013; Stasch JP, JCI, 2006
Targeting Impaired Cyclic GMP Signaling in HF-PEF

NO

sGC Stimulators

sGC Activators

0 Nitrates
10 Nitrite

ANP
BNP
CNP

NEP Inhibitors

NP Fragments

Redfield, ACC.14
Targeting Impaired Cyclic GMP Signaling in HF-PEF

NEAT-HFpEF
INDIE-HFpEF

SOCRATES-HF

sGC Activators

NO

sGC

pGCA

pGCB

cGMP

PKG

PDE

RELAX

5′ GMP

ANP
BNP
CNP

PARAGON-HF
NEP

NP Fragments

Redfield, ACC.14
Inhaled Nitrite Improves Exercise Hemodynamics in HFPoEF

**Effect on Exercise PCWP**

- Placebo
- Nitrite

**ANCOVA p=0.022**

Borlaug et al. JACC 2015;66(15):1672-82
Beetroot Juice in HFpEF ↑Aerobic Capacity

Zamani et al. Circulation 2015
PARAMOUNT: Significant Reduction in NT-proBNP with LCZ696 at 12 Weeks

LCZ696/Valsartan: 0.77 (0.64, 0.92)  
P = 0.005

p = 0.063

NT-proBNP (pg/ml)

Weeks Post Randomization

862 (733,1012)  
835 (710, 981)

783 (670,914)

605 (512, 714)

Solomon et al. Lancet 2012  
ESC Hotline 2012
PARAMOUNT (HF-PEF): Improvement in Left Atrial Size and NYHA Class with LCZ696 at 36 Weeks

No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks

No PHASE 2 CLINICAL STUDY IN HFrEF

Solomon et al. Lancet 2012
ESC Hotline 2012
**PARAGON-HF: study design**

**Target patient population:** ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

**Randomization 1:1**

- **Active run-in period**
  - Screening
  - Valsartan 80 mg BID*
  - LCZ696 100 mg BID

- **Double-blind treatment period**
  - LCZ696 200 mg BID
  - Valsartan 160 mg BID

- On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

- ~240 weeks

**Primary outcome:** CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BID=twice daily; CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association
A Therapeutic Approach

• Systematically confirm the diagnosis

• Optimize volume status, low threshold for invasive hemodynamic assessment

• Consider Use of Spironolactone

• Aggressively treat CAD, AF, HTN, PAH
A 61 year old man with no significant prior medical history presents with a 2 month history of increasing fatigue shortness of breath, and orthopnea. He takes no medications.

On examination, his pulse is irregular at 90 bpm and BP is 90/60 mm Hg. The jugular venous pressure is distended to the angle of the jaw. The lung fields are clear to auscultation. The apical impulse is diffuse in the midclavicular line with a soft S3 gallop and 3/6 apical holosystolic murmur. There is 2+ pitting edema of the calves bilaterally.

ECG reveals atrial fibrillation with low QRS voltage. Echocardiogram reveals normal left ventricular size, ejection fraction 60%, and concentric LV hypertrophy.
Question

Which of the following tests is most likely to yield a diagnosis?

A. Serum protein electrophoresis
B. Rectal fat pad biopsy
C. Endomyocardial biopsy
D. Fluorodeoxyglucose-PET Scan
E. Repeat echocardiogram with Doppler Tissue Imaging
Thank You!

www.brighamandwomens.org/heart