HFpEF: Novel therapies: hope or dream?

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Circulation: Heart Failure

HFpEF: Prevalence Increasing

GWTG-HF: N=110,621 patients hospitalized with HF
P<0.0001 for trend of increased HFpEF prevalence

Epidemiology of HFpEF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reduced Ejection Fraction (N=2429)</th>
<th>Preserved Ejection Fraction (N=2167)</th>
<th>P Value</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.7±12.1</td>
<td>74.4±14.4</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Male sex (% of patients)</td>
<td>65.4</td>
<td>44.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>28.6±7.0</td>
<td>29.7±7.8</td>
<td>0.002</td>
<td>0.17</td>
</tr>
<tr>
<td>Obesity (% of patients)</td>
<td>35.5</td>
<td>42.4</td>
<td>0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum creatinine on admission (mg/dL)</td>
<td>1.6±1.0</td>
<td>1.6±1.1</td>
<td>0.31</td>
<td>0.30</td>
</tr>
<tr>
<td>Hemoglobin on admission (g/dL)</td>
<td>12.5±2.0</td>
<td>11.8±2.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (% of patients)</td>
<td>48.0</td>
<td>62.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (% of patients)</td>
<td>63.7</td>
<td>52.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (% of patients)</td>
<td>28.5</td>
<td>41.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (% of patients)</td>
<td>34.3</td>
<td>33.1</td>
<td>0.42</td>
<td>0.61</td>
</tr>
<tr>
<td>Substantial valve disease (% of patients)</td>
<td>6.5</td>
<td>2.6</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>29±10</td>
<td>61±7</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
</tbody>
</table>


Outcomes

A. Patients with Reduced Ejection Fraction

B. Patients with Preserved Ejection Fraction

**HFpEF - Mechanisms**

- Clearly multifactorial
- Strongly associated with aging
- Fibrosis and stiffening of the ventricle seem to play a part
- Changes in renal function and volume avidity play a part
- Impaired contractile reserve seems to play a part
- Molecular mechanisms are largely unknown, although recent data suggest the sarcomeric protein titin may be important
- Improved patient phenotyping is critical to moving the field forward

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**Novel Therapies for HFpEF**
MRAs Beneficial in HFrEF and Post-MI LVD

**RALES**
(Severe HFrEF)
30% Risk Reduction

**EPHESUS**
(Post-MI)
15% Risk Reduction

**EMPHASIS**
(“Mild” HFrEF)
22% Risk Reduction


Why MRAs in HFP EF?

- **Aldosterone:**
  - Pro-fibrotic in the ventricle
  - Pro-fibrotic in the vasculature: arterial stiffening
  - Induces electrical remodeling: Pro-arrhythmic effects
  - Increases afterload
  - Is anti-diuretic
  - Decreases nitric oxide availability
  - Decreases baroreceptor sensitivity
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


Patient Participation

- **Randomized:** N=3445; **Mean follow-up:** 3.3 years
- **US** (1,151); **Russia** (1,066); **Rep. of Georgia** (612); **Canada** (326); **Brazil** (167); **Argentina** (123)

- **Mean Dose at 8 months:** spironolactone 25 mg; placebo 28 mg

<table>
<thead>
<tr>
<th>Spironolactone N=1,722</th>
<th>Placebo N=1,723</th>
</tr>
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<tr>
<td>% discontinued study medication:</td>
<td>% discontinued study medication:</td>
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<tr>
<td>1 year: 17.0%</td>
<td>1 year: 13.5%</td>
</tr>
<tr>
<td>2 year: 25.1%</td>
<td>2 year: 20.1%</td>
</tr>
<tr>
<td>End: 34.3%</td>
<td>End: 31.4%</td>
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| Vital status unknown: 67 (3.9%) | Vital status unknown: 65 (3.8%) |

Pitt B, et al, NEJM; 2014
1° Outcome (CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

**Spironolactone**

HR = 0.89 (0.77 – 1.04)

p = 0.138

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<td>1721</td>
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<tr>
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<td>1503</td>
<td>1461</td>
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<td>24 months</td>
<td>1166</td>
<td>1149</td>
</tr>
<tr>
<td>36 months</td>
<td>870</td>
<td>837</td>
</tr>
<tr>
<td>48 months</td>
<td>614</td>
<td>580</td>
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<tr>
<td>60 months</td>
<td>330</td>
<td>304</td>
</tr>
<tr>
<td>72 months</td>
<td>53</td>
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**Heart Failure Hospitalizations**

**Spironolactone**

HR = 0.83 (0.69 – 0.99)

p = 0.042

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Pitt B, et al, NEJM; 2014
Heart Failure Hospitalizations

![Graph showing total HF hospitalizations for Placebo and Spironolactone]

- **Total HF Hosp**
  - Placebo: 475
  - Spiro: 394
  - *P < 0.01*

- **Poisson regression**
  - 245/1723 (14.2%)
  - 206/1722 (12.0%)

- **Spironolactone**
  - **HR = 0.83 (0.69 – 0.99)**
  - **p = 0.042**

**Potassium**

<table>
<thead>
<tr>
<th>Potassium</th>
<th>Spiro</th>
<th>Placebo</th>
<th>P (chi-sq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>322</td>
<td>157</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(≥ 5.5 mmol/L)</td>
<td>(18.7%)</td>
<td>(9.1%)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>279</td>
<td>394</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(&lt;3.5 mmol/L)</td>
<td>(16.2%)</td>
<td>(22.9%)</td>
<td></td>
</tr>
</tbody>
</table>

- No deaths related to hyperkalemia were reported.

### Summary

<table>
<thead>
<tr>
<th></th>
<th>Spironolactone (N = 1722)</th>
<th>Placebo (N = 1723)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>320 (18.6%) 5.9/100pt-yr</td>
<td>351 (20.4%) 6.6/100pt-yr</td>
<td>0.89 (0.77-1.04) P=0.138</td>
</tr>
<tr>
<td>Hospitalization for Heart Failure</td>
<td>206 (12.0%) 3.8/100pt-yr</td>
<td>245 (14.2%) 4.6/100pt-yr</td>
<td>0.83 (0.69-0.99) P=0.042</td>
</tr>
</tbody>
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**Conclusions:** TOPCAT population with HFpEF:
- Rx with spironolactone did not alter the 1° composite
- Reductions in heart failure hospitalizations were observed
- Use of spironolactone in these patients requires careful monitoring of K+ and creatinine

Pitt B, et al, NEJM; 2014

### Subgroups

Of 22 pre-specified, only 1 - Stratum - showed a significant interaction with treatment

<table>
<thead>
<tr>
<th>Enrolled by:</th>
<th>Spiro</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptide</td>
<td>78/490 (15.9%)</td>
<td>116/491 (23.6%)</td>
<td>0.65 (0.49-0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart Failure Hosp</td>
<td>242/1232 (19.6%)</td>
<td>235/1232 (19.1%)</td>
<td>1.01 (0.84-1.21)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

*P=0.013 for interaction*
Exploratory (Post-hoc): Placebo Event Rate by Region

US, Canada, Argentina, Brazil
Placebo: 280/881 (31.8%)
US, Canada, Argentina, Brazil
Placebo: 71/842 (8.4%)
Russia, Rep Georgia
Placebo: 242/886 (27.3%)
Placebo: 78/836 (9.3%)

Exploratory (Post-hoc): Placebo vs Spiro 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
### Systolic Blood Pressure Change By Region

**Systolic Blood Pressure**

- **Russia/Georgia**
  - N = 1678
  - Average SBP Change (Spiro-Placebo) = -0.6 mmHg (NS)
- **Americas**
  - N = 1767
  - Average SBP Change (Spiro-Placebo) = -4.2 mmHg (p<0.001)

SBP delta differed by region (p<0.001), adjusted.* Circ 2014

### Potassium Change By Region

**Potassium**

- **Russia/Georgia**
  - Placebo
  - Spironolactone
- **Americas**
  - Placebo
  - Spironolactone

*B interaction p<0.001
Regional Discrepancies in the Reported Use and Actual Use of Spironolactone among Repository Participants in TOPCAT

Conclusions: TOPCAT Population With HFpEF

- Rx with spironolactone did not alter the 1° composite
- Reductions in heart failure hospitalizations were observed
- Use of spironolactone in these patients requires careful monitoring of K⁺ and creatinine

***********************************************************************

- Stepping outside of our statistical comfort zone: In the absence of any new data on the horizon, and in the face of the ongoing clinical need . . .
- Our post-hoc findings of improved prognosis with this use of spironolactone in those with event rates consistent with symptomatic heart failure warrants consideration.
Sacubitril/Valsartan in HFpEF

- Phase 2 study of sacubitril/valsartan in HFpEF
- 301 patients, mean age 71, 57% female, 94% controlled hypertension
- Randomized to sacubitril/valsartan or valsartan alone
- Primary outcome: Reduction in BNP
- Mean reduction in BP:
  - 9.3±14/4.9±10 mmHg with sacubitril/valsartan
  - 2.9±17/2.1±11 mmHg with valsartan

Adverse Events in HFpEF With Sacubitril/Valsartan

PARAGON-HF

- Phase 3 Trial of sacubitril/valsartan in HFpEF
- Completed enrollment Feb 2017
- 4822 participants in 43 countries
- Event-driven trial, estimated end date: Early 2019

Inorganic Nitrite Therapy

- Found in beet root juice
- Converted to nitrates in the presence of low pH/ischemia
- Hypothesized to deliver nitrate therapy to exercising muscle and improve exercise intolerance
- Several ongoing studies with different formulations in US
Other Therapies being Studied

- Exercise
- DASH diet
- sGC stimulators
- Ranolazine
- Endothelin Antagonists
- IL-1 Blockade
- Oxygen therapy

Implantable Hemodynamic Monitors in HFpEF
Cumulative Heart Failure Hospitalizations in Patients With Preserved Ejection Fraction With Treatment Patients Shown in Red and Control Patients in Blue

Implantable Hemodynamic Monitoring in HFpEF

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Transcatheter Therapeutics in HFpEF

- Proportion of patients with successful device implantation – 64/66 (97%)
- Percentage of patients with a reduction in PCWP at 6 months either at rest or during exercise
- Presence of persistent L→R shunting
- Major adverse cardiac and cerebrovascular events including death, stroke, MI or systemic embolic event, or need for device removal

6 month Secondary Outcomes
- HF hospitalization
- Changes in echocardiographic parameters
- 6 MW test
- Natriuretic Peptides
- QOL
Concerns exist, as the long-term effects of chronic elevation in R-sided output are unknown

- In the 75% of patients evaluated, device flow remains L⇒R in all
- Qp:Qs is stable between 6 and 12 months at 1.28
- Rate of death and stroke at one year is very low (4.6% mortality)
  - IN-Preserve rate of death 5.2% (placebo)
  - TOPCAT Americas rate of death 7.7% (placebo)
6 Minute Walk Time

- REDUCE-LAP
- RELAX - placebo
- First CRT report
- MIRACLE – CRT off
- MIRACLE – CRT on

MLWHF Score

- REDUCE-LAP
- RELAX - placebo
- First CRT report
- MIRACLE – CRT off
- MIRACLE – CRT on

MLWHF = Minnesota Living With Heart Failure Questionnaire
Conclusions

- No drug therapy has been shown to be definitely life-saving for all patients with HFpEF
- Active research to improve phenotyping of patients holds promise to guide future more effective intervention trials
- Implantable hemodynamic monitoring devices may be useful in this population
- Other catheter-based interventions being studied

Thank You