ALDOSTERONE ANTAGONIST IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

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ABBREVIATIONS

- BMP: basic metabolic panel
- CAD: coronary artery disease
- CC: chief complaint
- CHF: congestive heart failure
- CXR: chest x-ray
- DM: diabetes mellitus
- ECG: echocardiography
- HF: heart failure
- HFpEF: heart failure with preserved ejection fraction
- HPI: history of present illness
- HR: heart rate
- HTN: hypertension
- IVP: intravenous push
- LVEF: left ventricular ejection fraction
- NC: nasal cannula
- PMH: past medical history
- PO: by mouth
- SCr: serum creatinine
- SOB: shortness of breath

OBJECTIVES

- Describe the pathophysiology of HFpEF and how aldosterone antagonist may play a role
- Examine the current literature supporting the use of aldosterone antagonist in the management of HFpEF
- Discuss clinical implications of aldosterone antagonist use in HFpEF management based on current literature

PATIENT CASE

- HPI: AJ is a 58 y/o male with chief complaint of fatigue and shortness of breath for the past 8 days. (+) orthopnea. Patient was hospitalized 3 months ago for an episode of acute congestive heart failure.
- PMH: DM, HTN, CHF
- Admission Labs:
  - CXR: suspect bilateral pleural effusion
  - BMP:
    - SCr 1.78
    - K 3.9
    - Gluc 194
    - A1c 7.5
  - Cardiac:
    - LVEF 55%
    - NTproBNP 9,200
    - Troponin 0.177

- Vitals:
  - HR 90
  - BP 125/58
  - Temp 98.7
  - O2 Sat 97% on NC 2L/min
  - Furosemide 20 mg PO daily
  - Glyburide 5 mg PO daily
  - Lisinopril 10 mg PO daily
  - Metoprolol tartrate 50 mg PO BID
  - Metoprolol succinate 100 mg PO daily

- Is it appropriate to add spironolactone to this patient’s current treatment regimen?

  - Yes
  - No

BACKGROUND
EPIDEMIOLOGY

- Prevalence
  - Approximately 5.1 million patients in US have HF
  - Approximately 50% of patients with HF have HFrEF

- High mortality
  - 121 death per 1000 person-years

- Poor overall prognosis
  - Have substantial comorbidity, high rates of repeated hospitalization

Risk Factors
- Hypertension
- Older Age
- Female Sex
- CAD
- Atrial fibrillation
- Obesity
- Diabetes

PATHOPHYSIOLOGY

- Hypertensive remodeling
- Sedentary lifestyle Poor fitness
- Ventricular and vascular stiffening
- Obesity and metabolic stress
- Global loss of cardiac, vascular, and peripheral reserve

2013 ALDO-DHF STUDY – STUDY DESIGN

Objective
- Determine spironolactone superiority to placebo in improving diastolic function and maximal exercise capacity in patients with HFpEF

Design
- Multicenter, prospective, randomized, double-blind, placebo-controlled trial

Inclusion Criteria
- >50 y/o
- NYHA Class II or III
- LVEF ≥ 50%
- ECG evidence of diastolic dysfunction
- Peak VO2 ≤ 25ml/kg/min

Exclusion Criteria
- LVEF ≤ 40%
- Significant CAD
- MI or CABG within 3 months of enrollment
- Clinically relevant pulmonary disease

2013 ALDO-DHF STUDY – BASELINE CHARACTERISTIC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 209)</th>
<th>Spironolactone (n = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Hospitalization for HF in the past 12 months</td>
<td>75 (36%)</td>
<td>81 (38%)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>183 (88%)</td>
<td>180 (89%)</td>
</tr>
<tr>
<td>LVEF</td>
<td>189 (89%)</td>
<td>190 (89%)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>158 (74%)</td>
<td>164 (78%)</td>
</tr>
<tr>
<td>6-min walk distance</td>
<td>150 (70%)</td>
<td>151 (70%)</td>
</tr>
<tr>
<td>Baseline 65% (kg/m2)</td>
<td>140 (91 – 271)</td>
<td>179 (91 – 274)</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Median 65% – velocity (cm/s)</td>
<td>15.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Median 65% – velocity (cm/s)</td>
<td>16.4</td>
<td>16.3</td>
</tr>
</tbody>
</table>

LITERATURE REVIEW

2013 ALDO-DHF STUDY – METHODS

Intervention
- Spironolactone (n= 213) – spironolactone 25 mg once daily
- Placebo (n = 209)

Primary Outcome
- Co-primary endpoint:
  - E/e’ – an ECHO estimate of filling pressure for diastolic function
  - Peak VO2 – cardiopulmonary exercise testing for exercise capacity at 12 month

Secondary Outcome
- LVEF
- NT-proBNP
- 6-min walk distance

Statistical Methods
- Intention-to-treat analysis
- Student t-Test
- Fisher Exact Test

References
- JAMA. 2013;309(8):781-791
**2013 ALDO-DHF STUDY – RESULT: PRIMARY OUTCOME**

**Primary Endpoint**

<table>
<thead>
<tr>
<th>Outcome Spironolactone (n = 203)</th>
<th>Placebo (n = 195)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>67.2</td>
<td>65.9</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>152</td>
<td>145</td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>517</td>
<td>536</td>
</tr>
</tbody>
</table>

**Secondary Outcome**

<table>
<thead>
<tr>
<th>Outcome Spironolactone (n = 203)</th>
<th>Placebo (n = 195)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K &gt; 5 (%)</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Gynecomastia (%)</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Renal function worsening (%)</td>
<td>36</td>
<td>21</td>
</tr>
</tbody>
</table>

**2013 ALDO-DHF CRITIQUE**

- **Author’s Conclusion**
  - Spironolactone treatment improves diastolic function and left ventricular remodeling but did not alter the maximal exercise capacity
- **Limitations**
  - Study population: stable patients with moderate heart failure symptoms
  - NT-proBNP was not used as a specific inclusion criterion
  - Use of surrogate markers that have minimal clinical importance
- **Presenter’s Conclusion**
  - Spironolactone improves diastolic function in stable patients with moderate HFpEF
  - Study failed to show significant difference in maximal exercise capacity
  - Further studies are still necessary

**2014 TOPCAT TRIAL – STUDY DESIGN**

- **Objective**
  - Evaluate the effects of spironolactone in patients with symptomatic heart failure with preserved ejection fraction
- **Design**
  - Phase 3, multicenter, international, randomized, double-blind, placebo-controlled trial
  - Stratified according to enrollment (hospitalization stratum vs BNP stratum)
- **Inclusion Criteria**
  - ≥50 years old;
  - ≥1 sign/symptom of HF; LVEF ≥45%
  - Hospitalization stratum: ≥1 hospital admission in past 12 months
  - BNP Stratum: BNP in last 60 days ≥100pg/mL or NT pro-BNP ≥360pg/mL
- **Exclusion Criteria**
  - Severe systemic illness with life expectancy < 3 years
  - Severe renal dysfunction (eGFR < 30ml/min/1.73 m² or SCr ≥2.5 mg/dL)
  - Other specific coexisting conditions

**2014 TOPCAT TRIAL – METHODS**

- **Intervention**
  - Spironolactone (n = 1722) – 15 mg initial; titrate up to 45 mg within first 4 months
  - Control: placebo (n = 1723)
  - All patients continued to receive other treatment for heart failure
- **Primary Outcome**
  - Composite outcome of death from CV causes, observed cardiac arrest, or hospitalization for management of heart failure
- **Secondary Outcome**
  - Death or hospitalization from any cause, heart failure, hospital admission, elevated SCr
- **Statistical Methods**
  - 80% power (n = 551 with primary outcome); all tests were 2 sided at 5% significance level
  - Event-time analysis - emphasize Log-Rank Test
  - Cox Proportional-hazards model

**2014 TOPCAT TRIAL – BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spironolactone (n = 1722)</th>
<th>Placebo (n = 1723)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>68.7</td>
<td>68.7</td>
</tr>
<tr>
<td>M/F (male/ female)</td>
<td>1034 (60.4)</td>
<td>1104 (64.1)</td>
</tr>
<tr>
<td>Hospitalization stratum</td>
<td>1322 (77.5%)</td>
<td>1233 (71.7%)</td>
</tr>
<tr>
<td>BNP in past 60 days ≥100 pg/mL</td>
<td>234</td>
<td>233</td>
</tr>
<tr>
<td>Renal function worsening (%)</td>
<td>21.7 (12.1%)</td>
<td>24.1 (13.1%)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>357 (20.8%)</td>
<td>349 (20.2%)</td>
</tr>
</tbody>
</table>
| **Other specific coexisting conditions**
  - Severe renal dysfunction (eGFR < 30ml/min/1.73 m² or SCr ≥2.5 mg/dL)
  - Other specific coexisting conditions

2014 TOPCAT TRIAL – OUTCOMES

Study Drug mean dose at 8 months:
- Spironolactone: 25 mg/day
- Placebo: 27.7 mg/day

Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Spironolactone (n = 1732)</th>
<th>Placebo (n = 1732)</th>
<th>HR (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Outcome</td>
<td>320 (18.6%)</td>
<td>351 (20.4%)</td>
<td>0.89 (p=0.14)</td>
</tr>
<tr>
<td>Death from CV</td>
<td>160 (9.3%)</td>
<td>176 (10.2%)</td>
<td>0.90 (p=0.35)</td>
</tr>
<tr>
<td>Aborted cardiac arrest</td>
<td>3 (0.2%)</td>
<td>5 (0.3%)</td>
<td>0.6 (p=0.48)</td>
</tr>
<tr>
<td>Hospitalization from HF</td>
<td>206 (12%)</td>
<td>245 (14.2%)</td>
<td>0.83 (p=0.04)</td>
</tr>
</tbody>
</table>


Secondary Outcome: no statistically significant difference in secondary outcomes

2014 TOPCAT TRIAL – SUBGROUP ANALYSIS

- Randomization Stratum: Hospitalization vs BNP Stratum
  - Significant difference in primary outcome (p-value for interaction = 0.01)
  - BNP: significant for composite primary outcome (p = 0.003) & hospitalization for heart failure (p = 0.011)
  - Randomization: not significant for composite primary outcome or its components
- Geographic Region: Americas vs Eastern Europe
  - Between region and study group interaction was NS (p-value for interaction = 0.12)
  - Primary outcome significant in Americas (27.3%, p-value 0.026), not in E. Europe (9.3%, p-value 0.57)

2014 TOPCAT CRITIQUE

- Author’s Conclusion:
  - Spironolactone did not significantly reduce the composite primary end point of death
  - Significantly decreased the risk of hospitalization for heart failure
- Limitations
  - Unexplained regional difference in incidence rate of primary outcome
  - Significant difference in primary outcome between the 2 stratum (p-value for interaction = 0.01)
- Presenter’s Conclusion:
  - While spironolactone was not shown to significantly reduce the composite primary endpoint, it may still be a reasonable choice of medication to use in symptomatic HFpEF patients

2015 TOPCAT TRIAL – REGIONAL VARIATION

STUDY DESIGN

Objective:
- Reassess the regional difference in patients enrolled in Russia/Georgia v the Americas

Method
- Post-hoc analysis of the TOPCAT trial:
  - Russia/Georgia vs Americas (US, Canada, Brazil, Argentina)

Statistical Methods
- All analysis reported in the TOPCAT trial were repeated separately for the 2 regions
  - Chi-square test
  - Wilcoxon rank-sum test
  - Cox proportional-hazards regression model

BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Americas (n = 1767)</th>
<th>Russia/Georgia (n = 1678)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75</td>
<td>66</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>1134 (64%)</td>
<td>1151 (69%)</td>
<td>0.064</td>
</tr>
<tr>
<td>Class III</td>
<td>633 (36%)</td>
<td>511 (30%)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td>717 (41%)</td>
<td>719 (44%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current Status</td>
<td>117 (7%)</td>
<td>243 (14%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>59</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diuretic use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>1373 (78%)</td>
<td>1244 (74%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>1000 (56%)</td>
<td>1055 (63%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>spironolactone use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>201 (11%)</td>
<td>311 (18%)</td>
<td>0.014</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>376 (175, 702)</td>
<td>376 (175, 702)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

2015 TOPCAT TRIAL - REGIONAL VARIATION OUTCOMES

Mean follow up was 3.3 years (Americas: 2.9 years; Russia/Georgia: 3.7 years)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Americas (n = 1727)</th>
<th>Russia/Georgia (n = 1728)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily dose (spironolactone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.7 mg (p = 0.004)</td>
<td>26.4 mg (p = 0.003)</td>
<td></td>
<td>F=0.001</td>
</tr>
<tr>
<td>Mean daily dose (placebo)</td>
<td>25.9 mg (p = 0.004)</td>
<td>26.4 mg (p = 0.003)</td>
<td>F=0.001</td>
</tr>
<tr>
<td>N Engl J Med. 2015; 131:34-42</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Early permanent discontinuation as a result of breast tenderness or gynecomastia was more frequent in the spironolactone arm in both regions

2015 TOPCAT TRIAL - REGIONAL VARIATION OUTCOMES

Mean follow up was 3.3 years (Americas: 2.9 years; Russia/Georgia: 3.7 years)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Americas (n = 1724)</th>
<th>Russia/Georgia (n = 1728)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue drugs (%)</td>
<td>21.7</td>
<td>27.3</td>
<td>F = 0.001</td>
</tr>
</tbody>
</table>

Circulation 2015; 131:34-42
2015 TOPCAT TRIAL - REGIONAL VARIATION

**CLINICAL OUTCOMES**

Total of 671 patients had at least 1 confirmed primary outcome event

<table>
<thead>
<tr>
<th>Region</th>
<th>Hospitalization</th>
<th>BNP Stratum</th>
<th>HR (P-value)</th>
<th>Region</th>
<th>Hospitalization</th>
<th>BNP Stratum</th>
<th>HR (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas (n = 1767)</td>
<td>14.7</td>
<td>8.1</td>
<td>1.2 (p = 0.26)</td>
<td>Russia/Georgia (n = 1678)</td>
<td>2.4</td>
<td>2.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Adverse Reactions**

- Americas: significantly more hyperkalemia, less hypokalemia, more doubling of serum Creatinine above ULN, and decrease in SBP in spironolactone group vs placebo group.

**Discussion**

- The observed difference between the regions exceeded the anticipated variation in practice pattern.
- Unexplained regional differences and in renal and electrolyte response to spironolactone.

**Authors’ Conclusion**

- This post-hoc analysis indicates that 2 distinctly different population were enrolled.
  - only the America cohort shared characteristics observed in other randomized trials.

**Presenters’ Conclusion**

- Significant difference in baseline characteristics and response to spironolactone between Americas and Russia/Georgia patients suggests different patient population enrolled between the two regions.
  - Further studies necessary to assess the cause for the difference between the two regions.

2017 TOPCAT TRIAL – NEW INSIGHT INTO REGIONAL VARIATION

**STUDY DESIGN**

**Objective**

- Further explore the potential regional disparities in medication use between the patients enrolled in the Americas and those enrolled in Russia/Georgia.

**Methods**

- Measure concentration of canrenone in 366 patients.
  - United States/Canada: 206 patients.
  - Russia: 160 patients.
- The samples were taken from the serum samples during the 12-month study visit.

**Results**

- Self-reported compliance rate: Russia (90%); America (80%).
- Reported taking spironolactone but no detectable canrenone concentration.
  - Russia: 30%; Americas: 3% (p-value < 0.001).
2017 TOPCAT TRIAL – NEW INSIGHT INTO REGIONAL VARIATION

Author’s Conclusion
- Significant regional discrepancies in the reported use versus actual use of spironolactone as assessed by the metabolite concentration.
- The findings suggest that the trial results obtained in Russia do not truly reflect the actual therapeutic response of spironolactone.

Presenter’s Conclusion
- Compliance rate to the study medications in patients enrolled in Russia may be much lower than patients enrolled in the Americas.

OVERALL SUMMARY OF LITERATURE

<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
<th>Support aldosterone antagonist use?</th>
</tr>
</thead>
</table>
| 2013 Aldo-DHF      | - Improved left ventricular diastolic function.  
- No improvement in maximal exercise capacity, patient symptoms, or quality of life.  | NO                                |
| 2014 TOPCAT        | - No significant reduction in the composite primary endpoint.  
- Significantly decrease the risk of hospitalization for heart failure.  | POSSIBLY                          |
| 2015 TOPCAT – post-hoc analysis | - 2 distinctly different populations were enrolled between Americas and Russia/Georgia.  | UNCERTAIN                         |
| 2017 TOPCAT – canrenone analysis | - Significant regional discrepancies in the reported use and actual use of spironolactone.  | NO                                |

2017 ACCF/AHA HF TREATMENT GUIDELINE

- Non-pharmacologic Treatment:
  - Sodium restriction in symptomatic HF to reduce congestion symptoms.
  - Diuretics – used for symptom relief in volume overload patients (Class I, LOE C)
  - Coronary revascularization may be reasonable in patients with CAD in whom symptom is judged to have an adverse effect on symptomatic HF if [Class Ia, LOE C]

- Beta-Blocker & ACEI/ARB – reasonable for controlling BP in pt with HF (Class Ia, LOE C)

- Aldosterone Antagonist – may be used in appropriately selected patients to reduce hospitalization (Class Ia, LOE B-R)
  - LVEF > 45%
  - eGFR > 30 mL/min
  - SCr < 2 mg/dL
  - K < 5 mEq/L

PATIENT CASE

HPI: AJ is a 58 y/o male with chief complaint of fatigue and shortness of breath for the past 8 days. (+) orthopnea. Patient was hospitalized 5 months ago for an episode of acute congestive heart failure.

PMH: DM, HTN, CHF

Admission Labs:
- FBC: ER 90 BP 120/88 T 38.7 F
- Creactive protein (CRP) 5 mg/L
- Lipid panel
- Creatinine 1.1 mg/dL
- Cardiac: eGFR 55% 90 mL/min 1.73m²
- Troponin < 0.01
- CRP 0.177

CXR: suspect bilateral pleural effusion

PATIENT CASE

- Home Medications
  - Furosemide 20 mg PO daily
  - Glyburide 5 mg PO daily
  - Lisinopril 10 mg PO daily
  - Metoprolol fumarate 50 mg PO BID
- Inpatient Treatment Regimen
  - Metoprolol succinate 100 mg PO daily
  - Lisinopril 10 mg PO daily
  - Furosemide 20 mg IV PO
  - Glyburide 3 mg PO daily

Is it appropriate to add spironolactone to this patient’s current treatment regimen? [ ] Yes  [ ] No
KEY TAKEAWAYS

- HFpEF is a vaguely defined complex syndrome due to impaired ventricular filling or ejection with LVEF ≥ 50%
- Common risk factors includes: HTN, old age, CAD, atrial fibrillation, obesity, and diabetes
- Conclusion:
  - Further studies necessary to confirm the CV mortality benefit observed from the post-hoc trial
  - Further studies necessary to determine benefit of initiating spironolactone in acute setting
  - May consider spironolactone after maximizing other guideline-recommended treatment

ACKNOWLEDGEMENT

- Evan Peterson, PharmD., BCPS
- Y-Nha Nguyen, PharmD., BCPS, BCCCP
- Justin Gonzalez, PharmD., BCPS
- Andrew Orsa, PharmD
- Mario Varela, PharmD., BCPS
- Nathalie Quach, PharmD
- Ahmad Khalil, PharmD., BCPS, FCCP

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