ALDOSTERONE ANTAGONIST IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

PINHUI (JUDY) CHEN
PGY1 PHARMACY RESIDENT
VALLEY BAPTIST MEDICAL CENTER - BROWNSVILLE

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

2

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

3

PATIENT CASE

- **HPI:** AJ is 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:**

Vitals	HR 90	BP 125/58	Tmax 98.7F	O2 Sat 97% on NC 2L/min
BMP	SCr 1.78	K 3.9	Gluc 194	A1c 7.5
Cardiac	LVEF 55%	NTproBNP **9,200**	Troponin 0.177	

- **CXR:** suspect bilateral pleural effusion

4

PATIENT CASE

- Home Medications
  - Furosemide 20 mg PO daily
  - Glyburide 5 mg PO daily
  - Lisinopril 10 mg PO daily
  - Metoprolol tartrate 50 mg PO BID
- Inpatient Treatment Regimen
  - Metoprolol succinate 100 mg PO daily
  - Lisinopril 10 mg PO daily
  - Furosemide 20 mg IVP Q8H
  - Glyburide 5 mg PO daily
- Is it appropriate to add spironolactone to this patient's current treatment regimen?
  - ☐ **YES**
  - ☐ **NO**

5

6

BACKGROUND

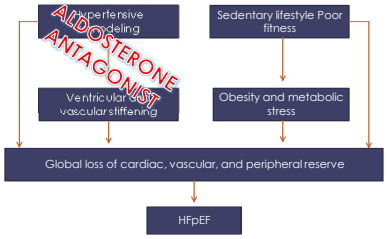
EPIDEMIOLOGY

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

Heart Fail Clin. 2014; 10(3): 377–388
Nature Reviews Cardiology 2017; 14: 591–602
Eur. Heart J. 33, 1750–1757 (2012)

7

PATHOPHYSIOLOGY



Nat Rev Cardiol 2014; 11:507-515

8

9

LITERATURE REVIEW

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	Exclusion Criteria
• >50 y/o • NYHA Class II or III • LVEF ≥ 50% • ECG evidence of diastolic dysfunction • peak VO2) ≤ 25ml/kg/min	• LVEF ≤ 40% • Significant CAD • MI or CABG within 3 months of enrollment • Clinically relevant pulmonary disease

JAMA. 2013;309(8):781-791

10

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

JAMA. 2013;309(8):781-791

11

2013 ALDO-DHF STUDY – BASELINE CHARACTERISTIC

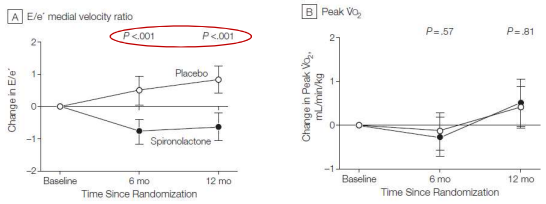
Characteristic	Placebo (n = 209)	Spironolactone (n = 213)
Mean age	67	67
Hospitalization for HF in the past 12 months	75 (36%)	81 (38%)
NYHA Class II	183 (88%)	180 (85%)
Hypertension	190 (91%)	197 (92%)
Concomitant Medications ACEI/ARB BB Diuretic	 158 (76%) 156 (75%) 109 (52%)	 167 (78%) 146 (69%) 118 (55%)
Baseline NTproBNP (ng/L)	148 (80 – 276)	179 (81 – 276)
Mean LVEF (%)	68	67
Median E/e' velocity (cm/s)	12.8	12.7
Mean peak VO_2 (ml/min/kg)	16.4	16.3

JAMA. 2013;309(8):781-791

12

2013 ALDO-DHF STUDY – RESULT: PRIMARY OUTCOME

Primary Endpoint



JAMA. 2013;309(8):781-791

13

2013 ALDO-DHF STUDY – RESULT: OTHER OUTCOMES

Secondary Outcome

Outcome	Spironolactone (n = 203)	Placebo (n=195)	P-value
LV ejection fraction, %	67.2	65.9	**0.04**
NT-proBNP (ng/L)	152	165	**0.03**
6-min walk distance (m)	517	536	**0.02**

Safety Outcome

Outcome	Spironolactone (n = 203)	Placebo (n = 195)	P-value
Serum K > 5 (%)	21	11	**0.005**
Gynecomastia (%)	4	<1	**0.02**
Renal function worsening (%)	36	21	**<0.001**

JAMA. 2013;309(8):781-791

14

2013 ALDO-DHF CRITIQUE

- Author's Conclusion
  - Spironolactone treatment improve 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 improve diastolic function in stable patients with moderate HFpEF
  - Study failed to show significant difference in maximal exercise capacity
  - Further studies are still necessary

JAMA. 2013;309(8):781-791

15

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

N Engl J Med. 2014;370(15):1383-1392

16

2014 TOPCAT TRIAL - METHODS

Intervention

- Spironolactone (n = 1722) – 15 mg initial; titrate up to 45 min 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, aborted cardiac arrest, or hospitalization for management of heart failure

Secondary Outcome

- Death or hospitalization from any cause, hyperkalemia, hypokalemia, elevated SCr

Statistical Methods

- 80% power (n = 551 with primary outcome); all tests were 2 sided at 5% significance level
- Intent-to-treat analysis - emphasize
- Log-Rank Test
- Cox Proportional-hazards model

N Engl J Med. 2014;370(15):1383-1392

17

2014 TOPCAT TRIAL – BASELINE CHARACTERISTICS

Characteristic	Spironolactone (n = 1722)	Placebo (n = 1723)
Median Age	68.7	68.7
Median LVEF (%)	56	56
NYHA Class II	1090 (63.3%)	1104 (64.1%)
Hospitalization Stratum	1232 (71.5%)	1232 (71.5%)
BNP Stratum Median BNP (pg/mL) Median NT-proBNP	490 (28.5%) 236 887	491 (28.5%) 235 1017
Diuretics	1401 (81.4%)	14.16 (82.3%)
ACEI or ARB	1452 (84.3%)	1448 (84.2%)
Beta-blockers	1346 (78.2%)	1330 (77.3%)

N Engl J Med. 2014;370(15):1383-1392

18

2014 TOPCAT TRIAL – OUTCOMES

Study Drug mean dose at 8 months:

- Spironolactone 25 mg/day
- Placebo 27.7mg/day

Primary Outcome

Outcome	Spironolactone (n = 1722)	Placebo (n = 1723)	HR (p-value)
Primary Composite Outcome	320 (18.6%)	351 (20.4%)	0.89 (p= 0.14)
Death from CV	160 (9.3%)	176 (10.2%)	0.90 (p= 0.35)
Aborted cardiac arrest	3 (0.2%)	5 (0.3%)	0.6 (p= 0.48)
Hospitalization from HF	206 (12%)	245 (14.2%)	**0.83 (p= 0.04)**

Secondary Outcome: no statistically significant difference in secondary outcomes

N Engl J Med. 2014;370(15):1383-1392

2014 TOPCAT TRIAL – SUBGROUP ANALYSIS

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)
  - Hospitalization: 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 0.576)

N Engl J Med. 2014;370(15):1383-1392

2014 TOPCAT CRITIQUE

- Author's Conclusion
  - Spironolactone did not significantly reduce the composite primary end point of death
  - significantly decrease 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
  - Significant baseline characteristic between randomization stratum (hospitalization vs BNP)
  - 1/3 of the participants in both group discontinued the study drug
- 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

N Engl J Med. 2014;370(15):1383-1392

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 hazard regression model

Circulation 2015; 131:34-42

2015 TOPCAT TRIAL - REGIONAL VARIATION BASELINE CHARACTERISTICS

Characteristic	Americas (n= 1767)	Russia/Georgia (n= 1678)	P-value
Age	72	66	**< 0.001**
NYHA Class II NYHA Class III	1043 (59%) 610 (35%)	1151 (69%) 511 (30%)	**0.006**
Hospitalization stratum BNP Stratum	976 (55%) 791 (45%)	1488 (89%) 190 (11%)	**< 0.001**
Current Smoker	117 (7%)	243 (14%)	**< 0.001**
BMI	32.9	29.4	**< 0.001**
Diuretic use	1573 (89%)	1244 (74%)	**< 0.001**
ACEI or ARB use	1395 (79%)	1505 (90%)	**< 0.001**
BNP	234 (145, 391) n = 430	376 (175 – 702) n = 38	**0.016**
NT-proBNP	900 (557, 1920); n = 257	1045 (585, 1885); n = 143	0.24

Circulation 2015; 131:34-42

2015 TOPCAT TRIAL - REGIONAL VARIATION OUTCOMES

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

	Americas (n = 1767)	Russia/Georgia (n = 1678)	P-value
Mean daily dose (spironolactone)	21.7 mg (n = 866)	28.4 mg (n = 823)	**P=0.001**
Mean daily dose (placebo)	25.9 mg (n = 846)	29.5 mg (n = 830)	**P=0.001**
Discontinue drugs (%)	21.7	7.3	**P< 0.001**

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

Region	Spironolactone (%)	Placebo (%)	P-value
Americas (n = 1767)	2.1	0.2	**P< 0.001**
Russia/Georgia (n = 1678)	2.9	0.4	**P< 0.001**

Circulation 2015; 131:34-42

2015 TOPCAT TRIAL - REGIONAL VARIATION CLINICAL OUTCOMES

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

	Americas (n = 522)	Russia/Georgia (n = 149)	P-value
Incidence rate (per 100 pt-yr)	11.5	8.9	**P< 0.001**

Primary event rate (per 100 patient-year)

Region	Hospitalization	BNP Stratum	HR (P-value)
Americas (n = 1767)	14.7	8.1	1.78 **(p< 0.001)**
Russia/Georgia (n = 1678)	2.4	2.4	NS

Primary Composite event rate (per 100 patient-year)

Region	Spironolactone	Placebo	HR (P-value)
Americas (n = 1767)	242 (10.4%)	280 (12.6%)	0.82 **(p= 0.06)**
Russia/Georgia (n = 1678)	78 (2.5%)	71 (2.3%)	NS

2015 TOPCAT TRIAL - REGIONAL VARIATION CLINICAL OUTCOMES

	Americas (n = 1767) (incidence rate per 100 pt-yr)			Russia/Georgia (n = 1678) (incidence rate per 100 pt-yr)			Regional difference
	Spironolactone (n – 886)	Placebo (n = 881)	HR (p-value)	Spironolactone (n = 836)	Placebo (n = 842)	HR (p-value)	
CV mortality	96 (3.6%)	127(4.9%)	0.74 **(p= 0.027)**	64 (2%)	49 (1.6%)	NS	**P_I< 0.001**
Aborted cardiac arrest	2 (0.08%)	4 (0.16%)	N/A	1 (0.03%)	1 (0.03%)	N/A	N/A
HF Hospitalization	184 (7.9%)	216 (9.7%)	0.82 **(p = 0.042)**	22 (0.72%)	29 (0.95%)	NS	**P_I< 0.001**

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

2015 TOPCAT TRIAL - REGIONAL VARIATION

- 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
- Author's Conclusion:
  - This post-hoc analysis indicates that 2 distinctively different population were enrolled
  - only the America cohort shared characteristics observed in other randomized trials.
- Presenter's 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

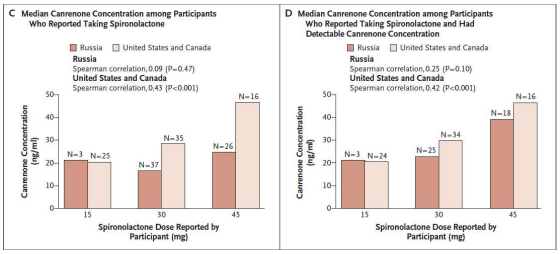
Methods

- 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

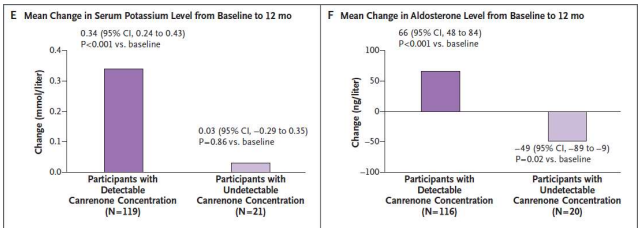
Results

- 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



TOPCAT TRIAL – REGIONAL VARIATION



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

N Engl J Med. 2017; 376:1690-1692

31

OVERALL SUMMARY OF LITERATURE

Study	Result	Support aldosterone antagonist use?
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 distinctively different population 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

32

2017 ACCF/AHA HF TREATMENT GUIDELINE

- Non-pharmacologic Treatment:
  - Sodium restriction in symptomatic HF to reduce congestive 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 HFpEF (Class IIa, LOE C)
- Beta-Blocker & ACEI/ARB – reasonable for controlling BP in pt with HTN (Class IIa, LOE C)
- Aldosterone Antagonist – may be used in appropriately selected patients to reduce hospitalization (Class IIb, LOE B-R)
  - LVEF > 45%
  - eGFR > 30 mL/min
  - SCr < 2.5 mg/dL
  - K < 5 mEq/L

Circulation 2017;136:e137-e161

33

34

PATIENT CASE

PATIENT CASE

- **HPI:** AJ is 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:**

Vitals	HR 90	BP 125/58	Tmax 98.7F	O2 Sat 97% on NC 2L/min
BMP	SCr 1.78	K 3.9	Gluc 194	A1c 7.5
Cardiac	LVEF 55%	NTproBNP **9,200**	Troponin 0.177	

- **CXR:** suspect bilateral pleural effusion

35

PATIENT CASE

- Home Medications
  - Furosemide 20 mg PO daily
  - Glyburide 5 mg PO daily
  - Lisinopril 10 mg PO daily
  - Metoprolol tartrate 50 mg PO BID
- Inpatient Treatment Regimen
  - Metoprolol succinate 100 mg PO daily
  - Lisinopril 10 mg PO daily
  - Furosemide 20 mg IVP Q8H
  - Glyburide 5 mg PO daily
- Is it appropriate to add spironolactone to this patient's current treatment regimen?

☐ YES

☑ NO

36

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

37

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

38

ALDOSTERONE ANTAGONIST IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

PINHUI (JUDY) CHEN
PGY1 PHARMACY RESIDENT
VALLEY BAPTIST MEDICAL CENTER - BROWNSVILLE