HEART FAILURE NETWORK

Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy – Heart Failure Trial

ATHENA-HF Trial

Javed Butler, Marvin A. Konstam, G. Michael Felker, Andreas P. Kalogeropoulos, Michael M. Givertz, Douglas L. Mann, Kenneth B. Margulies, Margaret M. Redfield, Marc J. Semigran, WH Wilson Tang, David J. Whellan, Steven E. McNulty, Kevin J. Anstrom, Monica Shah, Patrice Desvigne-Nickens, Adrian F. Hernandez, and Eugene Braunwald, on behalf of the NHLBI Heart Failure Network

U.S. Department of Health and Human Services
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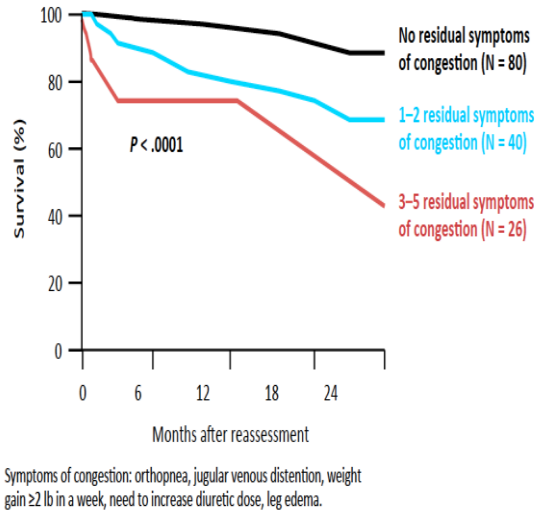
National Heart Lung and Blood Institute
People Science Health

Persistent Congestion and Outcomes in Acute Heart Failure

- Persistent clinical and sub-clinical congestion at discharge after an AHF hospitalization is associated with worse outcomes.

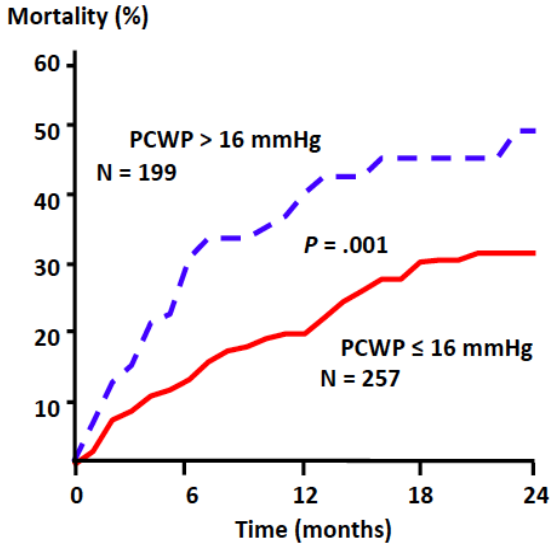
Signs and symptoms



Symptoms of congestion: orthopnea, jugular venous distention, weight gain ≥2 lb in a week, need to increase diuretic dose, leg edema.

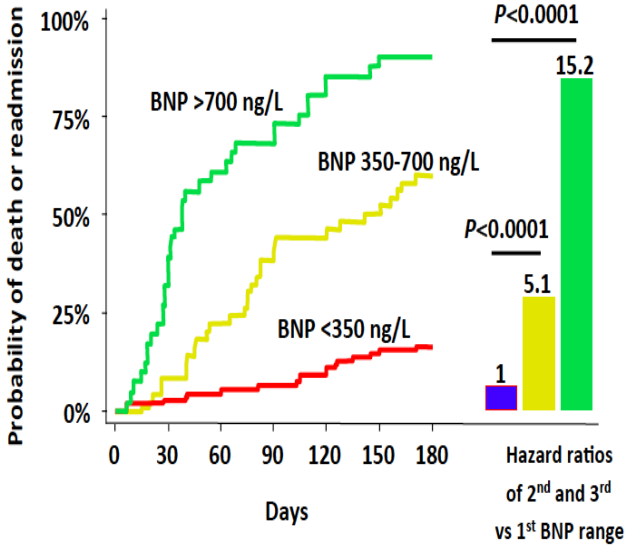
Lucas C, et al. *Am Heart J.* 2000;140:840-847.

Pulmonary Capillary Wedge Pressure



Fonarow GC, et al. *Circulation.* 1994;90(pt. 2):1-488.

Natriuretic Peptide Levels



Logeart D, et al. *J Am Coll Cardiol.* 2004;43:635-641

Acute Heart Failure

Aldosterone levels and high-dose MRA

- Patients with AHF have elevated aldosterone levels that are associated with
  - Diuretic resistance and persistent congestion
  - Worse post-discharge outcomes
    - Eur J Heart Fail. 2013;15(11):1228-35
- High-dose mineralocorticoid receptor antagonists (MRA) therapy has been shown to overcome diuretic resistance in HF. Circ Heart Fail 2009; 2: pp. 370-376
- In a single blind randomized trial of 100 patients, 50-100mg spironolactone use in AHF was associated with improved congestion and renal function.
  - Eur J Intern Med. 2014 Jan;25(1):67-72

Study Aim and Design

- To test the hypothesis that high-dose spironolactone use in patients with AHF will lead to greater reductions in NT-proBNP levels from randomization to 96 hr.
- Randomized, double blind, placebo-controlled, multicenter trial.
- Patients were randomized to usual care or usual care plus 100 mg spironolactone
  - Patients not on MRA at baseline were randomized to spironolactone 100 mg or placebo
  - Those on low-dose spironolactone were randomized to 100 mg spironolactone or 25 mg spironolactone

Other Objectives

96 hours

1. Congestion score (dyspnea, orthopnea, fatigue, JVP, rales, edema)
2. Dyspnea relief
3. Net urine output
4. Net weight change
5. Loop diuretic dose requirement
6. In-hospital worsening of HF

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Day 30	1. All-cause mortality 2. All-cause readmissions 3. Outpatient worsening HF (HF readmissions or ED visits or observational unit stays for HF or need for outpatients IV diuretics) 4. MRA use 5. Loop diuretic dose 6. Index hospitalization length of stay
Day 60	1. Vital status

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Day 60	1. Vital status
Safety	1. Change in serum creatinine 2. Hyperkalemia (>5.5mmol/L and >6.0mmol/L)

Key Inclusion Criteria

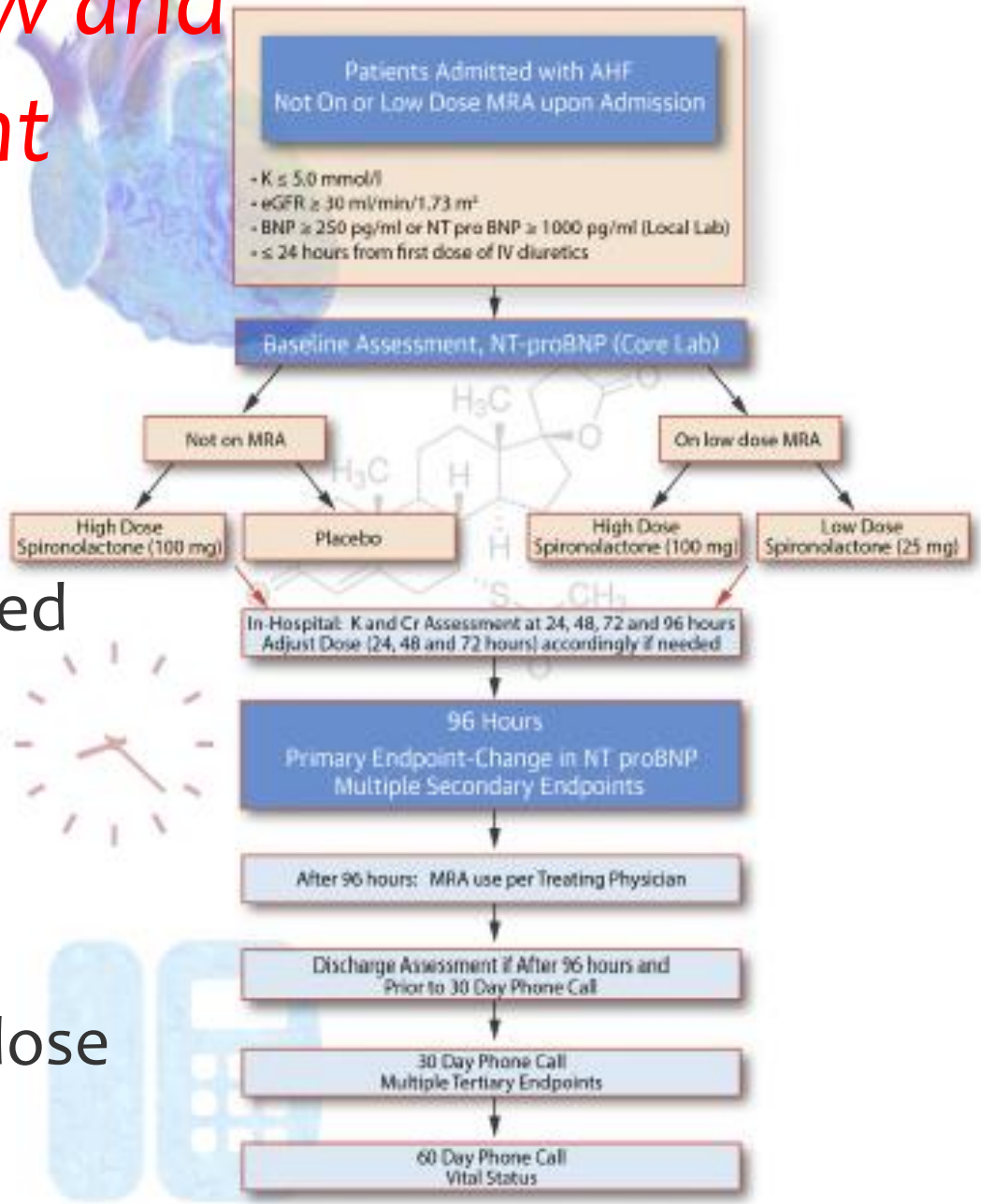
- Age ≥21 yrs
- At least 1 symptom and 1 sign of congestion
- eGFR of ≥30 mL/min/1.73m^2
- Serum K^+ ≤5.0 mmol/l
- NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL within 24h of randomization
- Not on MRA or on low-dose spironolactone (12.5 mg or 25 mg daily) at baseline
- Randomized within 24 hours of first IV diuretic dose

Key Exclusion Criteria

- Eplerenone or >25 mg spironolactone at home
- Systolic blood pressure <90 mmHg
- Significant arrhythmias or ICD shock within 1 wk.
- ACS currently suspected or within the past 4 wk.
- Current or planned LVAD within 30 days
- Post transplant or expected to receive one within 30d
- Current inotrope use

Study Flow and Enrollment

- 12/2014 to 4/2016
- 360 patients enrolled from 22 sites.
- 182 patients randomized to high-dose spironolactone
- 178 to usual care
  - 132 placebo
  - 46 continued low dose spironolactone



Butler, J. et al. J Am Coll Cardiol HF. 2016;4(9):726-35.

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Clinical Characteristics

	Usual Care	Spironolactone
Age (yr.)	65 (54, 74)	65 (57, 76)
Female (%)	36	36
White/Black (%)	56/43	55/41
Myocardial Infarction (%)	30	28
Hypertension (%)	81	87
Atrial fibrillation (%)	48	50
Diabetes Mellitus (%)	42	40
Chronic Kidney Disease (%)	31	24
Left Ventricular Ejection Fraction (%)	30 (20, 45)	35 (21, 50)
Proportion <45% (%)	79	69

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Baseline Treatment

	Usual Care (%)	Spironolactone (%)
ACE inhibitors or ARB	63	58
Beta blockers	74	74
MRA	28	27
Loop diuretics	95	97
Hydralazine	26	24
Nitrates	19	19
Implanted defibrillator	42	35
Biventricular pacemaker	37	42

Vitals and Laboratory Data

Baseline Characteristics	Usual Care	Spironolactone
Systolic Blood Pressure - mmHg	123 (108, 138)	120 (106, 138)
Heart rate - bpm	80 (70, 94)	78 (70, 90)
Body mass index	32 (27, 38)	30 (25, 35)
Sodium - mEq/L	140 (138, 142)	140 (138, 142)
Potassium - mEq/L	4.0 (3.6, 4.3)	3.9 (3.6, 4.3)
BNP, pg/ml (N=156)	1055 (502, 1581)	1131 (680, 1986)
NTproBNP, pg/ml (N=204)	4176 (1936, 7456)	4028 (2472, 10048)
Blood urea nitrogen - mg/dL	22 (17, 31)	23 (16, 33)
Creatinine - mg/dL	1.3 (1.0, 1.5)	1.2 (1.0, 1.5)
eGFR - ml/min/1.73 m^2	55 (46, 71)	58 (45, 75)

Results - *Primary Endpoint*

	Usual Care	Spironolactone	P
Log NTproBNP			
Baseline	8.23 (7.58, 8.94)	8.43 (7.90, 9.17)	
96 h (or discharge)	7.64 (6.93, 8.45)	7.89 (7.19, 8.68)	
Change	-0.49 (-0.98, -0.14)	-0.55 (-0.92, -0.18)	0.57
N-terminal pro B-type natriuretic peptide, pg/ml			
Baseline	3753 (1968, 7633)	4601 (2697, 9596)	
96 h (or discharge)	2080 (1025, 4675)	2672 (1326, 5896)	
Change	-1072 (-3182, -231)	-1796 (-3883, -571)	0.76

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Dyspnea and Congestion

	Usual Care	Spironolactone	P
Dyspnea - Likert Score	2 (1, 3)	2 (1, 3)	0.30
Dyspnea – Visual Analog Scale			
Baseline	65 (40, 75)	60 (45, 75)	
96 h	83 (70, 90)	80 (65, 90)	
96 h Change	15 (5, 30)	15 (2, 30)	0.61
Clinical congestion score			
Baseline	11 (9, 12)	10 (9, 12)	
96 h	4 (2, 6)	4 (2, 7)	
Change	-6 (-8, -4)	-6 (-8, -4)	0.416

Urine Output and Weight Change

	Usual Care	Spironolactone	P
Net urine output, mL (Cumulative)			
24 h	1183 (510, 1955)	1100 (483, 2131)	0.76
48 h	2282 (1155, 4135)	2484 (1203, 4411)	0.44
72 h	3810 (2011, 5565)	4171 (2053, 6040)	0.53
96 h	5584 (2924, 8132)	6086 (2780, 8420)	0.57
Weight change, lbs			
Baseline	207.1 (171.0, 250.4)	195.0 (162.6, 237.0)	
96 h or early discharge	198.9 (167.6, 243.6)	185.1 (158.5, 230.8)	
Change	-6.1 (-11.2, -1.8)	-7.3 (-13.0, -2.0)	0.33

Diuretic Use and Worsening Heart Failure

	Usual Care	Spironolactone	P
Furosemide equivalent diuretic dose, mg			
Baseline	160 (120, 320)	160 (100, 320)	
96 h	80 (40, 240)	80.0 (40, 200)	
96 h change	-80 (-160, 0.0)	-80.0 (-160, 0)	0.77
Worsening heart failure (%)			
Inpatient	18	19	0.76
Outpatient	10	11	0.76

Hyperkalemia

	Usual Care	Spironolactone	P
Change in serum potassium – mEq/L. Median (25th, 75th			
24 h	0.00 (-0.40, 0.30)	0.00 (-0.30, 0.30)	0.50
48 h	0.10 (-0.3, 0.40)	0.10 (-0.10, 0.40)	0.02
72 h	0.20 (-0.40, 0.55)	0.20 (-0.20, 0.60)	0.08
96 h	0.20 (-0.30, 0.60)	0.30 (0.00, 0.70)	0.08

- One patient in the placebo group developed serum K levels between 5.5-5.9 mmol/L
- No one developed K concentration > 6.0 mmol/L

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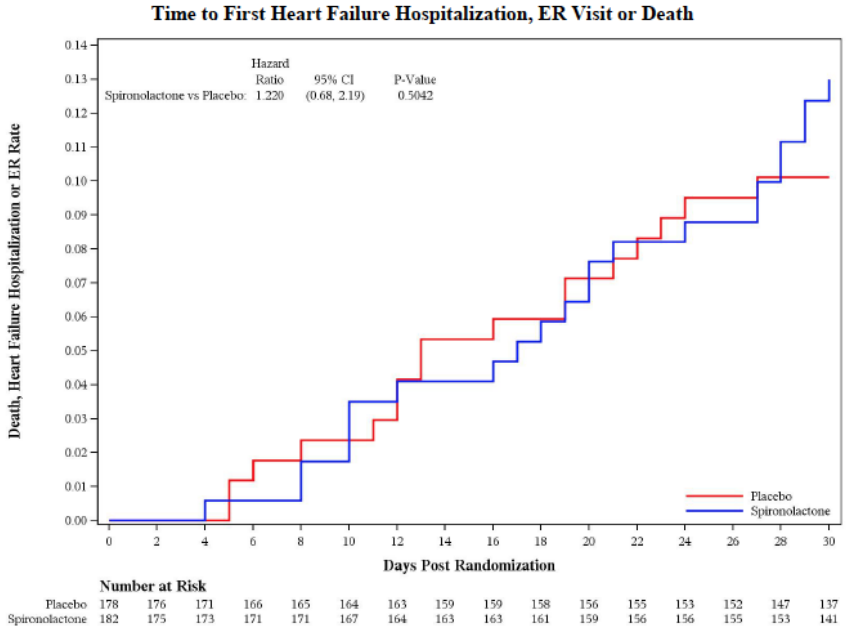
Renal Function

	Usual Care	Spironolactone	P
Change in serum creatinine - mg/dL. Median (25^{th}, 75^{th})			
24 h	0.05 (-0.05, 0.20)	0.05 (-0.03, 0.17)	0.76
48 h	0.02 (-1.10, 0.20)	0.10 (-0.03, 0.20)	0.67
72 h	0.08 (-0.08, 0.22)	0.10 (-0.03, 0.28)	0.85
96 h	0.10 (-0.02, 0.33)	0.10 (-0.05, 0.27)	0.77
Change in eGFR- ml/min/1.73 m^2. Median (25^{th}, 75^{th})			
24 h	-1.95 (-8.46, 2.79)	-2.58 (-7.83, 1.53)	0.87
48 h	-1.59 (-9.65, 3.71)	-4.12 (-8.87, 1.89)	0.95
72 h	-3.70 (-12.06, 4.09)	-3.71 (-10.67, 0.87)	0.82
96 h	-5.53 (-13.11, 0.79)	-4.35 (-11.06, 1.74)	0.56

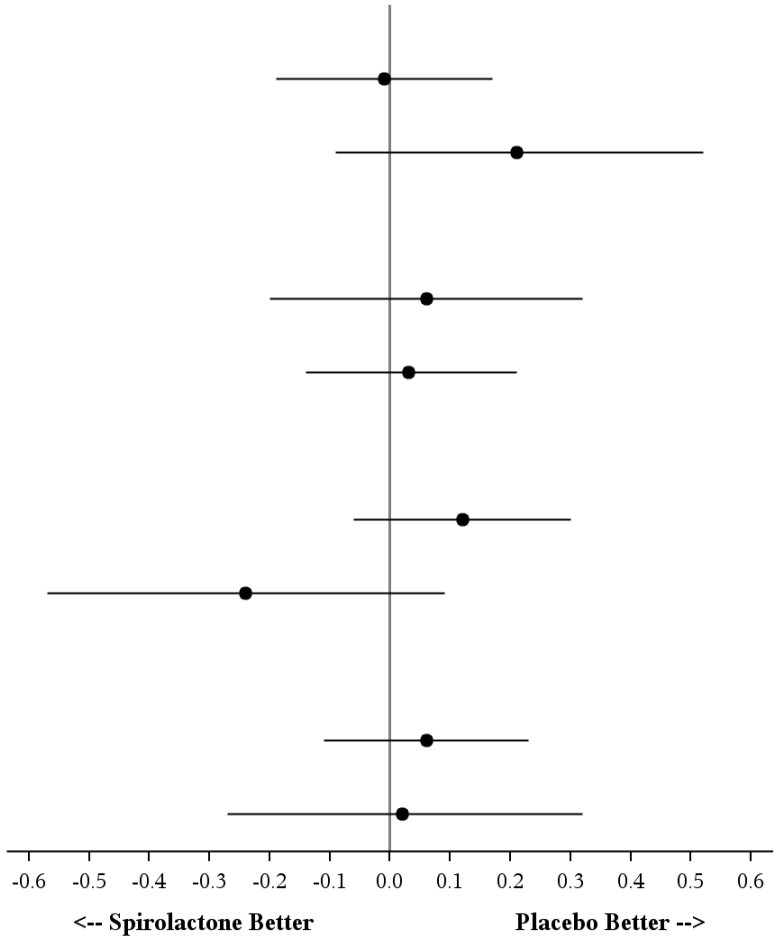
Post Discharge Outcomes

- Median time to discharge: 4 (2, 7) days in both groups.
- Two patients in each arm died in-hospital
- 7 patients in placebo and 5 in spironolactone arm died by day 30.
- No significant difference in post-discharge mortality, HF hospitalization, or ED visit.
- 47% in placebo and 43% in spironolactone arm had SAE by day 30



Sub-group analysis

Description	Treatment Difference	95% CI	Interaction P-Value
Spironolactone Naïve	-0.01	-0.19, 0.17	0.2154
Low Dose Spironolactone	0.21	-0.09, 0.52	
Age < 65	0.06	-0.20, 0.32	0.9678
Age ≥ 65	0.03	-0.14, 0.21	
LVEF ≤ 45	0.12	-0.06, 0.30	0.0776
LVEF > 45	-0.24	-0.57, 0.09	
Male	0.06	-0.11, 0.23	0.7452
Female	0.02	-0.27, 0.32	



Conclusion

- In ATHENA-HF, 100mg/day spironolactone for 96 hr in AHF did not achieve its primary aim of reducing NTproBNP level more than usual care alone
- None of the secondary endpoints differed between the 2 groups
  - Dyspnea relief, clinical congestion, net urine output, weight lose, or clinical events
- High dose spironolactone was well tolerated
  - No significant difference in worsening renal function or hyperkalemia between the two groups
- These data do not support the routine use of high dose spironolactone in AHF.
- The role of high dose MRA targeted to patients resistant to loop diuretics needs to be further studied.

Appreciation

- NHLBI Heart Failure Network
- Patients
- Investigators