Study Of Dietary Intervention Under 100 MMOL in Heart Failure

SODIUM-HF: A pilot study

Eloisa Colin-Ramirez BSc PhD, Finlay McAlister MD MSc, Yinggan Zheng MA MEd, Sangita Sharma PhD, Paul Armstrong MD, Justin A Ezekowitz MBBCh MSc

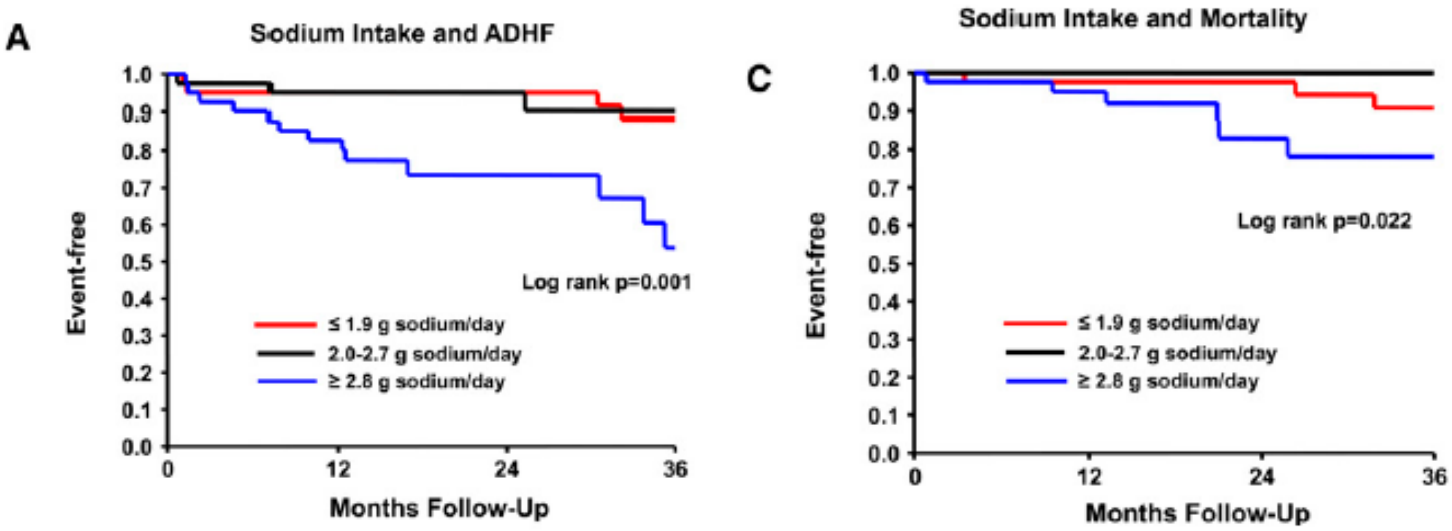
University of Alberta
Division of Cardiology, Department of Medicine

Background

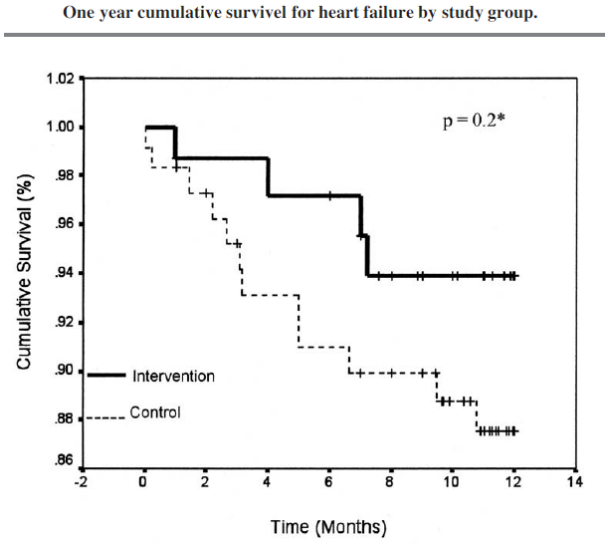
- Chronic heart failure (HF) remains a major and growing public health problem.
- 5-year mortality rate of ~20-50% after diagnosis.
- 20-30% of patients with HF have an ER visit or are hospitalized every year.
- HF is associated with neurohormonal activation and abnormalities in autonomic control that lead to sodium and water retention.
- Clinicians have focused on ***dietary sodium*** and ***water restriction*** to minimize the risk of acute volume overload episodes but ***little evidence*** supports this practice.

Roger VL et al. Circulation 2011;123:e18-e209.
Ezekowitz JA et al. Eur J Heart Fail 2011;13:142-147.

Observational study, n= 123 HF patients



Randomized Clinical Trial, n= 195 HF patients



Intervention group: Dietary recommendations for sodium restriction to <2400 mg/day provided by a dietitian.

Control Group: Usual dietary recommendations for dietary sodium reduction.

Arcand et al. Am J Clin Nutr. 2011.
Colin et al. Rev Chil Nutr, 2010.

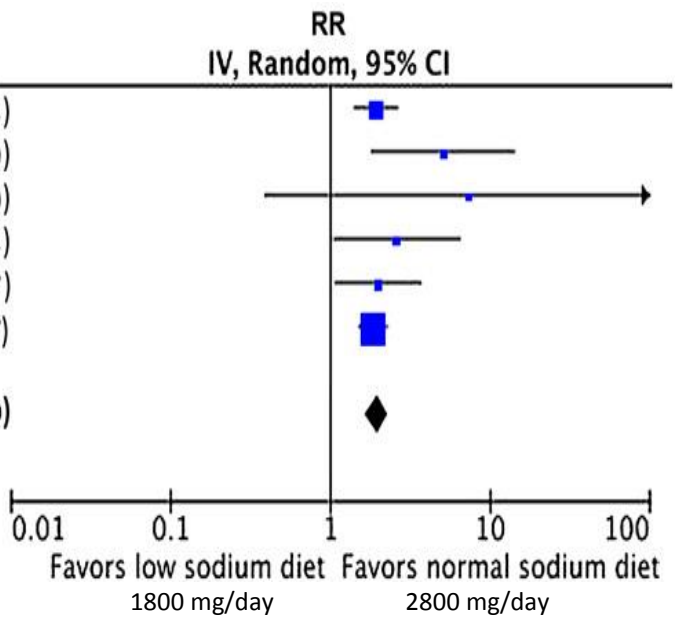
Background

Forest plot of relative risks for mortality

Study or subgroup	Low sodium Events	Total	Normal sodium Events	Total	Weight	RR IV, Random, 95% CI
Licata *et al*, 2003[9]	47	54	24	53	26.6%	1.92 (1.41 to 2.63)
Parrinello *et al*, 2009[7]	20	86	4	87	2.5%	5.06 (1.80 to 14.19)
Paterna *et al*, 2005[10]	3	46	0	48	0.3%	7.30 (0.39 to 137.50)
Paterna *et al*, 2008[13]	15	114	6	118	3.1%	2.59 (1.04 to 6.44)
Paterna *et al*, 2009[11]	26	179	14	191	6.9%	1.98 (1.07 to 3.67)
Paterna *et al*, 2011[12]	212	890	114	881	60.6%	1.84 (1.50 to 2.27)
Total (95% CI)		**1369**		**1378**	**100.0%**	**1.95 (1.66 to 2.29)**
Total events	323		162			

Heterogeneity: $\tau^2=0.00$; $\chi^2=4.73$, df=5 (p=0.45); $I^2 = 0\%$

Test for overall effect: Z=8.08 (p<0.00001)



Parenterally administered saline solutions
250–1000 mg of furosemide daily
Fluid restriction 1 litre/day

Retracted

DiNicolantonio JJ et al. Heart 2012. doi:10.1136/heartjnl-2012-302337
Retraction notice. Heart 2013;99:820

Dietary sodium recommendations in HF

Guideline and year	Sodium restriction recommendation
Canadian Cardiovascular Society (CCS) 2008	<2000 mg per day
Heart Failure Society of America (HFSA) 2010	2000 to 3000 mg per day
American Heart Association (AHA) 2013	No recommendation provided
European Society of Cardiology (ESC) 2012	No recommendation provided

Study objectives

Primary

- To determine the **feasibility** of conducting a randomized controlled trial comparing a low sodium diet to a moderate sodium diet in patients with HF.

Secondary

- To evaluate **changes** in **quality of life** and **B-type natriuretic peptide** (BNP) levels associated with a low sodium diet compared to a moderate sodium diet in patients with HF.

Study hypothesis

- Patients with HF following a low-sodium diet will have a reduction in BNP levels and improvement in quality of life when compared to patients following a moderate-sodium diet.

Key selection criteria

Inclusion

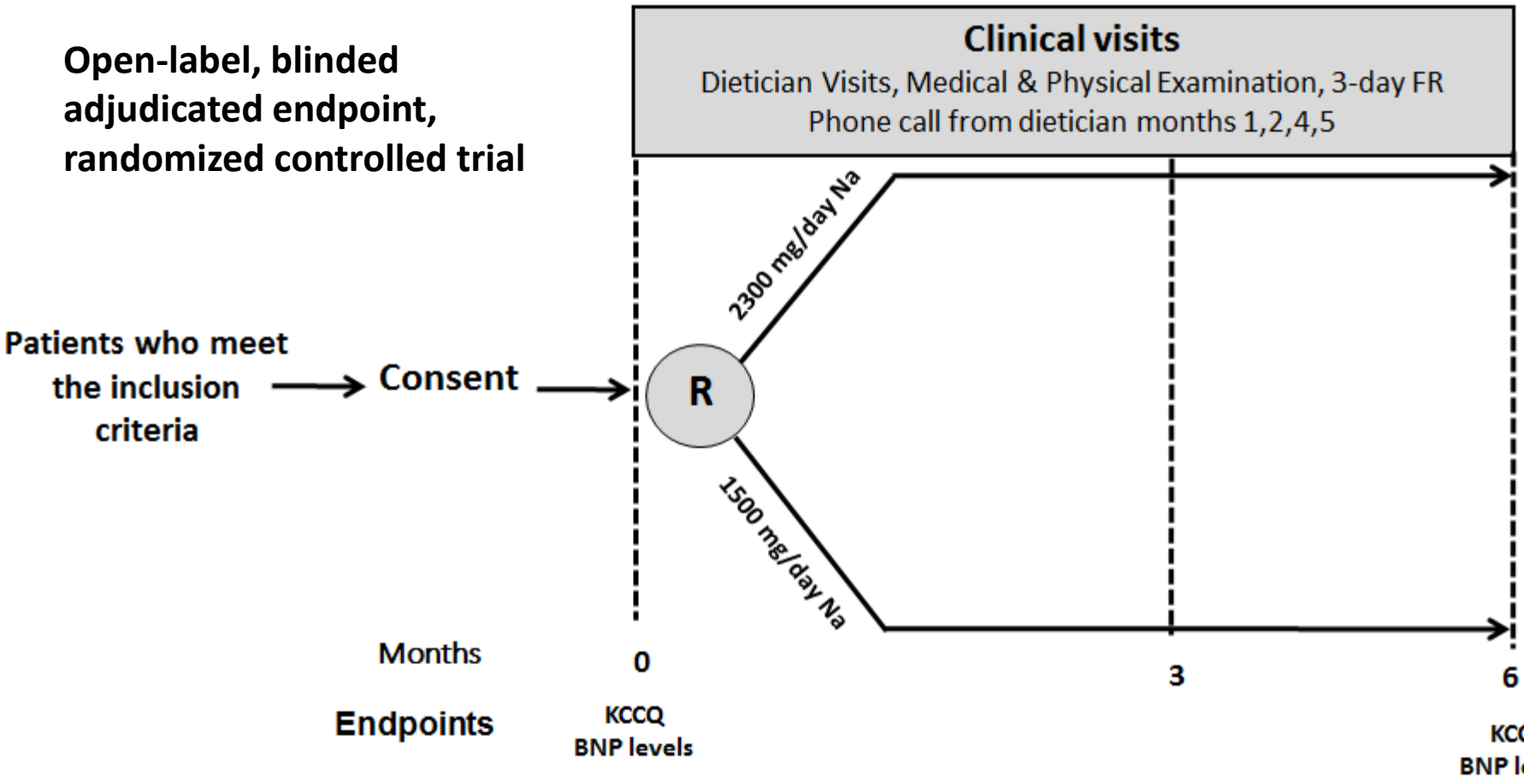
- Confirmed diagnosis of HF (both reduced and preserved systolic function),
- New York Heart Association (NYHA) class II-III

Exclusion

- Serum sodium <130 mmol/L
- GFR < 20 mL/min
- Another comorbid condition or situation which, in the opinion of the investigator, could preclude compliance with the protocol.

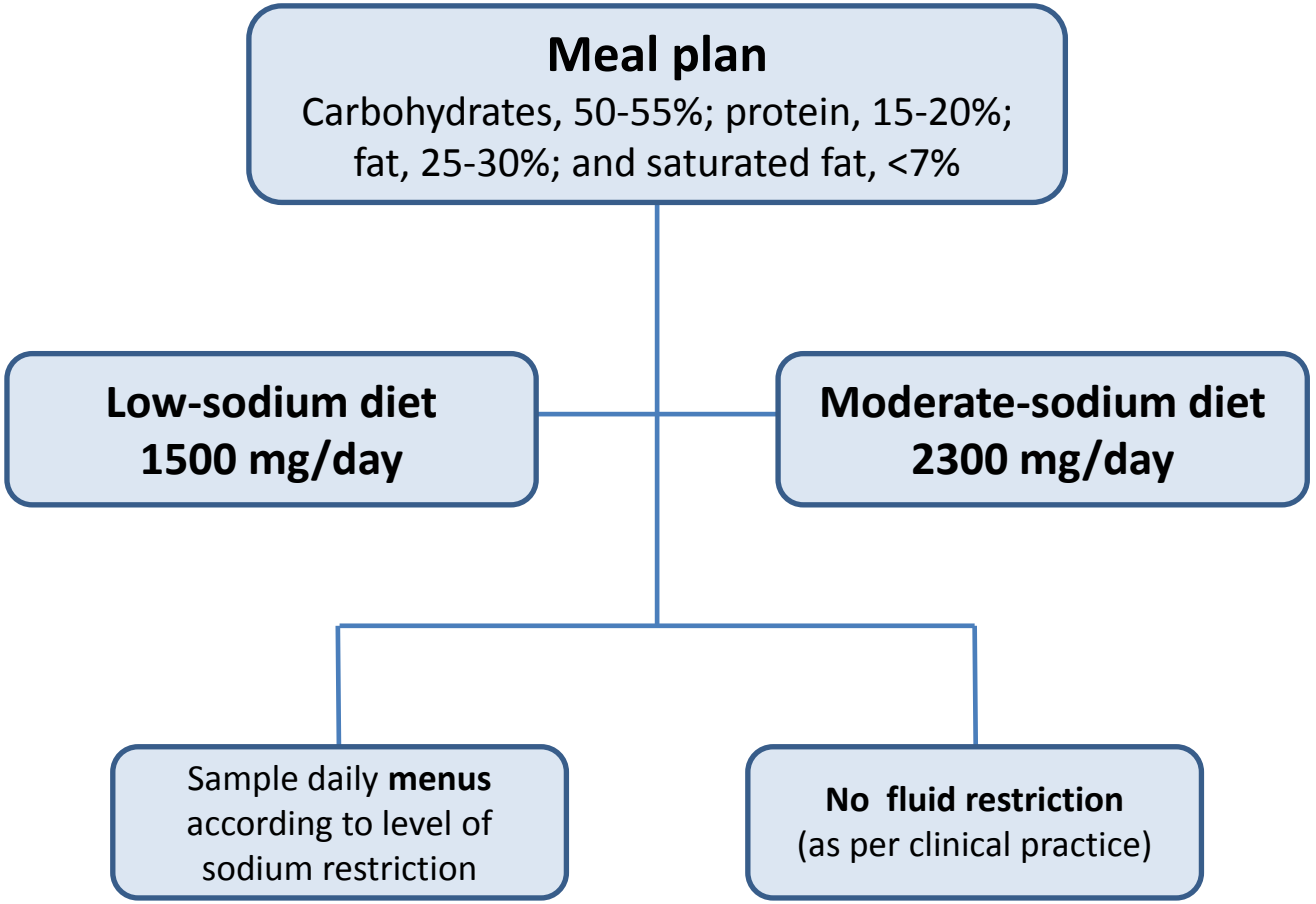
Study design

Open-label, blinded adjudicated endpoint, randomized controlled trial



The study was approved by the Health Research Ethics Board of the UofA

Dietary intervention

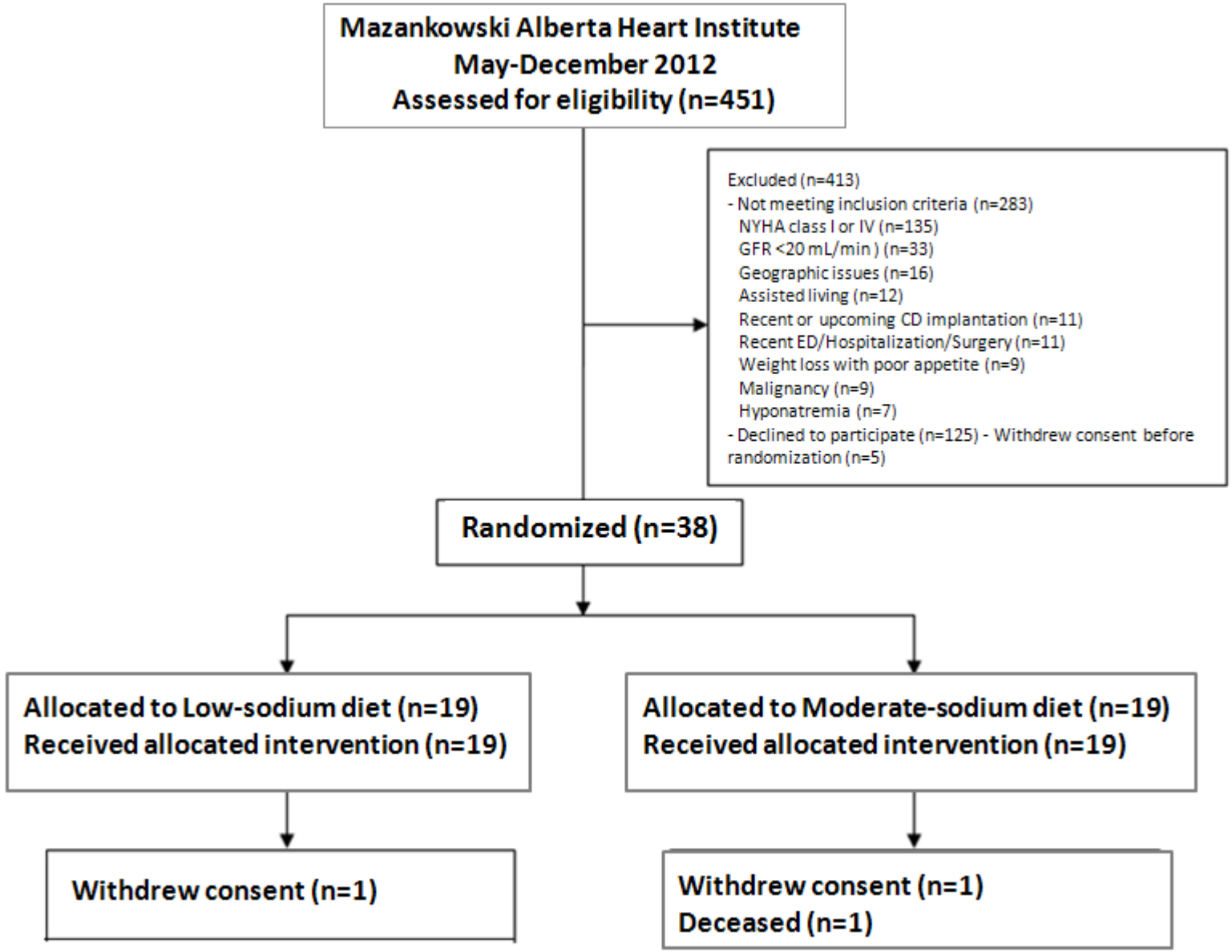


Adult Treatment Panel III. Circulation 2002;106:3143-3421.
Lichtenstein AH et al. Circulation 2006;114(82-96.

Statistical methods

- Primary efficacy endpoints:
  - Changes in KCCQ score and BNP levels.
- Between groups differences:
  - Chi-square test was used for categorical variables.
  - Wilcoxon rank sum test was used for continuous variables.
- Within group differences:
  - McNemar's test for categorical variables .
  - Wilcoxon signed-rank test was used for continuous variables.
- All statistical tests were two-sided with p-value <0.05 considered as statistically significant.

Study cohort



Results: Baseline characteristics

Characteristics	Overall (n=38)	Low-sodium diet (n=19)	Moderate-sodium diet (n=19)	P value
Age, years	66 (56-72)	66 (58-71)	64 (52-77)	0.98
Female, %	53	42	63	0.19
NYHA Class, %				0.29
II	90	84	95	
III	11	16	5	
BMI, kg/m^2	32.4 (28-36)	34.3(28-36)	30.3 (27-38)	0.60
Creatinine, umol/L	98 (75-130)	104 (75-138)	93 (75-118)	0.59
Ejection fraction, %	42 (25-51)	47 (30-60)	35 (24-45)	0.06

Values are medians (25th-75th percentiles)

Results: 6 month results

	Low-sodium diet (n=18)			Moderate-sodium diet (n=17)		
	Baseline	**6 months**	**P value**	**Baseline**	**6 months**	**P value**
Energy, kcal/day	1525 (1251-2410)	1402 (1274-2034)	0.18	1684 (1369-1891)	1397 (1252-1590)	0.1
Sodium intake, mg/day	2137 (1304-3118)	1398 (1090-2060)	**0.002**	2678 (1797-3018)	1461 (1086-1765)	**0.001**
Fluid, ml/day	1638 (1483-2204)	1493 (1203-2120)	0.13	1650 (1370-2070)	1670 (1290-2089)	0.59
Creatinine, umol/L	104 (75-138)	111 (93-133)	0.70	93 (75-118)	107 (78-114)	**0.03**

Values are medians (25^{th}-75^{th} percentiles)

Results: 6 month results

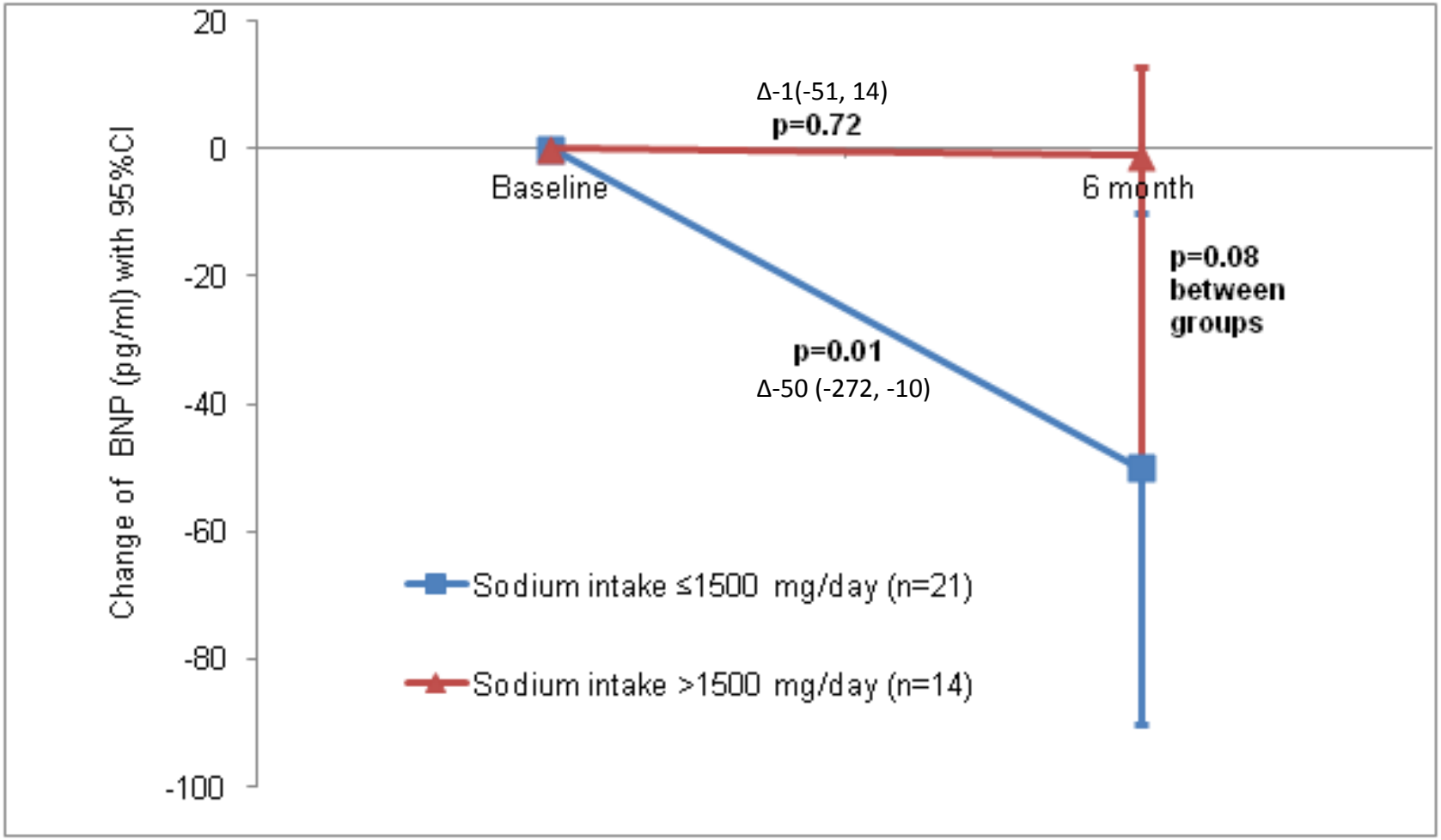
	Low-sodium diet (n=18)			Moderate-sodium diet (n=17)		
	Baseline	**6 months**	**P value**	**Baseline**	**6 months**	**P value**
BNP, pg/mL	216 (25-670)	71 (39-222)	**0.006**	171 (100-558)	188 (69-410)	0.67
KCCQ clinical summary score	62.8 (41.2-72.4)	75.3 (61.5-87.5)	**0.006**	66.4 (55.2-77.1)	72.9 (67.7-85.4)	0.07
KCCQ overall summary score	59.6 (39.1-73.2)	64.6 (50.3-86.1)	**0.04**	65.5 (47.7-82.3)	72.4 (63.8-86.3)	0.07

Values are medians (25^{th}-75^{th} percentiles)

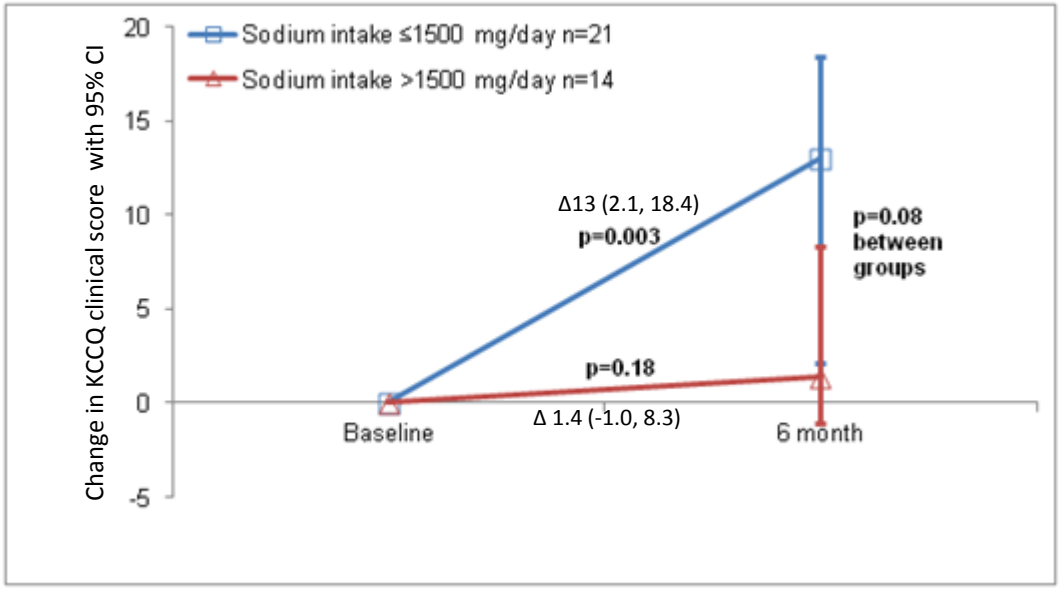
Post-hoc analysis

- Significant reduction in sodium intake observed at follow-up in both groups.
- To test the association between a low sodium intake and improvement in BNP levels and quality of life.
- All patients were divided into two groups according to the dietary sodium intake achieved at the end of the follow-up (**split at 1500 mg/day**), regardless of randomized treatment group.

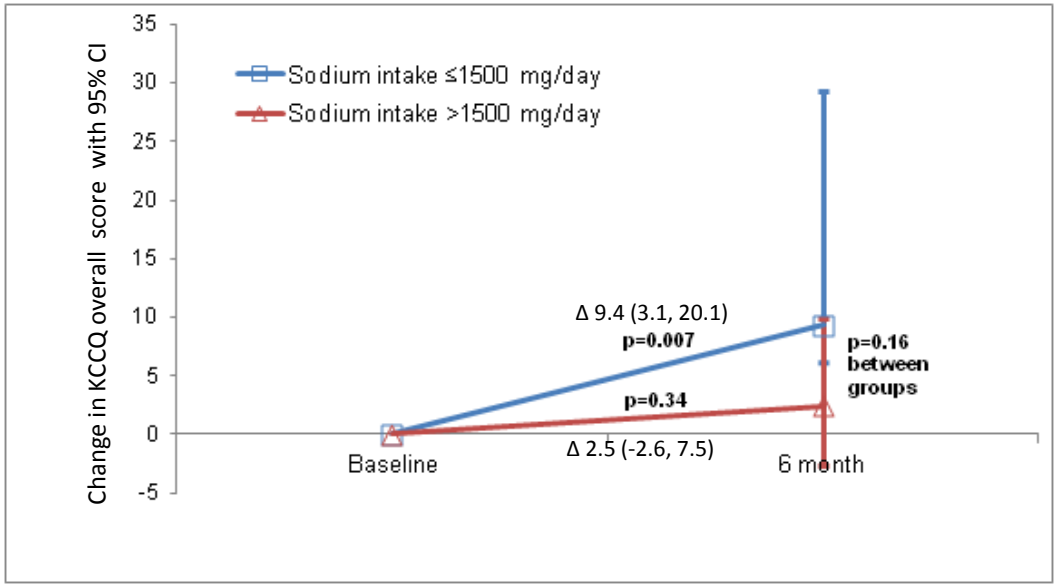
Post-hoc analysis: BNP



Post-hoc analysis: KCCQ



KCCQ clinical score



KCCQ overall score

Limitations

- Small sample size; strengths of an **RCT** design.
- Patients who achieved lower sodium intakes may have also been ***more adherent*** with prescribed medications, follow-up, and other lifestyle interventions that influence prognosis.
- The association between sodium intake of **<1500 mg/day and improvement in BNP and quality of life** cannot be considered proof of ***causation.***

Discussion

- Results of our pilot study suggest that the recent **AHA recommendation of 1500 mg/day sodium** for the general population may be applicable for patients with HF.

- **Larger RCTs with clinical outcomes** as primary endpoints are required to support this recommendation.

- The **SODIUM-HF trial**, a multicentre trial, is being conducted to test the effects of a low-sodium diet, compared to a Usual Care Group, on clinical outcomes as primary endpoints.
  - funded by CIHR
  - led by Canadian VIGOUR Centre

Whelton PK et al. Circulation 2012;126:2880-2889.

Conclusion

- The dietary intervention in this study was feasible in reducing sodium intake in patients with HF.

- An achieved sodium intake less than 1500 mg/day was associated with reduced BNP levels and improved quality of life in ambulatory patients with HF on optimal medical treatment.

Acknowledgements

- Dr. Justin Ezekowitz (PI)
- Quentin Kushnerik, RN
- Elizabeth Woo, RD
- Heart Function Clinic Staff

Selection criteria

Inclusion

- 18 y or older
- Willing/able to sign informed consent
- Confirmed diagnosis of HF (both reduced and preserved systolic function),
- New York Heart Association (NYHA) class II-III
- On optimally tolerated medical therapy according CCS guidelines

Exclusion

- Serum sodium <130 mmol/L
- GFRate < 20 mL/min
- Uncontrolled thyroid disorder
- End-stage hepatic failure
- Cardiac event within the prior month (implantation of a defibrillator or resynchronization pacemaker, a revascularization procedure or hospitalization due cardiovascular causes)
- Uncontrolled atrial fibrillation (resting heart rate >90 bpm)
- Active malignancy with an expected life expectancy <2 years
- Another comorbid condition or situation which, in the opinion of the investigator, could preclude compliance with the protocol.