



Canadian **VIGOUR** Centre  
Bridging Hearts and Minds

# Study of Dietary Intervention Under 100 MMOL in Heart Failure

SODIUM-HF 

Justin A. Ezekowitz, MBBCh MSc, on behalf of the SODIUM-HF  
investigators

Professor, University of Alberta  
Co-Director, Canadian VIGOUR Centre  
Cardiologist, Mazankowski Alberta Heart Institute  
Pragmatic Clinical Trials 2022



# Disclosures / COI / RWI / RWA

- Available online: [thecvc.ca](http://thecvc.ca)
- Funding from:



**University  
Hospital  
Foundation**

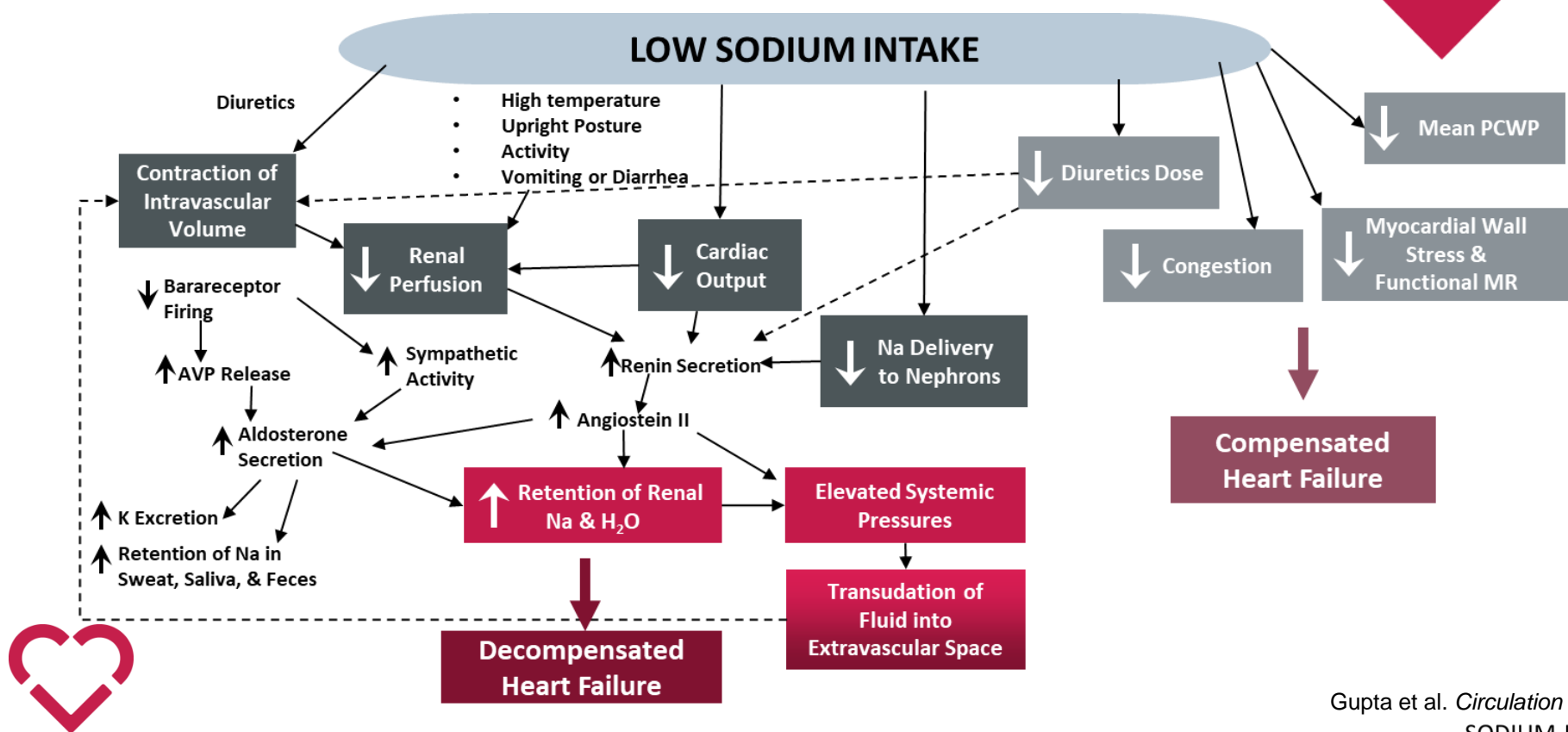


# Heart Failure and Dietary Sodium

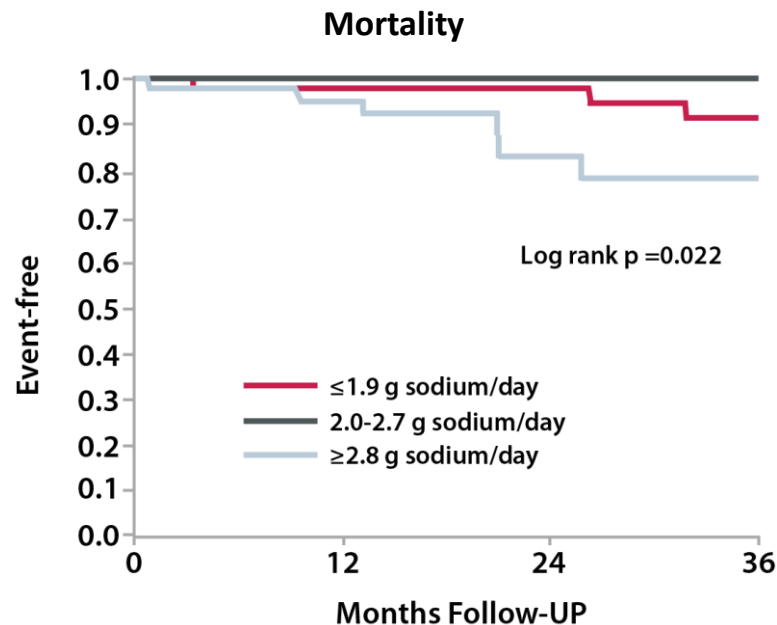
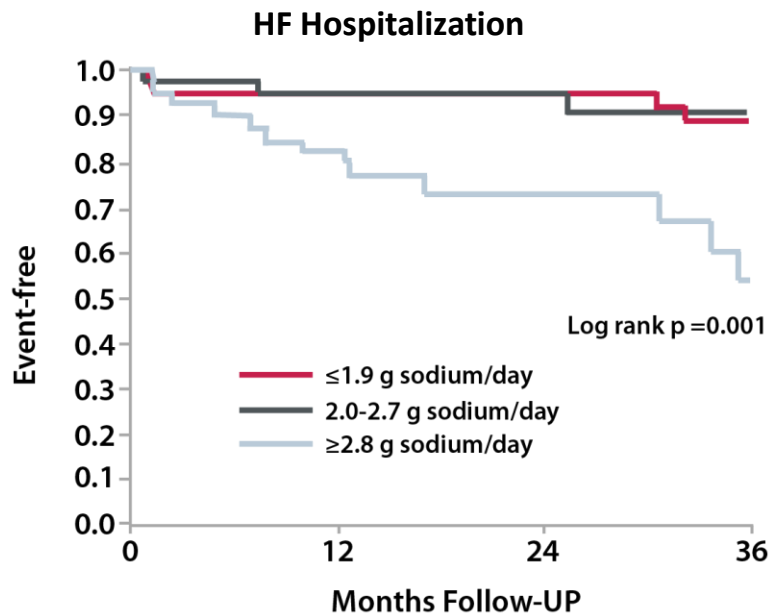
- HF is associated with:
  - neurohormonal activation
  - abnormalities in autonomic control
  - sodium and water retention
- Clinicians have focused on dietary sodium and water restriction to minimize the risk of volume overload for > 100 years
- Little evidence supports this practice



# Dietary Sodium Intake



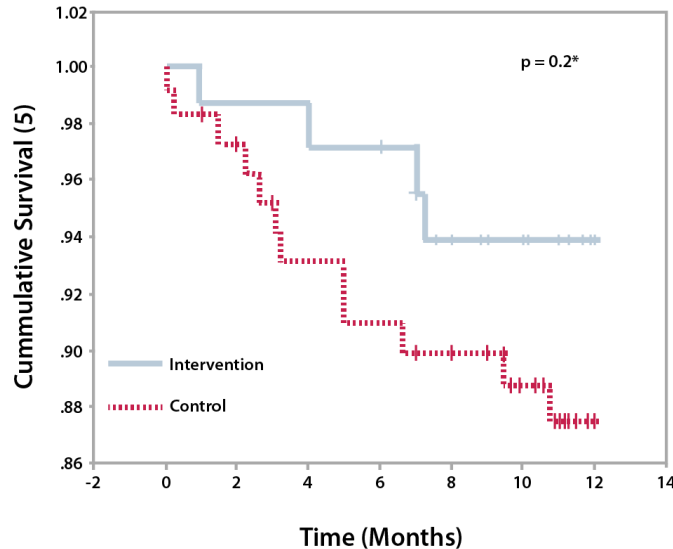
# Dietary sodium: Observational studies



n= 123 patients with HF

# Dietary sodium reduction: RCT

n= 195 patients with HF, Outpatient, Mexico city



Systematic review:

9 studies

All < 100 patients

Mixed interventions

***No consistent results on any outcome***

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

**Control Group:** Usual dietary recommendations for dietary sodium reduction.

# Clinical question

**Does advising a patient to lower the amount of sodium in their diet change the clinical outcome?**



# SODIUM-HF Objectives

Evaluate the effects of a low-sodium diet, compared to usual care, in patients with HF, on a 12 month outcome of:

- **Primary Endpoint:** Composite clinical outcome of All-cause mortality, CV hospitalizations, CV ED visits
- **Secondary Endpoints:**
  - Quality of life (by KCCQ)
  - Exercise capacity (by 6MWT)
  - NYHA class





# SODIUM-HF: Trial Design

**841 patients with heart failure (NYHA II-III) on optimally tolerated medical therapy**

Eligible patients identified via inclusion/exclusion criteria

Participants provide written consent and complete a baseline evaluation

**1500 mg/day Na**

**RANDOMIZATION  
(open label)**

**Usual care**

Clinical visits (12 months) and phone follow-up (12 months)

**Primary Endpoint:**

Composite outcome of all-cause mortality, CV hospitalizations, or CV ED visits

**Secondary Endpoints:**

Change in KCCQ, 6-minute walk test, and NYHA class



# SODIUM-HF: Sites



## SODIUM-HF



26 sites

Canada, Mexico, Chile, Colombia,  
Australia, New Zealand



# SODIUM-HF: In/Exclusion criteria

## SODIUM Inclusion Criteria

- ✓ 18 years or older and willing/able to sign informed consent.
- ✓ Confirmed diagnosis of HF (both reduced and preserved systolic function eligible)
- ✓ NYHA Class II-III
- ✓ On optimally tolerated medical therapy according to CCS guidelines

## SODIUM Exclusion Criteria

- ✗ Patients with an average dietary intake of <1500 mg Na/day
- ✗ Serum sodium <130 mmol/L
- ✗ Hemodialysis-dependent chronic renal failure (or glomerular filtration rate <20 mL/min)
- ✗ Uncontrolled thyroid disorder or end-stage hepatic failure
- ✗ Cardiac device or revascularization procedure in previous month or planned in the next 3 months
- ✗ Hospitalization due cardiovascular causes in the previous 1 month
- ✗ Uncontrolled atrial fibrillation (resting heart rate >90 bpm)
- ✗ Active malignancy with an expected life expectancy <2 years
- ✗ Another comorbid condition or situation which could preclude compliance with the protocol
- ✗ Enrolled in another interventional research study



# SODIUM-HF: Intervention

Patients randomized to one of two study arms:

## 1. Low-sodium containing diet

- <1500 mg daily (<65 mmol/daily)

## 2. Usual care

- general advice to limit dietary sodium as provided in routine clinical practice



# SODIUM-HF: Intervention

- Samples of **menus** at different levels of energy requirement (1400-2200 kcal)
- Patient might **interchange** any of the food items included in the menus by another one included in the recommended foods lists of the same food group that the original one included in the menu.
- Food **individualized** to local region/country
- If energy requirements were adjusted during a follow-up visit, new sample menus were provided.
- **3 day food records** for each visit



# SODIUM-HF: Sample Size / DMC

- Sample size:
  - Based on the primary composite outcome
  - Expected event rate of 25% in usual care arm
  - **30%** reduction in the primary outcome
  - **80%** power, two-sided type I error rate of 0.05
  - Total enrollment of **992** patients
- The Data Monitoring Committee
  - Reviewed data from the first **500** participants with complete 12-month follow-up
  - Mandate was to advise on *futility* (if conditional power was <20%) or *efficacy* (two-sided p-value <0.001).
  - This review, in addition to an assessment of trial operational feasibility and the impact of the COVID-19 pandemic, led to an early stopping with the last patient enrolled on December 09, 2020 and complete 12 month follow-up in December 2021.



# SODIUM-HF: Baseline Characteristics

	Low sodium diet group n=397	Usual care group n=409
<b>Age, years</b>	66 (57–73)	67 (58–75)
<b>Female Sex</b>	127 (32%)	141 (34%)
Geographical region		
Canada	230 (58%)	241 (59%)
Australia and New Zealand	79 (20%)	78 (19%)
Mexico, Chile, and Colombia	88 (22%)	90 (22%)
Diagnosed with HF for $\geq 1$ year	269 (68%)	282 (69%)
Hospitalised for HF in past 12 months	129 (32%)	141 (34%)
Ejection fraction	36 (28–48)	35 (27–50)



# SODIUM-HF: Baseline Characteristics

	Low sodium diet group n=397	Usual care group n=409
<b>Medical history</b>		
Coronary artery disease	187 (47%)	186 (45%)
Atrial fibrillation or flutter	156 (39%)	173 (42%)
Diabetes (type 1 or 2)	132 (33%)	156 (38%)
<b>Vital signs and physical findings</b>		
BMI, kg/m <sup>2</sup>	30 (26–35)	31 (27–36)
Heart rate, beats per min	69 (61–76)	69 (61–77)
Systolic blood pressure, mm Hg	118 (105–129)	118 (104–130)
<b>Laboratory values</b>		
BNP, pg/mL <sup>†</sup>	194 (74–470)	222 (85–541)
NT-proBNP, pg/mL <sup>†</sup>	763 (228–1161)	934 (418–2169)
eGFR, mL/min per 1.73m <sup>2</sup>	61 (46–75)	58 (42–71)

<sup>†</sup>within 90 days of enrollment

BNP available in 263 patients (127 low sodium, 136 usual care); NT-proBNP available in 62 (27 low sodium, 35 usual care) patients

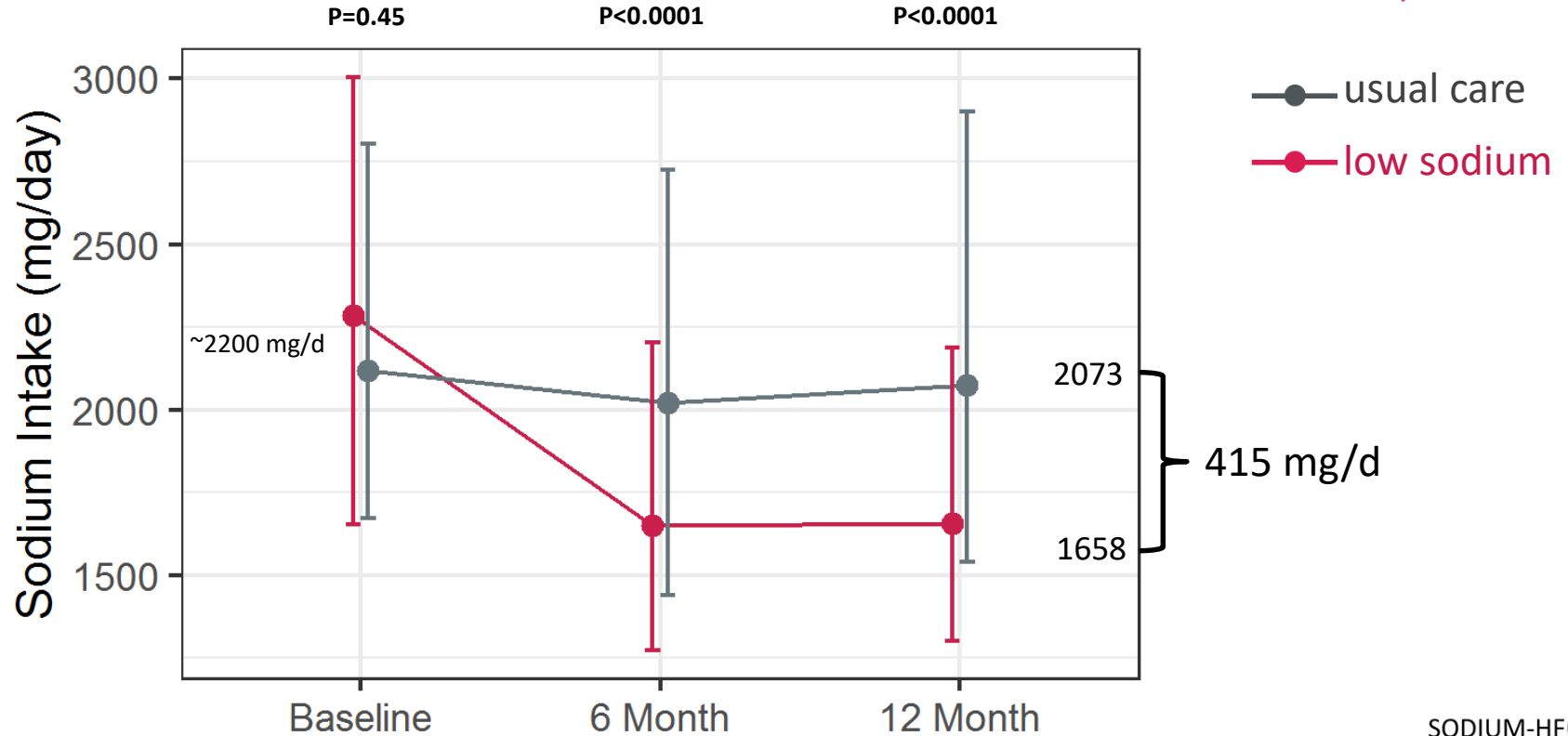


# SODIUM-HF: Baseline Characteristics

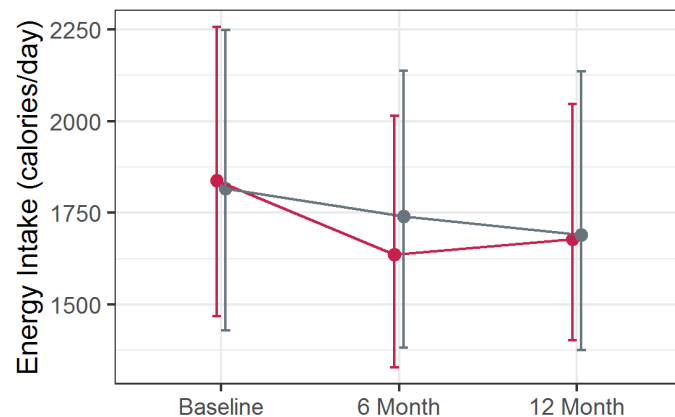
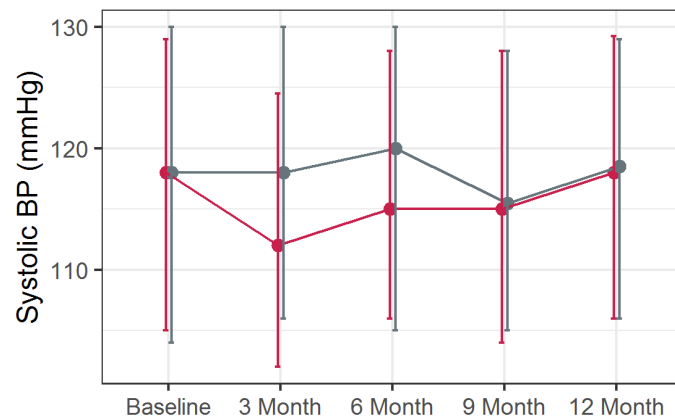
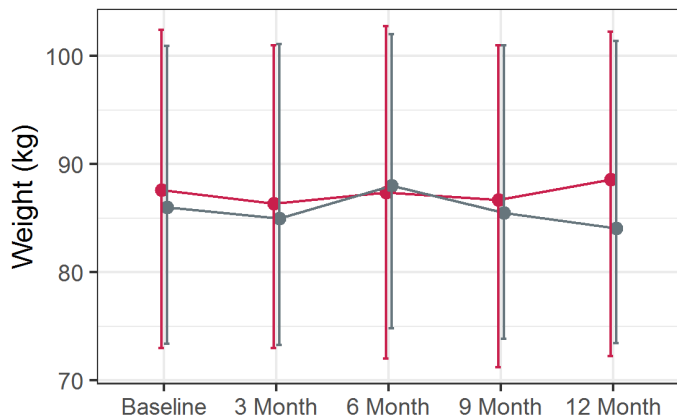
	Low sodium diet group n=397	Usual care group n=409
<b>Medical and Device Therapy, n (%)</b>		
Any RAAS inhibitor (ACE, ARB or ARNI)	314 (79.3)	335 (81.9)
ACE/ARB	256 (64.6)	284 (69.4)
ARNI (sacubitril-valsartan)	63 (16.5)	53 (13.4)
Beta-blocker	351 (88.6)	351 (85.8)
MRA	237 (59.8)	224 (54.8)
ICD	104 (26.2)	81 (19.9)



# Dietary sodium intake



# Blood pressure, weight and energy intake



—●— low sodium  
—●— usual care

All comparisons p=NS



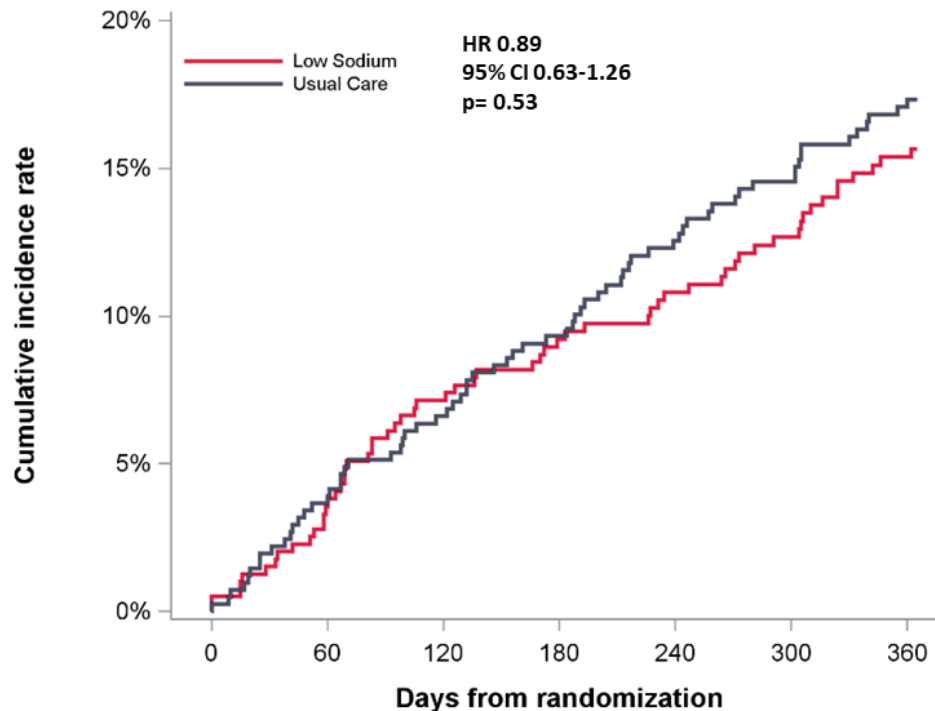


Canadian **VIGOUR** Centre  
Bridging Hearts and Minds

# Outcomes

# Primary Outcome

## CV related hospitalization/ED visit or all-cause mortality

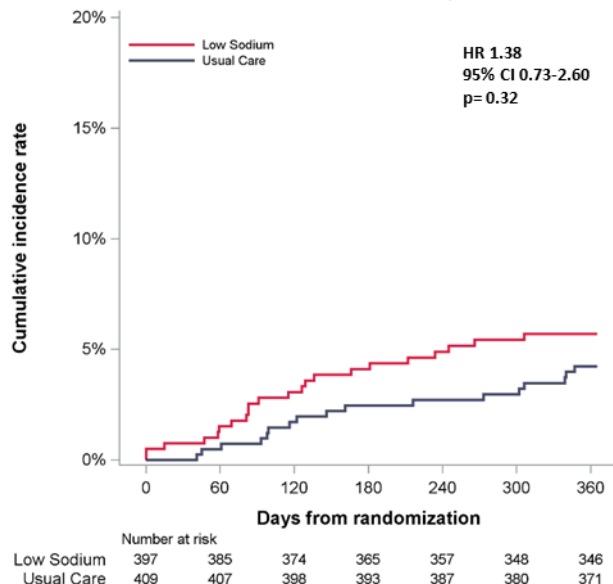


	Number at risk						
Low Sodium	397	377	359	347	336	323	312
Usual Care	409	394	379	367	350	339	326

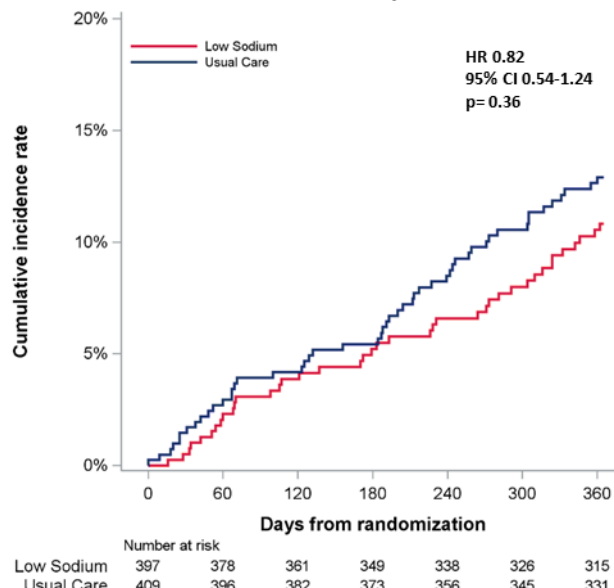


# Secondary Outcomes

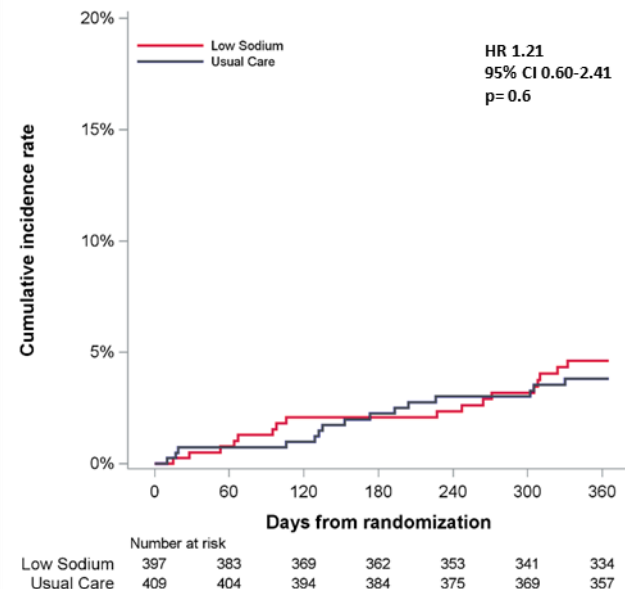
All-cause mortality



CV related hospitalization

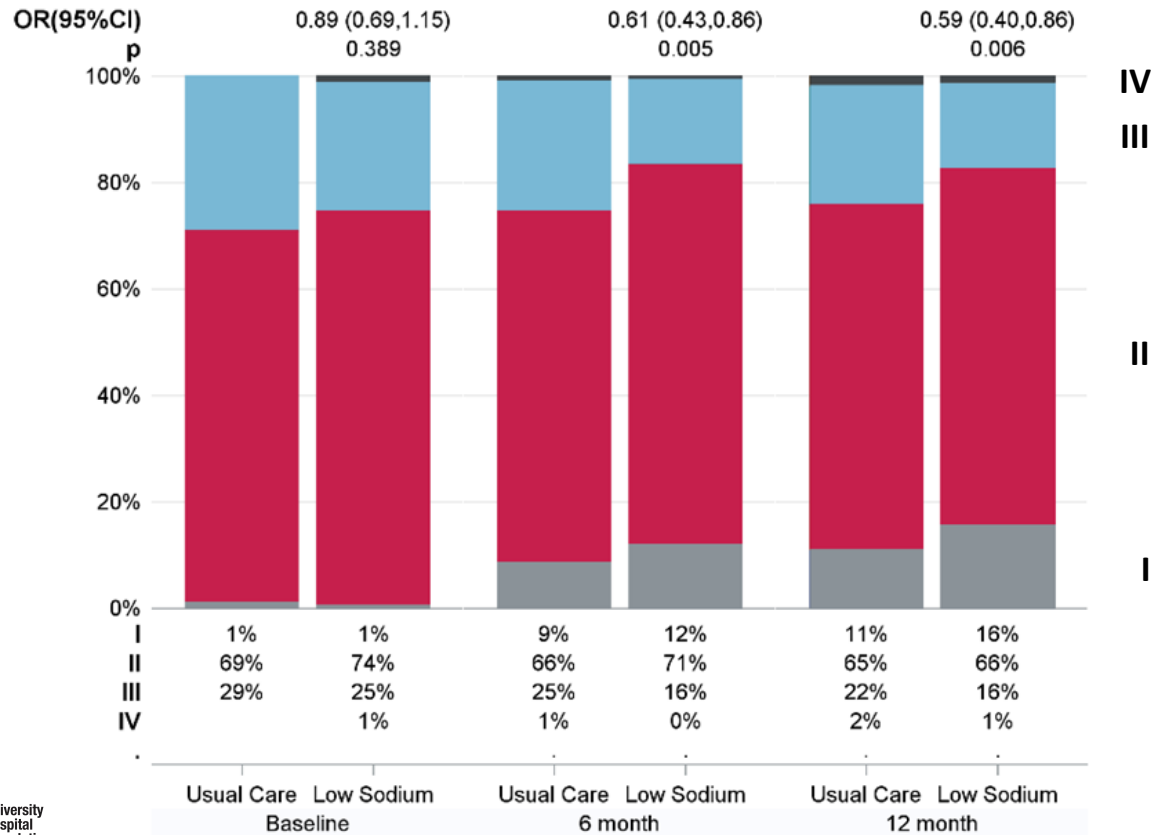


CV related ED visit



# Change in NYHA class

NYHA class:

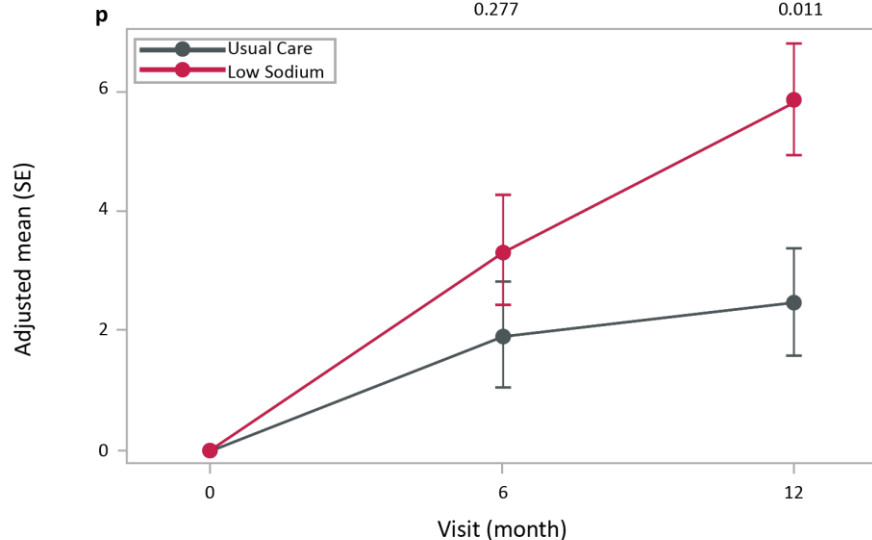


# Change in KCCQ score

## KCCQ OSS

1.42 (-1.1, 3.97)  
0.277

3.38 (0.79, 5.96)  
0.011



Usual Care  
Low Sodium

407  
393

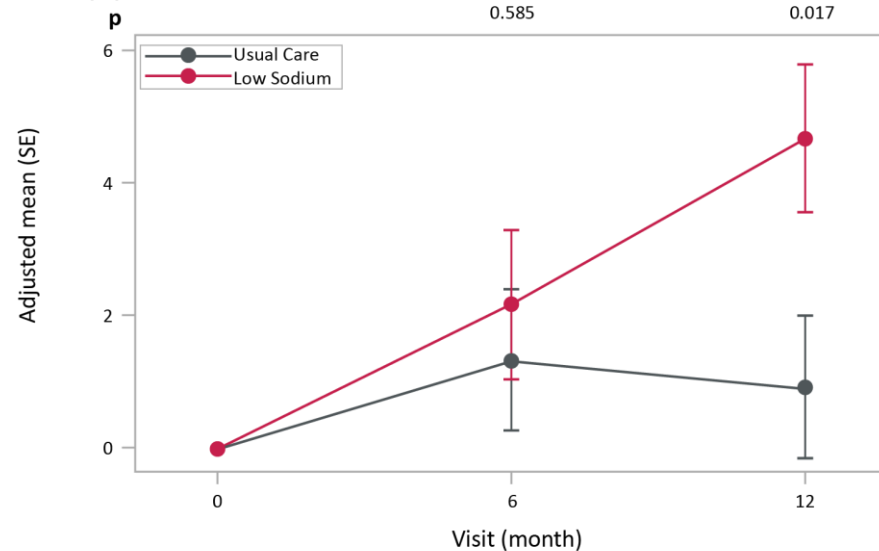
330  
309

316  
302

## KCCQ PLS

0.86 (-2.2, 3.93)  
0.585

3.77 (0.67, 6.87)  
0.017



Usual Care  
Low Sodium

402  
383

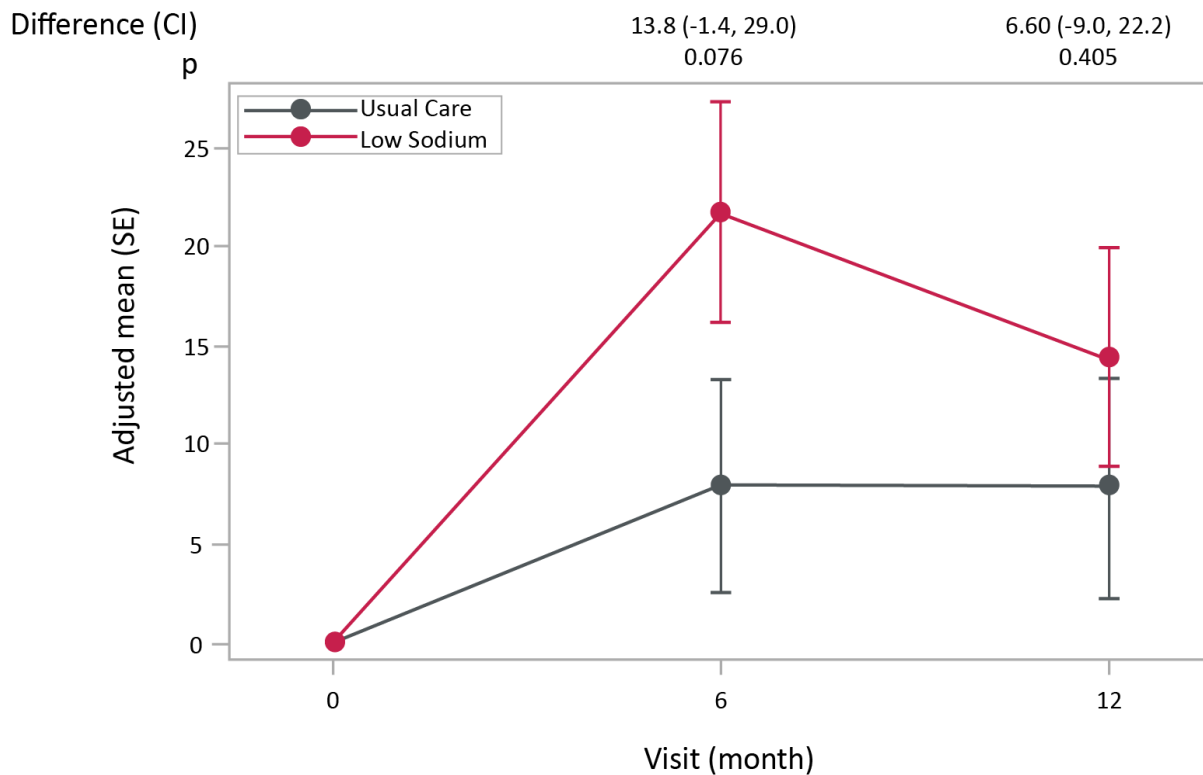
320  
296

308  
295





# Change in 6 min walk test distance



# Limitations

- There was a sodium reduction of 415 mg / day by 12 months, and greater reductions in daily sodium or alternatively, enrolling patients with markedly higher dietary sodium may or may not produce different results.
- The trial was stopped early
- Lower than anticipated event rate
- Inclusion criteria were pragmatic and no NT-proBNP required



# Conclusions

1. In ambulatory patients with HF, a dietary intervention to reduce sodium intake did not reduce clinical events.
2. There was a modest benefit on quality of life as measured by the KCCQ, and in NYHA class.
3. The 6-minute walk test was not statistically different between groups.



# Implications

A low-sodium diet as done in SODIUM-HF:

- Clinicians: as a therapy to improve QOL
- Patients: as part of an overall health strategy
- Guidelines: informs with best evidence



# SODIUM-HF Participants

- A special thank you to those patients who volunteered their time and effort to participate in the SODIUM-HF trial



# SODIUM-HF team

## **SODIUM-HF Investigators/Steering Committee**

Justin A. Ezekowitz (Chair), Eloisa Colin-Ramirez, Heather Ross, Jorge Escobedo, Peter Macdonald, Richard Troughton, Clara Saldarriaga, Wendimagegn Alemayehu, Finlay A. McAlister, JoAnne Arcand, John Atherton, Robert Doughty, Milan Gupta, Jonathan Howlett, Shahin Jaffer, Andrea Lavoie, Mayanna Lund, Thomas Marwick, Robert McKelvie, Gordon Moe, A. Shekhar Pandey, Liane Porepa, Miroslaw Rajda, Haunnah Rheault, Jitendra Singh, Mustafa Toma, Sean Virani, Shelley Zieroth

## **SODIUM-HF Food Core Lab**

Eloisa Colin-Ramirez (Chair), Caroline Kralka, Anita Naicker, Ana Medrano Chavez, Claire Kee, Meghan Rozmahel

## **SODIUM-HF Dietitians Working Group**

Eloisa Colin-Ramirez (Chair), Naomi Uchida, JoAnne Arcand, Margaret Brum, Leslie Jackson-Carter, Sneha Patel, Eva Jasielski, Darlene Manning, Rachel Thompson, Lisa Stein, Winnie Christopher, Jennifer Daniel, Amirhossein Sharifzad, Sinead Feeney, Minja Milic, Lauren Padilla, Martine Strumus, Ana Rebolledo, Solange Martinez, Lubia Velazquez, Grecia Mendoza, Helen Gunn, Sara Widdowson, Romina Delgado, Hayley Patterson, Tanith Lamaro, Marisa Nastasi, Kai Elmas, Emily Arthur, Tatiana Ballivan, Jenna Reinhart, Kate Morgan, Adrienne Young, Sheila Kelly, Elizabeth Woo, Nellie Wong, Lindsay Thompson

## **SODIUM-HF Independent Data Monitoring Committee**

Peter Jüni (Chair), Kevin E. Thorpe, Javed Butler, Robert Mentz

## **SODIUM-HF Clinical Endpoints Committee**

Shaun Goodman (Chair), Nawaf Almajed, Debraj Das, Nariman Sepehrvand, Abhinav Sharma, Mustafa Toma, Shelley Zieroth

## **SODIUM-HF Dietitians Study Coordinators & Dieticians**

Naomi Uchida, Enza De Luca, Sneha Patel, Carlos Fernando, Shahin Jaffer, Erin McAfee, Lisa Stein, Disha Shasti, Wendy Janz, Catherine McPherson, Elizabeth Grieve, Kelly Lehmann, Alison Magi, Quentin Kushnerik, Ana Rebolledo, Lubia Velazquez, Barbara Herrera, Lorraine Skelton, Stephanie Rose, Paz Bourke, Maria Sheehan, Joanne Harris, Estelle Beevors, Sonia Juranics, Linda Hindom, Jo-Anne Kurenoff, Paula Andrea, Garcia Amaya, Joanne Boyer, Mardi Heath, Vanessa Thorpe, Alice Cassidy, Margaret Brum, Eva Jasielski, Rachael Thomson, Darlene Manning, Winnie Christopher, Kristen Wolfe, Sinead Feeney, Lauren Padilla, Martine Strumas, Anita Naicker, Elizabeth Woo, Solange Martinez, Eva Meiklejohn, Romina Delgado, Hayley Patterson, Tanith Lamaro, Emily Arthur, Alice Doring, Emma Whitmore, Adrienne Young, Harriett Adsett, Kate Morgan, Elsa Gonzalez, Rochelle Anthony, Greer Logue, Serena Harris

# Simultaneous publication

## THE LANCET

**Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial**



*Justin A Ezekowitz, Eloisa Colin-Ramirez, Heather Ross, Jorge Escobedo, Peter Macdonald, Richard Troughton, Clara Saldarriaga, Wendimagegn Alemayehu, Finlay A McAlister, JoAnne Arcand, John Atherton, Robert Doughty, Milan Gupta, Jonathan Howlett, Shahin Jaffer, Andrea Lavoie, Mayanna Lund, Thomas Marwick, Robert McKelvie, Gordon Moe, A Shekhar Pandey, Liane Porepa, Mirosław Rajda, Haunnah Rheault, Jitendra Singh, Mustafa Toma, Sean Virani, Shelley Zieroth, on behalf of the SODIUM-HF Investigators*

www.thelancet.com Published online April 2, 2022 [https://doi.org/10.1016/S0140-6736\(22\)00369-5](https://doi.org/10.1016/S0140-6736(22)00369-5)



# Patient comments on Twitter

No real differences. 🤔 Honestly, my first take? This will come as a welcome relief to those patience who, quite honestly, overadhere to the >1200 mg sodium restriction to their detriment (insert ppl like me). Also, reduce the shame in thinking 'I am not doing enough'

Re-emphasis on a balanced diet with moderate activity (as manageable) is much more realistic -

It's massive. The guilt. Your heart is 'failing' you and now you are failing even more because of 'too much sodium' which is in everything?

I think the take home message here is the OCD on extra low sodium which involves a complete overhaul of everyone's diet and lifestyle has far worse and potentially deleterious effects on mental health -







Canadian **VIGOUR** Centre  
Bridging Hearts and Minds

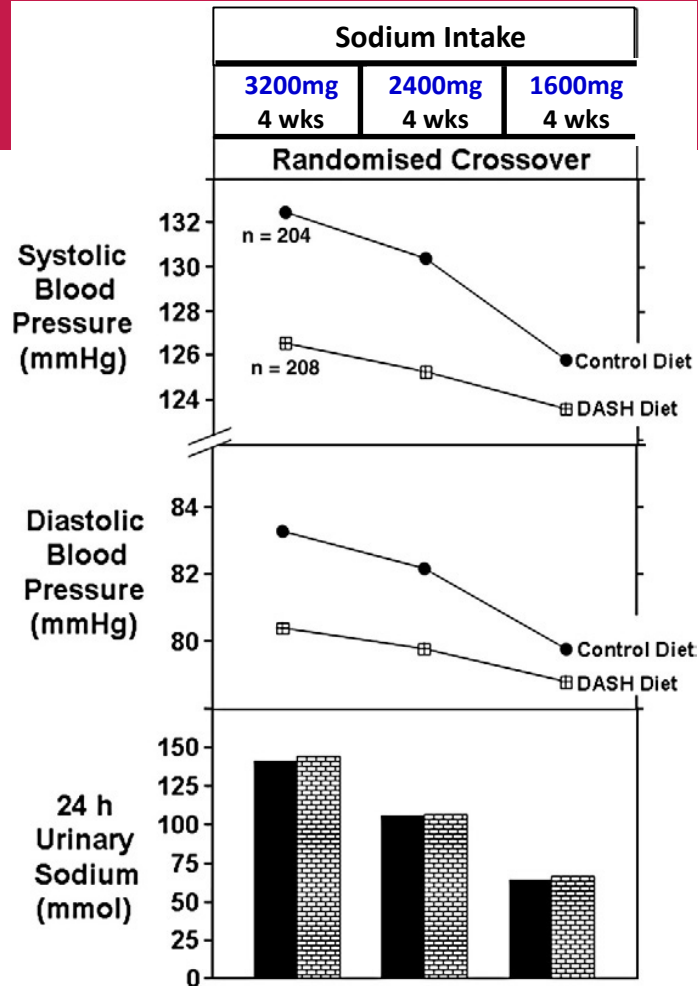
# Deeper dive

# Did we get the intervention right?

- Feeding trials (DASH)
  - Small, resource intensive, explanatory
  - Non-scalable
- Menu based
  - Low-tech, bespoke, pragmatic
  - Food variability, hard to isolate a nutrient
- Dietician involvement
  - Human effect, clinician time
  - Imbalance across arms



# DASH Trial



~400 patients w/HTN  
Metabolic kitchen making all meals  
12 weeks total  
Surrogate outcomes

Sacks F et al. N Engl J Med. 2001; 334: 3-10  
Figure adapted from: He J and MacGregor  
GA. Prog in Cardiovasc Dis. 2010; 52:363-82



# Effect of Salt Substitution on Cardiovascular Events and Death

Neal B et al. DOI: 10.1056/NEJMoa2105675

## CLINICAL PROBLEM

Salt substitutes that replace part of the sodium in regular salt with potassium chloride have been shown to decrease blood pressure, but their effects on cardiovascular and safety outcomes are unclear.

## CLINICAL TRIAL

**Design:** An unblinded, cluster-randomized trial examined cardiovascular and safety outcomes with a salt substitute as compared with regular salt in high-risk adults.

**Intervention:** 600 villages in rural China were assigned to use a salt substitute (75% sodium chloride, 25% potassium chloride) for all household cooking and food preservation or to continue using regular salt (100% sodium chloride). A total of 20,995 adults with a history of stroke or age  $\geq 60$  years with poorly controlled blood pressure were included. The primary outcome was stroke.

## RESULTS

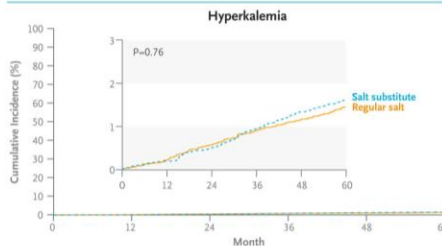
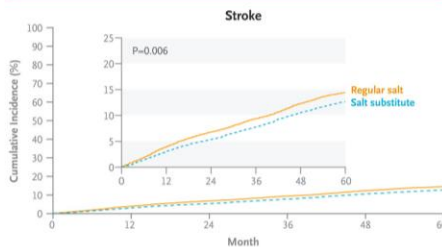
**Efficacy:** During a mean follow-up of 4.74 years, the incidence of stroke was significantly lower in the salt-substitute group than in the regular salt group. Secondary outcomes, including major cardiovascular events and death from any cause, also favored the salt substitute.

**Safety:** The incidence of clinical hyperkalemia did not differ between the groups.

## LIMITATIONS AND REMAINING QUESTIONS

- Participants were aware of the trial-group assignments.
- Whether the findings can be generalized to other settings or populations is unknown.
- Serum electrolytes were not measured serially, so some instances of hyperkalemia were likely to have been missed.

Outcomes	Salt Substitute N=10,504 (300 Villages)		Regular Salt N=10,491 (300 Villages)		Rate Ratio (95% CI)	P Value
	25% KCl	75% NaCl	100% NaCl			
Stroke		29.14	33.65		0.86 (0.77–0.96)	P=0.006
Major Adverse CV Events		49.09	56.29		0.87 (0.80–0.94)	P<0.001
Death from Any Cause		39.28	44.61		0.88 (0.82–0.95)	P<0.001
Hyperkalemia		3.35	3.30		1.04 (0.80–1.37)	P=0.76



## CONCLUSIONS

In this study among patients with a mean age of 65.4 years and a history of stroke or high blood pressure, use of a salt substitute lowered the risks for stroke, major cardiovascular events, and death from any cause.

# SSaSS Trial

~600 villages (21000 people) w/risk  
Salt substitute  
4.7 years  
Clinical outcomes (stroke)

Neal, *NEJM* 2021

# Was it the right population?

- Outpatient vs inpatient
- Relative vs absolute changes or targets
- Sodium intake:
  - Lower than average pt with CVD
  - Large HQ surveys lacking
    - UofT ~2400 mg/d
    - GOURMET-HF ~2900 mg/d





Canadian **VIGOUR** Centre  
Bridging Hearts and Minds

# Measurement

# Measuring Sodium and/or Adherence?



## Plasma

Easy

Tightly regulated,  
physiologically

Well-validated lab  
technique

Reflects acute change



## Urine

Easy (spot), hard (24H)

Variability/debate on methods

Depends on excretion /reabsorption

90-95% ingested is excreted (assumed)

Well-validated lab technique

Campbell, JCH 2019



## Diet

Easy-Hard

Variability in reporting

Need to know food (exact)

Well-validated technique

Reflects consumption



# Measurement: Food records

- Food recall: underestimates total c/w 24UNA
  - 15-25% underestimate
- Food records:
  - 1-14 days
  - Not much more info after 3-5 days
  - Actual record, not a recall
- Input into program (e.g. Food Processor, ESHA) which spits out every detail





# Food Records

- Prospective
- Recording and measurement of all food and beverages each day, for any # of days
- Weighted or volume measurements
- Not dependant on memory

			(include water, spices, and salt)	grams, tsp, #, # of shakes, etc.)	Prepared?
BREAKFAST	8:45am	HOME	HARLOWY 2% ORGANIC MILK	259g	
	:		BANANA BREAD (RECIPE INCL.)	90g	HOMEMADE
	:				
LUNCH	1:30pm	HOME	HABITANT PEA SOUP	190g	
	:		AFRICUS'NONAME SODA CRACKERS		
	:		(PLAIN TOPS)	12g	
	:		SALTED BUTTER	2g	
	:		2% ORGANIC MILK	509g	
	:		RAW CAULIFLOWER	41g	
	:		RAW KIWI	38g	
	:		CHOCOLATE EASTER EGG	6g	
	:				
DINNER	5:00pm	HOME	ROTINI (PASTA)	168g	
	:		CLASSICO TOMATO PESTO SAUCE	199g	
	:		PC BLUE MENU PARMESAN CHEESE	2g	
	:		CANADIAN GOURMET ITALIAN BEEF		
	:		MEATBALLS	146g	PRICE CHECK
	:		2% ORGANIC MILK	495g	
	:		COMPLIMENTS GARLIC BREAD	23g	PRICE CHECK
	:		YOPLAIT SOURCE STRAWBERRY YOGURT	97g	
	:				
SNACK	8:30pm	HOME	MANGO SOUP (RECIPE INCL.)	108g	
	:		ASTRO ORIGINAL BALKAN STYLE NATURAL		
	:		YOGURT	7g	
	:		CORIANDEK LEAVES (FRESH)	1g	
	:				
	:				



# Low Sodium vs Regular

## Nutrition Facts Valeur nutritive

Per 1/2 cup (125 mL) / par 1/2 tasse (125 mL)

Amount Teneur	% Daily Value % valeur quotidienne
------------------	---------------------------------------

**Calories / Calories** 20

**Fat / Lipides** 0 g 0 %

Saturated / saturés 0 g 0 %  
+ Trans / trans 0 g

**Cholesterol / Cholestérol** 0 mg 0 %

**Sodium / Sodium** 400 mg 17 %

**Carbohydrate / Glucides** 4 g 1 %

Fibre / Fibres 1 g 4 %

Sugars / Sucres 3 g

**Protein / Protéines** 1 g

Vitamin A / Vitamine A 6 %

Vitamin C / Vitamine C 10 %

Calcium / Calcium 8 %

Iron / Fer 2 %

## Nutrition Facts Valeur nutritive

Per 1/2 cup (125 mL) / par 1/2 tasse (125 mL)

Amount Teneur	% Daily Value % valeur quotidienne
------------------	---------------------------------------

**Calories / Calories** 20

**Fat / Lipides** 0 g 0 %

Saturated / saturés 0 g 0 %  
+ Trans / trans 0 g

**Cholesterol / Cholestérol** 0 mg 0 %

**Sodium / Sodium** 15 mg 1 %

**Potassium / Potassium** 260 mg 8 %

**Carbohydrate / Glucides** 4 g 1 %

Fibre / Fibres 1 g 6 %

Sugars / Sucres 3 g

**Protein / Protéines** 1 g

Vitamin A / Vitamine A 6 %

Vitamin C / Vitamine C 10 %

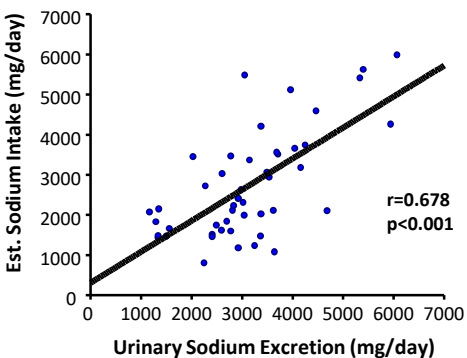
Calcium / Calcium 8 %

Iron / Fer 2 %

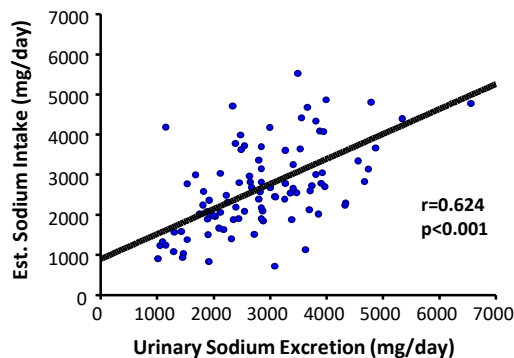


# Food vs. Urine: Diuretics

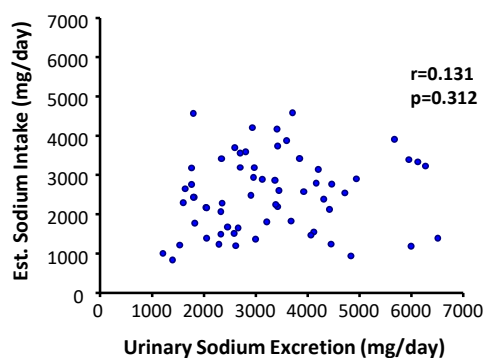
Patients with HF not on loop diuretics (n=47)



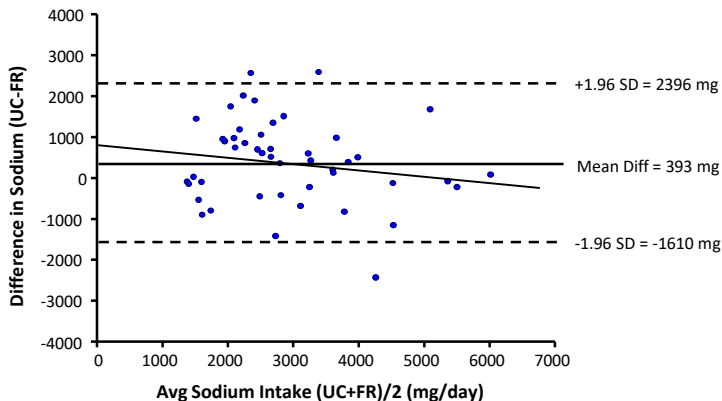
Non-HF cardiac patients (n=96)



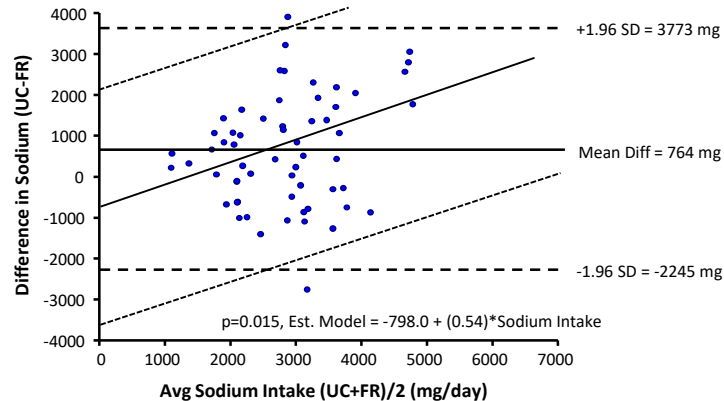
Patients with HF on loop diuretics (n=62)



HF patients not on a loop diuretic (n=47)



HF patients on a loop diuretic (n=62)



# Was this the right outcome?

- CVD/HFH = current standard
- All-cause mortality = totality of badness
- CV hospitalization = HFH + afib + ACS + ...
- CV ED = treat/street
- 1 vs 2 vs 5 years.....





# Summary / conclusions

A dramatic landscape photograph of a snow-capped mountain peak, likely Mount Everest, with a winding river in the foreground and a cloudy sky. The mountain is the central focus, with its peak partially obscured by clouds. The river flows from the left towards the right, creating a winding path through the valley. The sky is filled with large, white clouds, and the overall scene is one of natural grandeur.

Test unproven dogma  
Think about the patient, intervention, control  
Time for pragmatic RCT  
SODIUM-HF and other similar need to be done