THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ezekowitz J A, Colin-Ramirez E, Ross H, et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. *Lancet* 2022; published online April 2. https://doi.org/10.1016/S0140-6736(22)00369-5.

SODIUM-HF Supplementary Appendix

Table of Contents

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SODIUM- HF Inclusion / Exclusion Criteria

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

Exclusion Criteria

• Patients with an average dietary intake of < 1500 mg sodium / day by a quantitative or semi-quantitative method

• 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 (ICD or CRT) or revascularization procedure (PCI or CABG) 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, in the opinion of the investigator, could preclude compliance with the protocol such as moderate-severe dementia, prepared meals (e.g. Meals on Wheels) that cannot be modified or institutionalization.

• Enrolled in another interventional research study

SODIUM- HF Adjudication / Endpoint definitions

Hospitalization or Emergency Department visit

Hospitalization is defined as an admission to an inpatient unit (following discharge after the index hospitalization) or a visit to an emergency department after randomization that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available). Only hospitalizations that occur on an emergency (unplanned) basis will be considered as potential events (and hence adjudicated by the CEC). If competing causes of hospitalization or ED visits (i.e. CV and non-CV) judged to be of equal importance are at hand, the CV cause should take preference.

Non-fatal Events

Hospitalization or ED Events

Worsening heart failure

There must be:

1. clinical manifestations of worsening heart failure including at least one of the following:
    - New or worsening: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension, worsening renal function with no other apparent cause or radiological evidence of worsening heart failure. AND

2. additional/increased therapy specifically for the treatment of worsening heart failure with at least one of the following:
    - Intravenous treatment with diuretic, inotrope, vasodilator or other recognized intravenous heart failure treatment, or
    - Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function,) or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of heart failure.

Acute myocardial infarction

The Universal definition of myocardial infarction will be used to guide the CEC. This includes the following features:

1. Biochemical evidence
    - CK-MB greater than 2 x the upper limit of the normal (ULN) OR Troponin I or T greater than 2 x ULN, with a typical pattern of rise and fall consistent with myocardial infarction; AND

2. At least one of the two following criteria:
    - Typical clinical presentation consistent with myocardial infarction defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia OR Typical ECG changes consisting of any of the following:
    - new abnormal Q waves (or new R waves in lead V1-V2) in at least two consecutive leads,
    - evolving, ischemic ST segment or T wave changes in at least two consecutive leads,
    - new left bundle branch block.

Resuscitated sudden cardiac death

There must be:

1. Sudden cardiac death (see definition of sudden cardiac death, below) or cardiac arrest, with or without premonitory heart failure or myocardial infarction; AND

2. Identification of a life-threatening arrhythmia with resuscitation by cardiopulmonary resuscitation, cardioversion, defibrillation or other advanced cardiac life support measures (e.g. emergency cardiac pacing).

Identified causes of transient loss of consciousness, such as seizures or vasovagal episodes that do not reflect significant cardiac dysfunction, are excluded.

Sudden Cardiac Death refers to death that occurs unexpectedly and not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute myocardial infarction.

• Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator (ICD) review).

• Death after unsuccessful resuscitation from cardiac arrest. (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest).

• Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.

• Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the patient's clinical status preceding death should be provided, if available)

Other CV event

This category includes any CV events that do not fit any of the above definitions including chest pain, syncope NOS, brady- or tachyarrhythmias, and others that will be evaluated on a case-by-case basis.

Non-CV event

This includes all other events including social and organizational reasons for admission. The primary diagnosis will be assigned accordingly after review of the information.

Supplementary Table S1. Dietary Intake and Other Measurements

Measurement	Group	Baseline		3 month		6 month		9 month		12 month		Over all p-value
		N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Weight (kg)	Low Sodium	397	88 (73, 102)	330	86 (73, 101)	308	87 (72, 103)	278	87 (71, 101)	302	89 (72, 102)	0.12
	Usual Care	409	86 (73, 101)	363	85 (73, 101)	340	88 (75, 102)	307	86 (74, 101)	320	84 (73, 101)	
	p-value		0.91		0.96		0.98		0.94		0.62	
Systolic BP (mmHg)	Low Sodium	394	118 (105, 129)	327	112 (102, 124)	305	115 (106, 128)	274	115 (104, 128)	296	118 (106, 129)	0.15

	Usual Care	409	118 (104, 130)	360	118 (106, 130)	333	120 (105, 130)	304	116 (105, 128)	320	118 (106, 129)	
	p-value		0.36		0.14		0.43		0.93		0.91	
Diastolic BP (mmHg)	Low Sodium	394	70 (62, 79)	327	70 (60, 78)	305	70 (62, 78)	274	70 (62, 78)	296	70 (61, 80)	0.029
	Usual Care	409	70 (62, 78)	360	70 (64, 80)	333	70 (62, 78)	304	70 (62, 80)	320	70 (61, 80)	
	p-value		0.80		0.035		0.59		0.063		0.69	
Potassium Intake (mg/day)	Low Sodium	389	2334 (1711, 3034)			307	2378 (1889, 2963)			298	2336 (1746, 2970)	0.40
	Usual Care	403	2318 (1813, 2965)			328	2334 (1794, 2831)			314	2228 (1723, 2803)	

	p-value		**0.89**			**0.13**			**0.62**	
Sodium Intake (mg/day)	**Low Sodium**	**389**	**2286 (1653, 3005)**		**307**	**1649 (1272, 2202)**		**298**	**1658 (1301, 2189)**	**<.0001**
	Usual Care	**403**	**2119 (1673, 2804)**		**328**	**2021 (1440, 2726)**		**314**	**2073 (1541, 2900)**	
	p-value		**0.45**			**<0.0001**			**<0.0001**	
Fluid Intake (mL/day)	**Low Sodium**	**389**	**1782 (1322, 2294)**		**307**	**1707 (1293, 2212)**		**298**	**1777 (1397, 2212)**	**0.95**
	Usual Care	**403**	**1761 (1316, 2187)**		**328**	**1782 (1337, 2224)**		**314**	**1831 (1386, 2194)**	
	p-value		**0.84**			**0.59**			**0.71**	

Energy Intake (calories/day)	**Low Sodium**	**389**	**1838 (1468, 2257)**		**307**	**1636 (1329, 2014)**		**298**	**1679 (1401, 2047)**	**0.16**
	Usual Care	**403**	**1816 (1429, 2249)**		**328**	**1741 (1382, 2138)**		**314**	**1691 (1375, 2135)**	
	p-value		**0.60**			**0.18**			**0.33**	

IQR, interquartile range; BP, blood pressure

Supplementary Table S2. Quality of Life Outcomes

		Visit					
		Baseline		6 months		12 months	
Score	**Group**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Overall Summary Score	Low Sodium	393	66.6 (23.4)	309	71.4 (21.7)	302	74.8 (20.9)
	Usual Care	407	64.9 (22.3)	331	68.0 (22.1)	317	69.1 (23.1)
Clinical Summary Score	Low Sodium	393	70.8 (22.1)	309	74.8 (20.3)	302	77.4 (19.9)
	Usual Care	407	69.1 (21.9)	331	71.1 (22.0)	317	71.9 (23.2)
Physical Limitation Score	Low Sodium	383	70.6 (23.0)	300	73.3 (22.7)	298	76.4 (21.5)
	Usual Care	402	67.4 (23.8)	326	69.7 (24.4)	314	69.9 (25.6)

Supplementary Table S3. Quality of Life Outcomes Stratified by Sex

		Male						Female					
		Baseline		6 months		12 months		Baseline		6 months		12 months	
Score	**Group**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Overall Summary Score	Low Sodium	268	68.5 (22.9)	212	72.8 (21.4)	209	75.6 (20.9)	125	62.5 (23.9)	97	68.1 (21.9)	93	73.2 (20.7)
	Usual Care	267	67.0 (20.8)	222	69.1 (21.8)	211	69.7 (23.1)	140	61.0 (24.5)	108	65.6 (22.8)	105	67.9 (23.2)
Clinical Summary Score	Low Sodium	268	73.4 (20.9)	212	76.6 (20.0)	209	78.5 (19.4)	125	65.2 (23.6)	97	71.0 (20.5)	93	74.8 (20.7)
	Usual Care	267	72.5 (19.0)	222	73.1 (21.6)	211	73.4 (22.8)	140	62.8 (25.3)	108	66.8 (22.3)	105	68.8 (24.0)
Physical Limitation Score	Low Sodium	261	73.5 (21.4)	201	74.9 (22.1)	206	77.2 (21.3)	122	64.3 (25.0)	95	69.3 (23.7)	89	73.9 (22.0)
	Usual Care	263	70.1 (21.6)	216	70.7 (24.7)	205	70.6 (25.4)	139	62.2 (26.9)	104	67.1 (24.0)	103	67.8 (26.2)

Supplementary Table S4. Risk of the primary outcome by baseline dietary sodium intake

Dietary Sodium intake at baseline	**Hazard Ratio**	**95% CI**		**p-value**
< 1501 mg	ref	-		
1501 to 3000 mg	1.074	0.609	1.891	0.8060
> 3000mg	1.327	0.846	2.080	0.2179

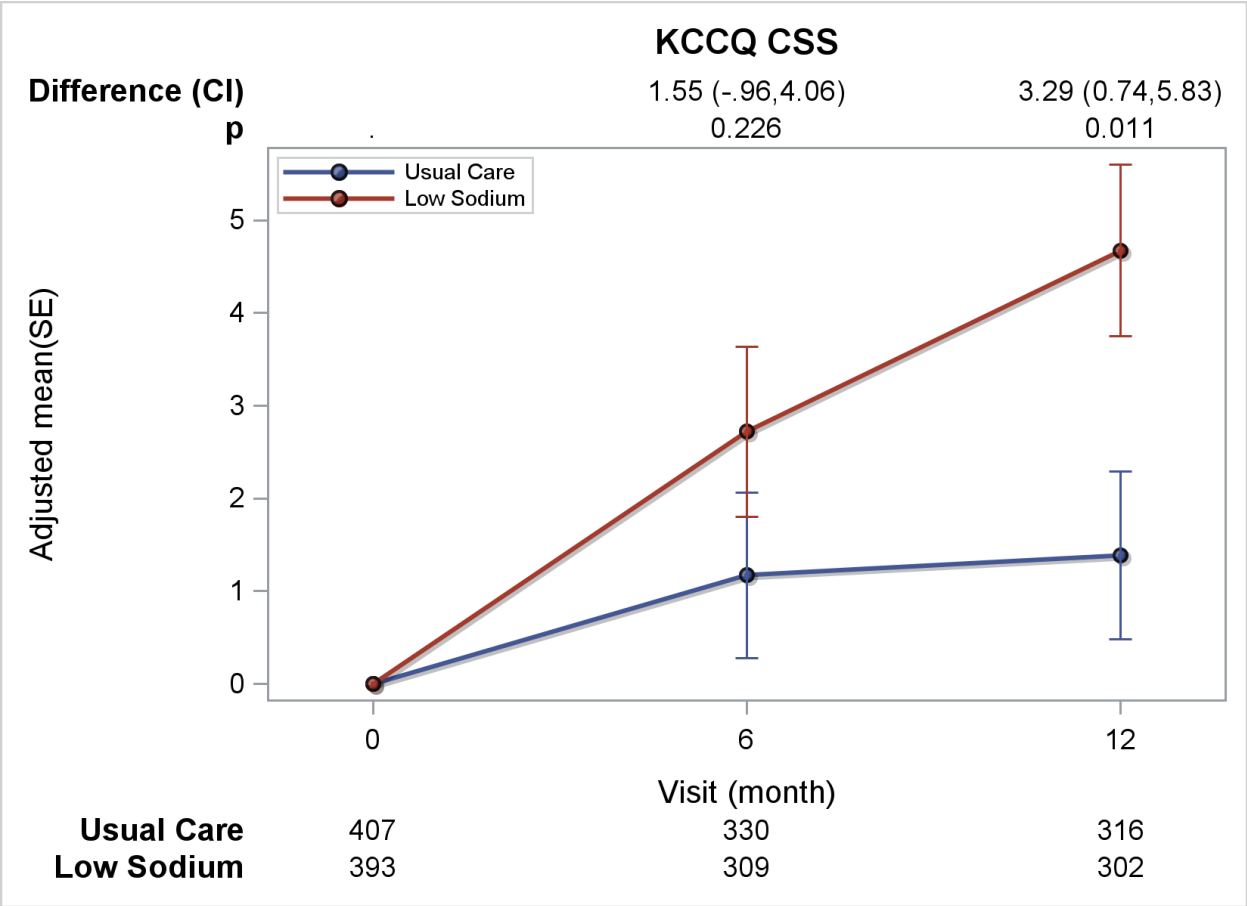
Supplementary Table S5. Association of the primary outcome, randomized group and baseline dietary sodium intake

Dietary Sodium intake at baseline	**Hazard Ratio (Low sodium vs Usual care)**	**95%CI**		**p-interaction**
< 1501 mg	1.22	0.54	2.79	0.63
1501 to 3000 mg	0.92	0.59	1.44	
> 3000mg	0.70	0.32	1.54	

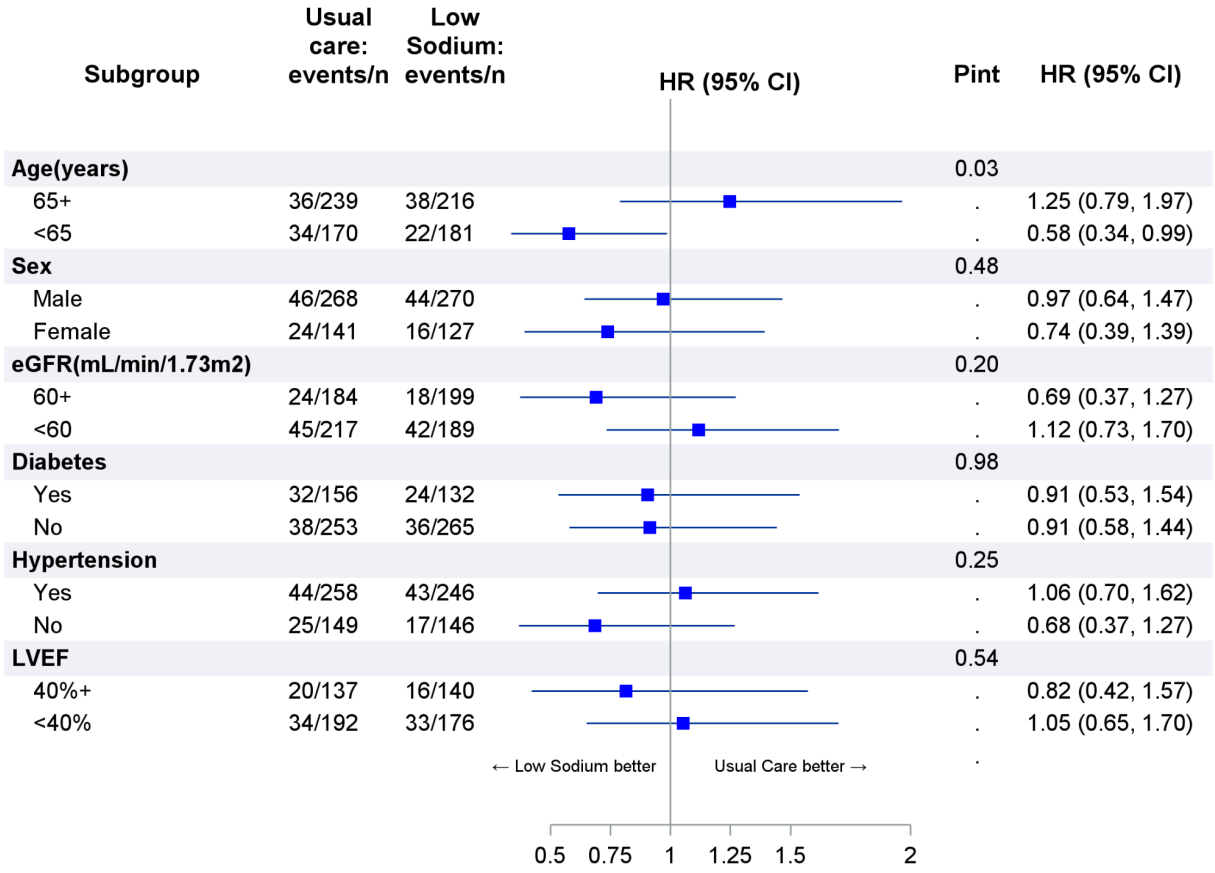
Supplementary Table S6. Risk of the primary outcome by use of renin angiotensin system inhibitors.

On renin angiotensin system inhibitor at baseline	Usual Care: events/N	Low Sodium: events/N	Hazard ratio (95%CI)	P-int
No	17/74	14/82	0.70 (0.35, 1.43)	0.46
Yes	53/335	46/314	0.95 (0.64, 1.42)	

Supplementary Figure S1. Quality of life outcomes. Clinical summary score



Supplementary Figure S2. Subgroup Analysis



Clinical Protocol

Study title:	The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure
Short title:	SODIUM-HF
Funding sources:	Canadian Institutes of Health Research.
Principal Investigator:	Dr. Justin A. Ezekowitz
Document type:	Clinical Study Protocol
Protocol date:	25 October 2019

STATEMENT OF CONFIDENTIALITY:

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the applicable ICH Guidelines and the principles of the Declaration of Helsinki and its amendments and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, where applicable, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the CIHR Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

Signature Page for Trial Management Group

Study title: The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure

Protocol date: 25 October 2019

Approved by the Principal Investigator: Dr. Justin Ezekowitz

Justin A. Ezekowitz, MBBCh MSc		20/01/2020
Name	**Signature**	**Date (dd/mmm/yyyy)**

Signature Page for Investigator

Study title: The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure

Protocol date: 25 October 2019

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Investigator Name	**Signature**	**Date (dd/mmm/yyyy)**
Please print		Please print

TABLE OF CONTENTS

Summary of Changes
Protocol V 1.3 4 Nov 2013 *to* Protocol V 3.0 25 Oct 2019
**NOTE: Protocol V 2.0 is not applicable to Canada*

Protocol Section	**Change**
Throughout	Updated Version and Date
Pg. 3 – Signature Page of Trial Management Group	Updated Protocol Version and Date
Pg. 4 – Signature Page for Investigator	Updated Protocol Version and Date
3.1	Updated to include participating regions and countries outside of Canada
4.1	Added new section re: optional sub-study
5.2.2	Added an additional secondary objective (#5) re: optional sub-study
8.1	Clarified the requirements for the screening visit
8.1	Added “Bioelectrical Impedance Analysis” and “Hand Grip Strength Test” to the Baseline, 6 Month and 12 Month Visits. Added the Optional Sub-Study assessments as a study procedure
8.2.8	Clarified that the KCCQ will be administered in English, French or Spanish
8.2.9	Added study procedures information for the Bioelectrical Impedance Analysis test
8.2.10	Added study procedures information for the Hand Grip Strength test
8.2.13	Added study procedures information for the Administrative Health Database Search (if applicable)
12.2.2	Added a sentence regarding CVC’s protection of patient identifying information per participation in the Optional Sub-Study
Appendix, Table 3	Modified to include study procedures for Optional Sub-Study

1. STUDY SYNOPSIS

Title:	The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure
Objectives:	The main objective is to evaluate the long-term effects of a low-sodium containing diet on a composite clinical outcome composed of all-cause mortality, cardiovascular hospitalizations or cardiovascular emergency department visits in patients with HF. Secondary objectives include the evaluation of a low-sodium containing diet on quality of life, exercise capacity, NYHA class, and longer term clinical outcomes (CV events and mortality) to 24 months.
Trial design:	Multicenter, randomized, open-label, blinded adjudicated endpoint.
Number of patients:	1000
Population:	Patients with HF (both reduced and preserved systolic function are eligible), 18 years or older, NYHA Class II-III, on optimally tolerated medical therapy and willing/able to sign informed consent.
Description of Intervention:	Patients will be randomly allocated to one of two study arms: low-sodium containing diet (65 mmol or 1500 mg daily) or Usual Care (general advice to limit dietary sodium as it is provided during routine clinic practice). Patients in both groups will receive conventional pharmacological and non-pharmacologic treatment for HF, according to current CCS guidelines.
Length of Study:	Study will be completed when all randomized patients have been followed for 24 months.
Efficacy	Primary endpoint: composite clinical outcome of all-cause mortality, CV hospitalizations or CV ED visits over 12 months. Secondary endpoints: include the individual components of the primary endpoint (all-cause mortality, CV hospitalizations, CV ED visits), change in exercise capacity as measured by the 6-minute walk test, change in NYHA class, and change in quality of life assessed by KCCQ.

2. INTRODUCTION

2.1 Background and Rationale

Heart failure (HF) remains one of the most common, disabling, expensive and fatal medical conditions.[1] The prevalence of HF in Canada is rising with an estimated 1.5% to 2% of the general population being affected at present with an increasing prevalence as patients survive acute myocardial infarction, live to an older age and have best medical and non-pharmacologic care available.[2] Despite dramatic improvements with therapies such as ACE inhibitors, beta-blockers, aldosterone blockers, implantable cardiac devices and other therapy, HF in the community or in modern-day clinical trials still carries a 1-year mortality risk of 5 to 15%.[3, 4] Further morbidity among HF cohorts is evidenced by the high rate of emergency department (ED) visits and admission (and repeat admissions) to hospital for HF or other cardiovascular causes which ranges from 20-30% per year.[2] Pharmacologic and non-pharmacologic interventions that can further reduce morbidity and mortality for this important public health concern are clearly needed.

Given that HF is associated with neurohormonal activation and abnormalities in autonomic control that lead to sodium and water retention, clinicians have focused on strategies to mitigate these physiological processes in order to realize improved patient outcomes. Recognizing the importance of sodium balance in HF, it has been presumed that reducing exogenous sodium intake in clinical situations characterized by an overtly fluid overloaded state would be an appropriate intervention.[5] Therefore, nutritional strategies in patients with HF are focused on self-care, including sodium and fluid restriction, to minimize the risk of acute volume overload episodes. Importantly, many urgent clinical visits, emergency department visits, and acute-care hospitalizations continue to be linked to dietary salt indiscretion.[6] Fully one of every 5 ED visits for patients with HF is traced back to dietary indiscretion.[7] However, recommendations for sodium intake for patients with HF are inconsistent **(Table 1)**.

Table 1 . Sodium restriction recommendation

Guideline and year	Sodium restriction recommendation
Canadian Cardiovascular Society (CCS) 2008[8]	<2000 mg per day
Heart Failure Society of America (HFSA) 2010[9]	2000 to 3000 mg per day
American Heart Association (AHA) 2009[10]	Moderate restriction (no value given). Less than 2000 mg/d if volume overload
American Heart Association (AHA) 2009 (self-care)[11]	< 2300 mg day
European Society of Cardiology (ESC) 2012[12]	No recommendation provided

Additionally, the guidelines for the treatment or prevention of hypertension are variable: 1500 mg/day,[13] 90 mmol/day,[14] or a reduction by 100 mmol/day.[15]

The reason for the inconsistent recommendations is clear: a ***lack of evidence on the impact of decreased dietary sodium on clinical events in HF populations***. As summarized below, the lack of truly representative clinical trials is evident despite emerging epidemiological data. In practice, over two thirds of HF patients consume >2000 mg of sodium per day, and sodium intake may be as high as 4418 ± 2033 mg/d in some sub-sets, despite education and counselling.[16] Efforts to provide solid efficacy data to date have been limited. Whether dietary sodium reduction reduces clinical events for patients with heart failure remains uncertain.

2.1.1 Sodium recommendations in healthy adults

The Canadian recommended upper intake limit for sodium in healthy adults is 2300 mg/day.[17] The Institute of Medicine Dietary Reference Intake suggests an adequate intake is 1500 mg dietary sodium/day.[17] However, whether HF patients would benefit from this lower amount of sodium intake is uncertain and requires further investigation.

2.1.2 High sodium diet is linked to clinical events in patients with heart failure

Observational[18-21] and experimental[22-31] studies evaluating the effects of sodium restriction in HF cohorts hitherto have shown mixed results. Recent data has even suggested that sodium restriction may be harmful in HF patients, as discussed below. In addition, clinical studies assessing the effect of sodium restriction on outcomes in this population have used different clinical and therapeutic approaches, making it challenging to compare data and draw definitive conclusions.

Prior epidemiological studies have linked a higher sodium diet to clinical events in patients with HF. A recent prospective observational study by Arcand *et al.* tested the hypothesis that high sodium intake is associated with increased morbidity in 123 ambulatory HF patients, and suggested that those who consume higher amounts of sodium are at greater risk of an acute decompensated HF (ADHF) event. Patients were classified into tertiles of sodium intake per day as follows: ≤1900, 2000-2700, and ≥2800 mg sodium/day with mean sodium intakes of 1400 ± 300, 2400 ± 300, and 3800 ± 800 mg sodium/day in the lower, middle, and upper tertiles, respectively. Even after adjustment for age, sex, energy intake, left ventricular ejection fraction, body mass index, beta-blocker use, and furosemide use, the hazard ratio (HR) was 2.55 (95%CI 1.61, 4.04; p=0.001) for the upper tertile compared with the lowest and middle tertiles for risk of an ADHF event, over a follow-up period of 3 years. High sodium intake (≥2800 mg sodium/day) was the only independent predictor of the primary endpoint of ADHF (HR: 1.66; 95%CI 1.23, 2.24). In the time-to-event analysis, a high sodium diet was related to all-cause mortality and ADHF events but no significant difference was seen for all-cause hospitalization. It is important to note that the mean fluid intake in this study was between 2.0-2.5 L/d in all groups and that mean doses of furosemide were 78±48, 78±46, and 94±69 mg/d for the lower, middle, and upper tertiles, respectively. These diuretic doses are lower than those used in RCTs showing poorer outcomes with a low-sodium diet.[27-29] [18]

2.1.3 Randomized clinical trials on sodium restriction

Few RCTs have been conducted to evaluate sodium restriction and its clinical effects in HF. Some of these trials were conducted to test the effects of dietary sodium intake in combination with parenterally administered saline solutions[32-35] or high doses of loop diuretics[27-29] and only a few studies have assessed the effect of dietary sodium restriction alone in HF.[22-26, 30, 31] RCTs of dietary sodium restriction in HF are summarized in **Appendix, Table 2.** Two trials summarized below (done by the co-applicant) have shown improvement in clinical outcomes; however the sample size of those previous trials has not been sufficient to inform clinical decisions or guideline development. Other studies have investigated the physiologic effects of sodium restriction, including changes in neurohormoral, hemodynamic, and metabolic profile.[22, 25, 26, 30] Colin *et al*. evaluated the effect of a sodium-restricted diet on HF patients in two studies. The first trial was conducted in 65 HF patients (NYHA class I-III) followed during 6 months.[23] Patients in the intervention group followed a restricted-sodium diet (<2400 mg/d Na), while those in the control group received only general counseling to reduce dietary sodium intake. At the end of follow-up, urinary sodium excretion decreased significantly in the intervention group and increased in the controls, representing a sodium intake of 1942 mg/day in the intervention group and 2535 mg/day in the controls. In addition, edema, fatigue and NYHA functional class improved significantly in the intervention group with respect to baseline, while no significant changes were found in the control group. Also, intervention group showed a greater increase in

overall quality of life score at the end of the study compared to the control group. The most recent trial was a 12-month RCT in 203 HF patients using clinical outcomes as the primary endpoint.[24] The same dietary intervention was used (<2400 mg/day versus control) and achieved, obtaining a mean sodium intake of 1581 mg/day and 2740 mg/day for the intervention and control group, respectively, after 12 months of follow-up. There were numerically fewer readmissions in the intervention group (11.1%) compared to the controls (15.7%, p=NS) and better 12-month survival in the intervention group (93.7%) compared to controls (88.1%, p=0.2). These results, although underpowered for clinical outcomes, are consistent with the prior study and additionally supported by similar changes in urinary sodium excretion, fatigue and extracellular water favoring the intervention group. Unlike other studies, catecholamines and serum aldosterone levels were not evaluated, but due the improvement in hydration and clinical status, a reduction in rate of admissions and rate of death, it is suggested that there was *no detrimental neurohormonal effect associated with a sodium-restricted diet in absence of high dose of loop diuretics*. Patients were taking 44.1±10.6 and 41.7±15.13 mg/d loop diuretics in the intervention and control groups, respectively. A larger sample size and/or longer time of follow-up are needed to demonstrate a significant effect of sodium restriction on clinical outcomes in this population.

One other trial deserves close evaluation. A study by Paterna *et al.*[28] has major limitations which, in our opinion, preclude its clinical relevance. This trial enrolled 232 HF patients one month following hospitalization for ADHF and followed them for 6 months after discharge. Patients were randomized into one of two groups: 80 mmol (1800 mg) or 120 mmol (2800 mg) dietary sodium/day. Patients in both groups were prescribed ***500–1000 mg of furosemide daily*** and a 1 litre fluid restriction. While patients following the sodium-reduced diet had a greater risk of hospitalization, this was likely due to the excessively high dose of diuretics employed in combination with aggressive fluid restriction. Patients in the low sodium group were likely hypovolemic as a result of this treatment combination and we would suggest that the results of this study should be interpreted with caution.

There have been three systematic reviews that deserve mention. First, a systematic review and meta-analysis[36] of prospective epidemiologic studies (n= 13 studies reporting on 19 independent cohorts; 177,025 participants) published between 1966-2008 assessed the relationship between the level of habitual salt intake and stroke or total cardiovascular disease outcomes. It showed that a higher salt intake was associated with a greater relative risk (RR) of stroke (RR 1.23, 95%CI 1.06 to 1.43) and other cardiovascular disease endpoints (RR: 1.14, 95%CI 0.99 to 1.32, p=0.07). The associations observed were greater the larger the difference in sodium intake and the longer the follow-up. The authors of this meta-analysis suggested that because of imprecision in the measurement of salt intake, these effect sizes are likely to be underestimated. In contrast, Taylor *et al*., in a meta-analysis of 7 RCTs (n= 6,489 participants),[37] including one RCT in a HF population,[28] found no strong evidence that salt reduction reduced all-cause mortality in normotensive (RR 0.67, 95%CI 0.40 to 1.12), or hypertensive patients (RR 0.97, 95%CI0.83 to 1.13). The single RCT in patients with HF showed an *increased* risk of all-cause death (RR 2.59, 95%CI 1.04 to 6.44) in those receiving a low salt diet. This review did not capture all relevant studies, including the two studies by Dr. Colin[23, 24] even though they were published in English and identifiable by their own search strategy. They additionally did not report on participant's health-related quality of life assessed based on validated generic or disease-specific instruments or other biomarker outcomes. They concluded that further rigorous large long-term RCTs are needed to demonstrate the cardiovascular benefit (or harm) of dietary salt reduction. A third meta-analysis of 6 RCTs (n=2747 participant)[38] evaluated the effects of a restricted sodium diet in patients with systolic HF concluded that a low sodium diet, compared with a normal sodium diet (2800 mg/d),

increased morbidity and mortality in systolic HF. It is worthy to note that all the trials included in this meta-analysis were all conducted by the same research group and included co-interventions of IV saline solutions or high doses of loop diuretics.[27-29, 32, 34, 35] This meta-analysis was subsequently retracted due to concerns related to the validity of the data.[39] Given the limitations in this meta-analysis, the real efects of a low sodium diet in patients with HF remain unclear.

2.2 Potential Risk

There are no known additional risks to following a low sodium diet beyond those described above. Safety risks are further mitigated as the current Canadian guidelines recommend 2 liters fluid restriction for patients with difficult to manage volume overload and also the lowest diuretic dose possible – counter to the 1L fluid restriction and up to 1000 mg furosemide used in the trial which showed harm. The doses of diuretics and fluid intake will be at the discretion of the site – experienced clinicians many of whom are on the CCS guidelines committee or involved with the Canadian HF Network (CHFN) or Society (CHFS). A low sodium containing diet has been advocated by the CCS, AHA and IOM and thus is already in clinical practice albeit variable across centers and advice. Patients will continue their regular clinical follow-up, and study personnel will inform clinicians if the study subject requires *ad hoc* clinical follow-up. In order to reduce the risk of suffering from nutritional inadequacies related to a low sodium diet, as mentioned above, the nutritional intervention employed in this study is designed to provide energy requirements according to the individual characteristics of a patient and to include foods from all the food groups.

3. INVESTIGATIONAL SITES

3.1 Investigational Sites

We have selected sites from across Canada, Latin America, Australia and New Zealand to ensure generalizability, take into account regional variations and to ensure a broad spectrum of patients are represented in the study population particularly given the scope of the HF epidemic globally.

3.2 Number of Patients and Duration of Study

Eligible patients will be recruited from HF and other cardiology or related clinics in each of the study centres. Overall, we anticipate a total of 18 months of recruitment.

4. OVERALL STUDY DESIGN

SODIUM-HF is a multicenter, open-label, blinded adjudicated endpoint, randomized controlled trial in ambulatory patients with chronic HF to evaluate the efficacy of a low sodium containing diet defined as 1500 mg/day compared to Usual Care defined as general dietary advice to limit dietary sodium, on a composite clinical outcome of all-cause mortality, cardiovascular hospitalizations and cardiovascular emergency department visits.

The total treatment period for each patient will be 12 months. The total duration of the follow-up will be 24 months. During the first 12 months, follow-up will occur in person (clinical visits) every 3 months for both groups (baseline, 3, 6, 9 and 12 months) **(Figure 1)**. Patients in the intervention group will also be contacted by phone by the dietician every month to reinforce dietary compliance and in person at 3, 6, 9 and 12 months. The second year of follow-up includes only telephone contacts at 18 and 24 months in both groups to verify clinical events. Dietary intake will be assessed by using 3-d food records. Food records will be collected as outline in **section 8** at each center and sent to CVC to be entered and analyzed. Labs will be collected and run locally (electrolytes and creatinine). The primary endpoint will be assessed at 12, 18 and 24 months, and secondary endpoints at 6 and 12 months.

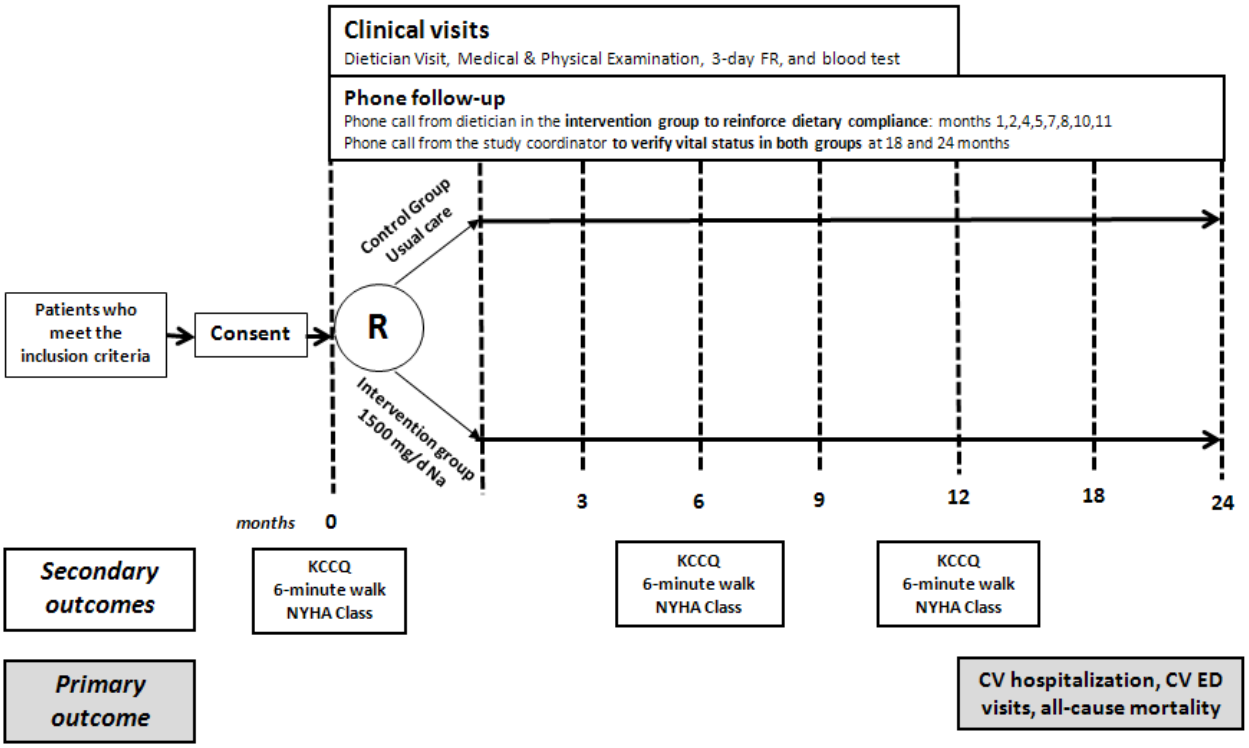


Figure 1. Study schema

4.1 Optional Sub-Study: Evaluating Long Term Outcomes via Administrative Health Data Linkages

Multiple administrative health databases (e.g., CIHI) will be searched for link long-term health outcomes to evaluate the long term effects of a low-sodium containing diet. After participant consent is provided, personally identifying information, including first and last name, date of birth and personal health number, will be provided by participating trial sites to the Canadian VIGOUR Centre [CVC], (see 10.1). Long-term health outcomes will include CV Emergency Department (ED) visits, CV hospitalizations, and all-cause mortality as per the primary endpoint (5.3.1) for a period of 5 years after the 24-month visit (total follow up period of 7 years). Identifiable patient information will be securely stored on CVC servers, as per data storage policies, with access restricted to limited personnel. Participation in this sub-study is optional and participants will be provided with a separate consent form.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Hypothesis

The hypothesis of this study is that patients following a low-sodium containing diet will have fewer clinical events (fewer hospital readmissions or emergency department visits, longer survival) than those on Usual Care.

5.2 Study Objectives

5.2.1 Primary objectives

The main objective is to evaluate the long-term effects of a low-sodium containing diet on a composite clinical outcome composed of all-cause mortality, cardiovascular hospitalizations or cardiovascular emergency department visits in patients with heart failure.

5.2.2 Secondary Objectives

1. To determine if a low-sodium containing diet, compared with Usual Care, improves quality of life [as measured by the Kansas City Cardiomyopathy Questionnaire] in patients with heart failure.
2. To evaluate if a low-sodium containing diet, compared with Usual Care, improves exercise capacity using the 6-minute walk test in patients with heart failure.
3. To identify whether a low-sodium containing diet, compared with Usual Care, results in an improved NYHA class in patients with heart failure.
4. To evaluate the longer term clinical outcomes (CV events and mortality) to 24 months.
5. To evaluate the long term clinical outcomes (CV events and mortality) to 84 months for applicable patients.

5.3 Study Outcome Measures

5.3.1 Primary Endpoint

The primary endpoint is a composite clinical outcome of all-cause mortality, CV hospitalizations or CV ED visits over 24 months.

We have selected all-cause mortality as part of the primary endpoint given the well-established relationship between sodium intake and blood pressure,[40, 41] the importance of mortality in HF and the relationship of sodium to mortality in other populations.[42] However, all-cause mortality may be difficult to impact in such a short time frame and therefore we have elected instead to include in as a component of our primary composite outcome. We selected CV hospitalizations as part of the primary endpoint given the risk that patients with HF face in terms of admissions for atrial fibrillation, ventricular arrhythmias, or coronary syndromes that may be in part linked to the underlying control of the HF syndrome. Additionally, ED visits are important: 35% of patients over 65 years of age are discharged home without admission and are at high risk for recurrent events.[43] These visits may be mixed due to the significant cardiovascular comorbid conditions hence inclusion of a broader CV cause has been incorporated.

5.3.2 Secondary Endpoint

Secondary endpoints include the individual components of the primary endpoint (all-cause mortality, CV hospitalizations, CV ED visits), change in exercise capacity as measured by the 6-minute walk test (6MWT), change in NYHA class treated as a categorical variable, and change in quality of life assessed by KCCQ.

Change in NYHA class has been utilized in trials of chronic HF therapy given the utility and ubiquitous nature of this measure in clinical practice.[44] Improvement by 1 NYHA class is clinically significant. The KCCQ has been validated in a broad community of patients with HF[45] and a minimum difference of 6 points is associated with a significant clinical improvement as evaluated by a 6MWT.[46] While we expect that quality of life will improve in the low-sodium group, however, it is conceivable that due to further restrictions of diet may, for some patients, lead to a worse quality of life. The 6MWT has been used in clinical trials given the low cost, reproducibility and representative of peak exercise capacity. An improvement of 25 to 30 meters is clinically significant.[44] If patients have fewer exacerbations of HF, and can maintain better exercise capacity due to better volume management, a positive effect will be seen in the duration of exercise in the 6MWT. We have avoided diuretic dosing as an endpoint given the variability in practice across Canada and the lack of agreement on dose, diuretic, schedule, and flexibility related to weight changes or a clinically meaningful difference. All analytic considerations are outlined below in **section 9**.

5.3.3 Outcomes adjudication

A Clinical Events Committee will adjudicate the primary outcome events based on data provided by the site, blinded to group allocation. The KCCQ has a standardized format and has been validated for paper, electronic or telephone delivery. NYHA class will be evaluated by same individual (typically the principal investigator of the site) in order to maintain consistency over the duration of the trial. The 6MWT will be performed using the procedure outlined by the American Thoracic Society and by an assessor blinded to treatment allocation.[47]

6. STUDY POPULATION

6.1 Inclusion Criteria

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

6.2 Exclusion Criteria

- Patients with an average dietary intake of < 1500 mg sodium / day by a quantitative or semi-quantitative method
- 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 (ICD or CRT) or revascularization procedure (PCI or CABG) 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, in the opinion of the investigator, could preclude compliance with the protocol such as moderate-severe dementia, prepared meals (e.g. Meals on Wheels) that cannot be modified or institutionalization.
- Enrolled in another interventional research study

Exclusion criteria have been selected carefully to reflect patients that could have a non-cardiovascular cause for dynamic weight or fluid changes (renal, hepatic, thyroid failure), inability to follow the protocol (dementia, institutionalization, prepared meals cannot be modified [e.g. Meals-on-Wheels]) or where the safety of the protocol may be uncertain (significant hyponatremia).

7. STUDY PLAN

7.1 Randomization

After providing written informed consent, patients will be randomly allocated by using a block randomization with variable block sizes via the automated web-based system. A patient's eligibility will be confirmed and a unique identifier and level of sodium restriction will be assigned. There is no run-in phase.

Patients will be randomly allocated to one of two levels of dietary sodium restriction: a low-sodium containing diet (65 mmol or 1500 mg daily) or Usual Care (general advice to limit dietary sodium as it is provided during routine clinic practice).

7.2 Dietary Intervention

7.2.1 Intervention Group: Low-sodium diet

Patients in the intervention group will be prescribed a normocaloric diet with the following energy distribution (Protein: 15-20%, Carbohydrates: 50-55%, Fat: 25-30%, Saturated fat: <7%) consistent with the guidelines for a cardiovascular healthy diet.[48] To achieve the energy requirement and energy distribution, patients will be provided with a specific meal plan containing common foods divided into groups based on Canada's Food Guide. Each group contains a list of recommended and non-recommended foods. Patients will be encouraged to select from the recommended foods the appropriate number of servings calculated for them based on their sex, age, height, and physical activity. This will be determined by the dietitian. The recommended number of servings will vary according to individual energy requirements. To determine the energy requirement of each patient, the Mifflin-St. Jeor equation will be used.[49] This equation has been validated for use in ambulatory adults, including those with a healthy BMI and those who are overweight or obese.[49] It has been found to estimate rest metabolic rate (RMR) most closely to indirect calorimetry, the gold standard for RMR.[50]
In order to achieve the desired level of sodium restriction (65 mmol or 1500 mg/day), patients will be told to avoid sodium rich foods (processed, packaged, pre-prepared, cured and fast foods) and condiments such as mustard, ketchup, soy sauce, teriyaki sauce, and salad dressings. They will also be asked to use low or free sodium cereals. Patients in this group will not be allowed to use salt for cooking or at the table; they will be encouraged to flavor foods with lemon juice, vinegar, herbs, spices, garlic, onions, and no added salt seasonings instead of salt.

Sample menus: Patients will also receive sample menus to guide their meal plan. These menus will be in accordance with the energy requirement and level of sodium restriction for each patient. Dietary intervention material (meal plans and menus) have been developed using funding from the University Hospital Foundation. The Dietician Working group **(see section 10)** will identify additional local adaptations to the menu material to reflect the diverse nature of Canadian diets with regional influence.

7.2.2 Control group: Usual Care

Usual Care will include general advice to limit dietary sodium as it is provided during routine clinic practice. No specific advice will be given on sodium other than mentioned above.

7.3 Blinding

Given the nature of the intervention, blinding of the patient or the research dietician was not felt to be feasible. Additionally, prepared meals from a metabolic kitchen was not felt to be feasible for the scope of the trial and would detract from the pragmatic nature of the intervention. Therefore, the level of blinding will be at the level of the outcome assessor. The primary outcome (clinical events) will be adjudicated by a Clinical Events Committee (CEC) blinded to the level of sodium restriction. An adjudication manual was designed to standardize adjudication. Additionally, the secondary endpoints such as the quality of life results, NYHA class assessment and 6-minute walk test will be performed by a member of the study team blinded to the group allocation (this strategy was used effectively in the HF-clinic based CIHR-funded trial RAFT which these centres participated in). To assess NYHA class and maintain consistency, a consistent site-selected individual (such as the site PI or designate) will be blinded to the allocated group when assessing NYHA class. Research dietitian at each site will randomize patients and inform them about their group assignment. Also, dietitian will ask the patients not to tell about their study group to any of the other members of the research team. All related to the diet will be discussed exclusively with the dietitian.

7.4 Concomitant Treatment

Throughout the study, patients in both groups will receive conventional pharmacological and non-pharmacologic treatment for HF, according to current CCS guidelines.[6]

8. CONDUCT OF THE STUDY

8.1 Schedule of Study Procedures

Visit time points and assessments are described in detail in the following text and summarized in **Appendix Table 3 "Study Flow Chart"**

Screening visit

As part of the eligibility evaluation, and when there is not sufficient dietary information on clinical records to determine whether or not patient's current daily sodium intake is more than 1500 mg, a patient may need to undergo a dietary sodium intake screening evaluation. **Specific written informed consent for this assessment must be obtained.**

After obtaining written informed consent from the patient for this dietary screening evaluation, dietary sodium intake will be evaluated by using the online Salt Calculator. If results of this evaluation indicate that patient's daily sodium intake is more than 1500 mg, investigator can proceed to obtain informed consent from the patient to participate in the study; this must be done prior to randomization or any study procedures. This assessment is appropriate for specific sites only and will be assessed on a site-by-site basis by the Canadian VIGOUR Centre.

During this visit, and after informed consent to participate in the study was obtained, the 3-day food record can be handed to the patient so he/she can complete this form prior to Visit 1 – Baseline, randomization.

Visit 1 – Baseline, Randomization

- Demographics
- Medical history
- Medical and physical examination
- NYHA class assessment
- Serum electrolytes and creatinine
- 3-day food record collection
- Kansas City Cardiomyopathy Questionnaire
- Six-minute walk test
- Dietary intervention (low-sodium diet or Usual Care) delivery
- Hand Grip Test (if applicable)
- Bioelectrical Impedance Analysis (if applicable)

Visit 2 – 3-month follow-up

- Medical and physical examination
- Recording of clinical events

Only for patients in the low-sodium group:

- Dietitian visit (dietary compliance reinforcement)
- 3-day food record collection

Visit 3 – 6-month follow-up

- Dietitian visit
- Medical and physical examination
- NYHA class assessment
- 3-day food record collection
- Kansas City Cardiomyopathy Questionnaire
- Six-minute walk test
- Recording of clinical events
- Hand Grip Test (if applicable)
- Bioelectrical Impedance Analysis (if applicable)

Visit 4 – 9-month follow-up

- Medical and physical examination
- Recording of clinical events

Only for patients in the low-sodium group:

- Dietitian visit (dietary compliance reinforcement)
- 3-day food record collection

Visit 5 – 12-month follow-up

- Dietitian visit
- Medical and physical examination
- NYHA class assessment
- Serum electrolytes and creatinine
- 3-day food record collection
- Kansas City Cardiomyopathy Questionnaire
- Six-minute walk test
- Recording of clinical events
- Hand Grip Test (if applicable)
- Bioelectrical Impedance Analysis (if applicable)

Eighteen-month telephone follow-up

- Phone call to verify clinical events

Twenty-four-month telephone follow-up

- Phone call to verify clinical events

***Optional Sub-Study*: Annually, every 12 months, until the 84 month time point**

- Review of administrative health databases for long-term clinical outcomes

8.2 Detail of Procedures

8.2.1 Informed Consent

Once deemed appropriate candidates for the study, the patient will be informed of the possibility of study participation. The benefits and risks of participating in the study will be explained to the patient, and the patient will be provided an opportunity to read the informed consent form and ask any questions he/she may have. Prior to conducting any study-related procedures, the patient must provide consent to participate by signing the local Ethics Review Board approved consent form.

8.2.2 Medical history
Using the structured layout of the CRF and the definitions given, a full medical history must be taken.

8.2.3 Medical and physical examination
A routine medical and physical examination is required at each clinical visit (baseline, 3, 6, 9 and 12 months). Any abnormality must be recorded.
Any subsequent change and new finding must be documented at each scheduled clinic visit.

This evaluation includes the following:

- Evaluation of systolic and diastolic blood pressure, heart rate, weight, height
- Signs and symptoms of heart failure: dyspnea, peripheral edema, fatigue.
- Cardiovascular medications (use and dose)

8.2.4 New York Heart Association classification
New York Heart Association (NYHA) class is to be recorded at baseline, 6 and 12 months. Definitions of NYHA classifications are listed in **Appendix.**

8.2.5 Serum electrolytes and creatinine
Serum electrolytes include sodium, potassium and chloride. Blood samples will be processed locally.

8.2.6 Three-day food record
Patients will be asked to complete a 3-day food record during the previous week to each clinical visit (at baseline, 3, 6, 9 and 12 months for the low-sodium group; and at baseline, 6 and 12 months for the Usual Care group), including 2 week days and 1 weekend day. Patients will be instructed to record all food and beverages consumed and if salt were added at the table or during cooking. If the amount of salt could not be measured in household measures, patients will be asked to record the number of pinches or shakes added to the food so that sodium could be estimated. All food record will be reviewed by the research dietitian to clarify food-item descriptions and to identify any missing food items. All food record will be sent to the Canadian VIGOUR Center to be entered and analyzed.

8.2.7 Six-minute walk test
A six-minute walk test will be used to assess functional capacity. Patients will walk as far as possible around a well-marked indoor course while supervised and encouraged by trained research personnel. The distance walked in 6 minutes will be recorded at baseline, 6 and 12 months post randomization

8.2.8 Kansas City Cardiomyopathy Questionnaire (KCCQ)
The KCCQ will be used to assess functional capacity. The patients will be given the questionnaire in English, French or Spanish at baseline, 6 and 12 months.

8.2.9 Bioelectrical Impedance Analysis (BIA) (if applicable):
The BIA test will be used to assess general body composition. Trained personnel will conduct the assessment with the patient and record the Bioelectric Impedance Resistance (R) and the Bioelectric Impedance Reactance (Xc) at baseline, 6 and 12 months post randomization. This assessment is appropriate for specific sites only and will be assessed on a site-by-site basis by the Canadian VIGOUR Centre.

8.2.10 Hand Grip Strength Test (if applicable):
The hand grip strength test will be used to assess the maximum isometric strength of the hand and forearm muscles. Trained personnel will conduct the assessment with the patient and record the score (in kilograms) at baseline, 6 and 12 months post randomization. This assessment is appropriate for specific sites only and will be assessed on a site-by-site basis by the Canadian VIGOUR Centre.

8.2.11 Clinical events
Clinical events are defined as: all-cause mortality, cardiovascular hospitalizations or cardiovascular emergency department visits. Events will be referred to the Clinical Events Committee for adjudication (refer to adjudication manual)

8.2.12 Phone follow-up
At 1, 2, 4, 5, 7, 8, 10, and 11 months after randomization in the low-sodium group patients by the research dietitian to reinforce dietary adherence.
At 18 and 24 months in both groups by the research coordinator to verify clinical events.

8.2.13 Administrative Health Database Search (if applicable):
Trained personnel (e.g., biostatisticians) will search relevant administrative health databases for CV ED visits, CV hospitalizations and all-cause mortality information for consenting patients on an annual basis. This assessment is appropriate for specific sites only and will be assessed on a site-by-site basis by the Canadian VIGOUR Centre.

9. STATISTICAL METHODS

9.1 Sample Size Estimation

We utilized four sources to determine the expected event rate of the primary endpoint: 1) Data from the Alberta provincial health registry were used to estimate population rates of ED visits, hospitalization and death among a community-based cohort of HF patients; 2) the mortality rates from the Canadian HF Network (CHFN) which was able to stratify the rates by NYHA class; 3) the death and hospitalization rates were compared with a recent Canadian/European-based trial of NYHA Class II and III outpatients and (4) those predicted by the Seattle HF Model. In a recent RCT of NYHA II patients, the annualized 1-year mortality rate was 5% to 8%,[51] and 15% in a Canadian cohort of patients followed in CHFN sites (personal communication, Malcolm Arnold, Chair of CHFN). We determined that our rates from the provincial registry were quite similar to the average 1-year mortality rate that we would expect from a 50/50 split of NYHA II and III class patients in our study population. Additionally the hospitalization rates observed in the provincial data were similar to those in the EMPHASIS trial. Given that the intervention is not expected to strongly impact one year mortality in this group of patients but, based on pilot data and the 2 prior trials, is expected to impact the likelihood of ED visits and hospitalization, we are expecting a 30% relative reduction in the composite endpoint. Given the unknown relationship with timing of events, we are basing the analysis on the event rate at the end of one year rather than a time-to-event analysis. Based on a **total sample size of 979 patients** the study will be adequately powered to detect a **30% relative reduction** assuming ß=0.80, 2-sided alpha 0.05, and a baseline control event rate of 25%. Even in the event that the baseline rate is as low as 20%, we are adequately powered to detect a 35% relative reduction **(Table 4).** If we include an additional 5% for patients lost to follow-up this bring the number of enrolled patients up to n=1000.

Table 4. Contingency table for power and sample size.

Baseline Event Rate	Relative Reduction				
	15%	**20%**	**25%**	**30%**	**35%**
20%	5521	3039	1902	1291	926
25%	4166	2298	1441	**979**	703
30%	3263	1803	1133	771	555
35%	2617	1451	913	623	450

We have additionally planned to systematically examine overall event rates to determine if we are adequately powered and if needed, will consider either adding additional patients or increasing the duration of the trial to ensure the number of primary endpoints is sufficient.

9.2 Statistical Analysis

All analyses will be based on the intention-to-treat principle. The primary analysis will be based on the differences in cumulative event-free survival between study groups by using the Kaplan-Meier method. Cox regression analysis will also be used to determine the risk of 12, 18 and 24-month clinical outcomes associated with a low sodium diet versus Usual Care, adjusting for potential confounders such as age, sex, NYHA class (at baseline), caloric intake, LVEF, BMI, and serum creatinine. If an interaction is found between the effect of sodium restriction on outcomes and any of the co-variables included in the model, a stratified analysis will be performed.

Secondary analyses based on quality of life and exercise capacity will be evaluated by repeated measures ANOVA at baseline, 6 and 12 months, and regression models developed where appropriate. Missing values for patients who are alive will be handled by last-value carried forward. If a patient dies after baseline the values will be treated as 'zero' and a conditional analysis of patients who were alive at 12 months will be conducted separately. Patients lost to follow-up will be treated as right-censored at their last known endpoint. Changes in NYHA class will be assessed as a score indicating their position relative to baseline (e.g. a patient who is NYHA III at baseline and then moves to II will have a score of +1 while a patient who was NYHA I at baseline and is a III at follow-up will receive a -2). These will then be tested and modeled using ordinal techniques. The change in 6MWT will be evaluated as a continuous variable and adjusted for age for comparison.

9.3 Interim Analysis

No interim analyses are planned outside of the analyses by the DSMB.

9.4 Planned Subgroup Analyses

We will evaluate the following key subgroups: (1) age (< or ≥ 65 years), (2) renal function (CrCl < or ≥ 40 mls/min), (3) diabetes mellitus, (4) hypertension, and (5) LVEF (< or ≥ 40%). We will explore the impact of other food nutrients including potassium, protein, and fat on outcomes for patients with HF. The information in the 3-day food record contains this information for this *post-hoc* and exploratory analyses. We will additionally explore the relationship between baseline to end of trial daily dietary sodium intake (expressed as a % reduction) on clinical outcomes.

10. ORGANIZATIONAL STRUCTURE

a. Executive Committee (EC): Drs. Ezekowitz, Colin and Armstrong form the EC that is responsible for the day-to-day conduct of the trial, as well as organization of all communication within the trial.
b. Steering Committee (SC): All co-applicants and collaborators will be involved in the SC. This SC oversees development of the scientific protocol and operational issues germane to all sites.
c. Dietician Working Group: This group is made up of dieticians to identify best practice within the trial. All the research-based dieticians from sites will be part of this working group, chaired by Dr. Colin.
d. Project Manager: A Project Manager will perform site start-up and management, contract management and any other specific issues. The Project Manager works closely with the PI, EC, SC and Dietician working group in order to facilitate timely and appropriate enrollment from all sites.
e. Data safety and monitoring committee: There will be a DSMC for SODIUM-HF. Individuals not connected to the applicants will serve on a committee. The DSMC will create a charter and specify the nature of analyses and oversee the conduct of the trial. An interim analysis will be performed when 50% of the patients have completed 6 month follow-up in order to evaluate achievement of sodium intake in the intervention group, and also to verify that sodium intake is not overlapped between the two groups. In addition, an all-cause mortality and futility analysis will be done once 50% of patients have completed 12 month follow-up to evaluate safety and efficacy of the treatment.

10.1 The Canadian VIGOUR Centre (CVC)

CVC (www.vigour.ualberta.ca) will handle trial management including study design, managing, monitoring, analyzing and reporting of trial results. The web-based case-report form will utilize REDCap.

10.2 Core Lab for Food Records

The 3-day food records are a crucial part of the trial and thus we have taken a core-lab approach to the data quality for this reason. Food records will be completed by patients, checked locally by the site-based research team, and then forwarded to CVC for data entry, quality assurance, audit and feedback. We anticipate given the number of 3-day food records (1000 patients, 5 records per patient in the intervention group and 3 in the control group) that data assurance and quality will require training of individuals by registered dieticians and core-lab personnel with iterative quality audits. A manual of operations has been developed and the Project Manager will ensure timely feedback to the Dietician Working Group and Executive Committee.

11. DATA COLLECTION AND MONITORING

11.1 Data Collection

The study will be using the REDCap System to capture data electronically. Data will be submitted by the study sites using web-based electronic data transfer.

11.2 Monitoring

Risk-based monitoring will be applied according to criteria developed by CVC.

11.3 Training

CVC will assure that appropriate training relevant to the study is provided by the PI, project lead and project dietician to the medical, dietetic, nursing and other staff involved in each centre.

12. INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

12.1 Local Ethics Review Board

12.1.1 Declaration of Helsinki

The study will be carried out in accordance with the provisions of the Declaration of Helsinki, last revised version, and with applicable local GCP standards.

12.1.2 Institutional review

According to local laws and regulations, the study protocol, the Patients Information Sheet and the Declaration of Consent (in the local language) must be approved by a local Ethics Review Board for each participating centre.

It is the responsibility of the investigator to submit the protocol for institutional review. A copy of the letter of approval from the local Ethics Review Board, with a content in accordance with local regulations, must have been received by the Project Lead prior to initiation of the Study. Major changes to the protocol, as well as change of principal investigator, must be approved by the local Ethics Review Board and documentation of this approval must be provided. Records of the local Ethics Review Board and approval of all documents pertaining to this study must be kept on file by the investigator in the Investigator's Study File.

Apart from the investigational procedures specified in the protocol, investigators are not allowed to perform ancillary studies without written approval from the Steering Committee and the local Ethics Review Board.

12.2 Informed Consent and Patient Protection

12.2.1 Patient information and consent

It is an obligation of the investigator to obtain informed consent from the patient by means of a dated and signed Declaration of Consent before any study related procedure is performed. The Declaration of Consent and the Patient Information Sheet must be written in the local language in accordance with local laws and regulations.

12.2.2 Patients Data Protection

The patients should be informed in writing that his/her medical data relevant to this study will be stored and analyzed while maintaining confidentiality in accordance with local data protection laws. All data transferred to the CRF and any process derived from the CRF will be handled anonymously. This will ensure that the identity of the individual will be protected. In the event the site or patient is participating in the Optional Sub-Study, personally identifying information will be stored on CVC's secure servers and access restricted to limited personnel.

12.3 Protocol Adherence

12.3.1 Protocol adherence

The protocol must be read thoroughly and the instructions must be followed exactly. The same applies to instructions given in the CRF and to any additional instructions issued from CVC.

12.3.2 Changes to protocol and related procedures

Changes to the protocol should only be made in the form of protocol amendments. CVC is

responsible for the distribution of a protocol amendment to investigators. Investigators are responsible for the distribution of an amendment to all staff involved in the study and to the local Ethics Review Board.

13. SAFETY

There are minimal risks associated to this dietary intervention as underlined in Section 2.2. Any subsequent clinical change and new finding after randomization must be documented, as well as any medical action taken related to it (e.g. changes in medication use or dose, surgical procedure, etc). If the patient, in the opinion of the investigator, is not clinically able to continue to follow the study dietary recommendation (e.g. need of initiating another specific dietary intervention such as indefinitely enteral or parenteral feeding), the patients must be discontinued of the study and the ***End of Study*** form must be completed.

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15. APPENDICES

Table 2. Summary of RCTs for the study of the effects of sodium restriction in patients with heart failure (HF)

Author (year)	Levels of sodium restriction	Patients	Endpoints and follow-up	Main findings
Alvelos *et al*. (2004)	Intervention group (IG): 2300 mg/d of sodium. Control group (CG): continued their usual-salt diet	Patients with mild-to moderate stable systolic HF. n=24	Primary: neurohumoral activation and renal dopaminergic system response Follow-up: 15 days	IG had lower blood pressure and urinary sodium excretion, a decrease in BNP, and more weight loss than the normal sodium group. However, IG had more activation of the sympathetic nervous and RAAS. All patients allocated to the low-sodium group were taking furosemide (mean dose 86,7±11,9 mg/d).
Damgaard *et al*. (2006)	1600 mg/d vs. 5700 mg/d of sodium. Water intake was free.	Patients with stable HF NYHA class II-III and age-matched controls. Cross-over design. n=24	Primary: hemodynamic and neuroendocrine response. Follow-up: 7 days for each level of restriction	High sodium intake improved cardiac performance, induced peripheral vasodilatation, and suppressed the release of vasoconstrictor hormones. Plasma pro-BNP unchanged.
*****Parinello, Paterna *et al*. (2008, 2009, **2009**)	Moderate-sodium diet (2800 mg/d) vs. a low-sodium diet (1800 mg/d) plus a fluid intake of 1000 ml/d in both groups. All patients were taking 125-250 mg bid of furosemide.	Compensated NYHA Class II HF outpatients who were recently hospitalized (previous 30 days) for ADHF. n=173	Primary: Hospital readmission Follow-up: 12 months	The moderate-sodium group had a lower rate of hospital readmissions and mortality compared with the low-sodium group. Plasma aldosterone, BNP, and renin activity levels were significantly higher in the low-sodium group.
Colin *et al*. (2004)	Intervention group (IG):<2400 mg/d sodium plus restriction of total fluids to 1.5 L/d Control group (CG): without specific restriction, general information.	Patients with stable systolic and diastolic HF. NYHA class I-III. n=65	Primary: decrease in HF symptoms related to volume overload Secondary: changes in extracellular water and quality of life. Follow-up: 6 months	The main signs and symptoms of HF decreased in the IG, with significant differences for edema and fatigue. No significant changes were found in the CG for symptoms. Extracellular water showed a significant decrease in the IG vs. an increase in the CG. IG had a greater increase in overall quality of life compared with the CG.
Colin *et al*. (2010)	Intervention (IG) <2400 mg/d sodium plus restriction of total fluids to 1.5 L/d Controls (CG): without specific restriction, general information.	Patients with stable systolic and diastolic HF. NYHA class I-III. n=203	Primary: Cardiovascular hospitalizations and survival. Secondary: decrease of symptoms. Follow-up: 12 months	Fatigue frequency was reduced in the IG compared with the CG. Hospital readmissions and survival tended to be better in the IG than in the CG (no significant difference). Mean dose of furosemide was 44.1 and 41.7 mg/d for the intervention and control group, respectively.
Nakasato *et al*. (2010)	Group 1) 800 mg vs. group 2) 2400 mg/d sodium. All patients were advised to maintain a fluid intake of approximately 1,000 ml/d	Stable outpatients with mild to moderate HF who reported previously consuming 6.6 g table salt/day, n=50	Primary: Not specified. Follow-up: Both groups were consuming 2640 mg/d Na diet, then were placed on 800mg/d diet x 7 days, and then randomized in group 1 vs. 2 x 7 more days	Salt-restriction was associated with lower macro- and micronutrients intake and increased neurohumoral activation associated with progression of HF, such as plasma norepinephrine and serum aldosterone.
Philipson *et al*. (2013)	Intervention group (IG): 2000-3000 mg/d of sodium and fluid restriction of 1.5 L/d. Control group (CG): without specific restriction, general information.	Stable HF patients NYHA class II – IV n=97	Primary: a composite endpoint of NYHA class, hospitalization, weight, peripheral oedema, QoL, thirst, and diuretics. Follow-up: Baseline investigations were repeated after 12 weeks and patients were contacted by telephone after 10-12 months.	After 12 weeks, significantly more patients in the IG than in the CG improved on the composite endpoint (51% vs. 16%; P , 0.001), mostly owing to improved NYHAclass and leg oedema. Nonegative effects were seen on thirst, appetite, or QoL.

*****The last RCT from this research group is summarized in the table.

Table 3. Schedule of assessments

Time (Months)	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	18	24	36	48	60	72	84
Dietician visit (in person)	X			X[#]			X			X[#]			X							
Dietician (phone)		X[#]	X[#]		X[#]	X[#]		X[#]	X[#]		X[#]	X[#]								
Medical & Physical Examination	X			X			X			X			X							
NYHA class assessment	X						X						X							
Serum electrolytes and creatinine	X												X							
3-day food record	X			X[#]			X			X[#]			X							
KCCQ	X						X						X							
6 minute walk test	X						X						X							
Clinical events/Vital Status				X			X			X			X	X*	X*					
Administrative Health Database Search **Optional*																X	X	X	X	X

***Phone follow-up by study coordinator to verify status**
[#]indicates only in the intervention group.

New York Heart Association (NYHA) Functional Classification

I	**No limitations of physical activity.** Ordinary physical activity does not cause undue fatigue, palpitations, dyspnoea or angina pain.
II	**Slight limitation of physical activity.** Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnoea, or angina pain.
III	**Marked limitation of physical activity.** Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or angina pain.
IV	**Inability to carry on any physical activity without discomfort.** Symptoms of cardiac insufficiency or of angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

SODIUM-HF
Statistical Analysis Plan
VERSION 2019-02-12
Drafted by: Wendimagegn Ghidey Alemayehu

1.1 Hypothesis

The primary hypothesis of this study is that patients following a low-sodium containing diet will have fewer hospitalizations, emergency department (ED) visits, or higher survival than those patients assigned to a usual care regime.

Null Hypothesis:

H_0: $HR_{Low\text{-}sodium\ containing\ diet:Usual\ care} = 1.0$

Alternative Hypothesis:

H_A: $HR_{Low\text{-}sodium\ containing\ diet:Usual\ care} \neq 1.0$

$HR_{Low\text{-}sodium\ containing\ diet:Usual\ care}$ represents the hazard ratio for the low-sodium containing diet regime versus usual care.

1.2 Objectives

1.2.1 Primary Objective

The primary objective is to evaluate the long-term effects of a low-sodium containing diet on the composite outcome of all-cause mortality, cardiovascular (CV)-related hospitalizations, or CV-related ED visits in patients with heart failure.

1.2.2 Secondary Objectives

(i) To evaluate if a low-sodium containing diet, compared with usual care, is associated with fewer CV events and deaths (individual event types in the primary composite endpoint) and through longer-term (i.e., 24 months) follow-up.

(ii) To determine if a low-sodium containing diet, compared with usual care, improves quality of life in patients with heart failure.

(iii) To evaluate if a low-sodium containing diet, compared with usual care, improves exercise capacity in patients with heart failure.

(iv) To identify whether a low-sodium containing diet, compared with usual care, results in improvement of NYHA class in patients with heart failure.

1.3 Primary and secondary endpoints

1.3.1 Primary endpoint

The primary endpoint is the rate of CV-related hospitalization, CV-related ED visit or all-cause death at 1 year post-randomization.

1.3.2 Secondary endpoints

Relative to the objectives outlined in Section 1.2.2, the secondary endpoints are:

(i) The time to first event within the event type (i.e., individual components of the primary composite endpoint: all-cause mortality, CV-related hospitalization, and CV-related ED visits) within 24 months, and all-events analyses will also be performed;

(ii) Improved quality of life as measured through the administration of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and 12 months (minimum difference of 6 points is considered clinically significant);

(iii) Improved exercise capacity as assessed by the 6-minute walk test at baseline and 12 months (an improvement of 25 to 30 meters is considered clinically significant); and

(iv) Improved function as measured by the NYHA class at baseline and 12 months (one-unit change is considered clinically significant).

1.3.3 Adjudication of endpoints

A clinical endpoint committee will be established to adjudicate all event types within the primary endpoint except mortality. The KCCQ will be administered according to its standardized format and has been validated for paper, electronic or telephone delivery. The 6-minute walk test will be performed according to the procedure outlined by the American Thoracic Society and by an assessor at the site who will be blinded to treatment allocation. The same assessor will ideally evaluate the NYHA class in order to maintain consistency in measurement.

1.4 Analysis Population

The primary objective of the study will be examined in the intention-to-treat (ITT) population; that is, all patients randomly assigned to low-sodium containing diet versus all patients randomly assigned to usual care. The secondary objectives will be studied similarly. Patients without any post-randomization information will be censored at Day 1 for time-to-event endpoints.

Companion analyses will be performed for the primary and secondary objectives in the per-protocol (PP) population, as well as in patients who achieved their target sodium levels as per randomized arm (i.e., achievement level analysis).

1.5 Statistical Methods

1.5.1 Analysis of primary endpoint

The primary endpoint will be analyzed in the ITT population according to the ITT principal and will be based on the adjudication conducted by the clinical endpoint committee. The analysis will be inclusive of all randomized patients.

Primary analysis will test the null hypothesis of $HR_{Low\text{-}sodium\ containing\ diet:Usual\ care}=1.0$ by applying the Cox proportional hazards model for the primary composite endpoint. If the level of statistical significance (two-sided, $p<0.05$) is achieved for the study treatment, the null hypothesis will be rejected in favour of the alternative hypothesis. Other baseline patient characteristics will be examined for their influence on the estimate of

the study treatment, and may include, but not limited to, age, sex, NYHA class, caloric intake, sodium intake, left ventricular ejection fraction, body mass index, and serum creatinine/eGFR. Unadjusted and adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) will be reported.

Kaplan-Meier estimates of the event rate by each group will be generated and presented in survival curves.

1.5.2 Analysis of secondary endpoints

1.5.2.1 Individual Event Types of the Primary Endpoint

The time to first event within each event type (i.e., CV-related hospitalization, CV-related ED visits, or all-cause death) of the primary endpoint will be examined through longer-term (i.e., 24 months) follow-up.

Additionally, extension of the Cox model will be applied for analysis of recurrent events that include all CV-related hospitalizations and of all CV-related ED visits using the Wei, Lin, Weissfeld method.[1]

1.5.2.2 Quality of Life

To determine if a low-sodium containing diet, compared with usual care, improves quality of life in patients with heart failure, the KCCQ will be administered at baseline, 6 months and 12 months. These repeated measure outcomes will be analysed based on the random effects model. The model will consist the treatment group (low sodium, standard), time (baseline, 6 months, 12 months) and the interaction effect as the fixed effects component and a random intercept component to account for the correlation of patient specific measurements.

Pair-wise differences between (i) baseline and 6 months, and (ii) baseline and 12 months will be estimated from the model and compared between the treatment groups. A minimum difference of 6 points between (two) time points will be considered clinically significant.

To measure the effect size between the two time points, Cohen's d effect size, which provides the magnitude of change relative to baseline variation, will be estimated to assess the responsiveness of the questionnaire to clinical change. In general, an effect size of 0.2 to 0.3 indicates a small effect; 0.5 is a medium effect; and ≥0.8 is a large effect. [2] Alternative effect size measure such as the probabilistic index will also be applied.[3]

1.5.2.3 Exercise Capacity

Exercise capacity will be assessed by the 6-minute walk test at baseline, 6 months and 12 months; an improvement of 25 to 30 meters is considered clinically significant. The analysis approach to this objective will be similar to that for quality of life (Section 1.5.2.2).

1.5.2.4 Functional Status

Functional status will be assessed by the NYHA class at baseline, 6 months and 12 months in patients with heart failure; an improvement of one class is considered clinically significant. The mixed effects ordinal logistic regression model will be used to determine whether there was differential improvement/change over time for the low-sodium group relative to the usual care.

1.5.3 Missing data

The use of the mixed effects model in the QoL, exercise capacity and the functional status analyses enables to handle the missing data problem. All the available data will be used and the maximum likelihood method provides unbiased estimate under the missing at random (MAR) assumption. In the time to event analysis, patients lost to follow-up will be treated as right-censored at their date of last contact.

1.6 Summaries of baseline characteristics, demographics and other analyses

Summaries of baseline characteristics, demographics and other analyses according to assigned study treatment will be presented in tabular or graphic formats. Descriptive statistics will be provided. No statistical testing will be performed.

1.7 Interim Analysis

The initial DMC review will occur after the first 50% of enrolled participants have been followed for 12 months. In addition, all-cause mortality and futility analyses will be performed once 50% of enrolled participants have completed 12 months of follow-up. This first assessment will evaluate sodium intake in the both groups. The intervention itself is not known to be related to any safety concerns; as such the focus for the DMC will be on the efficacy endpoints.

Guidelines for the recommendation of stopping or adapting the trial include:

- For futility: If the conditional power given the data is below 20% under the alternate hypothesis.
- For obvious benefit: If the improvement in the low-sodium arm is significant with a very extreme p-value (i.e., a two-sided p-value for the test of equality of proportions <0.001).

1.8 Determination of Sample Size

The sample size estimation is based on a 1:1 randomization of patients to either low-sodium containing diet or usual care. Based on an expected baseline control event rate of 25% (i.e., 1-year CV-related hospitalization, CV-related ED visits, or all-cause mortality), a sample size of 932 participants will yield 80% power to detect a 30% relative risk reduction (i.e., composite outcome rate of 17.5% in low-sodium group versus 25% in usual care comparator group), at a two-sided alpha of 0.05. Assuming a loss to follow up of up to 7%, the estimated sample size for the trial will be 1002 in total, or 501 per group.

1.9 Subgroup analyses and other exploratory analyses

The following subgroups will be examined in relation to the primary endpoint: (i) age (< or ≥ 65 years), (ii) renal function (creatinine clearance < or ≥ 40 ml/min), (iii) diabetes, (iv) hypertension, and (v) left ventricular ejection fraction (< or ≥ 40%). The presence of interaction effects with diet regimen groups will be formally tested in logistic regression model and subgroup specific OR (95%) will be estimated from the fitted model.

Additional exploratory analyses will include

- to examine the association of other food nutrients (including potassium, protein and fat) with outcomes. The source of information will be the 3-day food record. In addition, the association between baseline and end-of-trial daily sodium intake (% reduction) on clinical outcomes.
- to compare the days alive and out of hospital (DAAOOH) endpoint between the two randomized groups. DAAOOH for each patient will be calculated as the difference in the number of days between the total potential follow-up time (24 months) and total number of hospital days and/or days dead. For patients lost to follow-up, the censoring date will be used as the final date of their potential follow-up duration. If a patient dies, days dead is the number of days from death to the end of potential follow-up time. Linear regression model will be applied to evaluate the mean difference DAAOOH between the groups.

1.10 Compliance

Compliance for study treatment will be collected during the study. Deviation from protocol-directed administration will be summarized at the end of the study.

1.11 Extent of exposure

The extent of exposure will be summarized as the duration of study treatment (i.e., low-sodium containing diet or usual care) through the course of follow-up.

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