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Dietary Sodium Intake and Outcomes: a Secondary Analysis From Sodium-HF

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ABSTRACT

Objectives: This post hoc analysis of SODIUM-HF (Study of Dietary Intervention under 100 mmol in Heart Failure) assessed the association between baseline dietary sodium intake and change at 6 months with a composite of cardiovascular (CV) hospitalizations, emergency department visits and all-cause death at 12 and 24 months.

Background: Dietary sodium restriction is common advice for patients with heart failure (HF). Randomized clinical trials have not shown a beneficial effect of dietary sodium restriction on clinical outcomes.

Methods: A multivariable Cox proportional hazard regression model was used to assess the association of dietary sodium intake measured at randomization with primary and secondary endpoints.

Results: The study included 792 participants. Baseline sodium intake was ≤ 1500 mg/day in 19.9% (n = 158), 1501–3000 mg/day in 56.5% (n = 448) and > 3000 mg/day in 23.4% (n = 186) of participants. The factors associated with higher baseline sodium intake were higher calorie consumption, higher body mass index and recruitment from Canada. Multivariable analyses showed no association between baseline sodium intake nor magnitude of 6-month change or 12- or 24-month outcomes. In a responder analysis, participants achieving a sodium intake < 1500 mg at 6 months showed an association with a decreased risk for the composite outcome (adjusted HR 0.52 [95% CI 0.25, 1.07] $P = 0.08$) and CV hospitalization (adjusted HR 0.51 [95% CI 0.24, 1.09] $P = 0.08$) at 12 months.

Conclusion: There was no association between dietary sodium intake and clinical outcomes over 24 months in patients with HF. Responder analyses suggest the need for further investigation of the effects of sodium reduction in those who achieve the targeted dietary sodium-reduction level. (*J Cardiac Fail 2024;30:1073–1082*)

Introduction

Heart failure (HF) is a health problem with a rising prevalence that, overall, affects 1%–2% of the adult population worldwide.[1] More than 2 decades after it was declared an emerging epidemic, HF remains a clinical and public health problem that is associated with significant mortality rates and morbidity as well as frequent hospitalizations.[2,3] Optimal medical pharmacological treatment has an essential role in the management of and prognosis for improvement of HF, but also education, self-care and lifestyle advice are part of HF treatment.[4,5] Dietary sodium

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restriction is common self-care advice provided to patients with HF; however, recent evidence derived from the SODIUM-HF (Study of Dietary Intervention under 100 mmol in Heart Failure) trial and a subsequent meta-analysis failed to show a beneficial effect of dietary sodium restriction on all-cause mortality, cardiovascular (CV) hospitalization or emergency department (ED) visits in people with HF, but a moderate benefit in quality of life and functional New York Heart Association (NYHA) class was observed.[6,7]

SODIUM-HF was an international, open-label, randomized, controlled trial that tested the effects of dietary sodium restriction on clinical outcomes in ambulatory patients with HF. One of the strengths of this trial is the diversity of the population, which included participants from 6 countries, and the variety of diets and levels of dietary sodium intake at randomization.[6] Although this study involved an intervention of dietary sodium restriction of $<$ 1500 mg per day, the potential differences in sodium intake at baseline among participants from various regions and changes in sodium intake over time may be factors associated with clinical outcomes. Initial subgroup analysis did not identify any effect of heterogeneity according to baseline dietary sodium intake, and there was only a weak interaction of age related to clinical outcomes. However, this was based on outcomes at 12 months, did not explore outcome differences between those who achieved larger or smaller changes in dietary sodium consumption or patients' features related to dietary sodium intake, and was analyzed using tertiles rather than a continuous analysis.

Therefore, the objectives of this post hoc exploratory analysis were to describe the relationship between baseline dietary sodium and patients' characteristics, assess the association between baseline dietary sodium intake and the primary and secondary outcomes at 12 and 24 months, determine the relationship between change in dietary sodium intake at 6 months and outcomes at 12 and 24 months, and assess outcomes via a responder analysis of patients achieving dietary sodium intakes of $<$ 1500 mg/day.

Methods

Trial Design

This is a secondary analysis of the SODIUM-HF trial. SODIUM-HF was an international, open-label, randomized, controlled trial that enrolled patients in Australia, Canada, Chile, Colombia, Mexico, and New Zealand; the trial design, methods and results have been described previously.[6,8] In short, patients were randomly assigned (1:1) to either usual care according to local guidelines or a low-sodium diet of lower than 1500 mg/day. The primary outcome was the composite of CV-related admission to hospital, CV-related ED visit or all-cause death within 12 months in the intention-to-treat population (ie, all randomly assigned patients). The trial design and operations were led by the Canadian VIGOUR Centre at the University of Alberta (Edmonton, Canada). The full trial protocol was approved by the appropriate regulatory authorities in the participating countries and by individual institutional review boards or ethics committees at the participating sites, when required.

Participants

Participants were recruited from 26 sites in the participating countries. Eligible participants were aged 18 years or older, had chronic HF (defined as NYHA functional class 2−3), and were receiving optimally tolerated guideline-directed medical therapy. There were no ejection fraction or natriuretic peptide inclusion or exclusion criteria. Key exclusion criteria included an average dietary intake of fewer than 1500 mg/day of sodium at baseline, an estimated glomerular filtration rate (eGFR) of less than 20 mL/min/1.73m^2, and admission to hospital for a CV cause in the past month. A full list of eligibility criteria is reported elsewhere.[6] Dietary sodium intake was screened by several methods, particularly a food-frequency survey, which may have led to different results compared to the 3-day food record, the method used for assessing dietary sodium intake once the patient was enrolled in the trial. All patients provided written informed consent. Of the 806 participants recruited in SODIUM-HF between March 24, 2014, and December 9, 2020, 14 were excluded from this secondary analysis due to missing data for baseline sodium intake.

Variables

Participants were classified into 3 groups according to their baseline dietary sodium levels: $\leq$ 1500, 1501−3000, or $>$ 3000 mg/day, regardless of their trial allocation, for descriptive purposes. Additionally, participants were classified according to the region they were randomized from: Canada, Australia/New Zealand or Chile/Mexico/Colombia. Medical histories and demographic, anthropometric, dietetic, and clinical data were collected for all participants.

Dietary Sodium Intake

Dietary sodium intake was assessed by using 3-day food records (including 2 week days and 1 weekend day). Food records were reviewed by the dietitian during an interview with the patients to clarify food-item descriptions, discretionary use of salt or salty condiments and portion sizes and to identify any missing food items. Food records were analyzed by trained personnel in a core laboratory (Canadian VIGOUR Centre), using a nutrient software program (ESHA Food Processor SQL, version 10.11; ESHA Research, Salem, OR, USA). Calorie and dietary sodium intake were recorded. The 3-day food record is a widely

used method to estimate overall dietary intake and has been validated to estimate sodium intake in patients with HF.[8] For the purpose of this analysis, baseline and 6-month dietary intake information was included.

Outcomes

The intervention period in the SODIUM-HF trial was 12 months, and outcomes were measured at 12 and 24 months. The primary outcome was a composite of CV hospitalization, CV ED visit or all-cause death at 12 months, and, as a secondary outcome, at 24 months, after randomization. Secondary outcomes included the time to the first event for each component of the composite endpoint: all-cause mortality, CV hospitalization, and CV ED visits within 12 and 24 months. Outcomes were adjudicated by a clinical events committee using data provided by the site for events for the first 12 months. Events from 12−24 months were classified by the site investigator and/or provided from administrative data, where available.

Statistical Analysis

The continuous variables are summarized as median with interquartile range (IQR) and compared across the 3 categories of sodium intake using the Kruskal-Wallis test. Categorical variables are summarized as frequency with proportions and compared across the groups. Sodium intake was an ordinal variable, so baseline characteristics were compared using the Cochran-Armitage test for trend (for 2 levels), the Cochran-Mantel-Haenszel (for > 2 levels) and the Jochheere-Terpstra test (for continuous variables). A multivariable Cox proportional hazard regression model was used to assess the association of dietary sodium level measured at baseline (randomization) with primary and secondary endpoints, and adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were presented from the model. The multivariable model included baseline sodium level, age, sex, NYHA class, calorie intake, eGFR, body mass index (BMI), and region. These are prespecified variables, as described in the primary paper.[6] The pre-selection was based on the clinical knowledge and expected influence on the clinical outcome. The log (linearity) assumption for the relationship was first tested using the unrestricted cubic spline method. The assumption was not violated, and the log-transformed sodium level (using a base 2) was normally distributed; the estimates of outcomes per doubling of baseline sodium level are reported. The proportionality assumption in the Cox models was assessed using the Martingale residuals, and there was no evidence of violation of the assumption. In addition, we present the results of the multivariable Cox regression model, which included a restricted cubic spline for log sodium level with 4 knots (at the 5th, 35th, 65th, and 95th percentiles), age, sex, NYHA class, calorie intake, eGFR, BMI, and region. The HR was computed for changes in sodium levels relative to the mean sodium levels. By definition, patients who died before experiencing any of the nonfatal events were censored at time of death. This addresses the effect of death as a competing event to the CV hospitalization and CV ED visit outcomes by using the cause-specific Cox PH regression model. We also ran sensitivity analyses, considering each of the CV hospitalization and CV ED visit outcomes as competing risk events to death and to each other by using the cause-specific Cox PH regression model.

We used a 6-month landmark approach to assess the association of changes in dietary sodium intake from baseline to 6 months, with outcomes at 12 and 24 months. Patients who were alive and remained event free at 6 months and had dietary sodium intake data available both at baseline and at 6 months were included in this analysis. The outcomes were then modeled using the multivariable Cox regression that included the absolute differences in dietary sodium intake (baseline−6 months) as a linear spline with a knot at 0, age, sex, NYHA class, calorie intake, eGFR, BMI, and region. Furthermore, a responder analysis, the effect of achieving < 1500 mg at landmark (6 months) on the clinical outcome, was performed using multivariable Cox PH regression models. We also summarized the clinical outcomes as the proportion of patients who experienced the events and the rates per 100 person-years. While calculating rates, patients were censored by death or the development of a clinical outcome.

A multivariable linear regression model was used to identify the patient-specific and site-related factors associated with the dietary sodium intake at baseline. Dietary sodium intake was log transformed (with a base 2), as it was not normally distributed. The initial model included age, sex, NYHA class, calorie intake, BMI, eGFR, left ventricular ejection fraction, and region. To get the final model, we performed a stepwise variable selection approach using a prespecified P value of 0.9 for variables to enter the model and P values of 0.15 to stay in the model. The same model was selected when we used the lowest Akaike Information Criterion. The regression coefficients from the final model were transformed back to the original scale. Finally, the validity of regression model assumptions were checked by using diagnostic plots of residuals, and there was no indication of violation of any of the normality, independence or constant variance assumptions. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

Overall, 792 participants were included in this exploratory analysis (Fig. 1). Baseline dietary sodium intake was < 1500 mg/day in 19.9% (n = 158), 1501−3000 mg/day in 56.5% (n = 448) and > 3000 mg/day in 23.4% (n = 186) of the study participants. Women, older patients and those with lower eGFRs and higher ejection fractions were more

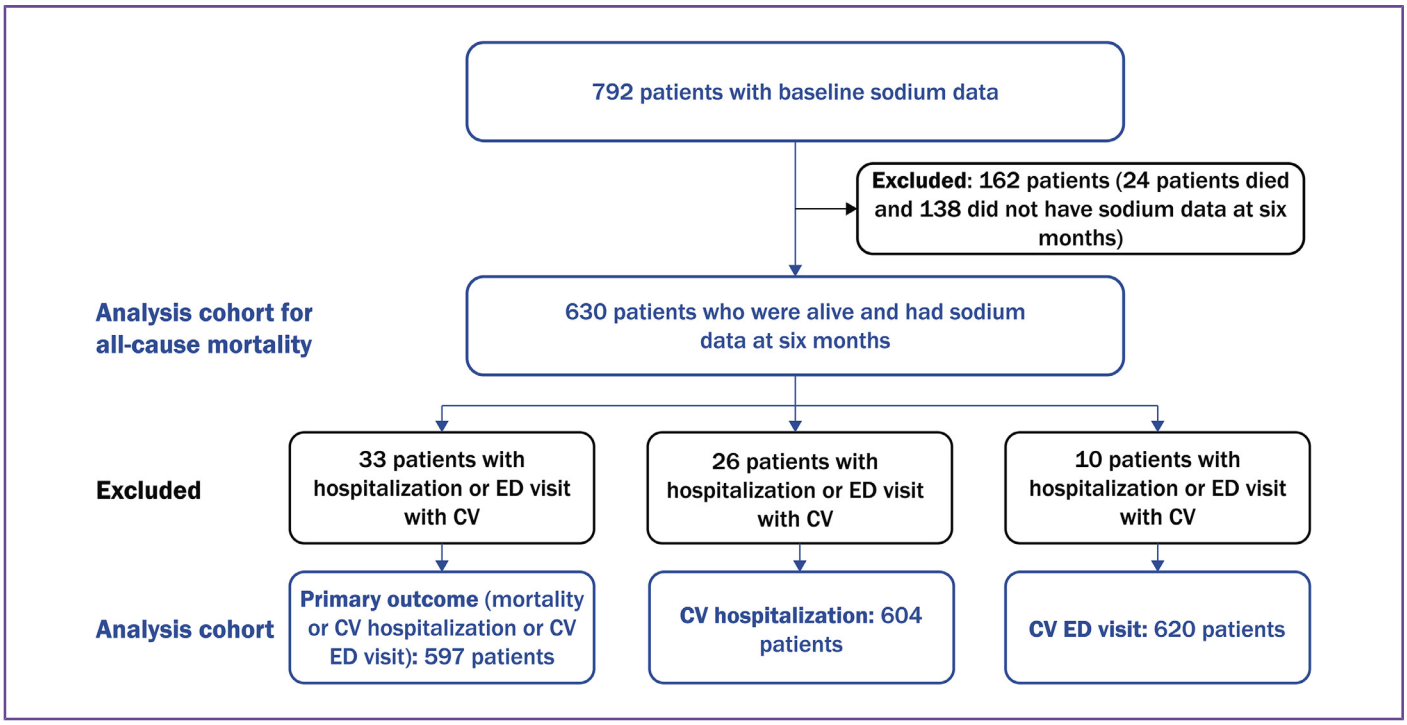

Fig. 1. Cohort selection for the analysis that used the landmark approach. CV, cardiovascular; ED, emergency department.

often represented in the group with lower baseline sodium intake (≤ 1500 mg/day). A higher proportion of patients with diabetes, smoking histories, use of mineralocorticoid receptor antagonists, and implantable cardioverter defibrillators were observed in the groups with higher sodium-intake levels. Patients with sodium intake > 3000 mg/day had the highest median BMIs. There were no significant differences according to the regions patients were recruited from or their baseline NYHA classes (Table 1).

Association Between Baseline Dietary Sodium Intake and Outcomes

Outcomes (composite outcome, all-cause mortality, CV hospitalizations or CV ED visits) distribution at 12 or 24 months, among 3 different levels of baseline sodium intake, are shown in Supplementary Table 1. Cox proportional hazard regression analysis showed no association between baseline dietary sodium intake (per doubling of baseline dietary sodium intake) with clinical outcomes at most time points. In unadjusted models, there was a trend toward fewer composite events and CV hospitalizations; however, in adjusted models there was only a trend toward a decreased risk of CV hospitalizations at 24 months (Table 2).

Relationship Between Change in Dietary Sodium Intake and Outcomes

Adjusted Cox proportional hazard regression analysis showed no associations between change in sodium intake in the first 6 months and 12- or 24-month outcomes (Fig. 2) and, as reported in Supplementary Table 2, per 500 mg increments, in absolute difference in baseline sodium intake and 6 months). This was consistent for patients across higher and lower baseline sodium intakes (Figs 3 and 4).

In the responder analysis, 212 (33.7%) of 630 patients who were alive at 6 months achieved < 1500 mg sodium levels at 6 months (Supplementary Table 3). Among 597 patients who were alive and did not experience composite outcomes at 6 months, a trend toward a lower risk in the composite outcome was observed in 5.0% responders vs 8.5% nonresponders at 12 months (aHR 0.52 [95% CI 0.25, 1.07] $P = 0.08$) (Supplementary Table 3, Table 3). Among 604 patients who were alive and did not experience a CV hospitalization, a CV hospitalization occurred in 4.5% responders vs 7.7% nonresponders at 12 months (aHR 0.51 [95% CI 0.24, 1.09] $P = 0.08$) after adjusting for baseline sodium intake, age, sex, NYHA class, calorie intake, BMI, eGFR, region, and baseline sodium (Supplementary Table 3, Table 3).

Relationship Between Baseline Dietary Sodium and Other Patient or Site Factors

Multivariable linear regression was used to assess the association between patients' factors and the levels of dietary sodium intake at baseline. Factors associated with higher baseline sodium intake were higher energy consumption, higher BMI and recruitment from Canada (Table 4).

Table 1 Baseline characteristics in the overall study sample and by levels of baseline daily dietary sodium intake

Variable Label	Statistic	≤1500 mg	>1500−3000 mg	>3000 mg	Total	*P* Value
Total n	n	158	448	186	792	
Age	Median (IQR)	68.5 (63.0, 76.0)	67.0 (58.5, 75.0)	63.0 (52.0, 71.0)	67.0 (58.0, 74.0)	<0.001
Women	n (%)	72 (45.6)	152 (33.9)	39 (21.0)	263 (33.2)	<0.001
Region						
Canada	n (%)	94 (59.5)	256 (57.1)	114 (61.3)	464 (58.6)	0.46
Australia/New Zealand	n (%)	31 (19.6)	85 (19.0)	40 (21.5)	156 (19.7)	
Chile/Mexico/Colombia	n (%)	33 (20.9)	107 (23.9)	32 (17.2)	172 (21.7)	
HF diagnosis ≤1 year	n (%)	106 (67.1)	303 (67.6)	134 (72.0)	543 (68.6)	0.31
HF hospitalization in past 1 year	n (%)	61 (38.6)	140 (31.3)	64 (34.4)	265 (33.5)	0.47
LVEF	Median (IQR)	38 (30, 50)	36.0 (28, 50)	34.5 (24, 47)	36.0 (27, 49)	0.018
Hypertension	n (%)	92 (59.7)	287 (64.5)	114 (61.3)	493 (62.8)	0.83
Coronary artery disease	n (%)	64 (41.3)	213 (48.2)	89 (49.2)	366 (47.0)	0.16
MI	n (%)	31 (19.6)	84 (18.8)	44 (23.7)	159 (20.1)	0.32
PCI	n (%)	19 (12.0)	73 (16.3)	36 (19.4)	128 (16.2)	0.067
CABG	n (%)	17 (10.8)	51 (11.4)	21 (11.3)	89 (11.2)	0.88
Peripheral arterial disease	n (%)	12 (7.9)	45 (10.4)	17 (9.2)	74 (9.6)	0.73
Cerebrovascular disease	n (%)	18 (11.6)	53 (11.9)	15 (8.2)	86 (10.9)	0.28
Atrial fibrillation/flutter	n (%)	62 (40.0)	181 (40.7)	80 (44.0)	323 (41.3)	0.45
Diabetes (type 1 or 2)	n (%)	43 (27.2)	171 (38.2)	68 (36.6)	282 (35.6)	0.090
COPD	n (%)	32 (20.6)	77 (17.4)	21 (11.5)	130 (16.7)	0.022
Ventricular fibrillation or tachycardia	n (%)	25 (16.1)	60 (13.5)	38 (20.7)	123 (15.7)	0.21
Smoking history	n (%)	61 (39.4)	201 (46.4)	107 (58.2)	369 (47.8)	<0.001
BMI (kg/m^2)	Median (IQR)	29.0 (25.2, 34.5)	30.2 (26.5, 35.0)	32.4 (27.6, 37.3)	30.5 (26.4, 35.4)	0.0020
Weight (kg)	Median (IQR)	82.9 (67.5, 95.6)	84.7 (72.2, 101.2)	92.8 (80.0, 108.5)	86.5 (73.0, 102.0)	<0.001
Hand-grip strength	Median (IQR)	30.0 (21.0, 36.0)	30.5 (22.0, 38.0)	38.0 (30.0, 46.0)	32.0 (22.5, 38.0)	0.034
Heart rate	Median (IQR)	67.0 (60.0, 75.0)	69.0 (60.0, 76.0)	70.0 (63.0, 77.0)	69.0 (61.0, 76.0)	0.073
Blood pressure, systolic	Median (IQR)	117.0 (103.5, 130.0)	118.0 (105.0, 128.0)	118.0 (104.0, 130.0)	118.0 (105.0, 129.0)	0.91
Blood pressure, diastolic	Median (IQR)	70.0 (60.0, 78.0)	70.0 (62.0, 78.0)	70.0 (63.0, 80.0)	70.0 (62.0, 78.0)	0.21
BNP (pg/mL)	Median (IQR)	186.4 (62.6, 661.9)	193.7 (83.2, 493.0)	195.9 (85.1, 433.5)	194.8 (83.1, 484.2)	0.89
NT-proBNP (pg/mL)	Median (IQR)	966.1 (228.0, 3476.0)	907.0 (407.0, 1729.7)	567.8 (211.4, 1308.5)	801.0 (335.0, 1552.0)	0.41
eGFR (mL/min/1.73m^2)	Median (IQR)	53.7 (38.5, 68.8)	59.0 (44.0, 71.1)	63.9 (52.0, 79.5)	59.0 (43.7, 72.5)	<0.001
Sodium (mmol/L)	Median (IQR)	139.5 (138.0, 141.0)	139.0 (137.0, 141.0)	139.0 (137.0, 140.0)	139.0 (137.0, 141.0)	0.28
Potassium (mmol/L)	Median (IQR)	4.3 (4.0, 4.8)	4.3 (4.0, 4.6)	4.3 (4.0, 4.6)	4.3 (4.0, 4.7)	0.15
Any RAAS (ACEi/ARB/ARNI)	n (%)	128 (81.0)	352 (78.7)	156 (83.9)	636 (80.4)	0.46
Beta-blocker	n (%)	137 (86.7)	386 (86.4)	167 (89.8)	690 (87.2)	0.37
ACEi/ARB	n (%)	111 (70.3)	294 (65.8)	122 (65.6)	527 (66.6)	0.38
ARNI	n (%)	18 (12.1)	62 (14.3)	36 (19.9)	116 (15.2)	0.043
Mineralocorticoid receptor antagonist	n (%)	77 (48.7)	244 (54.6)	129 (69.4)	450 (56.9)	<0.001
ICD	n (%)	25 (15.8)	108 (24.2)	49 (26.5)	182 (23.0)	0.022
Pacemaker	n (%)	14 (8.9)	35 (7.8)	15 (8.1)	64 (8.1)	0.81
CRT	n (%)	13 (8.2)	37 (8.3)	22 (11.9)	72 (9.1)	0.22
NYHA class						
Not recorded	n (%)	1 (0.6)	1 (0.2)	0 (0.0)	2 (0.3)	0.47
I	n (%)	1 (0.6)	6 (1.3)	1 (0.5)	8 (1.0)	
II	n (%)	118 (74.7)	313 (69.9)	133 (71.5)	564 (71.2)	
II	n (%)	38 (24.1)	127 (28.3)	50 (26.9)	215 (27.1)	
IV	n (%)	0 (0.0)	1 (0.2)	2 (1.1)	3 (0.4)	

AAS, renin-angiotensin-aldosterone system; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; RHF, heart failure; TIA, transient ischemic attack.

Discussion

The main findings of this secondary analysis of the SODIUM-HF trial are as follows. First, region of recruitment was identified to be associated with baseline dietary sodium intake; particularly, Canada was associated with a higher baseline sodium intake compared to the Mexico/Chile/Colombia combined region. Second, even among patients with HF, factors associated with high sodium consumption included being younger, having a higher BMI

Table 2 Association of dietary sodium intake (per doubling) at baseline with clinical outcomes

Outcomes	Unadjusted		Adjusted*	
	HR (95% CI)	*P* Values	HR (95% CI)	*P* Values
12 Months				
Composite	0.94 (0.73, 1.22)	0.66	0.97 (0.69, 1.39)	0.89
All-cause mortality	0.96 (0.59, 1.56)	0.88	1.29 (0.67, 2.52)	0.45
CV hospitalization	0.89 (0.65, 1.21)	0.46	0.88 (0.58, 1.33)	0.54
CV ED	1.47 (0.87, 2.51)	0.15	1.20 (0.60, 2.41)	0.60
24 months				
Composite outcome	0.83 (0.69, 1.00)	0.053	0.88 (0.68,1.13)	0.31
All-cause mortality	0.93 (0.67, 1.28)	0.64	1.18 (0.76, 1.85)	0.46
CV hospitalization	0.76 (0.60, 0.96)	0.019	0.74 (0.54, 1.00)	0.052
CV ED	1.24 (0.88, 1.75)	0.22	1.07 (0.68, 1.69)	0.77

*Adjusted for age, sex, NYHA class, calorie intake, BMI, eGFR, region.BMI, body mass index; CI, confidence interval; CV, cardiovascular; ED, emergency department; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association.

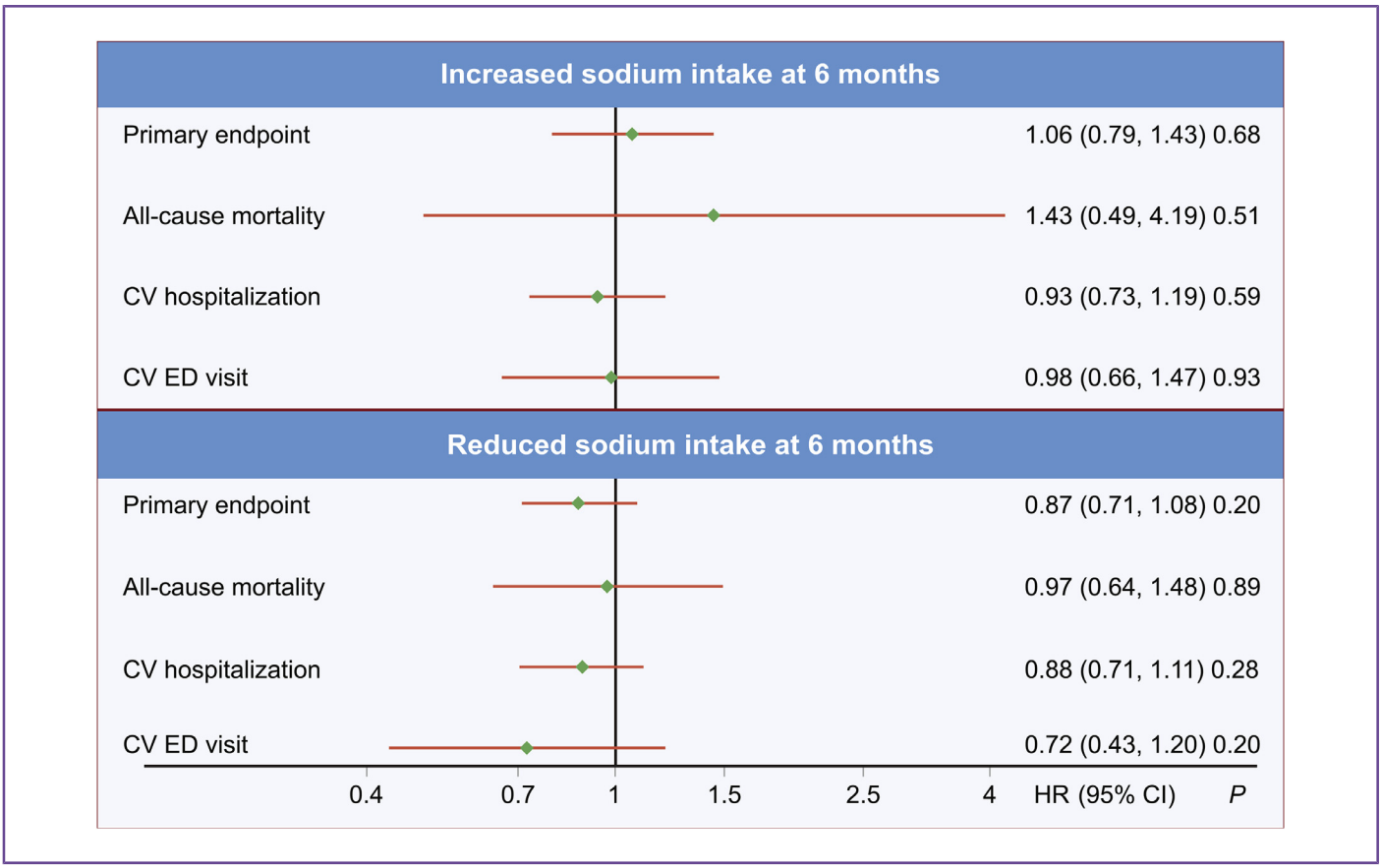

Fig. 2. Adjusted hazard ratio for 12-month outcomes per 500 mg/day increase in sodium intake according to the change in sodium intake at 6-month landmark from baseline; increased (a) or reduced (b). CI, confidence interval; CV, cardiovascular; ED, emergency department; HR, hazard ratio.

and a higher eGFR, among other factors. Whether or not interventions should specifically target sub-populations within HF to improve clinical outcomes is uncertain, but these factors may identify patients in whom an intervention to reduce dietary sodium may potentially be most beneficial. Third, no associations between magnitude of dietary sodium reduction and outcomes was observed, and no clear benefit or harm of achieving targeted dietary sodium reduction in the first 6 months or 12- or 24-month outcomes was found. Given the nature of post hoc responder analyses, these last results provide insight into the safety and potential associations for future trials.

A key consideration of all dietary interventions is adherence to the protocol and the diet itself. We found that only 212 (33.7%) of 630 patients who were alive at

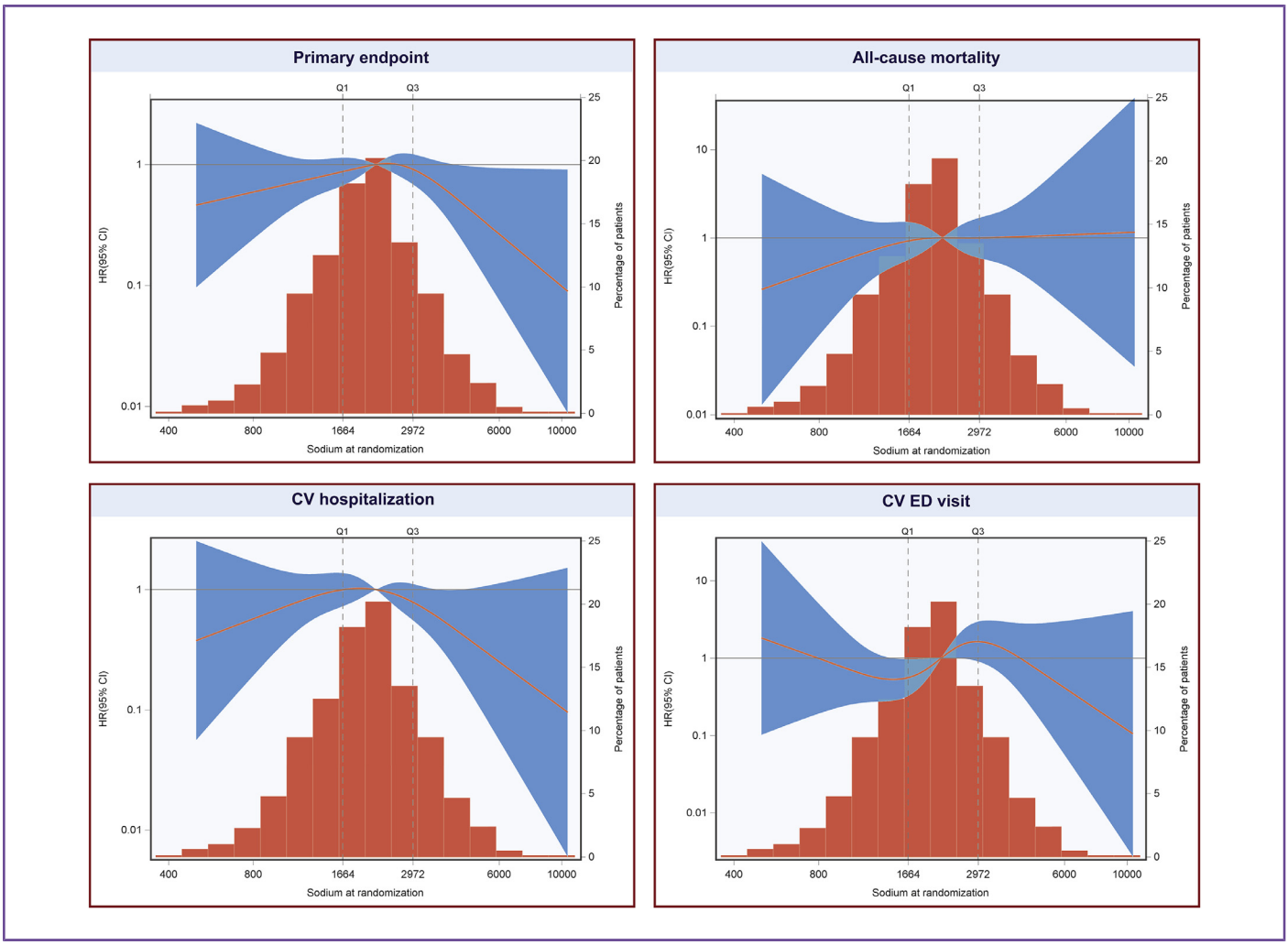

Fig. 3. Association (adjusted hazard ratio) of baseline dietary sodium intake with 12-month outcomes, across higher and lower baseline sodium intakes. CI, confidence interval; CV, cardiovascular; ED, emergency department; HR, hazard ratio.

6 months achieved < 1500 mg sodium level at 6 months. The Heart ABC (Self-management and Cognitive Function in Adults With Heart Failure) study reported that higher BMIs were present in patients with HF and with higher sodium consumption and were an independent predictor of nonadherence to sodium restriction.[9] We found no adjusted association between sex and sodium-intake reduction; however, we did find an association between sex and baseline sodium intake, with a higher proportion of women consuming less than 1500 mg/day at randomization. Other reports found that female sex is related to lower sodium consumption. An observational study in a French population with HF identified that decreased salt consumption was independently associated with female sex, living in a retirement home and having chronic HF.[10] These and other factors deserve exploration of the social or cultural factors surrounding sodium intake and the potential adherence to dietary restrictions in the broader community. It is important to point out that 19.9% (n = 158) of the participants exhibited baseline sodium intakes < 1500 mg/day; this may be explained by the fact that sodium intake was screened for but not estimated via 3-day food records during eligibility assessment. Thus, it is possible that once patients were recruited, baseline sodium intake, as measured by the 3-day food record, provided different results compared to the screening method (food frequency questionnaire).

In our analysis, baseline sodium intake was also closely related to caloric consumption. This relationship has previously been reported in patients with HF. In a longitudinal study, higher levels of energy intake were associated with higher amounts of sodium consumed.[11] Jefferson et al. reported that following a low-sodium diet as part of self-care in HF resulted in a decreased calorie intake, concluding that achieving a sodium reduction and adequate nutrition would require changes in eating patterns.[12] Colin-Ramirez et al. demonstrated that an intervention based on the DASH (Dietary Approaches to Stop Hypertension) dietary pattern was able to decrease sodium intake while maintaining recommended percentages of macronutrient intake.[13] These findings suggest that reducing dietary

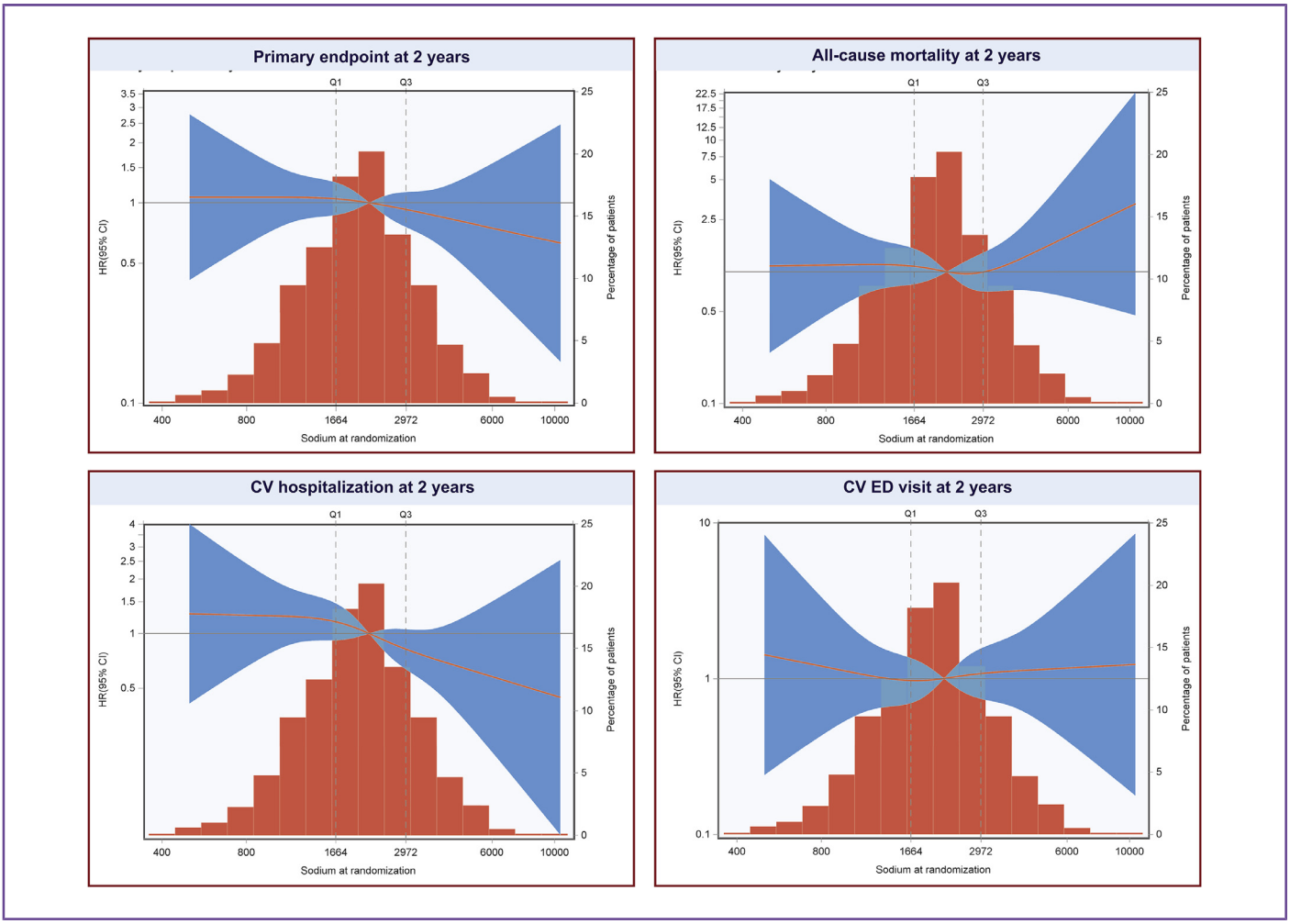

Fig. 4. Association (adjusted hazard ratio) of baseline dietary sodium intake with 24-month outcomes across higher and lower baseline sodium intakes. CI, confidence interval; CV, cardiovascular; ED, emergency department; HR, hazard ratio.

Table 3 Association of achieving sodium intake <1500 mg/day at 6 months with outcomes

Outcomes	Adjusted for Baseline Sodium		Adjusted for Baseline Sodium and Other Variables*	
	HR (95% CI)	*P* Values	HR (95% CI)	*P* Values
12 Months				
Composite	0.56 (0.27, 1.14)	0.11	0.52 (0.25, 1.07)	0.08
All-cause mortality	0.65 (0.13, 3.33)	0.61	0.72 (0.14, 3.81)	0.7
CV hospitalization	0.56 (0.26, 1.18)	0.13	0.51 (0.24, 1.09)	0.08
CV ED	0.46 (0.12, 1.67)	0.24	0.47 (0.12, 1.78)	0.26
24 Months				
Composite outcome	0.85 (0.59, 1.21)	0.37	0.83 (0.58, 1.20)	0.33
All-cause mortality	1.04 (0.57, 1.89)	0.91	1.06 (0.57, 1.98)	0.85
CV hospitalization	0.87 (0.57, 1.34)	0.52	0.84 (0.54, 1.30)	0.42
CV ED	0.60 (0.31, 1.15)	0.12	0.64 (0.33, 1.25)	0.19

*Age, sex, NYHA class, calorie intake, BMI, eGFR, region, and baseline dietary sodium intake.BMI, body mass index; CI, confidence interval; CV, cardiovascular; ED, emergency department; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association.

sodium intake would require keeping consumption of a healthful dietary pattern in order to promote a healthy dietary profile while reducing sodium intake.

Another important finding of this analysis is the lack of a statistically significant association between the reduction in sodium intake to < 1500 mg by 6 months and the

Table 4 Multivariable linear regression model for the identification of variables associated with baseline dietary sodium intake

Parameter	Estimates (95% CI)	*P* Values
Sex		
Women	ref	
Men	1.05 (0.99, 1.11)	0.08
Region		
Chile/Mexico/Colombia	ref	
Australia/New Zealand	1.06 (0.98, 1.15)	0.15
Canada	1.14 (1.06, 1.21)	<0.001
Energy (per 500 units increase)	1.25 (1.23, 1.28)	<0.001
BMI (per 5 units increase)	1.03 (1.01, 1.04)	0.004
eGFR (per 20 units increase)	1.02 (1.00, 1.05)	0.07

BMI, body mass index; eGFR, estimated glomerular filtration rate.

adjusted risk for the primary clinical outcome at 12 or 24 months. The associations demonstrated via the multivariable adjustment should be viewed cautiously, because many of the analyses may be underpowered and require further study. The overall results are consistent with the main analysis of the SODIUM-HF trial, where in ambulatory patients with HF, the reduction in sodium intake did not reduce clinical events compared to usual care.[6] This finding was also confirmed by a meta-analysis that included 17 randomized clinical trials that included 1683 patients; they found that sodium restriction was not associated with fewer deaths or hospitalizations in patients with HF, although sodium restriction may be associated with improvements in symptoms, as measured by NYHA class, or in quality of life.[7] Overall, these results raise questions about guideline recommendations for sodium restriction in the treatment of HF.[4,14–17] An update of these recommendations is likely to be needed after the generation of this new evidence.

Study Limitations

There are several limitations that should be noted. First, this is a post hoc analysis and, as such, should be considered hypothesis-generating. Nevertheless, the SODIUM-HF trial is the largest trial of its type and provides useful information for furthering our understanding of dietary sodium adherence and its relationship to HF outcomes. Second, all patient-related data on dietary components were self-reported; however, because they were routinely collected through standardized methods and then collated via a core lab, they should be viewed as an improvement over less rigorous methods for capturing this information. Third, the adherence to dietary sodium restriction can change after the intervention's finish and is a potential bias. Although the total intervention period was 12 months, participants were followed-up thereafter for an additional 12 months and had 2 extra visits during the second year (3 and 9 months) in the intervention group to support dietary adherence. Finally, although we collected detailed information and performed multivariable adjustments, there may be residual confounders that could further explain, in part, our results.

Conclusion

This post hoc analysis of the SODIUM-HF trial showed no association between dietary sodium intake at baseline on HF clinical outcomes over 2 years. We also found no association between the magnitude of dietary sodium reduction and outcomes, and no clear benefit or harm of sodium reduction over usual care was observed. Responder analyses suggest the need for further investigation of the effects of sodium reduction in those who achieve the targeted dietary sodium reduction level.

Lay Summary

Dietary sodium restriction is common advice for patients with heart failure (HF); however, randomized clinical trials have not shown a beneficial effect of dietary sodium restriction on clinical outcomes.

In this post hoc exploratory analysis of the SODIUM-HF trial, we assessed the association between baseline dietary sodium intake and change at 6 months, with a composite of cardiovascular hospitalizations, emergency department visits, and all-cause death at 12 and 24 months. We found that there was no association between dietary sodium intake at baseline on HF clinical outcomes over 2 years. Further, no association between the magnitude of dietary sodium reduction and outcomes and no clear benefit or harm of sodium reduction over usual care was observed.

Clara Saldarriaga

CRediT authorship contribution statement

CLARA SALDARRIAGA: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **ELOISA COLIN-RAMIREZ:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **SUNJIDATUL ISLAM:** Writing – review & editing, Visualization, Formal analysis. **WENDIMAGEGN ALEMAYEHU:** Writing – review & editing, Visualization, Validation, Formal analysis. **PETER MACDONALD:** Writing – review & editing, Investigation. **HEATHER ROSS:** Writing – review & editing, Investigation. **JORGE ESCOBEDO:** Writing – review & editing, Investigation.

FERNANDO LANAS: Writing – review & editing, Investigation. RICHARD W. TROUGHTON: Writing – review & editing, Investigation. FINLAY A. MCALISTER: Writing – review & editing, Investigation. JUSTIN A. EZEKOWITZ: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Disclosures

The authors confirm that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2024.04.031.

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