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

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

Summary

Background Dietary restriction of sodium has been suggested to prevent fluid overload and adverse outcomes for patients with heart failure. We designed the Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF) to test whether or not a reduction in dietary sodium reduces the incidence of future clinical events.

Methods SODIUM-HF is an international, open-label, randomised, controlled trial that enrolled patients at 26 sites in six countries (Australia, Canada, Chile, Colombia, Mexico, and New Zealand). Eligible patients were aged 18 years or older, with chronic heart failure (New York Heart Association [NYHA] functional class 2–3), and receiving optimally tolerated guideline-directed medical treatment. Patients were randomly assigned (1:1), using a standard number generator and varying block sizes of two, four, or six, stratified by site, to either usual care according to local guidelines or a low sodium diet of less than 100 mmol (ie, <1500 mg/day). The primary outcome was the composite of cardiovascular-related admission to hospital, cardiovascular-related emergency department visit, or all-cause death within 12 months in the intention-to-treat (ITT) population (ie, all randomly assigned patients). Safety was assessed in the ITT population. This study is registered with ClinicalTrials.gov, NCT02012179, and is closed to accrual.

Findings Between March 24, 2014, and Dec 9, 2020, 806 patients were randomly assigned to a low sodium diet (n=397) or usual care (n=409). Median age was 67 years (IQR 58–74) and 268 (33%) were women and 538 (66%) were men. Between baseline and 12 months, the median sodium intake decreased from 2286 mg/day (IQR 1653–3005) to 1658 mg/day (1301–2189) in the low sodium group and from 2119 mg/day (1673–2804) to 2073 mg/day (1541–2900) in the usual care group. By 12 months, events comprising the primary outcome had occurred in 60 (15%) of 397 patients in the low sodium diet group and 70 (17%) of 409 in the usual care group (hazard ratio [HR] 0·89 [95% CI 0·63–1·26]; p=0·53). All-cause death occurred in 22 (6%) patients in the low sodium diet group and 17 (4%) in the usual care group (HR 1·38 [0·73–2·60]; p=0·32), cardiovascular-related hospitalisation occurred in 40 (10%) patients in the low sodium diet group and 51 (12%) patients in the usual care group (HR 0·82 [0·54–1·24]; p=0·36), and cardiovascular-related emergency department visits occurred in 17 (4%) patients in the low sodium diet group and 15 (4%) patients in the usual care group (HR 1·21 [0·60–2·41]; p=0·60). No safety events related to the study treatment were reported in either group.

Interpretation In ambulatory patients with heart failure, a dietary intervention to reduce sodium intake did not reduce clinical events.

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Introduction

Evidence-based care of patients with heart failure has evolved substantially over the past few decades and includes pharmacological agents, devices, and self-care to improve clinical outcomes.[1,2] Recommendations regarding diet are used nearly uniformly in guidelines and clinical practice for all stages of heart failure, and could have global implications for heart failure management. Heart failure is associated with neurohormonal activation and abnormalities in autonomic control that lead to sodium and water retention; thus, dietary restriction of sodium has been historically endorsed as a mechanism to prevent fluid overload and subsequent clinical outcomes; however, more recent data has questioned the validity of these recommendations.

Previous clinical studies that enrolled patients with heart failure provided mixed results, with epidemiological data and clinical trials of varying designs highlighting beneficial,[3–8] neutral,[9,10] or potentially harmful[11–16] effects of a low sodium diet. Several of these differing results might be

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Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada (Prof J A Ezekowitz MBBCh, W Alemayehu PhD, F A McAlister MD); **Anáhuac University, Mexico City, Mexico** (Prof E Colin-Ramirez PhD); **Toronto General Hospital, Toronto, ON, Canada** (Prof H Ross MD); **Instituto Mexicano del Seguro Social, Mexico City, Mexico** (Prof J Escobedo MD); **St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia** (Prof P Macdonald MD); **University of Otago, Dunedin, New Zealand** (Prof R Troughton MD); **Centro Cardiovascular Colombiano Clinica Santa Maria (Clinica Cardio VID), Antioquia, Columbia** (C Saldarriaga MD); **University of Ontario Institute of Technology, Oshawa, ON, Canada** (J Arcand PhD); **The Royal Brisbane and Women's Hospital, Herston, QLD, Australia** (Prof J Atherton PhD); **Auckland UniServices, Auckland, New Zealand** (Prof R Doughty MD); **Brampton Research Associates, Brampton, ON, Canada** (M Gupta MD); **University of Calgary and Foothills Medical Centre, Calgary, AL, Canada** (J Howlett MD); **University of British Columbia, Vancouver, BC, Canada** (S Jaffer MD); **Prairie Vascular Research Inc, Regina, SK, Canada** (A Lavoie MD); **Middlemore Clinical Trials, Auckland, New Zealand** (M Lund MBChB); **Baker Heart and Diabetes**

Institute, Melbourne, VIC, Australia (Prof T Marwick PhD); **Hamilton Health Sciences, Hamilton, ON, Canada** (Prof R McKelvie MD); **St Michael's Hospital, Toronto, ON, Canada** (Prof G Moe MD); **Cambridge Cardiac Care Centre, Cambridge, ON, Canada** (A S Pandey MD); **Southlake Regional Health Centre, Newmarket, ON, Canada** (L Porepa MD); **Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada** (M Rajda MD); **The Prince Charles Hospital, Chermside, QLD, Australia** (H Rheault NP); **Red Deer Regional Hospital, Red Deer, AL, Canada** (J Singh MD); **St Paul's Hospital, Vancouver, BC, Canada** (M Toma MD); **Vancouver General Hospital, Vancouver, BC, Canada** (S Virani MD); **St Boniface Hospital, Winnipeg, MB, Canada** (Prof S Zieroth MD)

Correspondence to: Prof Justin A Ezekowitz, Canadian VIGOUR Centre, Katz Group Centre for Pharmacy and Health Research, University of Alberta, Edmonton, AB T6G 2E1 Canada
Jae2@ualberta.ca; @justinezekowitz

Research in context

Evidence before this study

Dietary recommendations have been provided to patients with heart disease for over 100 years, but very few of the recommendations have been based on evidence from randomised clinical trials. Updating a previous systematic review, we searched the scientific literature to identify trials enrolling outpatients with heart failure to a dietary intervention focused on sodium reduction. We searched MEDLINE and Google Scholar for publications in English between Jan 1, 2017, and Jan 31, 2022, using the terms ("sodium" OR "salt" OR "diet") AND ("heart failure" OR "cardiomyopathy" OR "congestive heart failure") AND ("random*" OR "clinical trials"). In an earlier systematic review, seven trials had been identified using this search strategy (including trials up until 2018), enrolling between 24 to 97 patients in each trial, and in our search we identified two extra trials set in the period after hospital discharge, which enrolled 27 and 66 patients, and an additional trial of 204 patients. Studies were between 4 weeks and 6 months in duration, used a variety of dietary sodium reduction strategies and targets, and had mixed effects on signs, symptoms, and clinical outcomes. No consistent result was seen across trials, and most were of low quality.

Added value of this study

To our knowledge, our study is the largest randomised clinical trial to test a strategy of dietary sodium reduction for patients with heart failure to date. We found that dietary sodium reduction (to a target of <1500 mg/day) in patients with heart failure did not reduce the clinical composite outcome of all-cause mortality, cardiovascular-related hospitalisation, or cardiovascular-related emergency department visits compared with usual care over 12 months. An improvement in the patient-reported outcome of quality of life and clinician assessed New York Heart Association functional class was noted; however, no significant between-group difference was seen in 6-min walk distance. Therefore, our study provides high-quality evidence to guide clinical decision making in a field that has thus far not had longer-term, pragmatically designed solutions to dietary interventions and guideline recommendations.

Implications of all the available evidence

Because the degree of dietary sodium reduction that would lead to a reduction in clinical events has not yet been defined, clinicians and patients should consider a dietary intervention similar to other medical therapies and balance the potential benefits on an individual basis.

due to the duration of study, the clinical and demographic characteristics of the patients included, location of care, level of sodium restriction reached, co-interventions, outcomes assessed, and rigour of the overall study design. Preprepared foods, such as those used in several feeding trials, are useful for short-term clinical studies but impractical for broad scale application and for inducing long-term eating habit modifications, and thus, menu-based or similar strategies might be preferred.

The Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF) trial was designed to assess the effects of dietary sodium reduction on clinical outcomes in a population with heart failure using a pragmatic design. Specifically, the study was designed to test whether or not a reduction in dietary sodium reduced cardiovascular-related admission to hospital (hereafter, referred to as hospitalisation), cardiovascular-related emergency department visits, and all-cause mortality within 12 months, and if it improved quality of life, New York Heart Association (NYHA) functional class, and 6-min walk distance.

Methods

Study design

SODIUM-HF was a pragmatic, multinational, open-label, randomised trial; the trial methods have been described previously.[17,18] The trial design and operations were led by the Canadian VIGOUR Centre (CVC) at the University of Alberta (Edmonton, AB, Canada). The full trial protocol (appendix pp 19–59) was approved by regulatory authorities in participating countries, where required, and by individual institutional review boards or ethics committees at participating sites. The CVC oversaw site monitoring, data management, and all analyses related to the trial.

See Online for appendix

Participants

Participants were recruited from 26 sites (including specialty centres, hospitals, primary care centres, and community, private, and public centres) in six countries (Australia, Canada, Chile, Colombia, Mexico, and New Zealand). Eligible participants were aged 18 years or older, with chronic heart failure (defined as NYHA functional class 2–3), and were receiving optimally tolerated guideline-directed medical therapy. Chronic heart failure was determined by local clinical guidelines and by clinicians with experience and expertise with the diagnosis and treatment of heart failure. There were no ejection fraction or natriuretic peptide inclusion or exclusion criteria. Exclusion criteria included an average dietary intake of less than 1500 mg/day of sodium, a serum sodium concentration of less than 130 mmol/L, an estimated glomerular filtration rate (eGFR) of less than 20 mL/min per 1·73 m² or haemodialysis-dependent renal failure, and admission to hospital for a cardiovascular cause in the past month. A full list of eligibility criteria is included in the appendix (p 5). All patients provided written informed consent.

Randomisation and masking

Participants were randomly allocated (1:1) to either usual care or to a low sodium diet. The randomisation lists

were generated by an independent statistician at the data coordinating centre (CVC) using a standard random number generator in randomly varying block sizes of two, four, or six and stratified by site. Randomisation and data collection were done centrally in REDCap (version 9.0). Study group allocation was concealed using a secure web-based randomisation system. Investigators, participants, and treating clinicians were aware of the assigned treatment strategy; however, outcome assessors for quality of life, NYHA functional class, and 6-min walk distance were masked to group allocation. A Clinical Events Committee, who were masked to the trial-group assignments, adjudicated all hospitalisations and emergency department visits for cardiovascular causes (definitions are in the appendix [pp 6–8]).

Procedures

In the low sodium diet group, a sodium target of less than 100 mmol (ie, 1500 mg/day) was selected on the basis of epidemiological data, previous randomised controlled trial data, and practical limits of dietary interventions. Dietary materials (ie, meal plans and menus) were developed and tested in a pilot study and locally adapted to reflect the regional nature of diets.[6] Participants were provided with a set of six daily sample menus according to their energy requirements, energy distribution, and extent of sodium restriction compared with their normal diet. Patients were prescribed a normocaloric diet with a distribution of 15–20% protein, 50–55% carbohydrates, 25–30% fat, and 7% saturated fat, consistent with most cardiovascular diet guidelines. The dietary intervention was supported by behavioural counselling by trained dietitians or physicians or nurses. Details of the dietary materials have been previously published.[6,18] The control group were given usual care, which included general advice to restrict dietary sodium, as provided during routine clinical practice. There was no run-in period or specific fluid restriction or dietary supplementation recommended.

The total intervention period was 12 months and participants were followed up thereafter for an additional 12 months. Patients had clinical visits at baseline, at 6 and 12 months, and two extra visits at 3 and 9 months occurred in the intervention group to support dietary adherence. Information on visits during the additional 12-month follow-up period are provided elsewhere.[17,18]

At each follow-up visit, vital signs, bodyweight, 3-day food records, and NYHA functional class were assessed, and participants were asked to complete quality-of life assessments. Safety was assessed by site personnel at each visit; no specific criteria for adverse events were used.

Dietary sodium intake was assessed using a 3-day food record (including 1 weekend day) at baseline, 6 months, and 12 months in both groups, and for the intervention group also at 3 and 9 months to monitor and support dietary adherence. Food records were analysed by trained personnel in a core laboratory (CVC), using a nutrient software program (ESHA Food Processor SQL version 10.11; ESHA Research, Salem, OR, USA).

Outcomes

The primary outcome was the composite of cardiovascular-related hospitalisation, cardiovascular-related emergency department visit, and all-cause death within 12 months after randomisation. Secondary endpoints were the time to first event within the event type (ie, individual components of the primary composite endpoint: all-cause mortality, cardiovascular-related hospitalisation, and cardiovascular-related emergency department visits) within 12 months and 24 months (24 month data are not available for all patients, so only 12 month data are reported here); quality of life as measured via the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, clinical summary score, and physical limitation score; change in 6-min walk distance; and change in NYHA functional class, all as change from baseline to 12 months.

Statistical analysis

We determined the sample size using the primary composite outcome. We estimated that a trial including 992 patients would have 80% power to detect a 30% reduction in the primary outcome in the low sodium diet group compared with an assumed event rate of 25% in the usual care group, and with a two-sided type 1 error rate of 0·05.

In a prespecified interim analysis, the Data Monitoring Committee reviewed data from the first 500 participants with complete 12-month follow-up data to advise on stopping the trial for futility (if conditional power was <20%) or efficacy (two-sided p value of <0·001). This review, in addition to an assessment of trial operational feasibility and the effect of the COVID-19 pandemic, led to an early stopping, with the last patient being enrolled on Dec 9, 2020, and complete 12 month follow-up in December, 2021.

We analysed the primary composite outcome and the individual component outcomes in the intention-to-treat (ITT) population as unadjusted analyses, as defined by Statistical Analysis Plan (appendix pp 60–65). The ITT population included all patients randomly assigned to treatment according to the treatment group they were assigned. Secondary outcomes were also assessed in the ITT population. Patients who withdrew or who were lost to follow-up before observing the event of interest or before completing their fixed 12-month follow-up period were right censored at the available time of withdrawal or last follow-up visit. We used a Cox proportional hazards model to estimate the relative risk measures in terms of hazard ratio (HR) and the 95% CIs. We checked the validity of the proportionality assumption by including time varying covariates, an interaction of treatment group with logarithm of the event time in the model, and testing its significance.

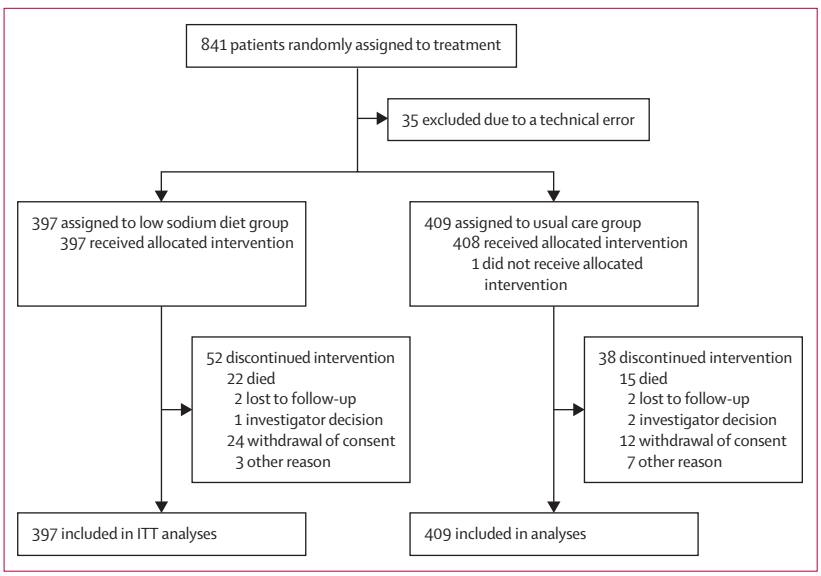


Figure 1: **Trial profile**
ITT=intention-to-treat.

We examined prespecified baseline patient characteristics (including age, sex, NYHA functional class, calorie intake, sodium intake, left ventricular ejection fraction, body-mass index, and eGFR) for their influence on the estimate of the study treatment effect using multivariable Cox regression model. We did prespecified subgroup analyses of the primary composite outcome on the basis of following covariates: age (<65 years *vs* ≥65 years), renal function (eGFR <60 mL/min per 1·73 m² *vs* ≥60 mL/min per 1·73 m²), diabetes (yes *vs* no), hypertension (yes *vs* no), and left ventricular ejection fraction (<40% *vs* ≥40%). Sex was also explored as a subgroup. We formally tested the interaction between these subgroups and assigned treatment groups in Cox models and we estimated subgroup-specific HRs with 95% CIs from the fitted model. In additional post-hoc sensitivity analyses we assessed the risk of the primary outcome by tertiles of baseline dietary sodium intake (≤1500, 1501–3000, and >3000 mg/day) and the effect of the intervention on patients across these tertiles, and by baseline use of a renin angiotensin system inhibitor and geographical region.

We generated Kaplan-Meier estimates of the primary and secondary outcomes by assigned treatment group and present these data as cumulative incidence curves. We visually assessed the distributions of the repeatedly measured KCCQ and 6-min walking distance and found them to not be skewed. We analysed changes in the scores of these tests using linear mixed-effects models consisting of the baseline score, treatment group, time (6 months or 12 months), and the interaction effect as the fixed-effect component and a random intercept component to account for the correlation of patient-specific measurements. We estimated the mean changes from baseline at 6 and 12 months from the model and tested whether the changes were different between the treatment groups. We also did additional post-hoc sex-stratified analyses for KCCQ. We analysed NYHA functional class via a proportional odds logistic regression model for repeated ordinal scores to determine whether there was a significantly different change over time for the low sodium diet group compared with the usual care group. Missing data in the KCCQ scores, 6-min walking distance, and NYHA functional class were not imputed. We analysed all the available data. Similarly, we used the linear mixed-effects model to estimate and test the significance of the differences in the least squares means of the dietary intake parameters (transformed to log-scale) between groups at baseline, 6 months, and 12 months.

We assessed safety in all patients randomly assigned to treatment. We present all patient characteristics as median (IQR) for continuous variables, and as counts and proportions for categorical variables. We did all statistical tests at an alpha level of 0·05, indicating statistical significance. We did all analyses using SAS software (version 9.4). This study is registered with ClinicalTrials.gov, NCT02012179.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 24, 2014, and Dec 9, 2020, 806 patients were enrolled and randomly assigned to either a low sodium diet (n=397) or usual care (n=409; figure 1). Baseline characteristics were balanced between groups (table 1). The median age was 67 years (IQR 58–74) and 268 (33%) were women and 538 (66%) were men. Data on race and ethnicity were not collected. 551 (68%) of 806 patients had heart failure for at least 1 year before enrolment, 270 (33%) had been admitted to hospital due to heart failure in the past 12 months, and the median ejection fraction was 36% (IQR 27–49). In the 325 patients with a natriuretic peptide measurement in the 90 days before enrolment, median B-type natriuretic peptide (BNP) was 197 pg/mL (IQR 83–492) and median N-terminal proBNP (NT-proBNP) was 801 pg/mL (IQR 335–1552). At randomisation, 649 (81%) of 806 patients were receiving an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or sacubitril–valsartan, 702 (87%) were receiving a β blocker, and 461 (57%) were receiving a mineralocorticoid receptor antagonist.

At baseline, the median sodium intake was 2286 mg/day (IQR 1653–3005) for the low sodium diet group and 2119 mg/day (1673–2804) for the usual care group (figure 2; appendix pp 9–11). In the usual care group, at 6 months the median sodium intake was 2021 mg/day (1440–2726) and at 12 months was 2073 mg/day (1541–2900), equating to an approximately 4% decrease

	Low sodium diet group (n=397)	Usual care group (n=409)
Age, years	66 (57–73)	67 (58–75)
Sex		
Female	127 (32%)	141 (34%)
Male	270 (68%)	268 (66%)
Geographical region		
Canada	230 (58%)	241 (59%)
Australia and New Zealand	79 (20%)	78 (19%)
Mexico, Chile, and Colombia	88 (22%)	90 (22%)
Diagnosed with heart failure for ≥1 year	269 (68%)	282 (69%)
Hospitalised for heart failure in past 12 months	129 (32%)	141 (34%)
Ejection fraction	36 (28–48)	35 (27–50)
NYHA functional class		
1	2 (1%)	6 (1%)
2	293 (74%)	283 (69%)
3	98 (25%)	119 (29%)
4	3 (1%)	0
Medical history		
Hypertension	246 (62%)	258 (63%)
Coronary artery disease	187 (47%)	186 (45%)
Peripheral arterial disease	33 (8%)	42 (10%)
Cerebrovascular disease (transient ischaemic attack or stroke)	45 (11%)	41 (10%)
Atrial fibrillation or flutter	156 (39%)	173 (42%)
Diabetes (type 1 or 2)	132 (33%)	156 (38%)
Chronic obstructive pulmonary disease	64 (16%)	72 (18%)
Previous ventricular fibrillation or tachycardia	65 (16%)	59 (14%)
Smoking history		
Ever smoker	197 (50%)	180 (44%)
Never smoker	200 (50%)	229 (56%)
Vital signs and physical findings		
BMI, kg/m²	30 (26–35)	31 (27–36)
Bodyweight, kg	88 (73–102)	86 (73–101)
Hand grip strength, kg*	30 (24–38)	33 (21–39)
Heart rate, beats per min	69 (61–76)	69 (61–77)
Systolic blood pressure, mm Hg	118 (105–129)	118 (104–130)
Diastolic blood pressure, mm Hg	70 (62–79)	70 (62–78)
(Continued from previous column)		
Laboratory values		
BNP, pg/mL†	194 (74–470)	222 (85–541)
NT-proBNP, pg/mL†	763 (228–1161)	934 (418–2169)
eGFR, mL/min per 1·73 m²‡	61 (46–75)	58 (42–71)
Serum sodium, mmol/L	139 (137–141)	139 (137–141)
Serum potassium, mmol/L	4 (4–5)	4 (4–5)
Medical and device therapy		
Any RAAS inhibitor (ACE, ARB, or ARNI)	314 (79%)	335 (82%)
β blocker	351 (88%)	351 (86%)
ACE or ARB	256 (64%)	284 (69%)
Sacubitril–valsartan	63 (16%)	53 (13%)
Mineralocorticoid antagonist	237 (60%)	224 (55%)
Implantable cardioverter-defibrillator§	104 (26%)	81 (20%)
Pacemaker	36 (9%)	29 (7%)
Cardiac resynchronisation therapy	41 (10%)	33 (8%)

Data are median (IQR) or n (%). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor blocker neprilysin inhibitor. BMI=body-mass index. BNP=b-type natriuretic peptide. eGFR=estimated glomerular filtration rate. NT-proBNP=N-terminal b-type natriuretic peptide. NYHA=New York Heart Association. RAAS=renin-angiotensin-aldosterone system. *Available in 118 patients. †Within 90 days of enrolment, and BNP records were available for 263 patients (n=127 in low sodium diet group, n=136 in usual care group) and NT-proBNP records were available for 62 patients (n=27 low sodium diet group, n=35 usual care group). ‡Significant difference between groups; p=0·036. §Significant difference between groups; p=0·037.

Table 1: **Baseline clinical and demographic characteristics**

from baseline to 6 months, and from baseline to 12 months. In the low sodium diet group, at 6 months the median sodium intake was 1649 mg/day (1272–2202) and at 12 months was 1658 mg/day (1301–2189), equating to an approximately 28% decrease from baseline to 6 months and from baseline to 12 months. The median difference between groups was 415 mg/day at 12 months (significance of difference of the least squares means on log-scale p<0·0001). No significant difference between the groups in bodyweight, systolic blood pressure, calorie intake, fluid intake, or potassium intake was seen up to 12 months (appendix pp 9–11).

Four patients were lost to follow-up (two [1%] of 397 in the low sodium diet group and two [<1%] of 409 in the usual care group). Ascertainment of the primary outcome within 12 months was available in 792 of the 806 patients (98%).

Within 12 months, the primary outcome had occurred in 60 (15%) of 397 patients in the low sodium diet group and 70 (17%) of 409 in the usual care group (HR 0·89 [95% CI 0·63–1·26]; p=0·53; figure 3A, table 2). All-cause death occurred in 22 (6%) patients in the low sodium diet group and 17 (4%) in the usual care group (HR 1·38 [0·73–2·60]; p=0·32), cardiovascular-related hospitalisation occurred in 40 (10%) patients in the low sodium diet group and 51 (12%) patients in the usual care group (HR 0·82 [0·54–1·24]; p=0·36), and cardiovascular-related emergency department visits occurred in 17 (4%) patients in the low sodium diet group and 15 (4%) patients in the usual care group (HR 1·21 [0·60–2·41]; p=0·60; figure 3, table 2). When adjusted for clinically important baseline characteristics, analyses of the primary outcome and its composites gave similar results (table 2).

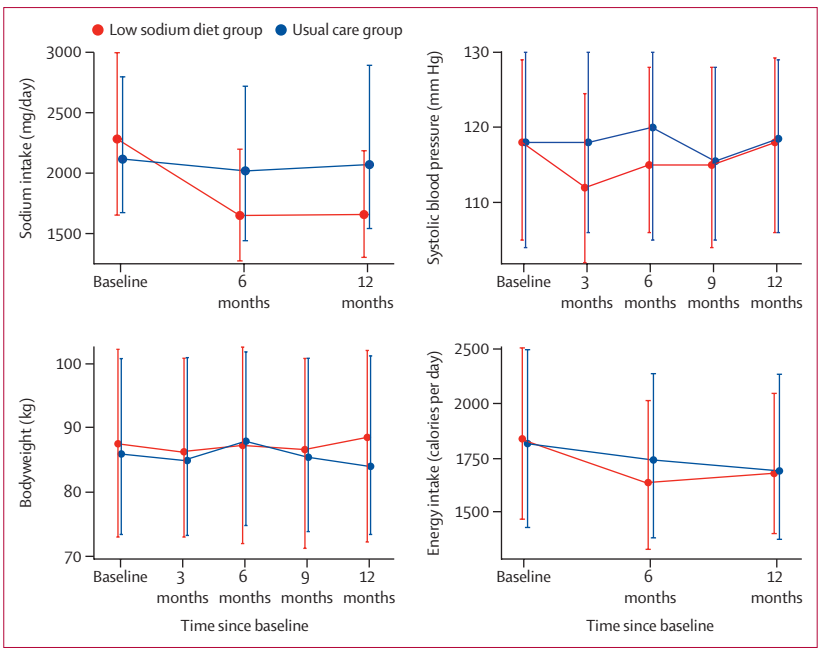


Figure 2: **Changes in sodium intake (A), blood pressure (B), bodyweight (C), and energy intake (D)**

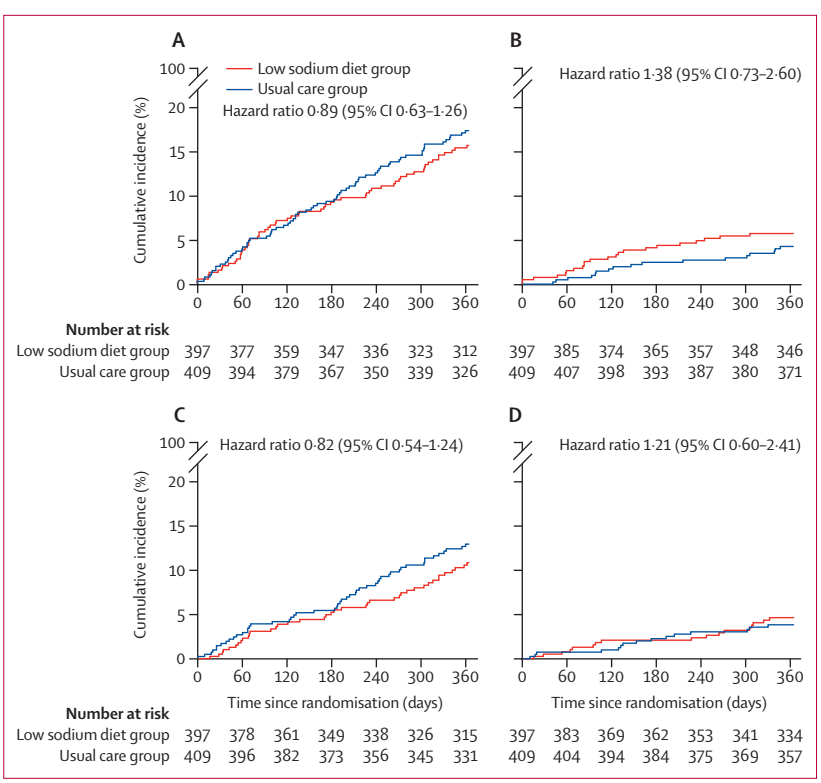


Figure 3: **Composite primary outcome (A) and secondary outcomes of all-cause mortality (B), cardiovascular-related hospitalisation (C), and cardiovascular-related emergency department visit (D)**

The increases in the overall summary score, the clinical summary score, and the physical limitation score on the KCCQ were significantly greater in the low sodium diet group than in the usual care group between baseline and 12 months (figure 4; appendix p 17). Adjusting for baseline score, the mean between-group difference in the change from baseline to 12 months in the overall summary score was 3·38 points (95% CI 0·79–5·96; p=0·011), clinical summary score was 3·29 points (0·74–5·83; p=0·011), and physical limitation score was 3·77 points (0·67–6·87; p=0·017). A sex-stratified analysis showed similar results with no significant treatment-sex interaction on quality of life (appendix p 14).

There was no difference in 6-min walk distance at 12 months between the low sodium diet group and the usual care group, with the adjusted mean difference in distance walked of 6·6 m (95% CI –9·0 to 22·2; p=0·41; figure 4).

There was a significant difference between groups in NYHA functional class at 12 months, with the low sodium diet group having greater likelihood of improving by one NYHA class than the usual care group (odds ratio 0·59 [95% CI 0·40–0·86]; p=0·0061; figure 4).

The absence of treatment effect for the primary outcome was consistent across prespecified subgroups (appendix p 19). A borderline interaction ($p_{interaction}$=0·032) was seen by age, with a greater reduction in the primary outcome seen for individuals younger than 65 years than for those aged 65 years and older. In post-hoc sensitivity analyses, we found no significant interaction between the primary outcome and baseline dietary sodium intake (≤1500, 1501–3000, and >3000 mg/day; $p_{interaction}$=0·63; appendix p 15). Additionally, we found no interaction between the primary outcome and baseline use of a renin angiotensin system inhibitor ($p_{interaction}$=0·46; appendix p 16) or by geographical region (p=0·54).

No safety events attributable to the trial were reported in either the low sodium diet or usual care groups.

Discussion

We found that in ambulatory patients with heart failure a strategy to reduce dietary sodium intake to less than 1500 mg daily was not more effective than usual care in reducing the risk of hospitalisation or emergency department visits due to cardiovascular causes or all-cause death. Despite the fact that the primary outcome was not met, there are several key findings that deserve consideration in interpreting these results. First, there was no difference in the composite clinical outcome over the 12-month follow-up period among patients with heart failure who were at moderate short-term risk for clinical events; longer-term follow-up (ie, >12 months) might or might not identify greater differences because a dietary sodium reduction strategy might take a long time to accumulate benefits. Second, we identified a moderate benefit on quality of life, as measured by the KCCQ, and in NYHA functional class, and these findings were consistent in sex-stratified analyses. 6-min walk distance, a commonly used functional test in randomised controlled trials, was not statistically different between groups. Whether the

	Low sodium diet group (n=397), events (per 100 patient-years)	Usual care group (n=409), events (per 100 patient-years)	Unadjusted hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)*	p value
Primary outcome						
Cardiovascular-related hospitalisation, cardiovascular-related emergency department visit, or all-cause death	60 (17·2)	70 (19·2)	0·89 (0·63–1·26)	0·53	0·99 (0·66–1·47)	0·95
Secondary outcomes						
Cardiovascular-related hospitalisation	40 (11·4)	51 (13·8)	0·82 (0·54–1·24)	0·36	0·94 (0·58–1·53)	0·82
Cardiovascular-related emergency department visit	17 (4·7)	15 (3·9)	1·21 (0·60–2·41)	0·60	1·06 (0·49–2·30)	0·88
All-cause death	22 (6·0)	17 (4·3)	1·38 (0·73–2·60)	0·32	1·35 (0·64–2·82)	0·43

*Adjusted for age, sex, New York Heart Association functional class, baseline calorie intake, baseline sodium intake, ejection fraction, body-mass index, estimated glomerular filtration rate, and presence of implantable cardioverter-defibrillator.

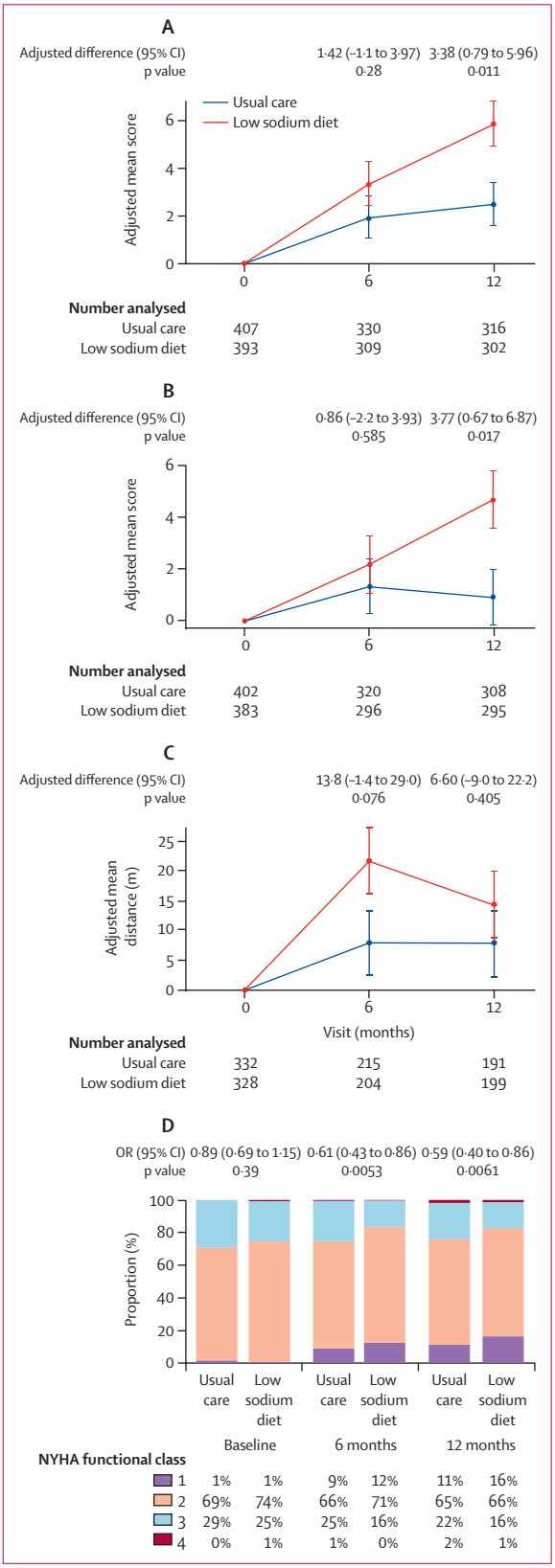
Table 2: **Primary and selected secondary outcomes**

moderate benefits in quality of life and overall safety of a dietary sodium strategy we tested are sufficient to warrant large-scale change in practice is uncertain.

SODIUM-HF provides a substantive update to the published evidence and differs from previous studies in its methods and findings. Heart failure guidelines have evolved and applied increased rigour to the assessment of data on which a recommendation is based; guidelines have downgraded the strength and grade of recommendations regarding dietary sodium restriction over time.[1,2] To our knowledge, SODIUM-HF is the largest trial of its type to date, with longer follow-up than short-term feeding studies. We enrolled a diverse group of patients from six countries with varied diets and follow-up that allows for increased generalisation of the results given the varying dietary content, methods of preparation, and habits or behaviours around food and nutrition. To maintain the pragmatic nature of the trial, we used a menu-based system rather than specially prepared foods, as is usually done in feeding studies. This method allows for increased translation into practice upon completion and was tracked using 3-day food records, a commonly used clinical tool. Previous smaller trials that used a dietary counselling approach with a personalised meal plan have shown no significant effects of sodium restriction on clinical outcomes in heart failure.[4,6] A trial of 203 ambulatory patients with heart failure found non-significantly fewer readmissions to hospital due to heart failure and increased 12-month survival in the group receiving dietary intervention with a targeted sodium intake of less than 2400 mg/day compared with the group receiving usual dietary recommendations for sodium restriction;[4] SODIUM-HF had similar non-significant results.

SODIUM-HF enrolled patients in an ambulatory setting at least 1 month after a cardiovascular hospitalisation to avoid the vulnerable period immediately after discharge. Two previous contemporary randomised clinical trials aimed to test the effects of sodium restriction on clinical outcomes or quality of life, or both, in patients recently discharged from hospital using the provision of meals. The Prevent Adverse Outcomes in Heart Failure by Limiting Sodium (PROHIBIT Sodium)[10] pilot trial randomly assigned 27 patients with heart failure to receive daily meals containing 1500 mg or 3000 mg of sodium. After a 12-week follow-up period, quality of life improved among patients in the 1500 mg group but remained unchanged in the 3000 mg group, and there was no difference in the change in NT-proBNP levels. The Geriatric Out-of-Hospital Randomized Meal Trial in Heart Failure study (GOURMET-HF)[7] randomly assigned 66 patients to 4 weeks of home-delivered sodium-restricted diets (1500 mg daily) on the basis of the Dietary Approaches to Stop Hypertension dietary pattern versus usual care. In GOURMET-HF, the KCCQ summary score increased similarly in both groups, and a non-significant increase in the KCCQ clinical summary score in the participants in the sodium-restricted diet group was observed. Similar to these studies, we also identified no attributable side-effects of a low sodium diet.

Several other design-related issues deserve consideration when interpreting our findings. We piloted the intervention to test the menu-based system and subsequently adapted this to regional differences.[18,19] This adaptation was necessary because of the ubiquitous nature of food, variations in preparing similar meals, and sociocultural differences in food intake. Adherence to the diet was good, as measured by 3-day food record sodium, calorie, and fluid intake, and maintained over the 12 months. Although 24 h urinary excretion is the gold standard dietary assessment method for sodium intake, food records are a valid dietary assessment technique in heart failure and the use of 24 h urine collections would have restricted trial feasibility and generated potentially misleading data for patients with heart failure on diuretics.[20] We captured but did not intentionally alter either caloric or fluid intake, diuretics, or other dietary supplements, and as such sought to modify in principle



the sodium content alone. This approach achieved its goals, as shown by the fluid and calorie content being similar in both groups over the course of the trial despite an additional two visits in the low sodium diet group of the trial. Finally, rather than assess surrogate endpoints (eg, changes in natriuretic peptides and ejection fraction), we wanted to understand if dietary modification to further reduce sodium intake altered clinical outcomes such as hospitalisation or death; we found that it did not.

This study has several important limitations. First, given the nature of the study intervention and the outcome assessor blinded to the intervention, the patients were not masked to study group assignment, which could be a potential source of bias especially for the secondary outcomes including NYHA functional class, KCCQ, and 6-min walking distance. Nevertheless, by capturing food record data in both study groups, and finding a reduction in the sodium content of the diet but no clinically significant differences in other diet-related parameters (eg, calories or fluid intake), it is unlikely that this is a major contributor of bias. Additionally, events were centrally adjudicated blinded to treatment assignment to further mitigate bias. Second, some patients might have decided to reduce their sodium intake even in the usual care group (contamination bias); however, this was not evident from the small (approximately 4%) reduction in sodium intake reported in the usual care group. We found a reduction in sodium of 415 mg/day by 12 months, and whether greater reductions in daily sodium or, alternatively, enrolling patients with substantially higher baseline dietary sodium than we did here might produce different results is uncertain. Third, we did not collect data on urinary or other biomarkers because such measurements were not possible with the resources we had available for this trial. Fourth, the trial was stopped early and so might overestimate the efficacy (or risk) of an intervention.[21] The lower than anticipated event rate of SODIUM-HF could limit the ability of the trial to detect a difference given the moderate effect size, and only a much larger trial or including patients at greater overall risk than we included here might be able to detect a clinically meaningful and significant reduction in clinical endpoints. Finally, the inclusion criteria were pragmatic and did not require NT-proBNP but instead relied on clinical diagnoses at sites familiar with the care of patients with heart failure. As a result, there is probably a mixture of higher and lower risk patients enrolled in the trial. Nevertheless, the event rate in SODIUM-HF was similar to that of other trials of ambulatory patients with heart failure.[22,23]

Figure 4: **KCCQ overall summary score (A), KCCQ physical Limitation Score (B), 6-min walk test (C), and NYHA functional class (D)**
In parts A–C, datapoints are adjusted means, with error bars showing SEs. KCCQ=Kansas City Cardiomyopathy Questionnaire. NYHA=New York Heart Association.

The dietary intervention in this study was feasible and effective in reducing sodium intake in patients with heart failure but did not result in changes in clinical outcomes, although small improvements were seen in quality of life and NYHA functional class.

Contributors

JAE and EC-R wrote the study protocol. WA planned and did the statistical analysis. All authors approved the study protocol. JAE wrote the first draft of the manuscript with input from EC-R and WA. All other authors provided substantial contribution to the acquisition of data and revision of the manuscript. WA and JAE accessed and verified the underlying study data. All authors had full access to all the data in the study and JAE had final responsibility for the decision to submit for publication. All authors have seen and approved of the manuscript before submission. JAE had unrestricted access to the data and drafted the initial version of the manuscript, which was reviewed and edited by all the authors. All the authors confirm the accuracy and completeness of the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Anonymised participant data can be made available upon requests directed to the corresponding author. Proposals will be reviewed on the basis of scientific merit, ethical review, available resources, and regulatory requirements and will be made available 12 months after the last participant has completed final follow-up. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. A steering committee will have the right to review and comment on any draft manuscripts based on these data before publication.

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