

Comparing Sodium Intake Strategies in Heart Failure Rationale and Design of the Prevent Adverse Outcomes in Heart Failure by Limiting Sodium (PROHIBIT) Study

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In the past 2 decades, heart failure (HF) research has focused primarily on drugs and devices. In contrast, evidence remains scarce and mostly observational for dietary sodium restriction,¹⁻³ arguably the most widely recommended self-care measure for patients with HF. In recent studies, patients with HF consumed an average of 3600 to 4200 mg sodium daily by 24-hour urinary sodium excretion,⁴ with 65% consuming >3000 mg.⁵ Although the evidence suggests that high-sodium intake worsens outcomes, the level of sodium intake that achieves optimal outcomes for patients with HF is unknown.⁶⁻¹² All current guidelines emphasize sodium intake restriction; however, there is no consensus on the actual level. Recommendations are either nonspecific or ranging between 2000 and 3000 mg/d,⁹ largely based on opinions or observational studies. In explicit acknowledgment of the evidence gap, the recent European Society of Cardiology guidelines for HF¹² have not assigned a level of evidence to sodium intake recommendations. The recent American College of Cardiology Foundation and American Heart Association guidelines recommend (class IIa) that sodium restriction is reasonable for patients with HF with congestive symptoms, but do not recommend a specific target level.¹³ The inconsistency of guidelines underlines the weak database that supports this cornerstone treatment.

Current Patterns of Sodium Intake Among Patients With HF

Current data indicate limited adherence with recommended sodium restriction among patients with HF. In a recent interventional study, when instructed to limit sodium intake to 2500 mg/d, patients with HF averaged a daily intake of 2700 to 3900 mg/d by 24-hour urinary sodium, depending on the assigned arm, after 8 months of intervention.⁴ Sodium intake reduction is difficult to adhere to even among patients with symptomatic HF, with less than one third of patients reporting sodium intake \leq 2500 mg/d by 3-day food diaries, which underestimate actual sodium

intake.⁴ Congruent with this observation, a recent study reported that only 34% of patients consume <3000 mg and only 15% consume <2000 mg sodium daily based on their 24-hour urinary sodium excretion.⁵ Sodium consumption <2000 mg/d is difficult to achieve even with dietitian education,¹⁴ and studies have demonstrated that sex¹⁵ and race¹⁶ affect dietary preferences and adherence to sodium restriction recommendations in patients with HF.

Challenge of Sodium Restriction in HF: Need for a Phase III Clinical Trial

HF may be associated with changes in cardiac output, systemic venous pressures, or shunting of blood away from the kidneys, leading to diminished renal perfusion and in turn activating the sympathetic¹⁷ and the renin angiotensin aldosterone system¹⁸ creating a vicious cycle of sodium and water retention, despite fluid overload (Figure 1).^{18,19} Moreover, inappropriate vasopressin levels are seen in HF. There is evidence that the natriuretic system is impaired early in the course of HF,^{20,21} causing sodium and water retention, which in turn provides the physiological basis for the low-sodium diet recommendation for patients with HF regardless of stage.

Although high-sodium intake can cause fluid retention and stimulate sympathoexcitation and inflammation, neurohormonal activation induced by low-sodium intake could potentially harm the failing heart also.²² In animal studies, a sodium-restricted diet leads to renin angiotensin aldosterone system activation,²³ and data suggest that dietary sodium restriction is associated with further neurohormonal activation in patients with HF also.²⁴⁻²⁹ It might be argued that further sympathetic and renin angiotensin aldosterone system activation is less clinically relevant in the presence of renin angiotensin aldosterone system–blocking agents and β -blockers. However, higher plasma renin activity was an independent predictor of mortality in the Valsartan in Heart Failure Trial (Val-HeFT) regardless of angiotensin-converting enzyme inhibitor or β -blocker treatment.²² In the Heart Outcomes Prevention Evaluation (HOPE) Trial, high

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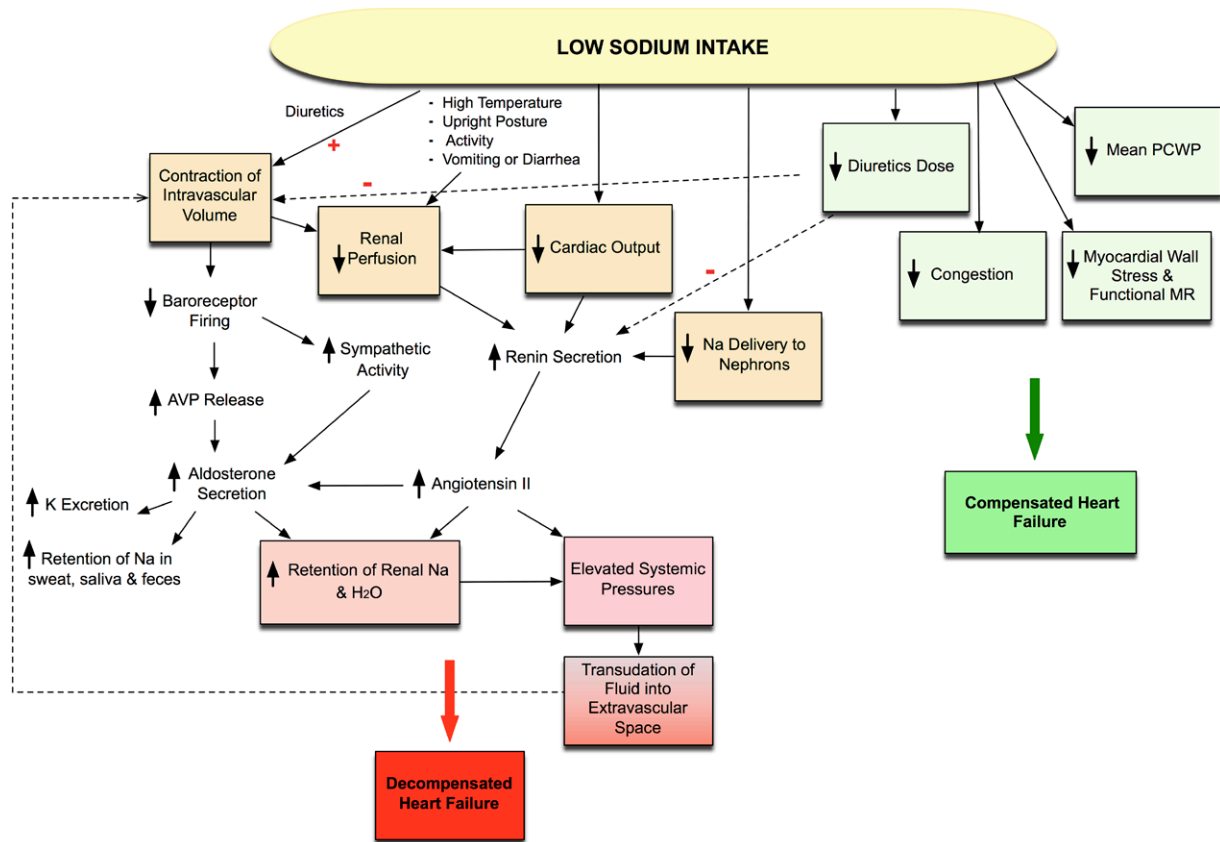


Figure 1. Effects of sodium intake in heart failure (HF). Low-sodium intake may have varied effect on HF. Intravascular volume contraction improves hemodynamics and reduces diuretic requirement, congestion, and myocardial wall stress, leading to compensated HF. Intravascular volume contraction, however, may also lead to a vicious cycle of increased sodium and water retention through neurohormonal activation predisposing to decompensated heart failure. AVP indicates arginine vasopressin; MR, mitral regurgitation; PCWP, pulmonary wedge capillary pressure; – (red), low diuretic doses reduce hormonal activation and contraction of intravascular volume; and + (red), diuretic action enhances contraction of intravascular volume. Adapted from Gupta et al¹⁹ with permission of the publisher. Copyright © 2012, Wolters Kluwer Health.

plasma renin activity was also an independent predictor of mortality in patients at high cardiovascular risk regardless of allocation to ramipril or placebo.³⁰ These data suggest that neurohormonal activation may nevertheless be important regardless of drug treatments that modulate neurohormonal activation.

Few studies, and only 1 in United States, have tested the impact of different sodium intake on clinical outcomes in HF.^{5,26–28,31–33} Observational and randomized studies have yielded contradicting results (Table 1). Several single-center randomized studies^{26–28,34–36} have suggested worse outcomes with strict sodium restriction in HF. However, these trials were conducted by the same investigators in a restricted geographic area, enrolled only postdischarge patients with HF, and in the largest of these studies there were multiple treatment arms, thus increasing the potential for type I error.¹⁹ Although a significant proportion of patients in these studies were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, few were on β -blockers or aldosterone antagonists. These shortcomings limit the generalizability of the findings.

Thus, although it seems reasonable to restrict sodium <3000 mg/d in HF, it is currently unknown how low is appropriate

for patients with HF. The net impact of sodium restriction on outcomes in patients with HF can only be addressed through a well-designed trial testing different levels of sodium restriction. However, critical knowledge gaps exist to develop a phase III trial of sodium restriction in HF.

Knowledge Gaps to Design a Phase III Clinical Trial of Sodium Restriction in HF: Rationale for a Clinical Trial Pilot Study

Target Population and Estimating Event Rates

Although the evidence base to support sodium restriction in HF and preserved ejection fraction (HFpEF) is inadequate,³⁷ the actual concerns with sodium restriction in HF have been raised for patients with HF and reduced EF (HFrEF) in the previous literature because of the neurohormonal activation and fluid retention with diuretic resistance in these patients.³⁸ Enrolling chronic stable patients with HFrEF would require a large sample size because of the lower event rates in this population.^{39,40} Patients with acute HF have mortality and readmission rates of $\leq 15\%$ and 30% , respectively, within 90 days post discharge, necessitating further research.⁴¹ These event rates increase power to detect an effect on outcomes

Table 1. Studies Investigating the Impact of Sodium Intake on Outcomes in Heart Failure

Source	Design	Intervention	Clinical Impact
Paterna et al ²⁶	Randomized N: 232; NYHA II post discharge; EF: <35%	Group 1: 2760 mg/d Na diet Group 2: 1840 mg/d Na diet Fluid intake: 1 L/d	6 mo (death, death+readmission) Group 1: 7.6%, 12.7% Group 2: 26.3%, 39.5%
Paterna et al ²⁷	Randomized N: 410; NYHA II post discharge; EF: <35%	Group A and B: 2760 mg Na+500/250 mg F Group C and D: 1840 mg Na+500/250 mg F Fluid Intake: 1 L/d Group E and F: 2760 mg Na+500/250 mg F Group G and H: 1840 mg Na+500/250 mg F Fluid intake: 2 L/d	6 mo (death, death+HF readmission) A: 1.9%, 7.7%; B: 3.9%, 29.4%; C: 9.8%, 49.0%; D: 13.7%, 54.9%; E: 9.6%, 51.9%; F: 12.0%, 58.0%; G: 11.5%, 71.1%; and H: 15.7%, 78.4%
Parrinello et al ²⁸	Randomized n: 173; NYHA II post discharge; EF: <35%	Group 1: 2760 mg/d Na+ (250–500) mg F Group 2: 1840 mg/d Na+ (250–500) mg F Fluid intake: 1 L/d	12 mo (readmission, death+ readmission) Group 1: 12%, 16% Group 2: 44%, 64%
Arcand et al ³¹	Observational n: 123 NYHA I-IV EF: <35%	Group 1: ≤1900 mg/d Na; Group 2: 2000–2700 mg/d Na; Group 3: ≥2800 mg/d Na Fluid intake: not mentioned	12-mo HF readmission: 5±3% (1), 5±3% (2), and 17±6% (3) 36-mo HF readmission: 12±6% (1), 15±7% (2), and 46±11% (3)
Lennie et al ⁵	Observational n: 302 NYHA I-IV EF: either < or ≥40%	Group 1: <3000 mg/d Na Group 2: ≥3000 mg/d Na Fluid intake: not mentioned	12 mo (death+admission+ED visits): NYHA I-II 1 vs 2: higher event-rate; NYHA III-IV 1 vs 2: lower event rate
Son et al ³²	Observational n: 232 NYHA I-IV EF: <40%	Group 1: <3000 mg/d Na Group 2: ≥3000 mg/d Na Fluid intake: not mentioned	12 mo (death+cardiovascular admission+cardiovascular ED visits): group 1 vs group 2: lower event rate
Song et al ³³	Observational n: 244 NYHA I-IV EF: either < or ≥40%	Group 1: <2000 mg/d Na Group 2: 2000–3000 mg/d Na Group 3: >3000 mg/d Na Fluid intake: not mentioned	12 mo (death+all-cause admissions) NYHA I-II: <2 g/d higher risk vs 2–3 g/d, >3 g/d lower risk vs 2–3 g/d NYHA III-IV: >3 g/d highest risk, no difference between <2 g/d and 2–3 g/d groups

ED indicates emergency department; EF, ejection fraction; F, furosemide; HF, heart failure; and NYHA, New York Heart Association.

within a feasible active feeding period (eg, 12 weeks). However, patients admitted for acute HF are given low-sodium diets different than their free-living state undergo adjustments in diuretics and other medications and are given self-care education, rendering assessment of usual sodium intake pattern unreliable at discharge. Enrolling patients at the 2-week follow-up visit would be more conducive to assessment of patients' usual dietary pattern and optimizing medications, while the patient is still within the postdischarge vulnerable phase. Waiting longer may lead to inclusion of lower risk patients.

Most acute HF studies reported cumulative 90- to 180-day outcomes.⁴¹ Thus, event rates among patients with HFrEF who are not readmitted 2 weeks after discharge can only be indirectly deducted from these data. Outcome data specifically among patients with HFrEF who are stable 2 weeks post discharge consuming >3000 mg/d sodium are unavailable. These estimates are needed to power a full-scale trial.

Proportion of Eligible and Willing Participants

Participating in a feeding trial for 12 weeks requires commitment. Although currently we do not know the optimal low sodium intake <3000 mg/d for HF, it is unlikely that sodium intake >3000 mg/d would be beneficial. Thus, out of ethical considerations, we will include patients who continue to consume ≥3000 mg/d sodium 2 weeks post discharge, despite education and instructions at discharge. The proportion of patients with HFrEF who are willing to participate meet the trial eligibility criteria and are eating ≥3000 mg sodium daily

is not known. This knowledge is essential to project enrollment rate in a full-scale trial.

Level of Sodium Intake and Relative Risk Between Trial Arms

A wide separation in sodium intake between trial arms, for example, more than the average American diet versus 1000 mg/d, would increase the probability to detect a difference in event rates. However, both extremely high- and extremely low-sodium intake would raise ethical and logistic concerns.^{24–29,34–36} Americans consume ≈3700 mg sodium daily,⁴² whereas the US Department of Agriculture and Department of Health and Human Services recommend 2300 mg/d in general and 1500 mg/d for blacks, those aged >50 years, or those with hypertension, diabetes mellitus, or kidney disease.⁴³ In a recent report, the Institute of Medicine concluded that there is inadequate evidence to suggest dietary sodium <1500 mg/d in any population and that, specifically for HF, more data are needed to establish appropriate targets.⁴⁴ Therefore, testing the recommended level for at-risk populations (1500 versus 3000 mg/d) would achieve a reasonable balance between ethical and trial concerns. No data exist on the effect of 1500 versus 3000 mg/d sodium diets on HFrEF outcomes to inform sample size for a full-scale clinical trial.

Long-Term Adherence, Safety, and Follow-Up

To assess efficacy of sodium restriction, the trial cannot rely on patients trying to reduce salt intake, as these attempts

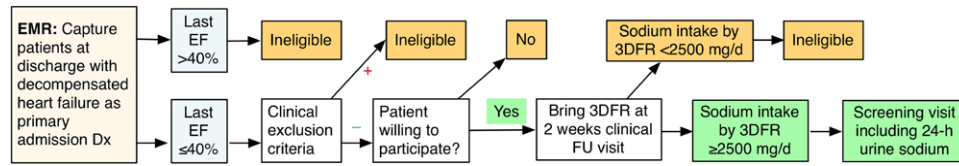


Figure 2. Design of the registry component. 3DFR indicates 3-day food record; EF, ejection fraction; EMR, electronic medical record system; and FU, follow-up.

are likely going to be inconsistent at best or not effective at worst. Provision of prepared food is preferable in a Phase III efficacy trial. A longer trial would increase power to detect a treatment effect, but adherence with provided food would likely decrease over time. The adherence of the target population with the provided meals during prolonged periods (eg, 12 weeks) is unknown. There are concerns about the effects of low dietary sodium on renal function and blood pressure in patients with HF taking diuretics,¹⁹ especially older adults, who constitute the majority of patients with HF. Currently, there are limited data to support the safety of strict sodium restriction in HF during a long-term (12 week) intervention.

A full-scale trial will need to include several follow-up visits to assess adherence with provided food and safety. However, to maintain logistic and fiscal feasibility of the trial, data on the minimum acceptable number and spacing of visits are required.

Fluid Intake

Data on the effects of fluid intake on outcomes and neurohormonal activation in HF are limited. One study suggested that fluid intake ≤ 1 L/d with a sodium intake of ≈ 2760 mg/d is associated with better outcomes and neurohormonal profile.²⁷ However, other studies suggest no difference in symptoms, weight, functional capacity, quality of life (QoL),⁴⁵ or time to achieve clinical stability.⁴⁶ To isolate the effect of sodium intake, we will advise participants to consume ≤ 2 L of fluids daily, as this level is recommended by most HF guidelines. However, we recognize that the evidence behind this recommendation is weak and more definitive data are needed.

Clinical Trial Pilot Study Design

Registry Component

We will approach consecutive patients with HFrEF with EF $\leq 40\%$ during admission for a primary diagnosis of acute HF (Figure 2). We will ask patients who do not meet any exclusion criteria (Table 2) to participate in a 12-week feeding trial followed by a 12-week follow-up period. We will instruct willing patients to complete and bring back a 3-day food record (3DFR) at the 2-week, standard-of-care postdischarge visit. The study dietitian will analyze food records using the Nutritionist Pro Diet Analysis software (Axxya Systems LLC, Redmond, WA) that allows for analysis of daily intake for 90 nutrients. The database of food and ingredients includes 52000 foods, including 500 brands from >7 manufacturers (www.nutritionistpro.com).

This component will estimate the proportion of (1) discharged patients with HFrEF who are both eligible and willing to participate and (2) among these patients, the proportion consuming ≥ 3000 mg/d 2 weeks post discharge, despite instructions. Our experience with previous acute and postdischarge HF trials has been that $>50\%$ of eligible patients will be willing to participate. Sodium intake data on patients with HF in United States are limited. In the National Institutes of Health-funded Education and Supportive Partners Improving Self-Care (ENSPIRE) trial, patients with HF consumed an average of 3600 to 4200 mg sodium daily by 24-hour urinary sodium excretion at baseline.⁴ However, these data are from chronic patients with HF. Patients admitted for HF receive dietary instructions. Therefore, the proportion of patients consuming >3000 mg/d sodium 2 weeks post discharge is unknown.

Because large-scale screening with 24-hour urine sodium would be impractical for a full-scale trial, we will prescreen patients with 3DFR.⁴⁷ This validated tool will provide an

Table 2. Eligibility Criteria for Entry in the Randomized Pilot Trial Component

Inclusion Criteria	Exclusion Criteria
Age ≥ 21 y at screening	Institutionalized patients
Recent (≤ 1 y) EF $\leq 40\%$	Communication barriers, including cognitive impairment; inability to communicate and understand and cooperate with the protocol
Admission for HF in the past 2 wk	Severe noncardiac illness that compromises life expectancy within the next 12 mo or the ability to participate in the study (eg, severe hepatobiliary disease, cancer undergound chemotherapy or radiotherapy)
Standard HF treatment, including ACEI/ARB, β -blockers, and aldosterone antagonists, unless contraindicated or intolerant	Any medical or surgical procedure planned in the next 6 mo
Able to consume research diet (eg, no dysphagia)	Participants planning to move to a different state within 6 mo
Systolic blood pressure ≥ 100 mm Hg	Participation in any other experimental protocol
>3000 mg/d sodium excretion (by 24-h urinary sodium)	Renal replacement therapy or stage 4 or 5 chronic kidney disease

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; and HF, heart failure.

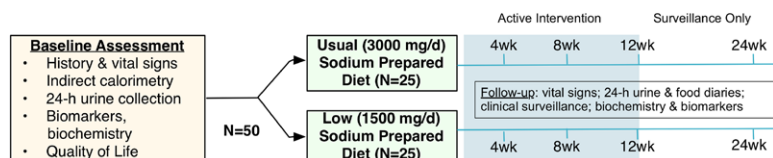


Figure 3. Design of the randomized pilot trial component.

estimate of sodium consumption to select patients for 24-hour urine sodium screening to determine eligibility for the randomized pilot trial component. The rationale for a lower sodium eligibility threshold (≥ 2500 mg/d) in the 3DFR is that food records systematically underestimate sodium intake compared with 24-hour urine collection,⁴⁷ especially in patients with HF taking loop diuretics.⁴⁸ Average daily sodium excretion by 24-hour urine was >750 mg higher than reported intake among 62 patients with HF receiving loop diuretics.⁴⁸ Therefore, we expect that most participants exceeding the 2500 mg/d sodium threshold by 3DFR will have ≥ 3000 mg/d sodium excretion by 24-hour urine collection. This approach will reduce the number of urine collections and improve feasibility of screening and at the same time confirm sodium intake by more objective testing.

Randomized Pilot Trial Component and Follow-Up Surveillance

Eligible patients will enter the randomized, double-blind pilot trial. We plan to randomize 50 patients to receive food with either 1500 or 3000 mg/d sodium for 12 weeks, followed by an additional 12 weeks of surveillance (Figure 3). Meals will be prepared under the nutritional and sodium-content surveillance of PurFoods, LLC (Ankeny, IA, www.purfoods.com), in a US Department of Agriculture–certified kitchen. PurFoods will ship all prepared meals to participants. Meals will be stored under temperature-controlled conditions at all times during shipment and storage, until delivered to the subject. Patients will be given food diaries to record any additional food or drink, as well as the portion of the prepared meal that they have consumed, and will be instructed to <2 L/d fluid restriction. The purpose of this component is to estimate

1. overall retention of patients on study and adherence with prepared food;
2. trends and between-arm differences in all-cause mortality, readmissions, and emergency department (ED) visits; N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels; QoL and satisfaction with food; and
3. safety of 1500 and 3000 mg/d sodium diets, including adverse events, vital signs, and biochemistry panels at 4, 8, and 12 weeks.

After the 12-week intervention, we plan 12 additional weeks of surveillance, including 2 office visits at weeks 1 to 2 and 12, and a phone call at 3 to 4 weeks.

Study Procedures

Screening and Baseline Visits

The dietitian will review the 3DFR and interview participants about diet habits and preferences to customize meal plans. Research coordinators will provide education for 24-hour

urine collection. If the urine collection shows >3000 mg/d sodium excretion, the patient will be invited to come back for the baseline visit (vital signs, blood draws, and QoL questionnaire) and start receiving individualized meal plans (either 1500 or 3000 mg/d).

Randomization

Participants will be randomly allocated to 3000 versus 1500 mg/d sodium diets with small blocks (6 subjects per block) permuted block randomization process to ensure balance between arms. The entire process will be managed by a study member without patient or clinical involvement and will be completely masked to investigators.

Masking Procedures

Coordinators, investigators, and participants will be blinded to arm assignment (double-blind design), and only an administrative member of the study team and the dietitians (from Stony Brook and PurFoods) responsible for the preparation of the meals will be aware of this. Also, to ensure blinding and neutrality, follow-up 24-hour urinary sodium values will not be disclosed to research personnel or participants until the end of the study. Adherence will be reinforced through standardized scripts.

Dietary Intervention

Participants will be given instructions to complete the 3DFR, including details about food preparation, brands, and amounts, and any dietary supplements (nutrients and herbals). Visual guides corresponding to portion size will be provided, including household measuring cups and spoons, rulers, etc, to help the recording process and quantification. The dietitians will review the 3DFR for fluid consumption, and participants will be able to continue to drink selected beverages (ie, water, coffee, and tea) but within the limit of 2 L/d total. Limits will be put on the type and amount of condiments to keep within study parameters. For caloric intake, basal metabolic rate will be calculated using indirect calorimetry. Protein intake will be adjusted to 0.8 g/kg of body weight.⁴⁹ All other nutrients will be between 70% and 100% of reference intake.⁴⁹ After randomization, patients will receive controlled diets that provide either 3000 or 1500 mg/d sodium for 12 weeks. All diets will have consistent macronutrients and caloric content throughout the feeding period to ensure weight maintenance. The menus will be planned with the collaboration of the 2 dietitians from Stony Brook and PurFoods. Food delivery will be conducted twice a week, with alternative arrangements in case of inadvertent circumstances. Participants will be instructed during all interactions to only eat what is provided to them. They will be also asked to keep a detailed diary of (1) any nonstudy food items consumed and (2) the proportion of the provided food consumed at each meal, with the option to provide reasons for deviations. To encourage adherence, the dietitians will keep in contact with the participants during phone or clinic visits with

standard scripts for reinforcement. Select discretionary seasonings (without sodium), but not salt, will be allowed. The caloric, fat, protein, and carbohydrate value of the meals will stay consistent throughout the trial.

Assessment of Adherence

Participants will be instructed to record (1) every nonstudy item they have consumed; (2) the proportion of study food consumed per meal; and (3) fluid intake, on a daily food diary, which will be reviewed at the 4 weekly visits. This approach was successful in the Dietary Approaches to Stop Hypertension (DASH) trial.⁵⁰ Between the clinic visits, the dietitian will contact subjects by phone to assess the diet adherence and to resolve any meal-related issues. Table 3 summarizes the schedule of visits and procedures.

Study End Points

Primary End Points: Patient On-Study Retention and Adherence

A longer (eg, 6 months) trial would increase power to detect a treatment effect. However, retention and adherence with study food would likely decline over time, compromising intention-to-treat analyses. For example, in the Treatment of Mild Hypertension Study,⁵¹ adherence with sodium intake declined over time as evident from the serial 24-hour urinary sodium determinations. Currently, there are no data to inform the optimal duration of an outcome-driven feeding trial in HF. Previous studies either provided food for a short time or relied on educational interventions to modify sodium intake. In the proposed study, we will track (1) retention, defined as the proportion of patients remaining on the study in the absence of clinical or safety events and (2) adherence, through patient diaries and 4 weekly 24-hour urine collections. In a recent HF study,⁴ the correlation between 3DFR-derived and 24-hour urine sodium was modest ($r < 0.5$), despite statistical significance and 3DFR systematically underestimated sodium intake, supporting therefore the need for objective assessment

of sodium intake adherence at least in the pilot phase. Our goal is to inform the optimal balance between trial duration and retention/adherence rates for a full-scale trial.

Secondary End Point: Clinical Outcomes

The secondary end point will be the composite of all-cause mortality, hospitalization, or emergency department visits, whichever occurs first (time-to-event analysis), to generate the most clinically relevant evidence for the appropriate level of sodium intake in HF. We opted for all-cause hospitalizations and emergency department visits because reduction in HF-related events might be offset by non-HF-related but still intervention-related events, for example, renal impairment or hypotension. In a recent study,³¹ patients with HF consuming < 2800 mg/d sodium were less likely to be admitted for HF compared with those consuming ≥ 2800 mg/d; however, there was no difference in all-cause admissions. Patients and caregivers will be asked to report any interim event at any institution to the study team during the regular encounters. We will contact the patient or family in case of a patient no-show. Additional data for healthcare system encounters will be collected through electronic health records and contact with patients and caregivers. For encounters in outside hospitals, we will obtain information through patient inquiry and a copy of the medical record will be requested for adjudication.

Tertiary End Points: NT-proBNP Levels and Patient-Oriented Outcomes (QoL and Food Palatability)

NT-proBNP levels are closely associated with prognosis in patients with HF regardless of functional class.⁵² Therefore, we will measure NT-proBNP levels, a sensitive, responsive to treatment, and widely available HF prognostic biomarker, as a surrogate for efficacy. QoL is an important therapeutic goal in HF, especially for dietary interventions, as food palatability may affect QoL.⁵³ Thirst and sodium appetite are physiological sensations aroused by perceived lack of water and sodium. Sodium deprivation stimulates aldosterone production, which promotes renal sodium conservation,⁵⁴ and angiotensin II

Table 3. Schedule of Study Visits and Procedures

Procedure	Screening (Day 2)	Baseline (Day 0)	Wk 2 (Phone)	Wk 4	Wk 6 (Phone)	Wk 8	Wk 10 (Phone)	Wk 12	Post Wk 2	Post Wk 2 (Phone)	Post Wk 12
Baseline diet assessment (3DFR)	X	X
24-h urine collection	X	X	...	X	...	X	X	...	X
Indirect calorimetry	X
History, physical examination, vital signs, and anthropometrics	...	X	...	X	...	X	...	X	X	...	X
Biochemistry, NT-proBNP, and HF biomarkers	...	X	...	X	...	X	...	X	X	...	X
Review of food diaries	X	...	X	...	X
Adherence assessment	X	X	X	X	X	X
Food palatability	X	...	X	...	X
Quality of life (KCCQ)	...	X	X
Adverse and clinical events	X	X	X	X	X	X	X	X	X

3DFR indicates 3-day food record; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; and NT-proBNP, N-terminal-pro-B-type natriuretic peptide.

stimulates sodium appetite and thirst (but does not, on its own, selectively stimulate the ingestion of sodium relative to water).^{55,56} Many patients with HF experience increases in sodium appetite,⁵⁷ further complicating any attempt to improve sodium restriction adherence. Few studies have investigated the effects of dietary sodium on QoL of patients with HF. In 1 study of 12 weeks of sodium and fluid restriction, thirst, appetite, and QoL were not affected.⁵⁸ However, 21% of patients complained about sodium restriction. Two studies reported better QoL among patients after the prescribed diet.^{29,59} We plan to investigate the effects of the prescribed diets both on QoL and food palatability.

Safety and Postintervention Surveillance

Several studies with sodium restriction in patients with HFrEF have reported a drop in blood pressure^{24,28,34} and worsening renal function^{25–29,34,60,61} in the low-sodium arm. We will collect data on blood pressure and renal function serially at 4, 8, and 12 weeks and withdraw those participants who meet prespecified safety criteria, despite appropriate modification of HF therapy. We will keep tracking blood pressure and renal function in the 2 planned office visits (at 1–2 weeks and 12 weeks post intervention) during the postintervention surveillance period.

Safety end points will include (1) systolic blood pressure (SBP) drop >20 mmHg for those with baseline SBP >120 mmHg, >10 mmHg for those with baseline SBP 100 to 120 mmHg, and any SBP <100 mmHg with symptoms, at any visit (planned or unplanned); (2) creatinine increase >0.5 mg over baseline at any visit. For patients meeting these criteria (except SBP <90 mmHg), medical therapy will be adjusted accordingly and patients will be re-evaluated after 1 week; if these effects persist, patients will be withdrawn. Patients with SBP <90 mmHg will be withdrawn immediately. Allergic responses or food poisoning events will be considered as safety events.

Because we cannot exclude the possibility of delayed or prolonged effects of dietary sodium on clinical and safety events, we will follow-up all participants for an additional 12 weeks, with 2 clinic visits and an interim phone, after the end of the intervention.

Analytic Plan

On-study retention (primary end point) will be calculated according to the Kaplan–Meier principle, that is, patients meeting a clinical event (death, admission, and emergency department visit) will be censored as on-study at the time of the event. For retention calculation purposes, safety end points will be considered as withdrawals. We will calculate adherence

(coprimary end point) on the basis of adherent days (days during which all study food was consumed and no nonstudy items were consumed) divided by the total number of days in the trial. A $\geq 90\%$ adherence will be considered adequate. In studies with fixed sodium intake,^{62,63} 90% of ingested sodium was excreted in the urine across a wide range of sodium intake (1500–4600 mg/d). Therefore, we expect average 24-hour urinary sodium to be 1350 mg in the 1500-mg/d group and 2700 mg in the 3000-mg/d group. The random variation of 24-hour urine excretion had a coefficient of variation of $\approx 15\%$ in these studies, estimated from the published data.^{62,63} We will therefore consider values outside the $\pm 15\%$ limits, that is, outside 1150 to 1550 mg for the 1500 mg/d sodium arm and 2300 to 3100 mg for the 3000 mg/d sodium arm, as evidence of nonadherence. We will provide average values per patient and per arm over time and the proportion of values outside the prespecified range.

Discussion

The results of the pilot study will provide necessary information to assess the feasibility and design of a efficacy trial of dietary sodium intake in HFrEF, including information on (1) expected patient willingness and eligibility rates; (2) patient retention and adherence with prepared food; (3) expected event rates in the target population and between the trial arms; (4) safety; and (5) appropriate follow-up scheduling to balance scientific rigor and feasibility. If the proposed pilot study suggests key impediments to a phase III trial, this will (1) prevent a costly, problematic full-scale trial and (2) provide the basis for alternative trial designs.

If the pilot results are encouraging, this will lead to an outcome-driven clinical trial to assess the efficacy of 2 different levels of sodium intake (3000 versus 1500 mg/d) in patients with HF with EF <40% recently discharged after an acute HF episode, with clinical events, healthcare resource utilization, and QoL as the end points of interest (Figure 4). Our hypothesis is that in recently hospitalized patients with HFrEF, a sodium intake of 1500 mg/d when compared with 3000 mg/d for 12 weeks will result in (1) reduction in the composite of death and all-cause hospitalization; (2) reduction in healthcare resources utilization; and (3) significant improvement in QoL. We expect the results of this study to inform HF guidelines and similar studies in HFpEF. If the full-scale trial proved efficacy of the low-sodium diet, then the low-sodium DASH diet would be a reasonable recommendation for HF, backed by advocacy efforts.

Adherence is an important component of any dietary intervention. Consistent results in terms of adherence to specified diet are difficult to produce even with coordinated efforts.⁴

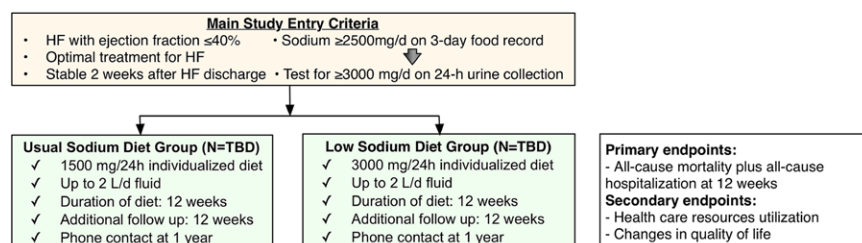


Figure 4. Outline of the proposed full-scale clinical trial. HF indicates heart failure. TBD indicates to be determined.

In our pilot study, we will provide prepared meals to reduce the uncertainty associated with educational and sociobehavioral components related to preparation of prescribed diets. However, for practical implementation of any level of sodium restriction, the effectiveness of behavior modification interventions and adherence to sodium restriction over time has to be explicitly tested.

This study will not include patients with HFpEF. There are no data on the appropriate level of sodium intake in these patients either, and sodium restriction is recommended on the basis of consensus. However, the underlying pathophysiology of HFpEF, especially in older adults who constitute the majority of patients with HFpEF, is different than HFrEF. For example, NT-proBNP levels are less elevated in patients with HFpEF, trials with neurohormonal blockade have not shown to improve outcomes, and unlike patients with HFrEF who have mostly cardiovascular adverse outcomes events, outcomes related to comorbidity play a more significant role in patients with HFpEF. Therefore, the appropriate level of sodium intake in this group of patients should be investigated in dedicated, well-designed studies.

If no separation trends in the efficacy end point are observed (mortality, readmission, and emergency department visits) in our study, this might signify the need to design a noninferiority trial. Finally, if safety concerns arise, we will propose a dose-finding study with multiple arms; these arms will be narrowly spaced in terms of dietary sodium intake spread to establish the safest level.

In trials of sodium intake in HFrEF, a lower sodium diet (1800 mg/d) was associated with increased all-cause mortality and HF readmission rates risk compared with a higher sodium diet (2800 mg/d). Although a single group has conducted all these trials and the results have not been independently validated, the potential impact of sodium intake recommendations on HF outcomes cannot be overemphasized. With over a million HF hospitalizations annually in United States, even a fraction of the treatment effect observed in previous studies, for example, a 20% relative risk between sodium arms, could lead to dramatic reductions in the absolute number of deaths and hospitalizations from HF and substantial savings for the healthcare system.

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Disclosures

None.

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KEY WORDS: clinical trial ■ heart failure ■ outcomes assessment ■ sodium, dietary

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