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## Comparing Sodium Intake Strategies in Heart Failure: Rationale and Design of the PROHIBIT Sodium (PREvent adverse Outcomes in Heart failure By limITing Sodium) Study

Javed Butler, MD, MPH<sup>1</sup>, Lampros Papadimitriou, MD, PhD<sup>1</sup>, Vasiliki Georgiopoulou, MD, MPH<sup>2</sup>, Hal Skopicki, MD, PhD<sup>1</sup>, Sandra Dunbar, RN, DSN<sup>3</sup>, and Andreas Kalogeropoulos, MD, MPH, PhD<sup>2</sup>

<sup>1</sup>Division of Cardiology, Stony Brook University, Stony Brook, NY

<sup>2</sup>Division of Cardiology, Emory University, Atlanta, GA

<sup>3</sup>Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA

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## Comparing Sodium Intake Strategies in Heart Failure: Rationale and Design of the PROHIBIT Sodium (PREvent adverse Outcomes in Heart failure By limITing Sodium) Study

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

**Correspondence to** Javed Butler, MD MPH, Cardiology Division, Health Sciences Center, T16, Rm080, Stony Brook, NY, 11794-8160. Telephone No: 631-444-1062; Fax No: 631-444-1054. javed.butler@stonybrookmedicine.edu.

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None.

## Current Patterns of Sodium Intake Among Patients with Heart Failure

Current data indicate limited adherence with recommended sodium restriction among HF patients. In a recent interventional study, when instructed to limit sodium intake to 2500 mg/day, HF patients averaged a daily intake of 2700 to 3900 mg/day by 24-h urinary sodium, depending on the assigned arm, after 8 months of intervention.<sup>4</sup> Sodium intake reduction is difficult to adhere to even among patients with symptomatic HF, with less than one-third of patients reporting sodium intake < 2500 mg/day by 3-day food diaries, which underestimate actual sodium intake.<sup>4</sup> 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-h urinary sodium excretion.<sup>5</sup> Sodium consumption below 2000 mg/day is difficult to achieve even with dietitian education,<sup>14</sup> and studies have demonstrated that gender<sup>15</sup> and race<sup>16</sup> affect dietary preferences and adherence to sodium restriction recommendations in patients with HF.

## The Challenge of Sodium Restriction in Heart Failure: Need for a Phase III Clinical Trial

Heart failure 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 sympathetic<sup>17</sup> and the renin angiotensin aldosterone system (RAAS)<sup>18</sup> creating a vicious cycle of sodium and water retention despite fluid overload (Figure 1).<sup>18, 19</sup> Moreover, inappropriate vasopressin levels are seen in HF. There is evidence that the natriuretic system is impaired early in the course of HF,<sup>20, 21</sup> causing sodium and water retention, which in turn provides the physiologic 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.<sup>22</sup> In animal studies, a sodium-restricted diet leads to RAAS activation,<sup>23</sup> and data suggest that dietary sodium restriction is associated with further neurohormonal activation in patients with HF also.<sup>24–29</sup> It might be argued that further sympathetic and RAAS activation is less clinically relevant in the presence of RAAS-blocking agents and beta-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 beta-blocker treatment.<sup>22</sup> In the Heart Outcomes Prevention Evaluation (HOPE) trial, high plasma renin activity was also an independent predictor of mortality in patients at high cardiovascular risk regardless of allocation to ramipril or placebo.<sup>30</sup> These data suggest that neurohormonal activation may nevertheless be important regardless of drug treatments that modulate neurohormonal activation.

Few studies, and only one in US, have tested the impact of different sodium intake on clinical outcomes in HF.<sup>5, 26–28, 31–33</sup> Observational and randomized studies have yielded contradicting results (Table 1). A number of single-center randomized studies<sup>26–28, 34–36</sup> 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 post-discharge HF patients, and in the largest of these studies there were multiple treatment arms,

increasing thus the potential for type I error.<sup>19</sup> Although a significant proportion of patients in these studies were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, few were on  $\beta$ -blockers or aldosterone antagonists. These shortcomings limit the generalizability of the findings.

Thus, although it seems reasonable to restrict sodium below  $<3000$  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 HF patients can only be addressed through a well-designed trial testing different levels of sodium restriction. However, critical knowledge gaps exist in order to develop a Phase III trial of sodium restriction in HF.

## **KNOWLEDGE GAPS TO DESIGN A PHASE III CLINICAL TRIAL OF SODIUM RESTRICTION IN HEART FAILURE: 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 EF (HFpEF) is inadequate,<sup>37</sup> the actual concerns with sodium restriction in HF have been raised for patients with HF and reduced EF (HFrEF) in the previous literature due to the neurohormonal activation and fluid retention with diuretic resistance in these patients.<sup>38</sup> Enrolling chronic stable HFrEF patients would require a large sample size due to the lower event rates in this population.<sup>39, 40</sup> Patients with acute HF have mortality and readmission rates of up to 15% and 30% respectively within 90 days post-discharge, necessitating further research.<sup>41</sup> These event rates increase power to detect an effect on outcomes within a feasible active feeding period (e.g. 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 post-discharge vulnerable phase. Waiting longer may lead to inclusion of lower risk patients.

Most acute HF studies reported cumulative 90-to-180 day outcomes.<sup>41</sup> Thus, event rates among HFrEF patients who are not readmitted 2 weeks after discharge can only be indirectly deducted from these data. Outcomes data specifically among HFrEF patients 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 below 3000 mg/day 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 3000mg/d sodium 2 weeks post-discharge, despite education and instructions at discharge. The proportion of HFrEF patients who are willing to participate, meet the trial eligibility criteria, and are eating 3000mg 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, e.g. more than the average American diet vs. 1000 mg/d, would increase the probability to detect a difference in event rates. However, both very high and very low sodium intake would raise ethical and logistic concerns.<sup>24–29, 34–36</sup> Americans consume ~3700 mg sodium daily<sup>42</sup>; whereas the US Department of Agriculture (USDA) and Department of Health and Human Services recommend 2300 mg/day in general and 1500 mg/day for African Americans, those over age 50, or those with hypertension, diabetes, or kidney disease.<sup>43</sup> In a recent report, the Institute of Medicine concluded that there is inadequate evidence to suggest dietary sodium <1500 mg/day in any population and that, specifically for HF, more data are needed to establish appropriate targets.<sup>44</sup> Therefore, testing the recommended level for at-risk populations (1500 mg/d) vs. (3000 mg/d) would achieve a reasonable balance between ethical and trial concerns. No data exist on the effect of 1500- vs. 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 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 over prolonged periods (e.g. 12 weeks) is unknown. There are concerns about the effects of low dietary sodium on renal function and blood pressure in HF patients taking diuretics,<sup>19</sup> especially older adults, who constitute the majority of HF patients. Currently, there are limited data to support the safety of strict sodium restriction in HF over a longer-term (12-week) intervention.

A full-scale trial will need to include a number of 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 is 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/day with a sodium intake of ~2760 mg/d is associated with better outcomes and neurohormonal profile.<sup>27</sup> However, other studies suggest no difference in symptoms, weight, functional capacity, quality of life (QoL),<sup>45</sup> or time to achieve clinical stability.<sup>46</sup> To isolate the effect of sodium intake, we will advise participants to consume 2L 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 HFrEF patients with EF  $\geq$  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 post-discharge visit. The study dietitian will analyze food records by 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 52,000 foods, including 500 brands from over 7 manufacturers ([www.nutritionistpro.com](http://www.nutritionistpro.com)).

This component will estimate the proportion of (1) discharged HFrEF patients 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 post-discharge HF trials has been that  $>$ 50% of eligible patients will be willing to participate. Sodium intake data on HF patients in US are limited. In the NIH-funded Education and Supportive Partners Improving Self-Care (ENSPIRE) trial, patients with HF consumed an average of 3600 to 4200mg sodium daily by 24-h urinary sodium excretion at baseline.<sup>4</sup> However, these data are from chronic HF patients. Patients admitted for HF receive dietary instructions. Therefore, the proportion of patients consuming  $>$ 3000mg/d sodium 2 weeks post discharge is unknown.

Because large-scale screening with 24-urine sodium would be impractical for a full-scale trial, we will pre-screen patients with 3DFR.<sup>47</sup> This validated tool will provide an estimate of sodium consumption to select patients for 24h urine sodium screening to determine eligibility for the randomized pilot trial component. The rationale for a lower sodium eligibility threshold ( $\leq$  2500 mg/d) in the 3DFR is that food records systematically underestimate sodium intake compared to 24-hour urine collection,<sup>47</sup> especially in HF patients taking loop diuretics.<sup>48</sup> Average daily sodium excretion by 24-hour urine was  $>$ 750mg higher than reported intake among 62 HF patients receiving loop diuretics.<sup>48</sup> Therefore, we expect that most participants exceeding the 2500-mg/d sodium threshold by 3DFR will have  $\geq$  3000 mg/d sodium excretion by 24-h 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](http://www.purfoods.com)), in a USDA 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 in

order to record any additional food and/or drink as well as the portion of the prepared meal that they have consumed and will be instructed to a <2L/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-arms differences in all-cause mortality, readmissions, and emergency department (ED) visits; NT-pro-B-type natriuretic peptide (NT-proBNP) levels; quality of life (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 1–2 and 12 and a phone call at 3–4 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-h 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, QoL questionnaire) and start receiving individualized meal plans (either 1,500 mg or 3,000 mg/d).

**Randomization**—Participants will be randomly allocated to 3000- vs. 1500-mg/d sodium diets with a 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 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 quantitation. The dietitians will review the 3DFR for fluid consumption and participants will be able to continue to drink selected beverages (i.e. water, coffee, tea) but within the limit of 2 L/day 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.<sup>49</sup> All other nutrients will be between 70–100% of reference intake.<sup>49</sup> 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 two 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 non-study 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 non-study 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.<sup>50</sup> Between the clinic visits the dietitian will contact subjects by phone in order to assess the diet adherence and to resolve any meal related issues. Table 3 summarizes the schedule of visits and procedures.

## Study Endpoints

**Primary Endpoints - Patient On-Study Retention and Adherence**—A longer (e.g. 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<sup>51</sup>, adherence with sodium intake declined over time as evident from the serial 24-h 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-h urine collections. In a recent HF study,<sup>4</sup> the correlation between 3DFR-derived and 24h-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 Endpoint - Clinical Outcomes**—The secondary endpoint 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 e.g. renal impairment or hypotension. In a recent study,<sup>31</sup> HF patients consuming  $< 2800$  mg/d sodium were less likely to be admitted for HF compared with those consuming  $\geq 2800$  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 Endpoints – NT-proBNP levels and Patient-Oriented Outcomes (QoL and Food Palatability)**—NT-proBNP levels are closely associated with prognosis in HF patients regardless of functional class.<sup>52</sup> 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.<sup>53</sup> Thirst and sodium appetite are physiologic sensations aroused by perceived lack of water and sodium. Sodium deprivation stimulates aldosterone production, which promotes renal sodium conservation<sup>54</sup> and angiotensin II stimulates sodium appetite and thirst (but does not, on its own, selectively stimulate the ingestion of sodium relative to water).<sup>55, 56</sup> Many HF patients experience increases in sodium appetite,<sup>57</sup> further complicating any attempt to improve sodium restriction adherence. Few studies have investigated the effects of dietary sodium on QoL of HF patients. In one study of 12 weeks of sodium and fluid restriction, thirst, appetite, and QoL were not affected.<sup>58</sup> However, 21% of patients complained about sodium restriction. Two studies reported better QoL among patients following the prescribed diet.<sup>29, 59</sup> We plan to investigate the effects of the prescribed diets both on QoL and food palatability.

### Safety and Post-intervention Surveillance

A number of studies with sodium restriction in HFrEF patients have reported a drop in blood pressure<sup>24, 28, 34</sup> and worsening renal function<sup>25–29, 34, 60, 61</sup> 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 two planned office visits (at 1–2 weeks and 12 weeks post-intervention) during the post-intervention surveillance period.

Safety endpoints will include (1) systolic blood pressure (SBP) drop >20mmHg for those with baseline SBP >120mmHg, >10mmHg for those with baseline SBP 100–120mmHg, and any SBP <100mmHg with symptoms, at any visit (planned or unplanned); (2) creatinine increase >0.5mg over baseline at any visit. For patients meeting these criteria (except SBP <90mmHg), 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 <90mmHg will be withdrawn immediately. Allergic responses or food poisoning events will be considered 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 two clinic visits and an interim phone, after the end of the intervention.



## Analytic Plan

On-study retention (primary endpoint) will be calculated according to the Kaplan-Meier principle, i.e. patients meeting a clinical event (death, admission, emergency department visit) will be censored as on-study at the time of the event. For retention calculation purposes, safety endpoints will be considered as withdrawals. We will calculate adherence (co-primary endpoint) on the basis of “adherent” days (days during which all study food was consumed and no non-study items were consumed) divided by the total number of days in the trial. A 90% adherence will be considered adequate. In studies with fixed sodium intake,<sup>62, 63</sup> 90% of ingested sodium was excreted in the urine across a wide range of sodium intake (1500 to 4600 mg/d). Therefore, we expect average 24-h 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-h urine excretion had a coefficient of variation (CV) of ~15% in these studies, estimated from the published data.<sup>62, 63</sup> We will therefore consider values outside the  $\pm 15\%$  limits, i.e. outside 1150–1550 mg for the 1500-mg/d sodium arm and 2300–3100 mg for the 3000-mg/d sodium arm, as evidence of non-adherence. We will provide average values per-person 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; (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 two different levels of sodium intake (3000 vs. 1500 mg/day) in HF patients with EF <40% recently discharged after an acute HF episode, with clinical events, health care resource utilization, and QoL as the endpoints of interest (Figure 4). Our hypothesis is that in recently hospitalized HFrEF patients, a sodium intake of 1500 mg/day as compared to 3000 mg/day for 12 weeks will result in: (1) reduction in the composite of death and all-cause hospitalization; (2) reduction in health care 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.<sup>4</sup> In our pilot study, we will provide prepared meals to reduce the uncertainty associated with educational and socio-behavioral 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 HFpEF patients. 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 HFpEF patients, is different than HFrEF. For example, NT-proBNP levels are less elevated in HFpEF patients, trials with neurohormonal blockade have not shown to improve outcomes, and unlike HFrEF patients who have mostly cardiovascular adverse outcomes events, outcomes related to comorbidity play a more significant role in HFpEF patients. 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 endpoint are observed (mortality, readmission, emergency department visits) in our study, this might signify the need to design a non-inferiority 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 to 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 US, even a fraction of the treatment effect observed in previous studies, e.g. 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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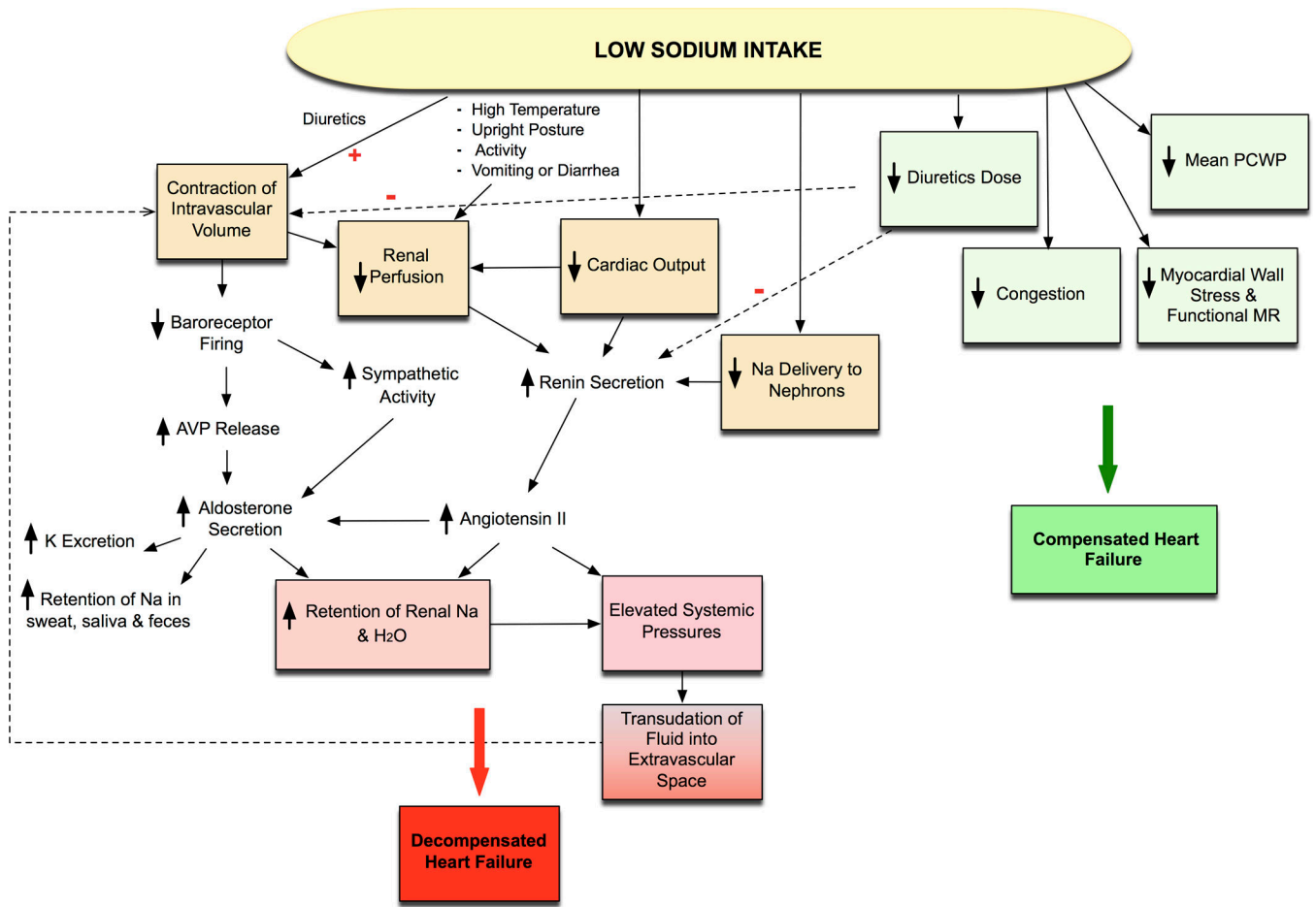
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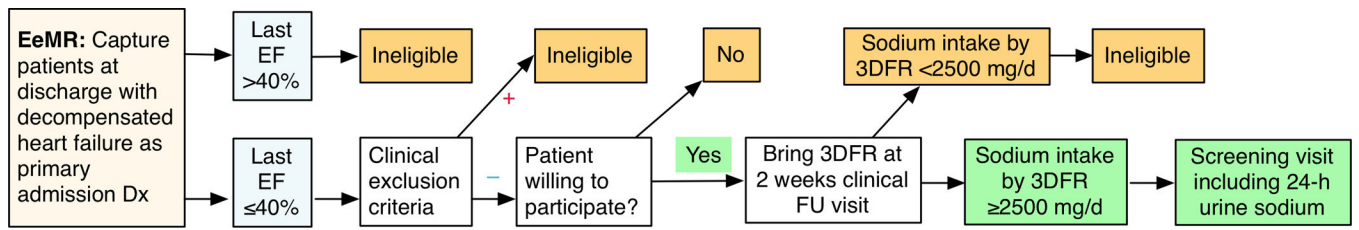
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**Figure 1. Effects of Sodium Intake in Heart Failure**

Low sodium intake may have varied effect on heart failure. Intravascular volume contraction improves hemodynamics and reduces diuretic requirement, congestion, and myocardial wall stress, leading to compensated heart failure. 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: arginine vasopressin; H<sub>2</sub>O: water; Na: sodium; K: potassium; MR: mitral regurgitation; PWCP: pulmonary wedge capillary pressure; red plus: diuretic action enhances contraction of intravascular volume; red minus: low diuretic doses reduce hormonal activation and contraction of intravascular volume). Reproduced with permission from *Circulation*. 2012;126:479–485.<sup>19</sup>



**Figure 2. Design of the Registry Component**

3DFR: 3-day food record; EeMR: Emory electronic medical record system; EF: ejection fraction; FU: follow-up



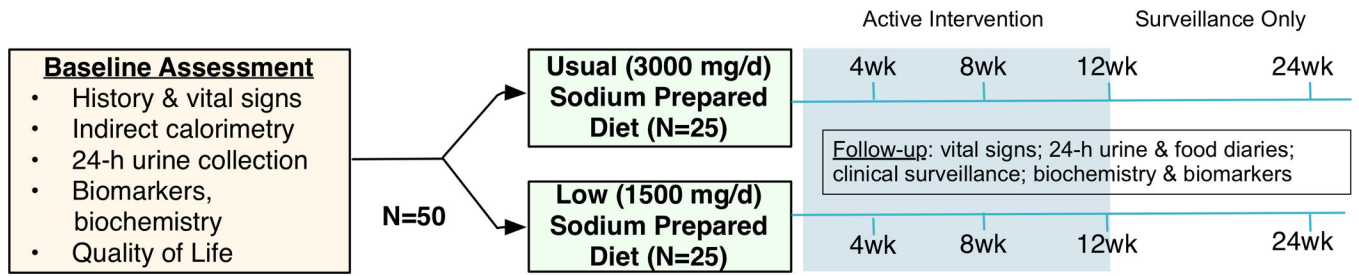


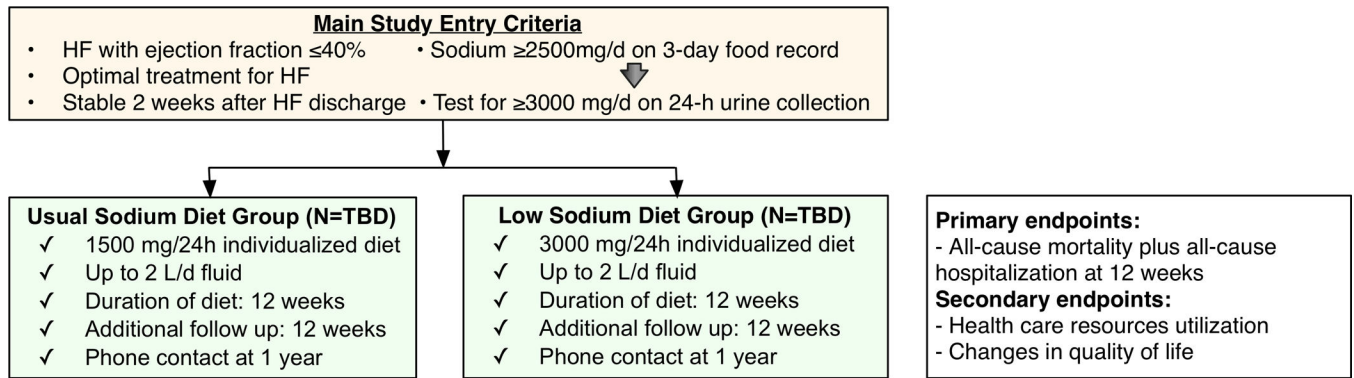
Figure 3. Design of the Randomized Pilot Trial Component

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**Figure 4. Outline of the Proposed Full-Scale Clinical Trial**

Table 1

## Studies Investigating the Impact of Sodium Intake on Outcomes in Heart Failure

Source	Design	Intervention	Clinical Impact
Paterna 2008 <sup>26</sup>	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	<b>6 months (death, death + readmission):</b> Group 1: 7.6%, 12.7% Group 2: 26.3%, 39.5%
Paterna 2009 <sup>27</sup>	Randomized N 410; NYHA II post discharge; EF: <35%	Group A & B: 2760 mg Na + 500 / 250 mg F Group C & D: 1840 mg Na + 500 / 250 mg F Fluid Intake: 1 L/d Group E & F: 2760 mg Na + 500 / 250 mg F Group G & H: 1840 mg Na + 500 / 250 mg F Fluid Intake: 2 L/d	<b>6 months (death, death + HF readmission):</b> <b>A:</b> 1.9%, 7.7% <b>B:</b> 3.9%, 29.4% <b>C:</b> 9.8%, 49.0% <b>D:</b> 13.7%, 54.9% <b>E:</b> 9.6%, 51.9% <b>F:</b> 12.0%, 58.0% <b>G:</b> 11.5%, 71.1% <b>H:</b> 15.7%, 78.4%
Parrinello 2009 <sup>28</sup>	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	<b>12 months (readmission, death+ readmission):</b> Group 1: 12%, 16% Group 2: 44%, 64%
Arcand 2011 <sup>31</sup>	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	<b>12 months HF readmission:</b> 5±3% (1), 5±3% (2), 17±6% (3) <b>36 months HF readmission:</b> 12±6% (1), 15±7% (2), 46±11% (3)
Lennie 2011 <sup>5</sup>	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	<b>12 months (death + admission + ED visits):</b> NYHA I–II 1 vs. 2: higher event-rate; NYHA III–IV 1 vs. 2: lower event rate
Son 2011 <sup>32</sup>	Observational N 232 NYHA I–IV EF: <40%	Group 1: <3000 mg/d Na Group 2: 3000 mg/d Na Fluid intake: not mentioned	<b>12 months (death + cardiovascular admission + cardiovascular ED visits):</b> Group 1 vs. 2: lower event rate
Song 2014 <sup>33</sup>	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	<b>12 months (death + all-cause admissions):</b> 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

HF: heart failure; ED: emergency department; EF: ejection fraction; F: furosemide; NYHA: New York Heart Association

**Table 2**

## Eligibility Criteria for Entry in the Randomized Pilot Trial Component

Inclusion criteria		Exclusion criteria	
1	Age ≥ 21 years at screening	1	Institutionalized patients
2	Recent ( 1 year) EF ≥ 40%	2	Communication barriers, including cognitive impairment; inability to communicate and understand and cooperate with the protocol
3	Admission for HF in the past 2 weeks	3	Severe non-cardiac illness that compromises life expectancy within the next 12 months or the ability to participate in the study (e.g. severe hepatobiliary disease, cancer undergound chemo- or radiotherapy)
4	Standard HF treatment, including ACEI/ARB & beta-blockers & aldosterone antagonists, unless contraindicated or intolerant	4	Any medical or surgical procedure planned in the next 6 months
5	Able to consume research diet (e.g. no dysphagia etc.)	5	Participants planning to move to a different state within 6 months
6	Systolic blood pressure < 100 mmHg	6	Participation in any other experimental protocol
7	>3000 mg/d sodium excretion (by 24-h urinary sodium)	7	Renal replacement therapy or Stage 4 or 5 chronic kidney disease

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; EF: ejection fraction; HF: heart failure

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 (3-day food record)	X										X
24-h urine collection	X			X		X		X	X		X
Indirect calorimetry	X										
History, physical exam, vital signs, 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

KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: N-terminal-pro-B-type natriuretic peptide