

EDITORIAL COMMENT

# The Uncertainty of Sodium Restriction in Heart Failure



## We Can Do Better Than This\*

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*Clinical vignette: a young woman develops a dilated cardiomyopathy with severe impairment of left ventricular (LV) function and corresponding symptoms consistent with advanced heart failure (HF). She is treated effectively with evidence-based medical therapy and experiences recovery of LV systolic function with at least a doubling of the ejection fraction (EF) and near complete resolution of her symptoms. She remains with reduced EF heart failure, New York Heart Association (NYHA) functional class II symptoms. She has been advised to continue indefinitely with Guideline-Directed Medical Therapy (GDMT)/device therapy and to follow a sodium restricted diet. Now stable after the acute illness, she reaches out to her physician to inquire about the necessity for sodium restriction as it is a nearly intolerable diet for her and comes at considerably more expense.*

*How would you proceed?*

- A. Advise her to unfailingly follow a sodium restricted diet (<1,500 mg/day)
- B. Liberalize sodium intake (<3,000 mg/day)
- C. Advise a reasonable diet as tolerated (goal Na intake ~4,000 mg/day)

**I**t is doubtful that there is unanimity in the community regarding the correct response to the above vignette—and therein lies the concern. Many of us have followed the traditional HF edict that

emphasizes the necessity to restrict sodium as a means of controlling excess volume, treating decompensation, and thwarting new episodes of congestion. Classic physiology has established salt and water retention as an important consequence of neurohormonal activation in HF and as a compensatory response to preserve cardiac output via Starling mechanisms. This modest compensatory response is quickly overwhelmed by the ensuing volume overload provoking symptoms of HF. Concomitant increases in wall stress lead to further ventricular remodeling and the disease is perpetuated. Subsequent heuristic logic has inferred that restricting sodium would be beneficial in the treatment of HF. Especially in those who are volume overloaded, legions of clinical experience have convinced us that patients fare better with sodium restriction and volume reduction.

This theme of sodium restriction has been a bedrock statement in all iterations of the American College of Cardiology/ American Heart Association (ACC/AHA) HF clinical practice guidelines and for the prevailing ACC Foundation/AHA 2013 Heart Failure Guidelines sodium restriction remains extant—albeit with much less vigor than before (1). The traditional logic has been so clear that to call for proof seemed heretical. Yet, an exhaustive search of available literature does not provide evidence supporting a threshold sodium intake, or the appropriate context for sodium restriction, that is, for prevention, at the time of hospitalization, and/or for advanced disease. There may even be a signal of harm (2). Thus, the more fundamental question becomes the very premise for sodium restriction. Does it exist?

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\*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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In this issue of *JACC: Heart Failure*, Doukky et al. (3) evaluate HART (Heart Failure Adherence

and Retention Trial) for evidence of sodium intake. This behavioral intervention trial compared self-management counseling versus education alone on the outcomes of death or HF hospitalizations. Multiple sites were involved enrolling 903 patients from 2001 to 2004. The study intervention involved 18 2-h group meetings of approximately 10 patients each over the course of 1 year. At each meeting, education was sourced from 18 Heart Failure Tip Sheets endorsed by the AHA. Among the various sheets was information on dietary sodium restriction. The a priori threshold for sodium restriction was an intake <2,000 mg/day based on a standardized food frequency questionnaire. There were an insufficient number of patients achieving a sodium restriction <2,000 mg, so a revised threshold for sodium restriction, empirically set at 2,400 mg/day, was used. The investigators have used these data to evaluate the association of a sodium restricted diet of <2,400 mg/day versus a sodium unrestricted diet, that is, >2,400 mg/day, on heart failure outcomes. Propensity matching was used to align patients for disease severity, diuretic use, ejection fraction, important comorbidities, and medical therapy. The consequent analysis identified an association between restricted sodium intake and a higher risk of death or heart failure (HF) hospitalization (hazard ratio: 1.83; 95% confidence interval: 1.21 to 2.84;  $p = 0.004$ ) driven mostly by an increase in the rate of HF hospitalization and a nonsignificant increase in the rate of death. The investigators surmise that recommendations for sodium restriction should be further downgraded in future guidelines and that a multicenter randomized trial is needed.

Now what? These are not the first data to question the advisability of sodium restriction in HF. d'Almeida et al. (4) randomized 75 patients with acute decompensated reduced EF HF to aggressive fluid, <1,000 ml/day, and sodium, <800 mg/day, restriction and found no significant difference in short-term outcomes with the exception of thirst in the intervention group. Conversely, Hummel et al. (5) in a very careful analysis provided a low-sodium Dietary Approaches to Stop Hypertension (DASH) diet to clinically stable and well compensated patients with HF with preserved EF over a 21-day period. The low sodium DASH diet reduced systolic blood pressure and was associated with improved diastolic function, improved arterial elastance and better ventricular-arterial coupling. Other investigators have even suggested that sodium loading at the time of decompensation may promote a more effective diuresis (6). A recently published clinical trial design, PROHIBIT (Prevent Adverse Outcomes in Heart Failure by

Limiting Sodium Study) included a tabular summary of the small trials done to-date to determine the benefit or harm of sodium restriction and the correct threshold. Some of these data show worsening neurohormonal activation with sodium restriction whereas other data, mostly observational, are consistent with worsening HF in the setting of dietary sodium excess (7).

It is evident that at present we have no clear direction. The current study adds to the momentum to call the question but does not provide answers. The patients studied in the HART database and reported by Doukky et al. (3) do not reflect the contemporary era of HF therapy and, despite very careful propensity matching, it remains likely that sodium restriction as shown in the present data serves more as a marker for advanced disease. Certainly, there are no data to infer causality. These data also highlight the difficulties in doing a proper dietary intervention trial. Food questionnaires that require self-reporting are problematic. The questionnaire used by the HART investigators "spotted" each patient at 1,250 mg/day sodium intake to account for sodium that is not apparent in the queried items and only 59 food choices were considered. In the PROHIBIT trial, the number of candidate food items is measured in the thousands. Measuring urinary sodium in a large number of patients is likely to be cost-prohibitive, but it at least provides objective data regarding sodium intake. Given the close interface of neurohormonal activation and sodium homeostasis, achieving an optimal background of neurohormonal antagonism is necessary in any rigorous trial, but what is optimal neurohormonal antagonism? Controlling dietary intake, specifically by providing all meals, which would nearly guarantee a true low-sodium diet, is likely not scalable to large numbers, again because of expense. The PROHIBIT study will compare 1,500 mg versus 3,000 mg/day diets over 24 weeks with the primary endpoints of dietary adherence, quality of life, and food palatability. Biomarkers will be assessed as well. But this trial, as a pilot, will begin with only 50 patients and then determine if a larger trial can be performed. The trials called for by Doukky et al. (3) and being piloted by the PROHIBIT investigators highlight the challenges and near impossibility of designing and executing a trial of sufficient rigor to fully address this important but vexing question.

At a time when more care is directed by clinical practice guideline statements, such statements increasingly need to be driven by evidence. On the issue of sodium restriction in HF, the 2012 European Heart Failure Guidelines officially offered no comment on the basis of insufficient evidence (8). The 2013

ACCF/AHA Heart Failure Guidelines endorsed sodium restriction as noted, but on the question of evidence, the ACC/AHA 2013 Heart Failure Guidelines impugned both the scant amount of data and the inconsistent quality of the data—typically with small numbers, nonrandomized, and without the benefit of optimal evidence-based guideline-directed medical therapy. As stated in those guidelines, “... these limitations make it difficult to give precise recommendations about daily sodium intake and whether it should vary with respect to the type of HF (e.g., HFrEF versus HFpEF), disease severity (e.g., NYHA class), HF-related co-morbidities (e.g., renal dysfunction), or other characteristics (e.g., age or race)...” The final recommendation varied according to the stage of HF. For stages A and B HF, alignment with the AHA recommendation of 1,500 mg/day was deemed appropriate as a means to prevent disease. For stages C and D HF, the data are insufficient; however, “...because sodium intake is typically high (>4 g/d) in the general population, clinicians should consider some degree (e.g., <3 g/d) of sodium restriction in patients with stage C and D HF for symptom improvement...”(1).

We can do better than this. The DASH diet is notably more expensive and consumes a greater percentage of available income for those with a lower socioeconomic status who frequently are at higher risk for HF (9). We should be certain of the need for

sodium restriction in those patients for whom such a diet may create hardship. Even more importantly, given the burden of HF and the billions of dollars expended each year to provide care, we cannot allow such a fundamental question as dietary recommendations to remain unanswered. If any component of the burden of hospitalization is driven by errant dietary directives, then we have done a disservice to the community and are now compelled to pursue this question and provide answers as soon as possible.

In our exuberance over new drugs and devices that may lead to modest improvements in HF outcomes, perhaps our greater opportunity is to revisit our core recommendations to patients. Those admonitions should be unwaveringly correct. That is not the case at present for sodium restriction. The advice many of us consistently give to our patients and their families may not be correct. We can do better than this. The time has come for a well-designed, appropriately powered dietary intervention trial. How can we not proceed?

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**KEY WORDS** guidelines, heart failure, sodium