Study of Dietary Intervention Under 100 MMOL in Heart Failure

SODIUM-HF

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ACC 2022
• Funding from:
# SODIUM-HF team

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Heart Failure and Dietary Sodium

- HF is associated with:
  - neurohormonal activation
  - abnormalities in autonomic control
  - sodium and water retention
- Clinicians have focused on dietary sodium and water restriction to minimize the risk of volume overload for > 100 years
- Little evidence supports this practice
Dietary Sodium Intake

LOW SODIUM INTAKE

- High temperature
- Upright posture
- Activity
- Vomiting or diarrhea

Diuretics

Contraction of Intravascular Volume

Baroreceptor Firing

↓ AVP Release

↑ Aldosterone Secretion

↑ K Excretion

↑ Retention of Na in Sweat, Saliva, & Feces

Renal Perfusion

↓ Baroreceptor Firing

↑ AVP Release

↑ Sympathetic Activity

↑ Aldosterone Secretion

↑ K Excretion

↑ Retention of Na in Sweat, Saliva, & Feces

↑ Retention of Renal Na & H2O

Decompensated Heart Failure

Elevated Systemic Pressures

Transudation of Fluid into Extravascular Space

Na Delivery to Nephrons

↓ Renin Secretion

Cardiac Output

↓ Diuretics Dose

↓ Mean PCWP

Congestion

↓ Myocardial Wall Stress & Functional MR

Compensated Heart Failure

Gupta et al. Circulation 2012
Dietary sodium: Observational studies

HF Hospitalization

- ≤1.9 g sodium/day
- 2.0-2.7 g sodium/day
- ≥2.8 g sodium/day

Log rank p = 0.001

Mortality

- ≤1.9 g sodium/day
- 2.0-2.7 g sodium/day
- ≥2.8 g sodium/day

Log rank p = 0.022

n= 123 patients with HF

Dietary sodium reduction: RCT

Systematic review:
9 studies
All < 100 patients
Mixed interventions

No consistent results on any outcome

Intervention group: Dietary recommendations for sodium restriction to <2400 mg/day provided by a dietitian.
Control Group: Usual dietary recommendations for dietary sodium reduction.

Mahtani JAMA: Internal Medicine 2018
Evaluate the effects of a low-sodium diet, compared to usual care, in patients with HF, on a 12 month outcome of:

- **Primary Endpoint:** Composite clinical outcome of All-cause mortality, CV hospitalizations, CV ED visits

- **Secondary Endpoints:**
  - Quality of life (by KCCQ)
  - Exercise capacity (by 6MWT)
  - NYHA class
SODIUM-HF: Trial Design

841 patients with heart failure (NYHA II-III) on optimally tolerated medical therapy

Eligible patients identified via inclusion/exclusion criteria

Participants provide written consent and complete a baseline evaluation

RANDOMIZATION (open label)

1500 mg/day Na  Usual care

Clinical visits (12 months) and phone follow-up (12 months)

Primary Endpoint:
Composite outcome of all-cause mortality, CV hospitalizations, or CV ED visits

Secondary Endpoints:
Change in KCCQ, 6-minute walk test, and NYHA class
SODIUM-HF: Sites

26 sites
Canada, Mexico, Chile, Colombia, Australia, New Zealand
SODIUM-HF: In/Exclusion criteria

**SODIUM Inclusion Criteria**

- 18 years or older and willing/able to sign informed consent.
- Confirmed diagnosis of HF (both reduced and preserved systolic function eligible)
- NYHA Class II-III
- On optimally tolerated medical therapy according to CCS guidelines

**SODIUM Exclusion Criteria**

- Patients with an average dietary intake of <1500 mg Na/day
- Serum sodium <130 mmol/L
- Hemodialysis-dependent chronic renal failure (or glomerular filtration rate <20 mL/min)
- Uncontrolled thyroid disorder or end-stage hepatic failure
- Cardiac device or revascularization procedure in previous month or planned in the next 3 months
- Hospitalization due cardiovascular causes in the previous 1 month
- Uncontrolled atrial fibrillation (resting heart rate >90 bpm)
- Active malignancy with an expected life expectancy <2 years
- Another comorbid condition or situation which could preclude compliance with the protocol
- Enrolled in another interventional research study
SODIUM-HF: Intervention

Patients randomized to one of two study arms:

1. Low-sodium containing diet
   - <1500 mg daily (<65 mmol/daily)

2. Usual care
   - general advice to limit dietary sodium as provided in routine clinical practice
• Samples of **menus** at different levels of energy requirement (1400-2200 kcal)
• Patient might **interchange** any of the food items included in the menus by another one included in the recommended foods lists of the same food group that the original one included in the menu.
• Food **individualized** to local region/country
• If energy requirements were adjusted during a follow-up visit, new sample menus were provided.
• **3 day food records** for each visit
Sample size:
- Based on the primary composite outcome
- Expected event rate of 25% in usual care arm
- 30% reduction in the primary outcome
- 80% power, two-sided type I error rate of 0.05
- Total enrollment of 992 patients

The Data Monitoring Committee
- Reviewed data from the first 500 participants with complete 12-month follow-up
- Mandate was to advise on futility (if conditional power was <20%) or efficacy (two-sided p-value <0.001).
- This review, in addition to an assessment of trial operational feasibility and the impact of the COVID-19 pandemic, led to an early stopping with the last patient enrolled on December 09, 2020 and complete 12 month follow-up in December 2021.
## SODIUM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low sodium diet group</th>
<th>Usual care group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=397</td>
<td>n=409</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>66 (57–73)</td>
<td>67 (58–75)</td>
</tr>
<tr>
<td><strong>Female Sex</strong></td>
<td>127 (32%)</td>
<td>141 (34%)</td>
</tr>
<tr>
<td><strong>Geographical region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>230 (58%)</td>
<td>241 (59%)</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>79 (20%)</td>
<td>78 (19%)</td>
</tr>
<tr>
<td>Mexico, Chile, and Colombia</td>
<td>88 (22%)</td>
<td>90 (22%)</td>
</tr>
<tr>
<td><strong>Diagnosed with HF for ≥1 year</strong></td>
<td>269 (68%)</td>
<td>282 (69%)</td>
</tr>
<tr>
<td><strong>Hospitalised for HF in past 12 months</strong></td>
<td>129 (32%)</td>
<td>141 (34%)</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td>36 (28–48)</td>
<td>35 (27–50)</td>
</tr>
</tbody>
</table>
# SODIUM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Low sodium diet group n=397</th>
<th>Usual care group n=409</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>187 (47%)</td>
<td>186 (45%)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>156 (39%)</td>
<td>173 (42%)</td>
</tr>
<tr>
<td>Diabetes (type 1 or 2)</td>
<td>132 (33%)</td>
<td>156 (38%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vital signs and physical findings</th>
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</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>30 (26–35)</td>
<td>31 (27–36)</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>69 (61–76)</td>
<td>69 (61–77)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118 (105–129)</td>
<td>118 (104–130)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>eGFR, mL/min per 1·73m²</td>
<td>61 (46–75)</td>
<td>58 (42–71)</td>
</tr>
</tbody>
</table>
Primary Outcome

**CV related hospitalization/ED visit or all-cause mortality**

- **Low Sodium**: HR 0.89, 95% CI 0.63-1.26, p=0.33
- **Usual Care**:  

<table>
<thead>
<tr>
<th>Days from randomization</th>
<th>Low Sodium</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>397</td>
<td>409</td>
</tr>
<tr>
<td>60</td>
<td>377</td>
<td>394</td>
</tr>
<tr>
<td>120</td>
<td>359</td>
<td>379</td>
</tr>
<tr>
<td>180</td>
<td>347</td>
<td>367</td>
</tr>
<tr>
<td>240</td>
<td>336</td>
<td>350</td>
</tr>
<tr>
<td>300</td>
<td>323</td>
<td>339</td>
</tr>
<tr>
<td>360</td>
<td>312</td>
<td>326</td>
</tr>
</tbody>
</table>
Secondary Outcomes

All-cause mortality

HR 1.38
95% CI 0.73-2.60
p = 0.32

CV related hospitalization

HR 0.82
95% CI 0.54-1.24
p = 0.36

CV related ED visit

HR 1.21
95% CI 0.60-2.41
p = 0.6
Change in NYHA class

NYHA class:

I
II
III
IV

<table>
<thead>
<tr>
<th></th>
<th>NYHA class</th>
<th>Usual Care Baseline</th>
<th>Low Sodium 6 month</th>
<th>Usual Care 12 month</th>
<th>Low Sodium 12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1%</td>
<td>1%</td>
<td>9%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>II</td>
<td>69%</td>
<td>74%</td>
<td>66%</td>
<td>71%</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>29%</td>
<td>25%</td>
<td>25%</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td>IV</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Change in NYHA class OR (95% CI):

- 0.89 (0.89, 1.15)  (P = 0.389)
- 0.61 (0.43, 0.86)  (P = 0.005)
- 0.59 (0.40, 0.86)  (P = 0.006)
Change in KCCQ score

### KCCQ OSS

<table>
<thead>
<tr>
<th>Difference (CI)</th>
<th>Adjusted mean (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.42 (-1.1, 3.97)</td>
<td>6.00</td>
<td>0.277</td>
</tr>
<tr>
<td>3.38 (0.79, 5.96)</td>
<td>6.20</td>
<td>0.011</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Visit (month)</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>12</td>
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### KCCQ PLS

<table>
<thead>
<tr>
<th>Difference (CI)</th>
<th>Adjusted mean (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.86 (-2.2, 3.93)</td>
<td>3.70</td>
<td>0.585</td>
</tr>
<tr>
<td>3.77 (0.67, 6.87)</td>
<td>4.45</td>
<td>0.017</td>
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<th>Visit (month)</th>
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<td>6</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

Usual Care: 407, 330, 316
Low Sodium: 393, 309, 302

Usual Care: 402, 320, 308
Low Sodium: 383, 296, 295
Change in 6 min walk test distance

![Graph showing the change in 6 min walk test distance with significantly higher mean distance for Low Sodium compared to Usual Care at 6 and 12 months.](Image)

- **Usual Care**
  - 0 months: 332
  - 6 months: 215
  - 12 months: 191

- **Low Sodium**
  - 0 months: 328
  - 6 months: 204
  - 12 months: 199

**Difference (CI)**
- Usual Care: 13.8 (-1.4, 29.0) 0.076
- Low Sodium: 6.60 (-9.0, 22.2) 0.405
Limitations

• There was a sodium reduction of 415 mg / day by 12 months, and greater reductions in daily sodium or alternatively, enrolling patients with markedly higher dietary sodium may or may not produce different results.

• The trial was stopped early

• Lower than anticipated event rate

• Inclusion criteria were pragmatic and no NT-proBNP required
Conclusions

1. In ambulatory patients with HF, a dietary intervention to reduce sodium intake did not reduce clinical events.

2. There was a modest benefit on quality of life as measured by the KCCQ, and in NYHA class.

3. The 6-minute walk test was not statistically different between groups.
Implications

A low-sodium diet as done in SODIUM-HF:

• **Clinicians**: as a therapy to improve QOL
• **Patients**: as part of an overall health strategy
• **Guidelines**: informs with best evidence
• A special thank you to those patients who volunteered their time and effort to participate in the SODIUM-HF trial