In-Hospital Sodium Intake for Acute Decompensated Heart Failure

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked

areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Dr. Paul Heidenreich
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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix I for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABBREVIATIONS TABLE

ACC	American College of Cardiology
ADHF	Acute decompensated heart failure
BNP	Brain (or B-type) natriuretic peptide
BUN	Blood urea nitrogen
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESP	Evidence Synthesis Program
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HF	Heart failure
HSS	Hypertonic saline solution
ICU	Intensive care unit
IQR	Interquartile range
IV	Intravenous
KQ	Key Questions
LVEDD	Left ventricle end-diastolic diameter
LVEF	Left ventricular ejection fraction
MD	Mean difference
NMD	Net mean difference
NR	Not reported
NRCS	Nonrandomized comparative study
NS	Not significant
NT-proBNP	N-terminal pro-brain (or B-type) natriuretic peptide
NYHA	New York Heart Association
PRA	Plasma renin activity
RCT	Randomized controlled trials
RD	Risk difference
RoB	Risk of bias
RR	Relative risk
SD	Standard deviation
TDS-HF	Thirst Distress Scale for Heart Failure
VAS	Visual analogue scale

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) was asked by the Veterans Health Administration (VHA) Hospital Medicine for an evidence review on interventions affecting sodium intake (*eg*, dietary sodium restriction and supplemental sodium chloride [NaCl] given as either hypertonic saline solution [HSS] infusion or oral NaCl tablets) for adults ≥18 years of age hospitalized for acute decompensated heart failure (ADHF). For decades, standard non-pharmacologic inpatient care for people with ADHF has included restricting dietary sodium intake. However, evidence on the benefit of sodium restriction in the inpatient setting is mixed and there are concerns of harms, particularly related to antidiuretic effects and poor nutritional intake. In contrast, several studies suggest that the use of supplemental sodium in combination with an intravenous diuretic regimen may improve kidney function and reduce mortality in patients with ADHF. Veterans and providers could benefit from clear guidance on the use of sodium intake interventions to manage ADHF in an inpatient setting. VHA Hospital Medicine intends to use this ESP review to inform national clinical guidance on sodium restriction during acute care for patients with ADHF.

BACKGROUND

Heart failure (HF) affects around 26 million people worldwide,[1] 6.2 million people in the United States (US) alone, and 5% of Veterans.[2,3] HF is also a leading cause of hospitalization and rehospitalization in the US.[4] Despite progress in evidence-based pharmacotherapies and device interventions, most HF patients are hospitalized within 5 years of a diagnosis.[5,6] Approximately 38% of hospitalizations of people with HF are for ADHF,[5] which is characterized by sudden or gradual onset of signs and symptoms of HF with pulmonary and/or systemic congestion related to increased left- and right-heart filling pressures (*eg*, dyspnea, orthopnea, weight gain, and lower limb swelling). People experiencing ADHF require immediate hospitalization or unplanned office or emergency room visits to stabilize their symptoms.[7,8]

The goal of treatment for patients hospitalized with ADHF is to reverse acute hemodynamic abnormalities and improve symptoms.[9] This is predominantly achieved by using diuretics (*eg,* loop diuretics) and vasodilators that decrease venous congestion and volume overload.[9] In addition to pharmacological therapies, for decades the standard inpatient management of ADHF has included restricting dietary sodium.[10] However, there is no consensus in clinical guidelines on the threshold of sodium intake per day. For example, the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of Heart Failure recommends a daily sodium intake of <2.3 g/day, and the 2021 European Society of Cardiology (ESC) guidelines recommend sodium intake of <5 g/day.[11,12]

The motivation to restrict dietary sodium is based on the clinical observation that excess sodium contributes to fluid retention.[13] However, sodium restriction can also have a negative effect by activating antidiuretic and anti-natriuretic systems, which leads to further development of congestion.[14] There is also concern that patients find low-sodium food less flavorful, which could negatively affect nutrition intake and lead to poor adherence to a low-sodium diet. Low

sodium intake may also reduce blood pressure that in turn increases heart rate and negates the effects of beta-blockers.[14] Most data on restricted dietary sodium come from studies conducted in outpatient settings.[15] Few studies have formally evaluated the effect of sodium restriction in inpatient settings.

Conversely, supplemental sodium (either HSS infusion or oral NaCl tablets) has been proposed as an adjuvant therapy to loop diuretics to improve diuretic efficacy in patients hospitalized with ADHF.[16] This therapeutic approach is motivated by the observation that volume expansion by HSS as a resuscitation fluid leads to the mobilization of fluid to the intravascular compartment, which is followed by increased urine output.[18] Randomized controlled trials (RCTs) conducted in inpatient and outpatient settings found that HSS with loop diuretics improved kidney function, urine output, weight loss, and electrolyte abnormalities, in addition to decreased plasma renin activity (PRA), inflammatory markers, and biomarkers including brain (or B-type) natriuretic peptide (BNP) levels.[17-19] Despite the potential clinical benefits, inpatient providers may be hesitant to adopt HSS given conceptual concerns that increased sodium intake may exacerbate HF symptoms.[18]

To date, most systematic reviews on sodium intake interventions have included studies combining data from both inpatient and outpatient settings.[20,21] We, therefore, conducted a systematic review on comparative effectiveness of various oral and/or intravenous prescribed sodium intake interventions in the treatment for ADHF patients during hospitalization.

METHODS

TOPIC DEVELOPMENT

We worked with representatives from VHA Hospital Medicine and our Technical Expert Panel (TEP) to refine the review scope and develop the key questions (KQ). We focus on studies that report on prescribed sodium intake to manage ADHF in an inpatient setting (*eg,* restricted dietary sodium intake or HHS). We excluded studies that did not prescribe sodium intake (*eg*, epidemiologic evaluation where daily sodium intake was evaluated as a continuous measure). We evaluated the effect that prescribed sodium intake had on intermediate measures (*eg,* neurohormonal activation and weight), clinical outcomes (*eg,* time to clinical stability and clinical congestion score), and health service use outcomes (*eg,* length of hospital stay and 30-day rehospitalization).

KEY QUESTIONS

KQ1: Among adults hospitalized for decompensated heart failure, what is the comparative effectiveness of different prescribed sodium intake interventions?

KQ1a: Does effectiveness differ as a function of patient characteristics, including by age, comorbid conditions (kidney function, hypertension, diabetes, stroke, body mass index), existing versus new onset heart failure, preserved versus reduced ejection fraction or pre-hospitalization dietary sodium intake, sex, and race/ethnicity?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42023410146).

DATA SOURCES AND SEARCHES

We searched Medline (via PubMed), Embase, ClinicalTrials.gov, CINAHL, and the Cochrane Database of Systematic Reviews from inception to February 13, 2023. We used Medical Subject Headings (MeSH) and free text terms for *decompensated heart failure* and related terms, *prescribed sodium intake*, and *inpatient*, together with filters for primary studies (see Appendix A for complete search strategies). We ensured that known relevant publications were captured by our searches. Additional citations were sought from hand-searching reference lists of relevant systematic reviews and consultation with content experts.

STUDY SELECTION

Citations were uploaded into EndNote, where duplicates were removed. We screened citations in Abstrackr (http://abstrackr.cebm.brown.edu),[22] which has machine learning algorithms to prioritize relevant citations. To ensure a common understanding of the eligibility criteria, we ran pilot rounds of 100 citations at a time, where all team members screened the same citations, until we achieved acceptable agreement. Subsequently, we screened citations in duplicate with conflicts adjudicated during team meetings or by a third senior researcher. Based on empirical evidence, we stopped screening when all remaining unscreened abstracts had a prediction value of <0.40 (on a 0–1 scale) and subsequently 400 abstracts in a row were rejected.[22] Accepted

abstracts underwent full-text review using an evidence mapping process independently by 1 researcher with confirmation of excluded articles by a second researcher. When necessary, the reviewers consulted a third senior researcher. A list of studies excluded at full-text review, with rejection reasons, is provided in Appendix B.

Eligibility criteria are listed in Table 1. In brief, eligible study participants were ≥18 years of age, hospitalized and treated for ADHF. Eligible studies evaluated the effect of prescribed sodium intake interventions, including restricted dietary sodium intake and supplemental sodium intake. We included any dietary sodium restriction, any concentration of intravenous supplemental NaCl (including HSS, half-normal saline, *etc*), and any prescribed supplemental oral NaCl intake. Studies were excluded if they were conducted in the emergency department (without an inpatient component) or outpatient setting, if they did not report patient-level interventions (*eg*, comparison of hospital policies that were not explicitly uniformly applied), or did not include a comparison group. We included RCT, nonrandomized comparative studies (NRCS), and other comparative observational studies, whether prospective or retrospective, and regardless of whether they were adjusted for potential confounders. We analyzed laboratory or intermediate measures, clinical outcomes, and health care utilization. We analyzed all outcomes except 30-day rehospitalization and 30-day mortality from the first in-hospital measurement to the end of the intervention or discharge.

Table 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults ≥18 years of age hospitalized for treatment of decompensated HF, including for exacerbation of a chronic condition or new onset or previously undetected heart failure	• Advanced HF requiring mechanical support or heart transplant • Patients in cardiogenic shock • Patients undergoing surgery • Patients on dialysis
Intervention	Prescribed sodium intake • Restricted dietary sodium intake • Increased oral sodium intake (*eg*, NaCl tablets) • Intravenous saline (hypertonic saline, normal saline, hypotonic [half normal] saline, other saline)	• Patients not prescribed sodium intake (*eg*, a hospital policy without explicit implementation in individuals) • Sodium intake evaluated as a continuous variable • Subgroups of patients based on average sodium intake or hospital policy
Comparator	• More (including normal/typical) sodium intake (as a comparator of restricted dietary sodium intake) • Less oral sodium intake (as comparator of sodium tablets) • Other intravenous saline regimen (including none)	
Outcomes	• Laboratory/Intermediate measures o RAAS activation o Neurohormonal activation o Kidney function (*eg,* serum creatinine, eGFR) o BNP / NT-proBNP o Urine output o Weight loss o Nutritional intake (calories and fluid)	

	Inclusion Criteria	Exclusion Criteria

	• Clinical outcomes
	  ○ Clinical congestion score
	  ○ Supplemental oxygen levels
	  ○ Duration or timing of IV diuretics
	  ○ Time to clinical stability (as defined by study)
	  ○ Mortality (inpatient and 30 days)
	  ○ Quality of life (generic or HF-specific)
	  ○ HF-related symptoms (*eg,* thirst, shortness of breath)
	  ○ Prescribed guideline recommended therapy after discharge (*eg,* ACE inhibitors)
	• Adherence to prescribed diet in the inpatient setting.
	• Discharge location (*eg,* home, skilled nursing, cardiac rehab)
	• Health care utilization
	  ○ Length of hospital stay
	  ○ Hospital readmission related to HF within 30 days
	  ○ Cardiovascular related ED visit within 30 days
	  ○ Transfer to ICU (proxy for clinical deterioration)
	  ○ Mechanical ventilation (proxy for clinical deterioration)	

Timing	• In-hospital (preferentially end-of-treatment or hospital discharge) for all except 30-days post discharge for hospital readmission and mortality	
Setting	• Inpatient	• Emergency department only • Outpatient
Study Design	• RCT • Nonrandomized comparative study, prospective or retrospective	• Single group (noncomparative) studies • Association between sodium as a continuous measure (not a prescribed intervention) and outcomes
Other	• No language restriction • No country restriction	

Abbreviations. ACE inhibitors=angiotensin converting enzyme inhibitors; BNP=brain (or B-type) natriuretic peptide; ED=emergency department; eGFR=estimated glomerular filtration rate; HF=heart failure; ICU=intensive care unit; NT-proBNP=N-terminal pro-brain (or B-type) natriuretic peptide; NRCS=nonrandomized comparative study; RAAS=renin-angiotensin-aldosterone system; RCT=randomized controlled trial.

DATA EXTRACTION AND ASSESSMENT

We created a data extraction form in the Systematic Review Data Repository-Plus (SRDR+) online system (https://srdrplus.ahrq.gov). We extracted the following data from eligible studies: study design, setting, baseline population characteristics, amount, and duration of sodium intake (intervention and comparator), and intermediate, clinical, and health service use outcomes. All data extraction was first completed by 1 reviewer and then checked by a second reviewer. Disagreements were resolved by consensus or discussion with a third reviewer.

Study risk of bias was independently assessed by 2 reviewers using questions derived from the Cochrane Risk of Bias and the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tools (Appendix C).[23,24] For all study designs, we also evaluated whether the article was free of discrepancies, and reporting of patient eligibility criteria, protocols, setting,

and outcome assessments were sufficiently clear. For RCTs, we evaluated the method of randomization, allocation concealment, and whether intention-to-treat analysis was used. For NRCSs, we evaluated whether patients in the treated and comparison groups were similar and what strategies were used to deal with potential confounders.

SYNTHESIS AND CERTAINTY OF EVIDENCE

For both KQs, we compared results in study groups using relative risks (RR) for dichotomous outcomes. When a study had no events in 1 group, we calculated risk differences (RD). We compared continuous data using net mean differences (NMD; *ie*, difference-in-differences or between-intervention comparisons of within-intervention changes from baseline to follow-up) or mean differences (MD) between interventions for outcomes evaluated only post-intervention (*eg,* length of stay). When necessary, we estimated NMDs or MDs and their standard deviations from reported data, including from reported medians and ranges.[25,26] Adjusted analyses were preferentially extracted over unadjusted (crude) comparisons. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted meta-analyses using the restricted maximum-likelihood estimation (REML) random-effects models in the "meta" package for R version 4.3.0 (2023-04-21). Statistical heterogeneity was estimated using the I^2 statistic, which estimates the percentage of heterogeneity ascribed to statistical heterogeneity (not ascribed to random chance).

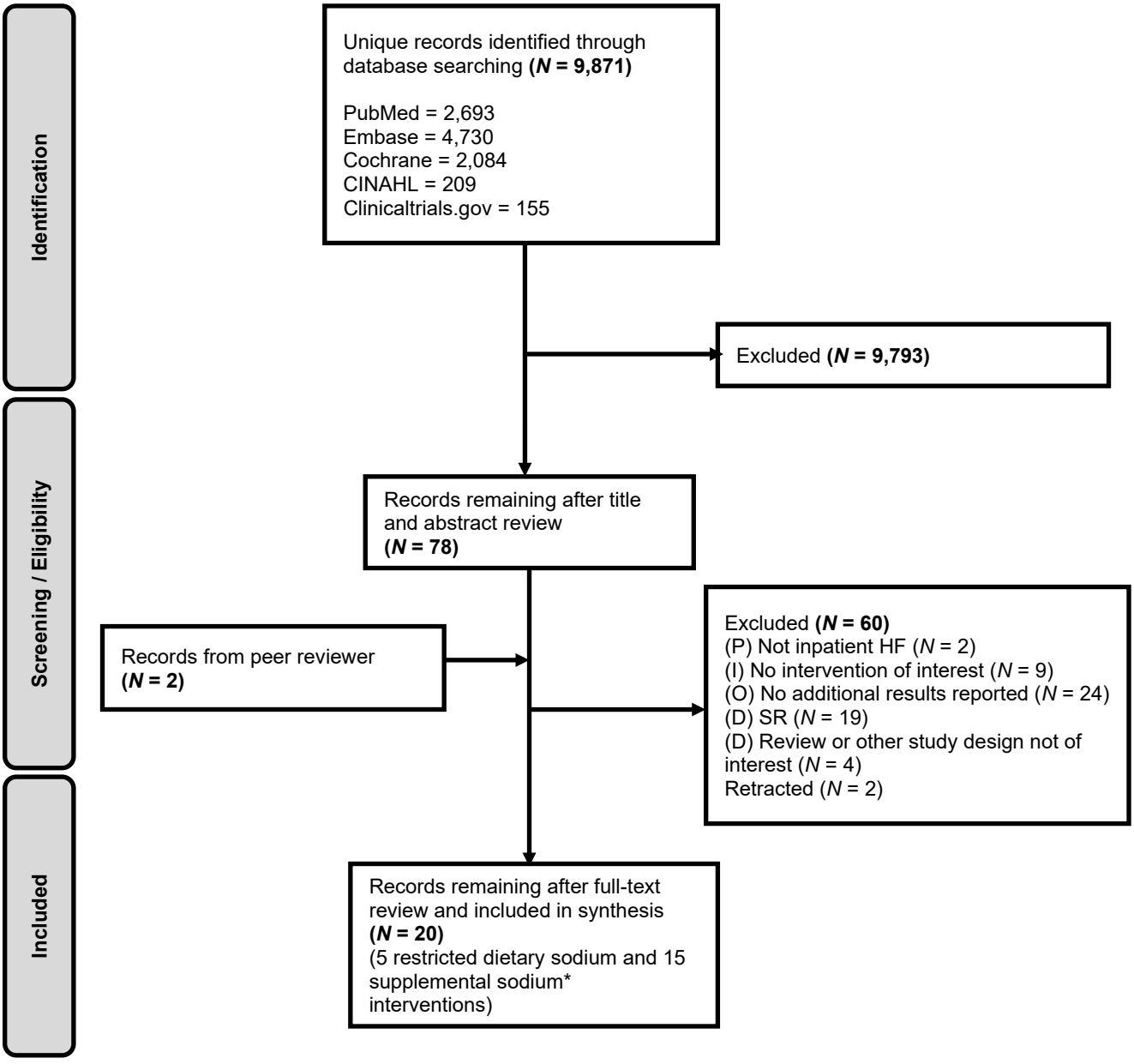
We assessed the certainty of evidence following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[27] We compiled key study findings in evidence profiles, which provide the basis for determination of certainty of evidence and summarize conclusions for outcomes prioritized by the stakeholders: serum creatinine, BNP, NT-pro BNP, caloric intake, clinical congestion score, weight loss, 30-day all-cause mortality, 30-day readmission, and length of hospital stay. Within each priority outcome, we considered the study design, the number of studies (and participants), methodological limitations (*ie,* risk of bias), directness of the evidence, precision of the findings, consistency across studies, and other issues. Based on these, we determined certainty of evidence, which could be high, moderate, or low. Where we found few or no comparable studies, we report that there is insufficient evidence to draw conclusions. We did not determine certainty of evidence for non-prioritized outcomes.

RESULTS

LITERATURE FLOW AND OVERVIEW

Of 9,871 unique records screened, 78 studies were accepted for full-text review. Upon reviewing these, 20 studies[28-47] were eligible (Figure1). The most common reasons for exclusion included records without additional outcomes of interest ($N = 24$), systematic reviews ($N = 19$), and not an intervention of interest ($N = 9$). We found no additional studies from the existing systematic reviews.

Figure 1. Literature Flowchart



Notes. *14 studies evaluated HSS and 1 study evaluated supplemental oral NaCl.
Abbreviations. D=design; HF=Heart failure; HSS=hypertonic saline solution; I=intervention; NaCl=sodium chloride; O=outcome; P=population; SR=systematic review.

Twenty studies were included and reported the effectiveness of dietary sodium intake[28,29,31,32 30] (*N* = 5), intravenous HSS with furosemide[33-46] (*N* = 14), or oral NaCl supplementation[47] (*N* = 1*)* for patients hospitalized with ADHF. Table 2 shows the summary characteristics of the eligible studies, Appendix D presents design details, and Appendix E presents baseline characteristics. There were 17 RCTs[28,29,31-33,35,37-43,45-47] and 3 NRCSs.[30,36,44] The 5 studies that evaluated the effectiveness of restricted dietary sodium intake intervention included 381 patients total (4 RCTs *N* = 191[28,29,31,32] and 1 NRCS *N* = 190[30]). Fourteen studies that evaluated the effectiveness of HSS with furosemide included 3,483 patients (13 RCTs *N* = 3,166[33-35,37-43,45-47] and 2 NRCSs *N* = 317[36,44]). One RCT evaluating HSS with furosemide conducted in Italy was large (*N* = 1,927).[37] One RCT (*N* = 65) compared oral NaCl with furosemide to furosemide alone and was included in the synthesis of the HSS studies.[47] Two studies[30,44] were published as conference abstracts. The majority of the studies were conducted in Europe (*N* = 9),[33-39,44,45] followed by South America (N = 5),[28,29,31,32,40] Asia (*N* = 3),[30,41,43] the Middle East (*N* = 2),[42,46] and the US (*N* = 1).[47]

Appendix F.1 describes the dietary sodium restriction interventions and Appendix F.2 describes the sodium supplementation with furosemide interventions. Appendix G presents categorical outcomes and Appendix H presents continuous outcomes.

Table 2. Summary Characteristics of Eligible Studies

Characteristics	Restricted Dietary Sodium Intake (*N* = 5)	Supplemental Sodium Intake[a] (*N* = 15)
Design		
RCT (*N* = 16)	4	13
NRCS (*N* = 3)	1	2[b]
Risk of Bias		
Low (*N* = 9)	2	8
Moderate (*N* = 4)	1	3
High (*N* = 6)	2	4
Countries		
Brazil (*N* = 5)	4	1
China (*N = 1)*	--	1
France (*N* = 1)	--	1
Italy (*N = 8*)	--	8
Iran (*N* = 1)	--	1
Japan (*N* = 2)	1	1
Turkey (*N* = 1)	--	1
United States (*N* = 1)	--	1
Interventions		
Restricted prescribed sodium diet (*N* = 5)	5	--
Hypertonic saline solution with IV furosemide (*N* = 14)	--	14
Oral NaCl tablets with IV furosemide (*N* = 1)	--	1
Intermediate Measures		
Aldosterone (*N* = 4)	1	3
BNP (*N* = 9)	2	7

Characteristics	Restricted Dietary Sodium Intake (*N* = 5)	Supplemental Sodium Intake[a] (*N* = 15)
Caloric intake[c] (*N* = 2)	2	--
Diuretics dose during hospitalization (*N* = 4)	3	1
Fluid intake (*N* = 1)	1	--
Kidney function (creatinine[d]) (*N* = 14)	3	11
Kidney function (blood urea nitrogen) (*N* = 15)	3	12
Kidney function (eGFR) (*N* = 6)	--	6
Kidney function (serum cystatin C) (*N* = 2)	--	2
NT-proBNP (*N* = 4)	1	3
Plasma renin activity (*N* = 2)	1	1
Renin (*N* = 1)	--	1
Serum sodium (*N* = 16)	3	13
Clinical Outcomes		
Clinical congestion score (*N* = 2)	2	--
Composite HF-related symptoms[e] (*N* = 1)	--	1
HF-related symptom (change in NYHA functional class) (*N* =3)	--	3
HF-related symptom (general well-being) (*N* = 1)	1	--
HF-related symptom (shortness of breath[f]) (*N* = 3)	1	2
HF-related symptom (thirst[g]) (*N* = 3)	2	1
All-cause mortality[h] (*N* = 8)	4	4
Percent of patients received diuretics in hospital (*N* = 2)	2	NA
Time on IV diuretics[i] (*N* = 2)	2	NA
Time to clinical stability (*N* = 1)	1	--
Urine output (*N* = 13)	1	12
Weight change (*N* = 18)	4	14
Adherence Outcomes		
Adherence to prescribed interventions (*N* = 2)	2	NA
Health Service Utilization Outcomes		
Length of hospital stay (*N* = 14)	3	11
Readmission (HF-related or all-cause) (*N* = 5)	3	2
Transfer to ICU (*N* = 1)	--	1

Notes. [a] 14 studies evaluated HSS and 1 study evaluated supplemental oral NaCl; [b] One retrospective and 1 prospective NRCS; [c] One NRCS reported the incidence of low caloric intakes (caloric intakes less than 20 kcal/kg per day); [d] One NRCS reported worsening of renal function, represented by an increase in serum creatinine ≥0.3 mg/dL; [e] Composite includes dyspnea, lower edema, weakness, palpitation and fatigue; [f] One RCT reported perceived dyspnea using visual analogue scale in dietary sodium interventions; [g] Perceived thirst using visual analogue scale or Thirst Distress Scale for Heart Failure (TDS-HF); [h] Reported in-hospital and at 30-day follow up; [i] The time to transition from IV to oral diuretic therapy.
Abbreviations. BNP=brain (or B-type) natriuretic peptide; eGFR=Estimated Glomerular Filtration Rate; HF=heart failure; HSS=hypertonic saline solution; ICU=intensive care unit; IV=intravenous; N=number; NA=not applicable (not an outcome of interest for supplemental NaCl interventions), NRCS=non-randomized comparative studies; NT-proBNP=N-terminal pro-brain (or B-type) natriuretic peptide; RCT=randomized clinical trials.

RESTRICTED DIETARY SODIUM INTAKE

Five studies (4 RCTs and 1 NRCS) conducted between 2008 and 2016 involving 381 analyzed participants (243 intervention, 138 control) compared a low sodium diet to higher sodium diet

(unrestricted in 4 studies).[28-32] All 5 studies had similar inclusion and exclusion criteria (Appendix D).

The 4 RCTs were all conducted in Brazil in a single-center hospital setting.[28,29,31,32] Patients in the RCTs were, on average, from 54 to 72.3 years old (Appendix E).[28,29,31,32] Most participants (in 3 of the 4 RCTs with data) were male (56.3–69%).[28,29,32] Only 2 RCTs reported data on race/ethnicity, with White participants making up 81% and 84% of the study samples (no data on other patients).[29,31] Three of the RCTs reported patient HF classification at baseline on the New York Heart Association (NYHA) scale, with 9.5% of patients being classified as NYHA Class II in 1 study,[31] 47% and 50.9% as NYHA Class III in 2 studies,[29,31] and 39.6% and 45% as NYHA Class IV in 2 studies.[29,31] One RCT reported baseline NYHA classification for patients randomized to the low sodium group only, with 28.6% and 71.4% of participants classified as NYHA Classes III and IV, respectively.[28] Three RCTs reported mean (SD) of left ventricular ejection fraction (LVEF) at baseline from 26.0% (8.7) to 60.9% (7.5),[29,31,32] and 1 study reported mean (SD) of left ventricle end-diastolic diameter (LVEDD) 63.2% (12.2).[32]

The single NRCS ($N = 190$) was conducted in Japan, included participants with a median age of 79 years, did not report information on race/ethnicity, and 100% of participants were classified as NYHA II-IV at baseline.[30]

Although it was not possible to blind participants or personnel, all the RCTs studies had independent outcome assessors. One of the RCTs was, in fact, "quasi-randomized" in that it allocated patients based on medical record number. It was downgraded for high risk of bias randomization and allocation concealment (Appendix C).[28] Another RCT was also judged to be at high risk of bias because of incomplete outcome data due to missing follow-up data.[32] The NRCS was presented in a conference abstract,[30] reported minimal methodological details, and was at moderate risk of bias.

Appendix F.1 describes the dietary sodium interventions. Prescribed sodium intake in the intervention groups ranged from a maximum of 0.8 g/day (in 3 studies) to 2.4 g/day (the NRCS). Sodium intake in higher sodium groups (*ie*, control) ranged from 2.8 g/day to 3-5 g/day. Two studies restricted fluid intake in both intervention and higher sodium diet groups (ranging from 800 mL/day and 1000 mL/day),[28,32] and 2 studies did not indicate any fluid restriction in both intervention and higher sodium diet groups.[29,31] In 2 studies, fluid intake did not differ between the intervention and control groups.[28,32] Two studies described implementing a restricted diet until discharge or hospital day 7 (whichever came first),[29,31] and in 1 study, patients received a restricted diet until hospital day 7 unless there was a clinical indication to end it early.[32] Two of the studies did not report the duration of the intervention.[28,32]

EFFECT OF RESTRICTED DIETARY SODIUM

In summary (Table 3), there was no statistically significant difference in serum creatinine (moderate confidence) or BNP (low confidence) between a low sodium and a higher sodium diet. Fewer calories were consumed by patients on a low sodium diet compared with a higher sodium diet (low confidence). There were no significant differences in clinical congestion score (moderate confidence), 30-day readmission, and length of stay between a low sodium diet and higher sodium diet (low confidence). Studies provided insufficient evidence (no conclusion) for

effects on NT-pro BNP, weight loss, and mortality, due to imprecise estimates and very serious methodological limitations.

Other findings (certainty of evidence not assessed) included no statistically significant difference in blood urea nitrogen, urine output, prescribed diuretics or dose of diuretics, serum sodium, aldosterone, or PRA for patients on a low sodium diet compared to a higher sodium diet. There was an increase in thirst but no difference in shortness of breath and general well-being for patients on a low sodium diet compared to a higher sodium diet. There was no difference in days to compensation. Patients were adherent to the prescribed sodium diet. No study reported data on estimated glomerular filtration rate (eGFR) or serum cystatin C.

Table 3. Summary of Findings for Restricted Dietary Sodium Interventions

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Creatinine	3 (159); RCT[29,31,32]	Serious[a]	Direct	Precise	Consistent	None	Moderate	Pooled NMD = 0.08 mg/dL, 95% CI (−0.08, 0.23)
BNP	2 (128); RCT[29,31]	No limitations	Direct	Not precise[c]	Consistent	Sparse data	Low	Net *median* difference = 525 and −13 pg/mL
NT-pro BNP	1 (31); RCT[32]	Very serious[a]	Direct	Not precise[d]	NA	Single Study	Insufficient	No conclusion
Caloric intake	2 (243); RCT[30,31] NCRS[30]	Serious[b]	Direct	Precise	Consistent	Sparse data	Low	Consume <20 kcal/kg/day RR = 3.4, 95% CI [1.70, 6.86]) MD = −4.4 kcal/kg/day, 95% CI (−7.26, −1.53). MD in percent estimate of daily requirement: −16, 95% CI (−6.6, −25.4)
Clinical congestion score	2 (128); RCT[29,31]	No limitations	Direct	Precise	Consistent	Sparse data	Moderate	NMD = −0.5, 95% CI (−1.76, 0.76) and 0.4, 95% CI (−1.6, 2.4)
Weight change	4 (191); RCT[28,29,31,32]	Serious[a,b]	Indirect[e]	Not precise[f]	Serious[g]	None	Insufficient	No conclusion
Mortality (All cause)	4 (191); RCT[28,29,31,32]	Serious[a,b]	Indirect[e]	Not precise[h]	Consistent	Sparse data[i]	Insufficient	No conclusion
Readmission	3 (159); RCT[28,29,31,32]	Serious[a]	Direct	Precise	Serious[j]	None	Low	Pooled RR = 1.07, 95% CI (0.68, 1.69)
Length of hospital stay	3 (159); RCT[29,31,32]	Serious[a]	Direct	Not precise[k]	Consistent	None	Low	Pooled NMD = 3.06 days, 95% CI (−0.61, 6.72)

Notes. [a] One study was high risk of bias due to incomplete outcome data and no intent to treat analysis; [b] One study was moderate risk of bias due to uncertainty about the completeness of the outcome data and selective reporting; [c] One study had a wide IQR at baseline and follow-up for both groups; [d] Wide IQR at baseline and follow-up measures for both groups; [e] Data reported at different time points; [f] At least 1 study had a large SD; [g] Two of 4 studies reported a decrease in weight for higher diet and 2 reported a decrease for low sodium diet; [h] At least 1 study had a wide confidence interval; [I] Only 5 events per group (total events for all participants = 10) across all of the included studies; [j] Two studies reported a lower risk for low sodium diet, and 1 study reported a higher risk for low sodium diet; [k] At least 1 study had a wide confidence interval.

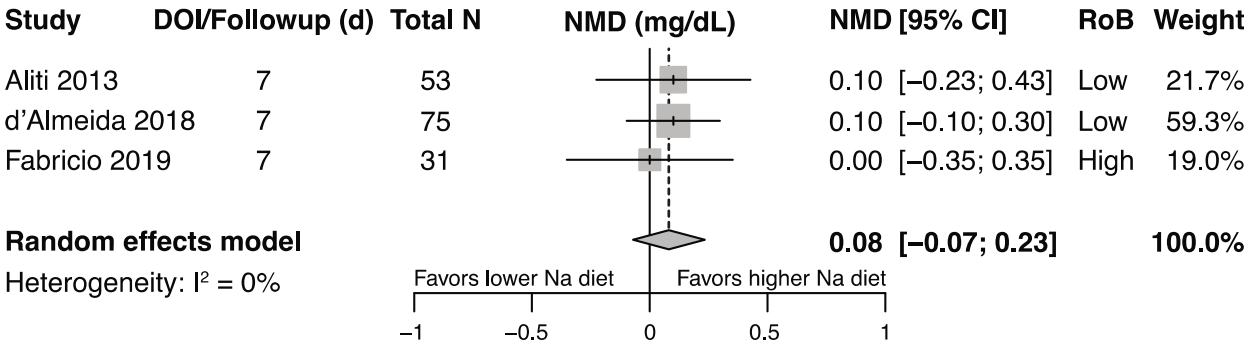
Abbreviations. BNP=brain (or B-type) natriuretic peptide; CI=confidence interval; MD=mean difference; NA=not applicable; NMD=net mean difference; NRCS=non-randomized controlled study; NT-proBNP=N-terminal pro-brain (or B-type) natriuretic peptide; RCT=randomized controlled trial; RR=relative risk.

Intermediate Outcomes

Serum Creatinine

Three RCTs found no significant difference in serum creatinine from baseline to 7 days between the diet intervention arms (pooled NMD = 0.08 mg/dL, 95% CI [−0.07, 0.23]; Figure 2).[29,31,32] The duration of intervention was 7 days in all studies. One RCT (Fabricio et al) yielded a highly imprecise estimate regarding difference in the likelihood that serum creatinine would increase by ≥0.3 mg/dL over 7 days between patients randomized to a low sodium diet of 1.2 g/day Na compared to a higher sodium diet of 2.8 g/day Na (RR = 0.94, 95% CI [0.43, 2.04]).[32] (Note that we use the abbreviation for sodium, Na, when reporting a dose or serum level.)

Figure 2. Serum Creatinine: Low Sodium versus Higher Sodium Diet

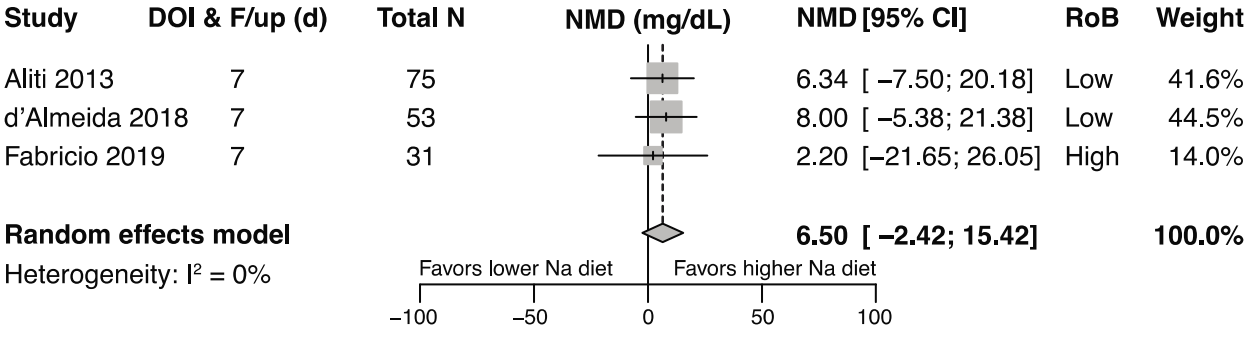


Notes. Net reduction in serum creatinine is considered to be a favorable outcome.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; Na=sodium; NMD=net mean difference; RoB=risk of bias.

Blood Urea Nitrogen (BUN)

Three studies found no significant difference in BUN from baseline to 7 days (the duration of the intervention and follow-up) for patients who received a low sodium diet compared to higher sodium diet (pooled NMD = 6.5 mg/dL, 95% CI [−2.4, 15.4]; Figure 3),[29,31,32] although all 3 studies found a small net increase in BUN among patients on low sodium diets compared with higher sodium diets.

Figure 3. Blood Urea Nitrogen (BUN): Low Sodium versus Higher Sodium Diet



Notes. Net reduction in BUN is considered to be a favorable outcome.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; Na=sodium; NMD=net mean difference; RoB=risk of bias.

Estimated Glomerular Filtration Rate (eGFR) and Serum Cystatin C

No study reported data on eGFR or serum cystatin C.

Natriuretic Proteins (BNP and NT-proBNP)

Two RCTs reported change in BNP from baseline to 7 days or discharge and 1 study reported change in NT-proBNP. One RCT found no significant difference in median BNP from baseline to 7 days between patients on a low sodium diet (0.8 g/day Na) compared to higher sodium diet (~3-5 g/day Na; net *median* difference = 525 pg/mL, $p = 0.51$).[29] A second RCT found no significant difference in median BNP between intervention (0.8 g/day Na) and control arms (~4 g/day Na) from baseline to 7 days (net *median* difference = −13 pg/mL, $p = 0.85$).[31] Finally, 1 RCT found no significant difference in change in serum NT-proBNP between a low (1.2 g/day Na) and higher sodium diet (2.8 g/day Na) groups from baseline to 7 days (net *median* difference = 139 pg/mL, NS).[32]

Weight Change

Four RCTs reported no significant difference in change in weight from baseline to 3 or 7 days.[28,29,31,32] We did not meta-analyze these studies because of the inconsistent time points when weight was reported. One RCT found no significant difference in change in weight from baseline to the primary end point of 3 days (middle of intervention) between the low sodium diet (0.8 g/day Na) and higher sodium diet (~3-5 g/day Na; NMD = 0.3 kg, 95% CI [−1.9, 2.4]).[29] The same study reported no significant difference in weight change from baseline to 7 days (means not reported, $p = 0.12$).[29] A second RCT found no significant difference in mean change in weight from baseline to 3 days and baseline to 7 days ($p > 0.99$ and $p = 0.49$, respectively) between a low sodium diet (0.8 g/d Na) and higher sodium diet (~4 g/day Na).[31] A third RCT found no significant difference in mean change in weight from baseline to 7 days between a low sodium diet (1.2 g/day Na) and higher sodium diet (2.8 g/day Na; NMD = −1.0 kg, 95% CI [−18.2, 16.2]).[32] Finally, the fourth RCT found no significant difference in percent change in weight from baseline to time of compensation (the study did not clearly report mean days to compensation) between patients on a low sodium diet of 0.8 g/day compared to higher sodium diet of 4 g/day (MD = 2.2%, 95% CI [−3.5, 7.9]).[28]

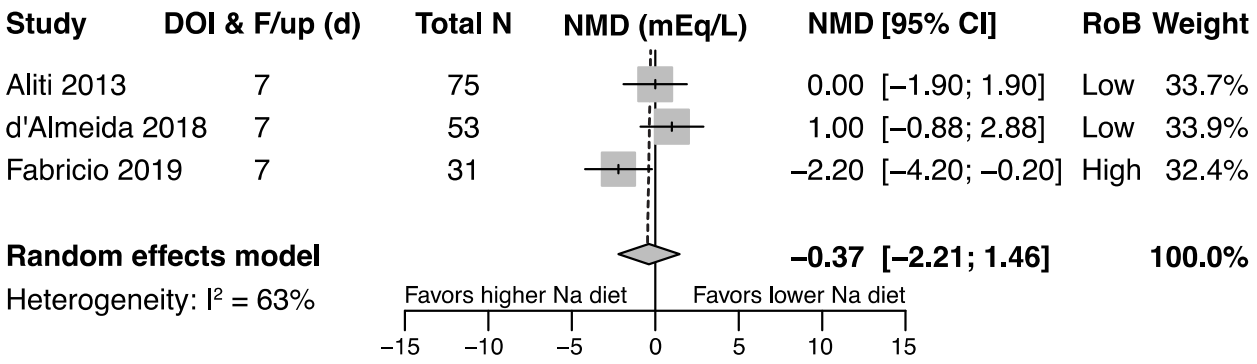
Urine Output

One RCT found no significant difference in urine output between the low sodium diet (1.2 g/day Na) and higher sodium diet (2.8 g/day Na) groups from baseline to 7 days (MD = 1.4 L/24 hr, 95% CI [−0.6, 3.4]).[32]

Serum Sodium

Three RCTs, overall, found no significant difference in serum sodium from baseline to day 7 (duration of intervention and follow-up) between the low and higher sodium arms (pooled NMD = −0.4 mEq/L, 95% CI [−2.2, 1.5]; Figure 4).[29,31,32] One study found a statistically significant, but clinically small, net *decrease* (*ie*, worsening) in serum sodium in the patients given the low sodium diet.[32] The authors hypothesize that the effect of natriuresis caused by the loop diuretics and the restricted sodium intake combined to lower serum sodium levels.

Figure 4. Serum Sodium: Low Sodium versus Higher Sodium Diet



Notes. Net increase in serum sodium is considered to be a favorable outcome.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; Na=sodium; NMD=net mean difference; RoB=risk of bias.

Prescribed Diuretics

Two RCTs reported no significant difference in the proportion of patients who received diuretics while hospitalized between the low sodium diet and higher sodium diet (RR = 0.97, 95% CI [0.89, 1.07] and 1.00, 95% CI [0.83, 1.20]).[29,32]

Three RCTs reported prescribed diuretic dose during the hospitalization.[28,31,32] One RCT reported no significant difference in change in diuretic (furosemide) dose from baseline to 7 day between the low sodium diet of 0.8 g/day Na and higher sodium diet of ~4 g/day Na (NMD = 4.3 mg/day, 95% CI [−12.0, 20.6]).[31] One RCT found no difference in cumulative loop diuretic dose during hospitalization between the low sodium (1.2 g/day Na) and higher sodium diet groups (2.8 g/day Na; MD = 103.5 mg/day, 95% CI [−14.2, 221.2]).[32] One RCT found no difference in daily and cumulative diuretic (furosemide) dose during the compensation period between the low sodium diet 0.8 g/day Na and higher sodium diet of 4 g/day Na (MD = −0.2 mg/day, 95% CI [−0.6, 0.3] and −31.0 mg/day, 95% CI [−265.7, 203.7], respectively).[28] Finally, 2 RCTs found no significant difference in the time to transition from an intravenous to an oral diuretic administration (median difference = 0 days and MD = 0.3 days, 95% CI [−0.86, 1.46]).[29,31]

Nutritional Intake

One NRCS found that the risk of consuming fewer calories (defined as <20 kcal/kg/day) was significantly greater for people who received a low sodium diet (2.4 g/day Na) compared to higher sodium diet (4 g/day Na; RR = 3.4, 95% CI [1.70, 6.86]).[30] The NRCS and an RCT also reported calorie intake as a continuous measure. The NRCS found fewer calories (defined as the percent of estimated daily requirement) were consumed by patients prescribed a low sodium diet compared to those prescribed a higher sodium diet (MD = −16.0%, 95% CI [−6.6, −25.4]).[30] Similarly, an RCT found fewer calories were consumed by patients on a restricted sodium diet (0.8 g/day Na) compared to those on a higher sodium diet (~4 g/day Na; MD = −4.4 kcal/day, 95% CI [−7.3, −1.5]).[31] This RCT also found fewer liquids were consumed over 7 days in the low sodium diet group which also restricted fluids to 800 mL/day compared to those in the higher sodium diet group which did not restrict fluid intake (median difference = −312.7 mL/day, $p < 0.001$).[31]

Other Intermediate Measures

One RCT found no significant difference in aldosterone from baseline to day 7 of admission or discharge between those on a low sodium diet (0.8 g/day Na) compared to higher sodium diet (~4 g/day Na; NMD = 11 pg/mL, $p = 0.85$).[31] Similarly, 1 RCT reported no difference in PRA from baseline to day 7 or discharge in patients on a low sodium diet (0.8 g/day Na) compared to patients on a higher sodium diet (~4 g/day Na; NMD = −0.9 ng/mL/h, $p = 0.42$).[31]

Clinical Outcomes

Clinical Congestion Score

Two RCTs reported clinical congestion scores between the low sodium and higher sodium diet groups from baseline to 3 or 7 days.[29,31] One RCT found no significant difference in scores between the low sodium (0.8 g/day Na) and higher sodium (~3-5 g/day Na) groups from baseline to 3 and 7-days (NMD = −0.6, 95% CI [−2.1, 0.9] at 3 days and −0.5, 95% CI [−1.8, 0.8] at 7 days).[29] A second RCT reported no significant difference in scores from baseline to day 7 of the intervention between the low sodium diet of 0.8 g/day Na and higher sodium diet of ~4 g/day Na (NMD = 0.4, 95% CI [−1.6, 2.4]).[31]

Heart Failure Related Symptoms

Two RCTs evaluated thirst via a 10-point visual analogue scale.[29,31] In both studies, patients randomized to the low sodium diet compared to higher sodium diet reported greater feelings of thirst from baseline to 7-day follow-up.[29,31] An RCT found a significant increase in thirst for patients in the low sodium diet (0.8 g/day Na) compared to higher sodium diet group (~3 to 5 g/day Na; NMD = 1.5, 95% CI [0.4, 2.7], $p = 0.01$).[29] In this study, fluid intake was limited to a maximum of 800 mL/day in the intervention group, while liberal fluid intake of ≥2500 mL/day was allowed in the higher sodium group. Similarly, 1 RCT reported significantly greater perceived thirst during the study period for patients on a diet of 0.8 g/day Na and a restriction of 800 mL/day fluid compared to a diet of ~4 g/day Na and unlimited fluid intake ($p = 0.03$).[31]

One study found no significant difference in shortness of breath and general well-being, both measured by a 10-point visual analogue scale, for patients randomized to a low sodium diet (1.2 g/day Na) compared to higher sodium diet (2.8 g/day Na) from baseline to day 7 (NMD = 0.8, 95% CI [−0.3, 1.9] and 0.6, 95% CI [−0.9, 2.1], respectively).[32]

Mortality

Four studies reported all-cause mortality at different time points.[28,29,31,32] Two RCTs reported no deaths in either group during the 7-day intervention period[29] or during hospitalization.[30] Two RCTs reported 30-day mortality outcomes. The event rates were low in both studies, yielding very imprecise estimates (RR = 0.93, 95% CI [0.15, 5.84][32] and RR = 0.77, 95% CI [0.12, 5.04][31]). One RCT also reported a highly imprecise estimate of mortality *not* related to HF (RR = 1.29, 95% CI [0.09, 18.8], time frame unclear).[28]

Other Clinical Outcomes

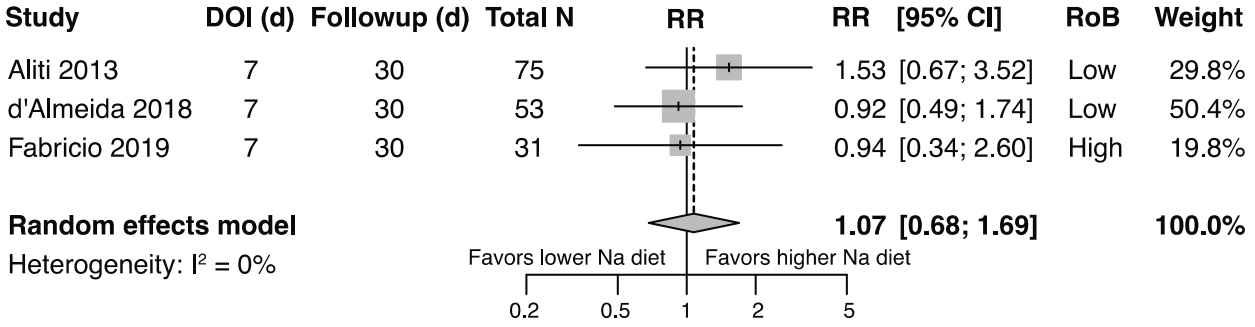
One RCT found no significant difference in days to compensation between a low sodium (0.8g/day Na) and higher sodium diet (4 g/day Na; MD = 0.9, 95% CI [−0.3, 2.1]).[28]

Health Service Utilization Outcomes

Readmission

Three RCTs reported no significant difference in 30-day readmission between patients on a low sodium diet compared to higher sodium diet (pooled RR = 1.07, 95% CI [0.68, 1.69]; Figure 5).[29,31,32] One RCT reported 30-day readmission due to HF,[29] while the other 2 RCTs[31,32] reported all-cause 30-day readmission.

Figure 5. 30-Day Readmission: Low Sodium versus Higher Sodium Diet

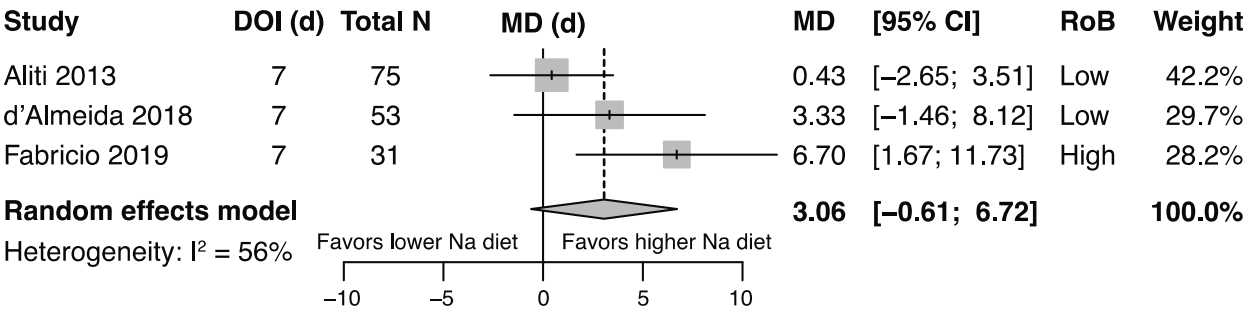


Notes. Lower rate of readmission is considered to be a favorable outcome.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; Na=sodium; RoB=risk of bias; RR=risk ratio.

Length of Hospital Stay

Three RCTs reported a nonsignificant longer length of stay for patients on a low sodium diet compared to the higher sodium diet (pooled MD = 3.1 days, 95% CI [−0.6, 6.7]; Figure 6).[29,31,32] None of the studies, though, provided a hypothesis for why a low sodium diet would increase length of stay. There was a moderate degree of heterogeneity across studies, with differences ranging from 0.4 to 6.7 days.

Figure 6. Length of Hospital Stay: Low Sodium versus Higher Sodium Diet



Notes. Shorter hospital stay is considered to be a favorable outcome.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; Na=sodium; MD=mean difference; RoB=risk of bias.

Adherence

Two RCTs evaluated adherence to the hospital diet by measuring the amount of sodium consumed.[31,32] The 2 RCTs found significantly less sodium was consumed over 7 days by patients who received a low sodium diet compared to higher sodium diet (median difference = −1.3 g/day Na, $p < 0.001$ and MD = −1.5 g/day, 95% CI [−1.7, −1.2]).[31,32] A third RCT found no significant difference in the acceptance of the hospital diet defined as consuming 80% of the entire meal between the low (1.2 g/day Na) and higher sodium diet (2.8 g/day Na; mean 79.6% [14.3] vs 88.1% [12.3], $p = 0.08$).[32]

SUPPLEMENTAL SODIUM INTERVENTIONS (WITH DIURETICS)

Fifteen studies[33-47] including 13 RCTs[33-35,37-39,41-43,45-47] and 2 NRCSs[36,44] (conducted between 1996 and 2022) involving 3,483 participants (1,707 intervention, 1,776 control) evaluated the effectiveness of HSS with diuretics ($N = 14$) or oral NaCl with diuretics ($N = 1$) in patients hospitalized with ADHF. Appendix D shows the design details and Appendix E shows the baseline characteristics of the studies. Nine studies were conducted in Europe,[33-40,44,45] 2 in Asia,[41,43] 2 in the Middle East,[42,46] 1 in the US,[47] and 1 in South America.[40] Most studies were conducted in single-center hospitals,[34,36-46] but 2 studies did not report the hospital settings.[33,35] The mean age of patients ranged from 47 to 76 years. The percentage of male population ranged from 38.3% to 81.3% and males were the minority in only 2 studies. Only 1 study, which was conducted in the US, reported data on race/ethnicity (86% White and 14% Black or African American). In 11 studies,[33-35,37-40,42,43,45] mean (SD) of left ventricular ejection fraction (LVEF) at baseline ranged from 23.9% (6.3) to 56.4% (10.6), and 2 studies[36,41] reported median (IQR) of LVEF at baseline [(34.5) (26.5, 41) and 37 (28.5, 42.5)]. Mean (SD) of LVEDD 71.6 mm (9.7) was reported in 1 study.[40]

In 1 RCT, an independent physician assigned patients to treatment groups, and 1 RCT had major discrepancies within the text and poor methodological reporting of outcome definitions (therefore both are high risk of bias).[35,43] Three RCTs had moderate risk of bias due to concerns over the method of allocation concealment and blinding.[33,45,46] Finally, 2 NRCSs had high risk of bias because they either conducted crude unadjusted analyses or did not report a method to address confouding.[36,44]

Appendix F.2 describes the sodium supplementation interventions including saline solution, sodium dose, diuretics, fluid intake, other intervention (*eg*, dietary sodium), and duration of interventions. In 7 studies, the concentration of HSS (between 1.4% and 4.6% NaCl) was tailored based on the patients' serum sodium levels.[33-37,39,45] In 6 studies,[38,40-42,46] HSS concentration was fixed (ranging from 1.94% to 7.5% NaCl). One study used compound HSS (NaCl 2.8%, KCl 0.2%, and $MgSO_4$ 0.9%)[43] and 1 study did not report concentration of HSS.[44] One study (conducted in the US) used an oral NaCl formulation to replicate neurohormonal effects of HSS intervention and for easy administration to the study population.[47] Dietary sodium intake was reported in 11 studies during the intervention period.[33-39,41,43,45,47] Total sodium intake (calculated by the research team from all sources including diet) in the supplemental sodium arms ranged from 1.15 to 8.1 g/day, and in furosemide alone arms ranged from 0.7 g/d to 2.9 g/d. All but 1 study (a conference abstract) explicitly noted that HSS or oral sodium was combined with furosemide. In 9 studies sodium supplementation was combined with a conventional dose of furosemide (≤250 mg/d),[37-39,41-43,45-47] in 3 studies HSS was combined with high doses of furosemide (500-1000 mg/d),[33-35] and 1 study combined HSS with 125-1000 mg of furosemide.[36]

Ten studies compared supplemental sodium with furosemide to furosemide alone,[33-37,39,42,43,45,47] 3 studies compared HSS with furosemide to furosemide with normal saline,[38,40,46] 1 study compared HSS with furosemide to furosemide with glucose (5%),[41] and 1 study did not report whether patients in the comparison arm received furosemide.[44] Intervention durations varied across the studies (ranging from 1 day to 12 days), and 3 studies did not clearly define or report the duration of intervention period.[37,39,44]

In summary (Table 4), there were significant net decreases in creatinine, BNP, and weight from admission to last in-hospital measurement for patients administered supplemental sodium and furosemide compared to furosemide alone (low confidence for BNP and moderate confidence for others). Hospital length of stay was shorter for patients who received supplemental sodium (moderate confidence). There was no significant difference in NT-pro BNP (low confidence). Studies provide insufficient evidence (no conclusion) for mortality and 30-day readmission, and the studies did not report calorie intake or clinical congestion score.

For other outcomes (certainty of evidence not assessed), there was a significant net decrease in BUN; a significant net increase in eGFR, urine output, and serum sodium; and no significant difference in cystatin C, aldosterone, or PRA for patients administered supplemental sodium and furosemide compared to furosemide alone. Patients who received supplemental sodium with furosemide had a greater likelihood of improving on the NYHA functional class from admission to discharge. Two studies had conflicting findings related to dyspnea. Two RCTs found that fewer patients who were administered HSS and furosemide experienced dyspnea. One RCT, though, found no difference in a composite measure of clinical symptoms (dyspnea, lower limb edema, weakness, palpitations, and fatigue) at discharge between groups. One RCT found a reduction in thirst at the end of the 4 day intervention. Finally, 1 RCT found no difference in intensive care unit admissions.

Table 4. Summary of Findings for Supplemental Sodium Interventions

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
Creatinine	11 (2,766); RCT[33-35,37-42,46,47]	No limitations	Indirect[a]	Precise	Consistent	None	Moderate	Pooled NMD = −0.38 mg/dL, 95% CI (−0.54, −0.22)
BNP	7 (2,848); 6 RCT[35,37-40,43] and 1 NRCS[36]	Serious limitations[b,c,d]	Indirect[a]	Precise	Consistent	Sparse data	Low	Pooled NMD = −62.84 pg/mL, 95% CI (−103.61, −22.08)
NT-pro BNP	3 (235); RCT[41,45,47]	Serious limitations[e]	Indirect[a]	Imprecise[f]	Consistent	Sparse data[g]	Low	Pooled NMD = −1614.17 pg/mL, 95% CI (−3581.66, 353.31)
Caloric intake	0	NA	NA	NA	NA	NA	NA	No evidence
Clinical congestion score	0	NA	NA	NA	NA	NA	NA	No evidence
Weight change	14 (3,333); 13 RCTs[33-35,37-43,45-47] and 1 NCRS[44]	No limitations	Indirect[a]	Precise	Consistent[h]	None	Moderate	Pooled NMD = −2.66 kg, 95% CI (−4.70, −0.62)
Mortality (all cause)	4 (2,317); RCT[35,37,40,43]	Serious limitations[b]	Indirect[a]	Imprecise	Inconsistent[i]	Sparse data	Insufficient	No conclusion
Readmission	2 (159); RCT[35,47]	Serious limitations[b]	Direct	Precise	Inconsistent[j]	None	Insufficient	No conclusion
Length of hospital stay	11 (3,243); 9 RCTs[33-35,37-39,42,44,47] and 2 NRCS[36,44]	Serious limitations[b, c, k]	Direct	Precise	Consistent	Large effect[l]	Moderate	Pooled NMD = −2.90 days, 95% CI (−4.02, −1.79

Notes. [a] Studies reported outcomes at different time points; [b] One RCT was high risk of bias due to randomization decided by an independent physician and no allocation concealment, [c] One RCT was high risk of bias due to outcome not clearly being defined and uncertainty about blinding; [d] One NRCS was high risk of bias because treatment and comparison groups were matched by age and sex and no adjusted comparisons; [e] One RCT was moderate risk of bias due to no blinding of participants and personnel and unclear allocation concealment; [f] One RCT reported significant net decrease in NT-proBNP and 2 RCTs reported non-significant decrease in outcome result; [g] Two RCTs reported outcome in median (IQR) and 1 RCT reported outcome in mean (SD); [h] One RCT reported a small weight gain (0.12 kq) in HSS group after 24-hr HSS intervention compared to furosemide alone while the remaining RCTs reported weight loss; [I] Two RCTs reported no death during hospitalization, 1 RCT reported greater mortality risk in HSS group during hospitalization, and 1 RCT reported higher mortality risk in control group at 30-day follow-up; [j] 1 RCT found reduction in 30-day readmission and another RCT found no difference in 30-day readmission outcome; [k] 1 RCT was moderate risk of bias due to no blinding and incomplete outcome data; [l] 1 NRCS being an outlier of longer length of stay in HSS group after the intervention.
Abbreviations. BNP=brain (or B-type) natriuretic peptide; CI=confidence interval; kg=kilogram; NA=not applicable; NMD=net mean difference; NRCS=non-randomized controlled trial; NT-proBNP=N-terminal pro-brain (or B-type) natriuretic peptide; RCT=randomized controlled trial; RR=relative risk.

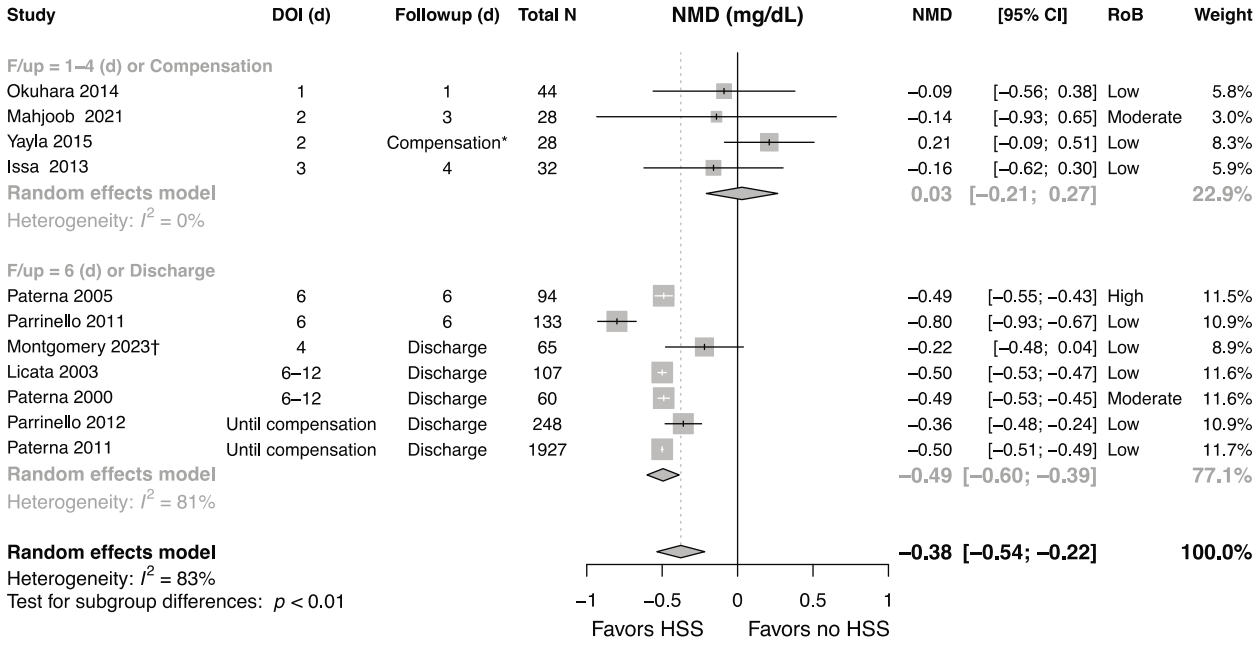
Intermediate Outcomes

Serum Creatinine

Eleven RCTs[33-35,37-42,46,47] found a significant net decrease in serum creatinine from baseline to the last in-hospital measurement for patients randomized to HSS or oral NaCl with furosemide compared to furosemide alone (pooled NMD = −0.38 mg/dL, 95% CI [−0.54, −0.22]; Figure 7). Duration of intervention varied among studies (from 1 to 6 or more days, or until compensation), as did the timing of the last in-hospital measurement (24 hours to 6 days or discharge).

Meta-analysis revealed statistical heterogeneity in NMDs across studies. As shown in Figure 7, studies with shorter durations of intervention (1-3 days), which also had shorter duration of follow-up (1 to 4 days or compensation), found no difference in NMD for serum creatinine (pooled NMD = 0.03 mg/dL, 95% CI [−0.21, 0.27]), but after about 4 or 6 or more days of treatment and follow-up, serum creatinine levels were significantly lower in the sodium supplementation group (pooled NMD = −0.49 mg/dL, 95% CI [−0.60, −0.39]). The NMD was significantly greater in longer duration studies than shorter duration studies ($p < 0.001$).

Figure 7. Serum Creatinine: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net reduction in serum creatinine is considered to be a favorable outcome.
* Time to compensation; † Compared oral NaCl with furosemide to furosemide alone.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; NMD=net mean difference; RoB=risk of bias.

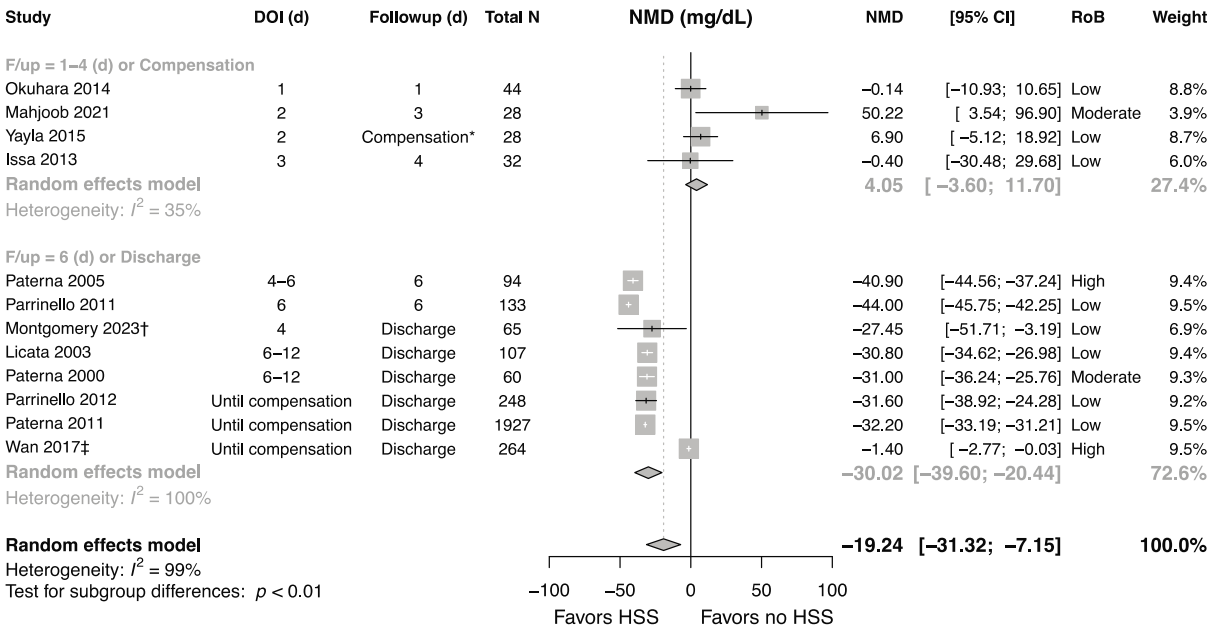
Blood Urea Nitrogen (BUN)

Twelve RCTs found a significant net decrease in BUN from baseline to last reported in-hospital measurement (24 hours or 6 days or discharge) for patients randomized to supplemental sodium with furosemide compared to furosemide alone (pooled NMD = −19.2 mg/dL, 95% CI [−31.3, −7.2]; Figure 8).[33-35,37-43,46,47] Mahjoob et al was the only study to report a large, statistically

significant effect that favored furosemide alone (NMD = 50.2 mg/dL, 95% CI [3.5, 96.9]).[46] In this study, patients were randomized to either HSS with furosemide or furosemide alone for 48 hours. The study did not offer an explanation for why BUN may have risen to such a degree. A *post hoc* sensitivity analysis excluding Mahjoob et al did not alter the conclusion (pooled NMD = −22.3 mg/dL, 95% CI [−33.2, −11.3]).

Meta-analysis revealed statistical heterogeneity in NMDs across studies. As shown in Figure 8, similar to serum creatinine, studies with shorter durations of intervention (1-3 days), which also had shorter duration of follow-up (1 to 4 days or compensation), found no difference in NMD for BUN levels (pooled NMD = 4.1 mg/dL, 95% CI [−3.6, 11.7]), but after about 4 or 6 or more days of treatment and follow-up, BUN levels were significantly lower in the sodium supplementation group (pooled NMD = −30.0 mg/dL, 95% CI [−39.6, −20.4]). Excluding the 1 outlier longer-term study with no effect (Wan et al) in a post hoc sensitivity analysis yielded an even greater, more precise NMD (pooled NMD = −21.2 mg/dL, 95% CI [−33.8, −8.5]). With or without Wan et al, the NMD was significantly greater in longer duration studies than shorter duration studies ($p < 0.01$).

Figure 8. Blood Urea Nitrogen (BUN): Supplemental Sodium (With Furosemide) versus Furosemide



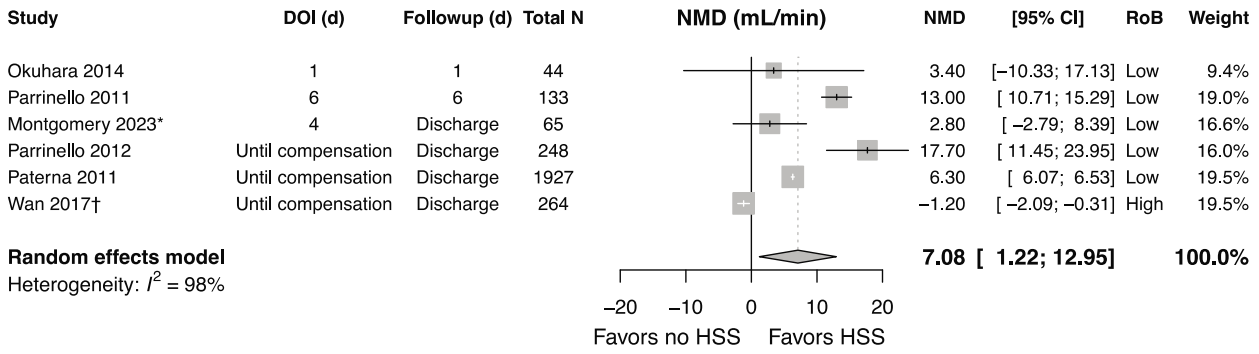
Notes. Net reduction in serum BUN is considered to be a favorable outcome.
* Time to compensation. † Compared oral NaCl with furosemide to furosemide alone; ‡ Potential outlier among longer-duration studies; excluded in a post hoc sensitivity analysis of the subgroup.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; NMD=net mean difference; RoB=risk of bias.

Estimated Glomerular Filtration Rate (eGFR)

Six RCTs reported a significant net increase in eGFR from baseline to last in-hospital measurement (24 hours to 6 days or discharge) for patients randomized to HSS or oral NaCl with furosemide compared to furosemide alone (pooled NMD = 7.1 mL/min, 95% CI [1.2, 13.0]; Figure 9).[37-39,41,43,47] Statistical heterogeneity was very large across studies, but no clear

explanation was found. The single short duration study (1 day) did not differ from longer duration studies. Wan et al was the only study to report a small and significant net decrease in eGFR for patients who received HSS with furosemide compared to furosemide alone (NMD = −1.2 mL/min, 95% CI [−2.1, −0.3). This study had major discrepancies between text and tables and unclear outcome definitions (high risk of bias). A post hoc sensitivity analysis excluding Wan et al yielded a larger and more precise effect relative to the main analysis (pooled NMD = 9.2 mL/min, 95% CI [3.7, 14.7]; I^2 = 91%), although heterogeneity remained comparable to the main analysis.

Figure 9. Estimated Glomerular Filtration Rate (eGFR): Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net increase in eGFR is considered to be a favorable outcome.
* Compared oral NaCl with furosemide to furosemide alone; † Wan 2017 was excluded in post hoc sensitivity analysis.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; HSS=hypertonic saline solution (or oral sodium with furosemide); N=sample size; NMD=net mean difference; RoB=risk of bias.

Serum Cystatin C

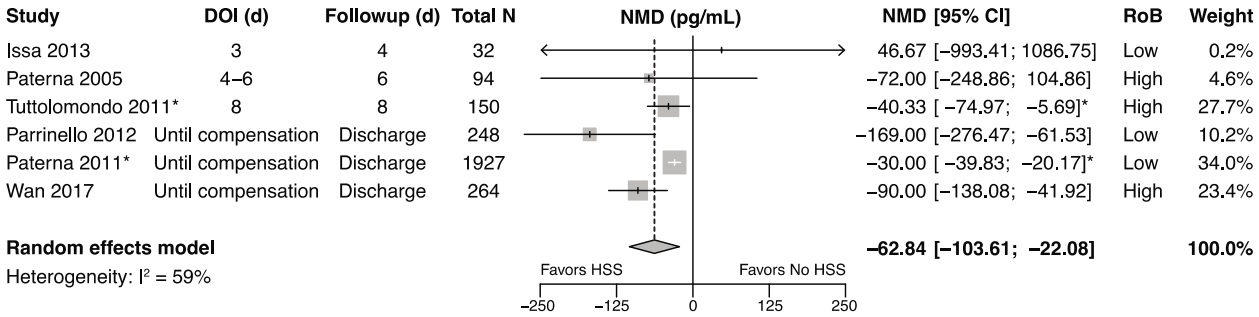
Two RCTs found no significant difference in serum cystatin C between HSS and furosemide from baseline to last in-hospital measurement.[40,41] One RCT found no significant difference in serum cystatin C between HSS with furosemide and furosemide alone from baseline to day 4, which was 24 hours after the intervention period (NMD = −0.15 mg/L, 95% CI [−0.50, 0.20]).[40] Similarly, a second RCT found no significant difference in serum cystatin C between HSS with furosemide to furosemide with glucose (5%) from baseline to the end of 24-hour intervention (NMD = −0.10 mg/L, 95% CI [−0.65, 0.45]).[41]

Natriuretic Proteins (BNP and NT-proBNP)

Seven studies in total reported on BNP; however, only 4 reported BNP at baseline and follow-up,[35,39,40,43] while 2 studies only reported BNP at follow-up[36,37] and 1 study graphically reported BNP (means were not extracted).[38] Across 6 studies reporting extractable data, there was a significant net decrease in BNP among patients who received HSS with furosemide compared to furosemide alone (pooled NMD = −62.8 pg/mL, 95% CI [−103.6, −22.1]; Figure 10).[35-37,39,40,43] One RCT graphically reported a decrease in BNP from baseline to 6 days for patients who received HSS with furosemide compared to furosemide alone ($p < 0.001$). In a post hoc sensitivity analysis with the 4 studies reporting baseline and follow-up data, the net effect was greater and remained statistically significant (pooled NMD = −103.3 pg/mL, 95% CI [−151.8,

−54.8]; I^2 = 0%). The shorter duration studies were imprecise and thus did not clearly differ in findings from longer duration studies.

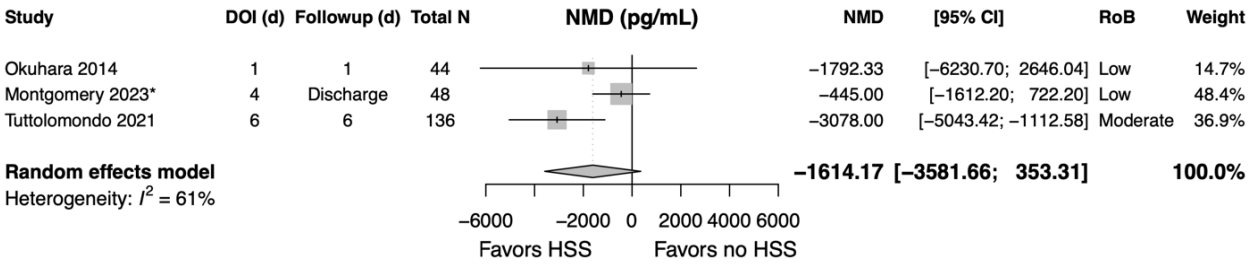
Figure 10. BNP: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net reduction in BNP is considered to be a favorable outcome.
* Mean difference at follow-up time point (no baseline data reported). Excluded from post hoc sensitivity analysis.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; NMD=net mean difference; RoB=risk of bias.

Three RCTs found no significant difference in NT-proBNP from baseline to last in-hospital measurement (pooled NMD = −1614.2 pg/mL, 95% CI [−3581.7, 353.3]; Figure 11).[41,45,47] The last in-hospital measurement varied between 1 to 6 days or discharge. One RCT found a significant net decrease in NT-pro BNP between HSS with furosemide compared to furosemide alone from baseline to the end of 6-day intervention period (NMD = −3078.0 pg/mL, 95% CI [−5043.4, −1112.6]).[45] The remaining 2 RCTs found nonsignificant net decreases in NT-pro BNP between either HSS or oral NaCl and furosemide compared to furosemide alone.[41,47]

Figure 11. NT-proBNP: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net reduction in NT-proBNP is considered to be a favorable outcome.
* Compared oral NaCl with furosemide to furosemide alone.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; HSS=hypertonic saline solution (or oral sodium with furosemide); N=sample size, NMD=net mean difference, RoB=risk of bias.

Weight

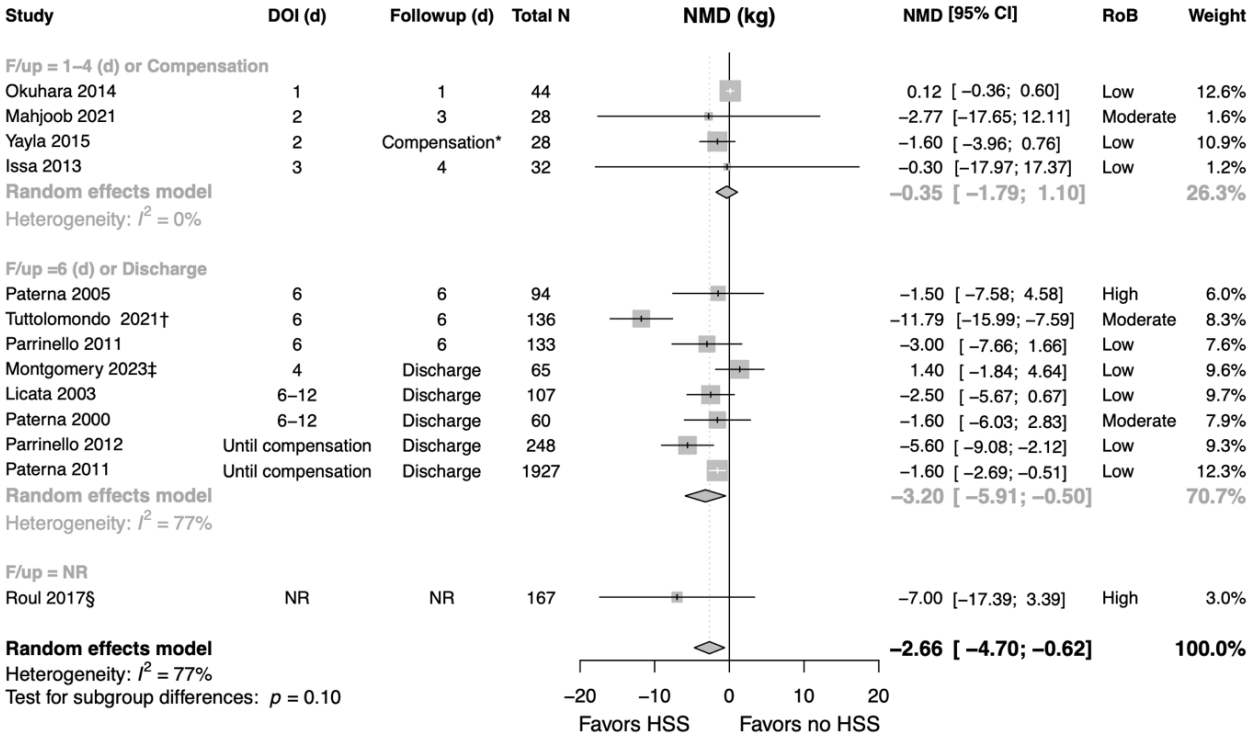
Fourteen studies (13 RCTs[33-35,37-43,45-47] and 1 NRCS[44]) reported change in body weight from baseline to in-hospital follow up (3 to 6 days or discharge). Wan et al presented weight data that was inconsistent with adult patients (*eg*, 23.44 kg mean weight at baseline) and was excluded from meta-analyses.[43] Roul et al reported median weight without data to allow an estimate of variance (net median difference = −7 kg), so we used the median SD from the other 11 RCTs in

the meta-analysis. In pooled data from 13 studies,[33-35,37-42,45-47] there was a significant net decrease in weight from baseline to last in-hospital measurement for patients who received supplemental sodium with furosemide compared to furosemide alone (pooled NMD = −2.7 kg, 95% CI [−4.7, −0.6]; Figure 12).

Meta-analysis revealed statistical heterogeneity in NMDs across studies. As shown in Figure 12, studies with shorter durations of intervention (1-3 days), which also had shorter duration of follow-up (1 to 4 days or compensation), found no difference in NMD for weight (pooled NMD = 0.4 kg, 95% CI [−1.8, 1.1]), but after about 4 or 6 or more days of treatment and follow-up, weight changes were significantly greater in the sodium supplementation group (pooled NMD = −3.2 kg, 95% CI [−5.9, −0.5]). The NMD was not significantly greater in longer duration studies than shorter duration studies ($p = 0.10$).

Montgomery et al compared oral NaCl with furosemide to furosemide alone and was the only study to report an increase in weight, but the effect size was small and nonsignificant. In a post hoc sensitivity analysis, we excluded Roul et al (for which we estimated the SD) and the pooled NMD was minimally changed (pooled NMD = −2.5 kg, 95% CI [−4.6, −0.5]). In another post hoc sensitivity analysis, we excluded Tuttolomondo 2021 et al, which reported a much larger reduction in weight than the other studies. The net effect remained statistically significant, but with a substantially smaller effect size (pooled NMD = −1.5 kg, 95% CI [−2.7, −0.3]; $I^2 = 56\%$).

Figure 12. Weight: Supplemental Sodium (With Furosemide) versus Furosemide

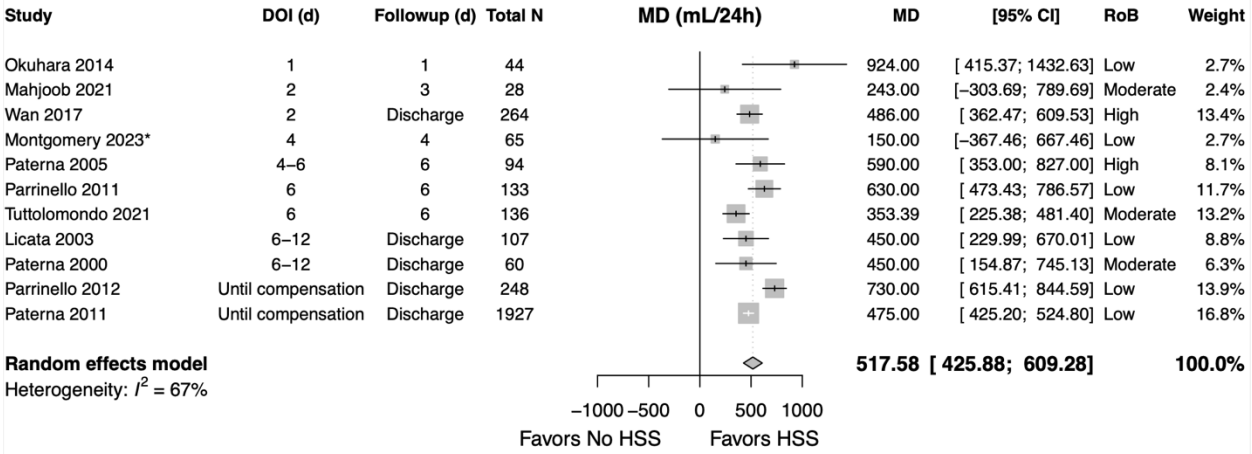


Notes. Net reduction in weight is considered to be a favorable outcome.
* Time to compensation; † Compared oral NaCl with furosemide to furosemide alone; ‡ Potential outlier. Excluded in a post hoc sensitivity analysis; § NMD and 95% CI estimated from reported median data. Excluded in a post hoc sensitivity analysis.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; HSS=hypertonic saline solution (or oral sodium with furosemide); N=sample size; NMD=net mean difference; RoB=risk of bias.

Urine Output

Twelve RCTs reported urine output at various periods of follow-up (24 hours to 4 days or 6 days or discharge).[33-35,37-41,43,45-47] Most reported average daily (24 hour) urine output for the duration of follow-up. One study (Issa et al) reported only urine output (per kg per hour) on selected days and was excluded from meta-analyses.[40] Meta-analysis of the 11 RCTs that reported average daily urine output (or equivalent data) found a clinically large, statistically significant greater urine output in the sodium supplementation with furosemide groups (pooled MD = 517.6 mL/24 hr, 95% CI [425.9, 609.3]; Figure 13). Although there was some heterogeneity in the estimate of the MD, the studies were consistent in finding favorable effects of sodium supplementation with furosemide, which were mostly clinically large and statistically significant. The study by Issa et al, which reported day-specific data for 3 days plus 24 hours post-intervention, in contrast found a nonsignificant, small effect ($p = 0.07$). If we assume that their reported data represent the full duration of follow-up for all patients, then the estimated MD was 43.6 mL/24 hr (95% CI [−3.6, 90.8]). Including this in the meta-analysis would reduce the pooled MD to 459.4 mL/24 hr (95% CI [327.0, 591.8]).

Figure 13. Urine Output: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net increase in urine output is considered to be a favorable outcome. * Compared oral NaCl with furosemide to furosemide alone.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size; NMD=net mean difference; RoB=risk of bias.

Caloric Intake

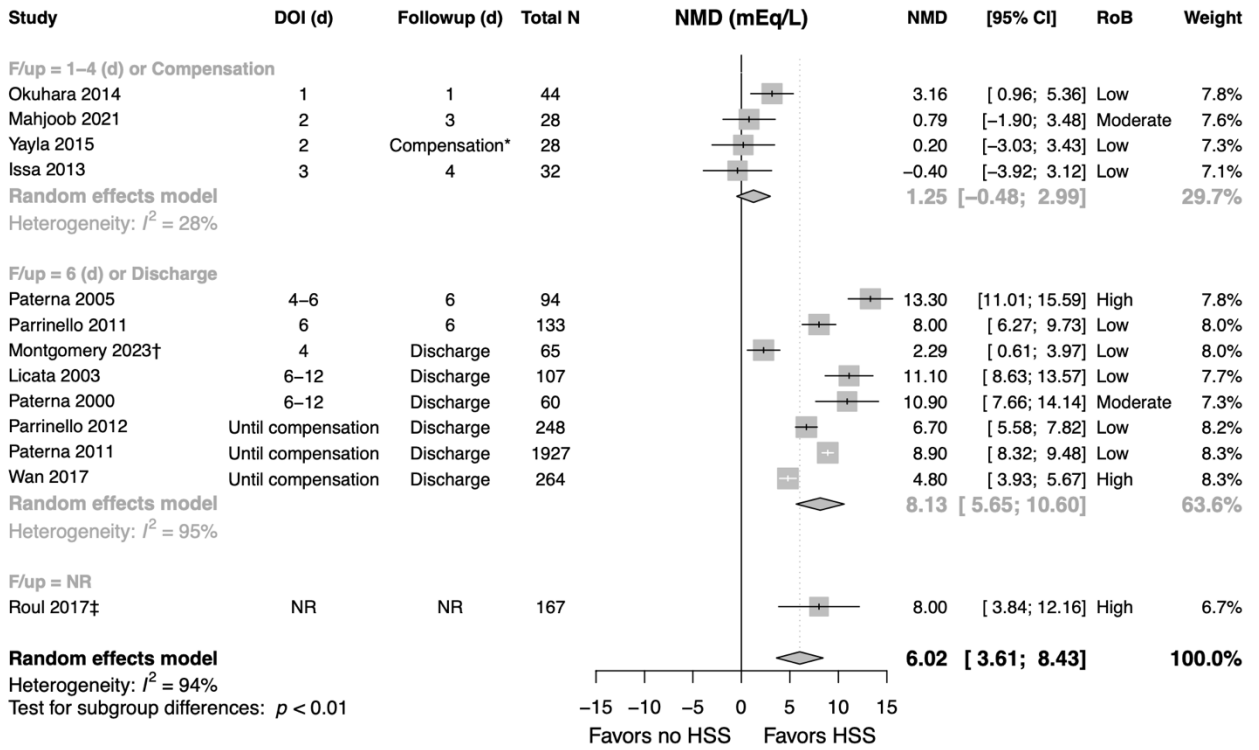
No study reported data on caloric or fluid intake.

Serum Sodium

Thirteen studies (12 RCTs[33-35,37-43,46,47] and 1 NRCS[44]) evaluated serum sodium at baseline and at the end of intervention or discharge. Pooled data from 13 studies found a significant net increase in serum sodium from baseline to last in-hospital measurement (24 hours to 6 days or discharge) for patients who received sodium supplementation with furosemide compared to furosemide alone (pooled NMD = 6.0 mEq/L, 95% CI [3.6, 8.4]; Figure 14**)**. Results remained consistent in a post hoc sensitivity analysis that excluded data from the NRCS that only reported serum sodium at follow-up (pooled NMD = 5.9 mEq/L, 95% CI [3.4, 8.5].[44]

Meta-analysis revealed large statistical heterogeneity in NMDs across studies (I^2 = 94%). As shown in Figure 14, studies with shorter durations of intervention (1-4 days), which also had shorter duration of follow-up (1 to 4 days or compensation), mostly found no difference for serum sodium (pooled NMD = 1.3 mg/dL, 95% CI [-0.5, 3.0]), but after about 4-6 or more days of treatment and follow-up, NMD for serum sodium was larger (pooled NMD = 8.1 mg/dL, 95% CI [5.7, 10.6]). The NMD was significantly greater in longer duration studies than short duration studies ($p < 0.01$). While the statistical heterogeneity across the longer duration studies remained high, they all consistently found a relatively large, statistically significant improvement with sodium supplementation.

Figure 14. Serum Sodium: Supplemental Sodium (With Furosemide) versus Furosemide

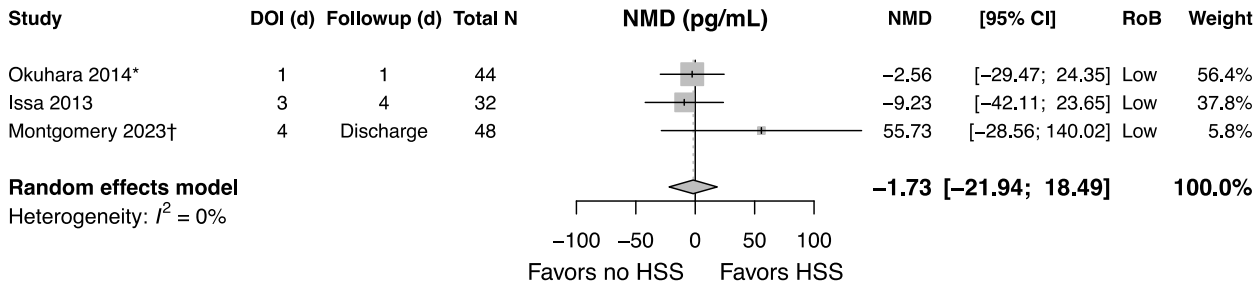


Notes: Net increase in serum sodium is considered to be a favorable outcome.
* Time to compensation. † Compared oral NaCl with furosemide to furosemide alone. ‡ NMD and 95% CI estimated from reported median data. Excluded in a post hoc sensitivity analysis.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; N=sample size, NMD=net mean difference; RoB=risk of bias.

Serum Aldosterone

Three RCTs found no significant difference in serum aldosterone from baseline to end of intervention (1 day to discharge) for patients who received HSS or oral NaCl with furosemide compared to furosemide alone (pooled NMD = −1.7 pg/mL, 95% CI [−21.9, 18.5]; Figure 15).[40,41,47] Montgomery et al reported a nonsignificant net increase in aldosterone, but the estimate was imprecise with a large confidence interval.

Figure 15. Serum Aldosterone: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Net decrease in serum aldosterone is considered to be a favorable outcome.
* Unit used for aldosterone was not reported; † Compared oral NaCl with furosemide to furosemide alone.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; HSS=hypertonic saline solution (or oral sodium with furosemide); N=sample size; NMD=net mean difference; RoB=risk of bias.

Plasma Renin Activity (PRA)

One RCT found no significant difference in PRA from baseline to at the end of 24-hr intervention in patients who received HSS with furosemide compared to furosemide alone (net *median* difference = −0.1 ng/mL/hr).[41] One study reported no significant difference in renin levels from baseline to in-hospital follow-up (4 days) for patients who received HSS with furosemide intervention compared to furosemide alone (net *median* difference = 2.2, unit not reported).[40]

Clinical Outcomes

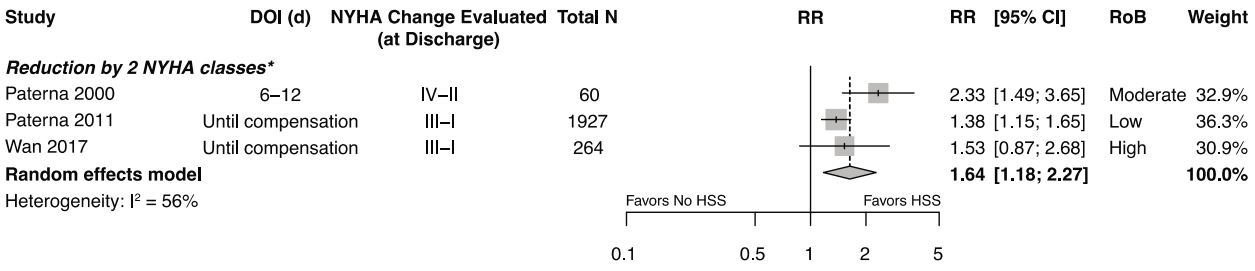
Clinical Congestion Score

No study reported data on a clinical congestion score.

Heart Failure–Related Symptoms

Three RCTs reported the change in NYHA functional class from admission to discharge.[33,37,43] In 2 studies (Paterna 2000 and Paterna 2011), all patients had a reduction in NYHA class prior to discharge (by 1 or 2 classes); in Wan et al, 88% had improvement. Pooling data from the 3 studies found that those randomized to HSS and furosemide were more likely to *improve* by 2 NYHA functional classes (*eg*, from class IV to II or from class III to I) than those on furosemide only (pooled RR = 1.64, 95% CI [1.18, 2.27]; Figure 16).[33,37,43] In the study by Wan et al (where 12% of patients did not improve in NYHA class), the RR for improving by 1 *or* 2 classes was not statistically significant (RR = 1.42, 95% CI [0.68, 2.96]).

Figure 16. NYHA Functional Class, Change in Class: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. The analyzed outcome is an improvement (in NYHA class). Thus, RR > 1 favors HSS (improved heart function is more likely with HSS).
* All patients improved by 1 or 2 NYHA classes in Paterna 2000 and Paterna 2011.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention; RoB=risk of bias; RR=relative risk.

Thirst

One RCT reported reduction in symptoms of thirst (TDS-HF score) from baseline to the end of 4-day intervention among patients randomized to oral NaCl with furosemide compared to furosemide alone. The score ranged from −1.2 to 0.11, with higher scores indicating greater thirst symptoms. No significant difference was found (NMD = −1.3 unit, 95% CI [−4.2, 1.5]).[47]

Shortness of Breath

Two RCTs reported data on shortness of breath.[41,45] One RCT reported fewer patients experienced dyspnea and systematic venous congestion 24 hours after treatment among patients randomized to HSS with furosemide compared to furosemide with 5% glucose (RR = 1.73, 95% CI [1.10, 2.71]).[41] A second RCT reported no significant difference in resting dyspnea and work effort dyspnea between the groups at the end of the intervention (RR = 0.46, 95% CI [0.1, 2.03] and RR = 0.52, 95% CI [0.278, 0.99], respectively).[45]

Composite Clinical Parameters

One RCT[43] found no significant difference in a composite measure of clinical symptoms (dyspnea, lower limb edema, weakness, palpitations, and fatigue) at discharge for patients administered HSS with furosemide or furosemide alone (RR = 0.99, 95% CI [0.92, 1.07]).

Mortality (All-Cause)

Four RCTs reported all-cause mortality.[35,37,40,43] Two RCTs reported no deaths in both groups during hospitalization.[37,43] One RCT (Issa et al) reported an atypically large number of in-hospital deaths compared with other studies. They reported 10 (50%) in-hospital deaths among patients randomized to HSS with furosemide and 4 (33.3%) in-hospital deaths for patients randomized to furosemide alone (RR = 1.5, 95% CI [0.60, 3.74]).[40] The fourth RCT reported 3 deaths during 30-day follow-up in patients treated with furosemide alone (0 vs 3 deaths, RD = −0.065, 95% CI [−0.145, 0.015].[35]

Health Service Utilization Outcomes

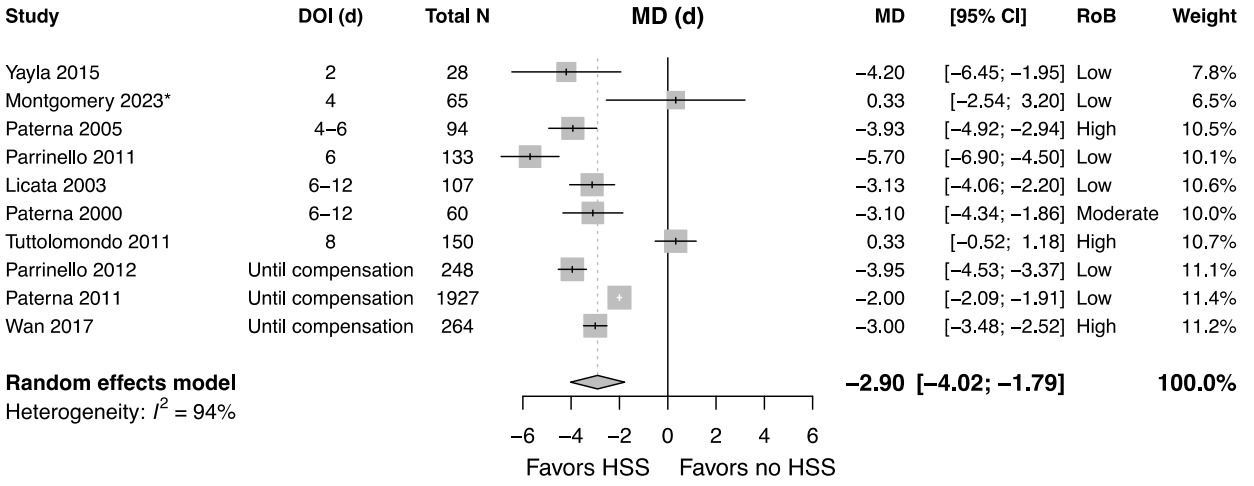
Readmission

One RCT[35] found a decrease in 30-day heart failure–related readmission for HSS with furosemide compared to furosemide alone (0 vs 12 events; RD = −0.26, 95% CI [−0.39, −0.13]). Another RCT found no significant difference in 30-day readmissions for oral NaCl with furosemide compared to furosemide alone (RR = 0.91, 95% CI [0.36, 2.31]).[47]

Length of Stay

Eleven studies (9 RCTs[33-35,37-39,42,43,47] and 2 NRCSs[36,44]) reported hospital length of stay. One NRCS[44] reported a longer median length of stay for patients who received HSS compared to no HSS (median difference = 11 days). This study did not report data to estimate a variance between groups and thus was excluded from meta-analysis. Of note, this study was an outlier both in direction and magnitude of difference in length of stay. The pooled estimate of the 10 remaining RCTs showed a shorter length of stay for sodium supplementation with furosemide compared to furosemide alone (pooled MD = −2.9 days, 95% CI [−4.0, −1.8]; Figure 17).[33-39,42,43] Among these 9 RCTs, there were 2 outlier studies that found no difference (Tuttolomondo 2011 et al and Montgomery 2023 et al). Excluding these studies in a post hoc sensitivity analysis yielded a slightly greater effect, with greater precision (pooled MD = −3.5 days, 95% CI [−4.3, −2.7], I^2 = 94%). Of note, Montgomery 2023 et al was the only study conducted in the US, and it found no significant difference between oral NaCl with furosemide compared to furosemide alone (MD = 0.3 days, 95% CI [-2.5, 3.2]).

Figure 17. Length of Hospital Stay: Supplemental Sodium (With Furosemide) versus Furosemide



Notes. Shorter length of stay is considered to be a favorable outcome.
* Compared oral NaCl with furosemide to furosemide alone.
Abbreviations. CI=confidence interval; d=day; DOI=duration of intervention N=sample size; MD=Mean difference; RoB=risk of bias.

Transfer to Intensive Care Unit (ICU)

One US-based RCT found no significant difference in intensive care unit admission during hospitalization for oral NaCl with furosemide compared to furosemide alone (RR = 0.56, 95% CI [0.15, 2.15]).[47]

DISCUSSION

We identified 5 studies (4 RCTs and 1 NRCS) that compared a low sodium diet to higher sodium diet, and 15 studies (13 RCTs and 2 NRCSs) that compared HSS with furosemide or, in 1 instance, oral NaCl with furosemide, to furosemide alone. The most frequently evaluated outcomes for dietary sodium interventions were weight loss, diuretic dose during hospitalization, and all-cause mortality. For sodium supplementation studies, weight was the most frequently reported outcome followed by urine output, serum sodium, serum creatinine, and length of hospital stay. Only 1 study was conducted in the US and was not in the VA system. Key findings include the following:

Dietary Sodium Interventions

Intermediate Outcomes

- There is no evidence of a difference in serum creatinine (moderate confidence), BNP (low confidence) or BUN, urine output, serum Na, aldosterone, PRA, prescribed diuretics, or dose of diuretics between a low sodium and higher sodium diet (certainty of evidence not assessed).
- It is unknown if a low sodium diet affects NT-pro BNP (insufficient evidence).
- Fewer calories may be consumed by patients on a low sodium diet (low confidence).
- The studies did not evaluate eGFR or serum cystatin C.

Clinical Outcomes

- There is no evidence of a difference in clinical congestion score between a low sodium diet compared to higher sodium diet (moderate confidence).
- Perceived thirst, but not other HF symptoms (shortness of breath or general well-being), may be greater for patients who receive a low sodium diet compared to higher sodium diet (certainty of evidence not assessed).
- It is unknown if a low sodium diet affects weight loss or mortality (insufficient evidence).
- Patients were adherent to the prescribed sodium diet (certainty of evidence not assessed).

Health Service Utilization Outcomes

- There were no significant differences in 30-day readmission or length of stay between a low sodium diet compared to higher sodium diet (low confidence).

Sodium Supplementation With Furosemide

Intermediate Outcomes

- Sodium supplementation with furosemide may decrease serum creatinine (moderate confidence) and BNP (low confidence), but not NT-proBNP (low confidence).

- Sodium supplementation with furosemide may increase urine output, serum sodium, and eGFR, and may decrease BUN. There is no evidence of differences in cystatin C, serum aldosterone, or PRA (certainty of evidence not assessed).
- The studies did not evaluate caloric intake.

Clinical Outcomes

- Sodium supplementation with furosemide may decrease weight (moderate confidence), reduce thirst symptoms (certainty of evidence not assessed), and improve NYHA functional class from admission to discharge (certainty of evidence not assessed).
- There may be no difference in shortness of breath or a composite measure of HF symptoms (certainty of evidence not assessed).
- It is unknown if sodium supplementation with furosemide affects mortality (insufficient evidence).
- The studies did not evaluate a clinical congestion score.

Health Service Utilization Outcomes

- Sodium supplementation with furosemide may reduce length of hospital stay (moderate confidence).
- It is unknown whether sodium supplementation with furosemide reduces 30-day readmission or intensive care unit admission during hospitalization (insufficient evidence).

SUMMARY

ADHF is 1 of the leading causes of hospitalization and rehospitalization in the US.[4] For decades, patients hospitalized with ADHF have been prescribed a restricted sodium diet with diuretic therapy. One surprising finding from this review was that only 5 relatively small studies, with only 381 analyzed patients, evaluated the effect of restricting dietary sodium in an inpatient setting. The goal of restricting sodium in ADHF patients is to reduce fluid retention and congestion. Yet there were no significant differences in weight change, urine output, and clinical congestion score from baseline to last in-hospital measurement between patients who received restricted or higher sodium diets. Furthermore, for most prioritized intermediate, clinical, and health service utilization outcomes, there was no significant difference between patients who received a restricted or higher sodium diet. Importantly, restricting dietary sodium may be associated with harms. Fewer calories were consumed by patients who received a restricted diet (presumably because they did not like the taste of their food), and 2 studies reported increased thirst for patients who received a restricted sodium diet combined with fluid restriction.[29,31] It is possible that this may partially explain why this strategy did not reduce hospital length of stay or other HF symptom metrics. Based on these data, the results suggest that a restricted sodium diet may *not* improve inpatient outcomes and may potentially result in poor experience with care. Unfortunately, these additional outcomes were not reported in all the included studies. Also, these findings are based on only small studies, mostly conducted in Brazil.

Unlike the restriction of dietary sodium, there is a larger evidence base evaluating the effect of combining furosemide with bolus sodium in the form of HSS or oral NaCl (15 studies and total analyzed $N = 3,483$). HSS is hypothesized to ameliorate diuretic resistance by shifting water from interstitial compartment, thus restoring effective intravascular volume and improving renal blood flow. In addition, HSS is expected to reduce hyperactivation of the renin-aldosterone-angiotensin pathway and help reduce the sodium-avid state of the kidneys.[18] Consistent with this hypothesis, we found that HSS (or in 1 instance oral NaCl tablets) and furosemide compared to furosemide alone yielded a significant net improvement in kidney function (net reductions in serum creatinine and BUN and a net increase in eGFR), increased urine output, and reduced weight. Indirect evidence (across studies) suggests that improvements in kidney function and serum sodium become evident after about 4 to 6 days of treatment.

Despite evidence to suggest the efficacy of sodium supplementation as an adjuvant therapy for loop diuretics, providers may still have concerns that administering sodium to people with ADHF can lead to sodium overcorrection or pulmonary edema. Notably, though, the average sodium increase in these interventions was ~6 mEq/L, which is lower than the maximum of 8 mEq/L per 24 hour change in sodium that is deemed safe in acute correction. There were no reports of worsening pulmonary edema or hypoxia with administration of sodium supplementation in these studies, while shortness of breath symptoms and NYHA class improved across studies.

STRENGTHS AND LIMITATIONS OF THE EVIDENCE BASE

The evidence base on restricting dietary sodium has several important limitations. First, only 5 small studies evaluated restricted dietary sodium interventions in an inpatient setting. Second, 2 of the 4 RCTs had major methodological limitations due to missing outcome data, not following an intent-to-treat analysis, or using hospital record number to randomize patients. Third, 2 studies did not clearly define how long patients were administered a restricted diet, which we assumed was for the duration of their hospitalization.[28,30] Lastly, the few, small studies combined with heterogeneity in maximum sodium consumption (range 0.8 g/day to 2.4 g/day) makes it challenging to know whether outcomes may differ by the amount of prescribed sodium.

Most studies evaluating HSS (or oral sodium) and furosemide had low risk of bias (*ie*, no major methodological weaknesses). We synthesized data based on the last in-hospital measurement; however, there was meaningful variation across studies in the timing of outcome assessment. Some studies evaluated outcomes immediately after the intervention and others at discharge. At a minimum, future studies should report outcomes at admission, after the intervention, and at discharge. In addition, studies inconsistently reported whether they restricted dietary sodium. Lastly, variation across studies in the duration of intervention (24 hours to 12 days) and dose of furosemide (conventional or high dose) makes it challenging to identify the best sodium supplementation with diuretic strategy.

Although of importance to stakeholders, studies were inconsistent in whether they reported HF-related symptoms (and which symptoms), and none of the diet studies reported change in NYHA class. Of crucial importance to determine who might benefit most (or least) from the interventions, the studies did not report differences in effectiveness by patient characteristics (age, sex, or race/ethnicity), comorbid conditions, or community dietary sodium intake. Only 2 dietary studies reported baseline data on race/ethnicity[29,31] (only reporting the proportion of

White participants), and only the US-based sodium supplementation study (or oral sodium) reported data by race/ethnicity (only reporting the proportion of White and Black participants). The studies did not report outcomes by existing versus new-onset HF or preserved versus reduced ejection fraction. However, 3 studies found that HSS and furosemide resulted in meaningful improvements in NYHA functional class from admission to discharge. Finally, no study compared a dietary sodium restriction to HSS and furosemide.

IMPLICATIONS FOR VA POLICY AND PRACTICE

HF is highly prevalent among the Veteran population and is an important cause of hospitalization, morbidity, and mortality in the VA.[3] Providing the best care to Veterans hospitalized with decompensated heart failure is paramount to the VA's mission. No study was conducted in the VA and only 1 study (oral sodium tables) was conducted in the US. All 4 dietary sodium RCTs were conducted in Brazil and most HSS studies were conducted in Europe. Two separate author groups each conducted 2 of the European studies,[36,38,39,45] and a third author group conducted 3 of the European studies.[33,35,37] Men were the majority in most studies (range 32%–81%; the VA population is 89% male) and no study reported effectiveness by sex. Despite these differences, the main overall findings likely translate to the VA population, as the underlying biology and pathophysiologic mechanisms are not likely different by country. It is also reasonable to hypothesize that the finding of a reduction in length of stay for sodium supplementation with diuretics may be reproduced in the VA, but it is likely that the magnitude of change in length of stay (a measure particularly sensitive to a health system's characteristics) may be substantially different than found in mostly European studies. Veterans Integrated Services Networks with strong transitional care programs (*eg,* Hospital in Home and Cardiac Rehabilitation programs) are likely in the best position to leverage the observed reductions in length of stay for sodium supplementation. However, the single US study found no significant difference in hospital length of stay between oral sodium tablets with furosemide compared to furosemide alone.

As a high reliability organization, the VA should consider adapting and implementing the best evidence for Veterans with ADHF within its care delivery system. Our findings call for the careful review of the routine inpatient practice of severely restricting sodium intake for patients admitted with ADHF. While physiologic measures were largely unchanged with low sodium diets, the reduction in calories is a serious concern for the Veteran population who may be fluid overloaded ("overweight") and malnourished. The use of HSS (or oral sodium supplementation) with loop diuretics to augment diuresis deserves consideration for inclusion in hospital protocols as a strategy for ADHF.

As VA Medical Centers and providers evaluate the merits of sodium supplementation, they will also need to consider broader implementation needs and barriers. Providers and systems may be reluctant to change practice. The pathophysiology of sodium in HF is generally discussed in medical curricula as something to be avoided. The counterintuitive nature of administering a high-sodium solution to patients in ADHF, concerns of over-correction or precipitation of pulmonary edema, and limited experience of providers will require education, partnership with cardiovascular and renal specialists, buy-in from leadership, and clear protocols. In addition, HSS will require greater utilization of clinical resources for patient monitoring with an appropriate safety protocol in place. Furthermore, clinical experience with the use of HSS for

ADHF likely varies between facilities, and training of medical staff will be critical to promote the safe use of HSS in selected patients with ADHF.

Limited evidence of RCT data from North America suggests a unique opportunity for VA hospitals to evaluate effectiveness and implementation of this strategy in the US and to fill the gaps in evidence for VA providers and policy makers. Conducting studies in the US would be particularly informative to understand the effect of intervention on health system outcomes pertinent to the US (such as length of hospital stay), which are likely to differ substantially across different health systems and countries. In addition, interviews with Veterans, providers, and Medical Center leadership can identify barriers and facilitators to implementation of clinical interventions employing sodium supplementation with loop diuretic protocols. After systems adopt these protocols, effectiveness and safety measures can be evaluated by using the VA data.

RESEARCH GAPS/FUTURE RESEARCH

Despite millions of people affected by HF worldwide, there is limited evidence on the effect of prescribed sodium interventions in an inpatient setting. Fewer than 400 people contributed data to the dietary sodium intake studies and fewer than 3,500 people contributed data to the sodium supplementation studies. There is a need for a well-designed, adequately powered RCT of pragmatic design to assess the effectiveness of HSS infusion (and possibly separately oral supplementation) for patients admitted with ADHF. There was variation in HSS administration (concentration ranged from 1.15% to 7.5%), tailoring dosage (tailoring or fixed), and duration of treatment. There are several broader research needs. Future studies should focus on examining differences in effectiveness by patient characteristics (age, sex, or race/ethnicity), HF phenotypes, chronicity of HF, and comorbid conditions. There is also a need to understand patient quality of life, experience, and satisfaction with care. As protocols are translated into practice, there will be a need to evaluate implementation efforts which can be incorporated into the pragmatic research design.

The evidence regarding restricted in-hospital dietary sodium is small. Future, well-conducted, larger studies would be needed to effectively evaluate the dietary sodium restriction. However, given the reluctance of patients to have their dietary sodium restricted (as evidenced by decreased caloric intake), the lack of evidence of a beneficial effect of restricted dietary sodium (to date), and the apparent effectiveness of sodium supplementation with furosemide treatment, it is unclear whether future studies of restricted in-hospital dietary sodium are warranted.

STRENGTHS AND LIMITATIONS OF THE SYSTEMATIC REVIEW PROCESS

Our review represents the most up-to-date report evaluating the evidence the practice of dietary sodium restriction and the use of HSS (or oral sodium supplementation) with furosemide among hospitalized patients with ADHF. This evidence review has several limitations. There was variation in the dietary sodium intake and sodium supplementation administration strategies, and we were unable to compare effects by dosing or duration. Outcomes of 30-day mortality and 30-day readmission may be affected by care after discharge, but we were unable to evaluate corresponding outpatient care protocols. We were likewise unable to investigate potential sources of heterogeneity of treatment effects (explanations for differences across studies) because of small numbers of studies and lack of reporting on many characteristics of interest or

of subgroup analyses. A strength of our review was the focus on hospitalized patients. Studies examining dietary interventions in outpatient settings are challenging to conduct because sodium consumption is documented via patient reported diaries. Documenting (and managing) sodium consumption in an inpatient setting is likely easier, and thus reported intakes are likely more accurate. While we did not define a priori sensitivity analyses, the post hoc sensitivity analyses based on removing substantive outliers provide important supportive evidence.

CONCLUSIONS

Findings from this review call into the question the conventional practice of restricting dietary sodium for managing ADHF in an inpatient setting. Only a few studies examined the effect of restricting dietary sodium, and these studies had important methodological limitations. There was no evidence of differences in most intermediate, clinical, or health service use outcomes for patients prescribed a restricted sodium diet compared to a higher sodium diet, but patients consumed fewer calories on a low sodium diet compared to a higher sodium diet. Studies provide insufficient evidence for the effect of numerous outcomes, including mortality. Patients who received HSS (or in 1 instance, oral sodium supplementation) and furosemide, compared to furosemide alone, had clinical improvements in intermediate, clinical, and health service use outcomes, particularly related to effective diuresis and length of hospital stay, without evidence of deleterious kidney or HF effects. The effects of sodium supplementation and furosemide therapy may not become evident until at least 4 to 6 days of treatment. However, especially since little research has been conducted in the US, there is a need for well-designed and large RCTs to further assess the effectiveness of sodium supplementation and furosemide treatment for inpatients with ADHF. There is a particular need for future research to examine heterogeneity of treatment effects based on patient characteristics and to identify the optimal duration, dose, and protocol of sodium supplementation treatment. While more rigorous trials would be needed to determine whether restricted dietary sodium is effective in the inpatient setting, the apparent benefit of sodium supplementation and furosemide treatment may preclude the need for additional dietary studies.

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