Circulation: Heart Failure

ORIGINAL ARTICLE

Sodium Restriction in Patients With Heart Failure: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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BACKGROUND: Sodium restriction is a nonpharmacologic treatment suggested by practice guidelines for the management of patients with heart failure (HF). In this study, we synthesized the data from randomized controlled trials (RCTs) evaluating the effects of sodium restriction on clinical outcomes in patients with HF.

METHODS: In this aggregate data meta-analysis, Cochrane Central, MEDLINE (Medical Literature Analysis and Retrieval System Online), Embase Ovid, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus databases were searched up to April 2, 2022. RCTs were included if they investigated the effects of sodium/salt restriction as compared to no restriction on clinical outcomes in patients with HF. Outcomes of interest included mortality, hospitalization, change in New York Heart Association functional class, and quality of life (QoL).

RESULTS: Seventeen RCTs were identified (834 and 871 patients in intervention and control groups, respectively). Sodium restriction did not reduce the risk of all-cause death (odds ratio, 0.95 [95% CI, 0.58–1.58]), hospitalization (odds ratio, 0.84 [95% CI, 0.62–1.13]), or the composite of death/hospitalization (odds ratio, 0.88 [95% CI, 0.63–1.23]). The results were similar in different subgroups, except for the numerically lower risk of death with reduced sodium intake reported in RCTs with dietary sodium at the 2000 to 3000 mg/d range as opposed to <2000 mg/d (and in RCTs with versus without fluid restriction as a co-intervention). Among RCTs reporting New York Heart Association change, 2 RCTs (which accounted for two-thirds of the data) showed improvement in New York Heart Association class with sodium restriction. Substantial heterogeneity existed for QoL: 6 RCTs showed improvement of QoL and 4 RCTs showed no improvement of sodium restriction on QoL.

CONCLUSIONS: In a meta-analysis of RCTs, sodium restriction was not associated with fewer deaths or hospitalizations in patients with HF. Dietary sodium restriction may be associated with improvements in symptoms and QoL.

Key Words: heart failure ■ meta-analysis ■ randomized controlled trial ■ salts ■ sodium

Heart failure (HF) is a major public health concern that affects >64 million people worldwide.[1] The prevalence of HF is expected to increase due to the aging population and improvements in pharmacologic and nonpharmacologic care, which will further impact hospitalization rates and health care costs.[2] Importantly, and despite improvements in HF therapy and survival, patients' health-related quality of life (QoL) is substantially affected and the risk for future events remains high; the 1- and 5-year survival has been estimated to be 87% and 57%, respectively.[1]

The potential contribution of dietary sodium consumption to fluid overload in the context of HF has been acknowledged, and restricting dietary sodium consumption is a common self-care recommendation for patients with HF. This stems from an understanding of the pathophysiologic basis of sodium and fluid handling within

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WHAT IS NEW?

- Following the recent publication of the SODIUM-HF trial (Study of Dietary Intervention Under 100 mmol in Heart Failure), it is still unclear what the totality of randomized controlled trial data to date suggests about the efficacy of this nonpharmacologic measure in the management of patients with HF.
- In an aggregate data meta-analysis, we identified 17 randomized controlled trials investigating the effects of dietary sodium restriction compared with a less salt-restrictive intake or no sodium restriction on clinical outcomes in patients with HF.
- Sodium restriction did not reduce the risk of all-cause death, hospitalization, or the composite of death/hospitalization in patients with HF.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The current evidence does not support dietary sodium restriction for reducing mortality or hospitalization, but the therapy may have a role in improving symptoms and quality of life in patients with HF. Despite the lack of significance, more strict sodium restriction (<2000 mg/d) was associated with worse outcomes compared with less strict sodium restriction (ie, 2–3 g/d). As the baseline sodium intake was generally moderate in our pooled study population, the findings might not be generalizable to populations with higher dietary sodium intake and further studies might be warranted to explore the impact of sodium restriction in those populations.

Nonstandard Abbreviations and Acronyms

GOURMET-HF	Geriatric Out of Hospital Randomized Meal Trial in Heart Failure
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
NYHA	New York Heart Association
OR	odds ratio
QoL	quality of life
RCT	randomized controlled trial
SODIUM-HF	Study of Dietary Intervention Under 100 mmol in Heart Failure

different basic and clinical models of HF. For example, patients with HF have diminished renal perfusion that leads to an activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system as a compensatory mechanism to maintain cardiac output by increasing sodium and water retention. Vasoconstriction and volume overload are further affected in HF by alterations in the systems that normally counteract sympathetic nervous system and renin-angiotensin-aldosterone system activation.[3] However, current clinical evidence supporting the practice of dietary sodium restriction is inconsistent, leading to a lack of consensus on the recommended level of restriction among the major guidelines for the management of HF (Table 1).[4–10]

The interest in investigating the effects of dietary sodium restriction on QoL and clinical outcomes in patients with HF has increased over the last decade.[11–14] In 2018, a systematic review of 9 randomized clinical trials of sodium restriction in patients with HF highlighted the inconsistency of outcomes, trial design, and interventions.[15] New evidence has emerged since the prior systematic review, thus, the purpose of this work was to provide an updated review and meta-analysis of the evidence of the effects of dietary sodium restriction on clinical outcomes in adult patients with HF.

METHODS

The study protocol and data that support the findings of this study are available upon reasonable request from the corresponding author (J.A. Ezekowitz). Randomized controlled trials (RCTs; both cross-over and parallel groups designs) in any language, with any length of follow-up and any outcome measure used, were considered if they studied the effect of sodium or salt restriction (with or without fluid restriction as a co-intervention) in patients with HF (both inpatient and outpatient settings, any New York Heart Association [NYHA] class, any left ventricular ejection fraction status) as compared with no sodium/salt restriction or less strict sodium restriction regimens. RCTs that merely investigated the effect of educational programs on the patients' adherence to sodium restriction were excluded. The PICOS (population, intervention, comparator, outcomes, study design) that was used in this aggregate data meta-analysis is provided in Table S1. The systematic review was previously registered in PROSPERO (International Prospective Register of Systematic Reviews; Study Unique Identifier: 326954).

The following databases were screened for eligible RCTs published from inception until April 2, 2022: Cochrane Central Register for Controlled Trials in the Cochrane Library, MEDLINE (Medical Literature Analysis and Retrieval System Online), Embase Ovid, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus. The search strategy for each database is provided in Table S2. The bibliographies of the included articles were also reviewed for identifying potential eligible studies. No language restriction was applied for the search, and there were no specific restrictions on the publication date. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, 2 investigators (N. Sepehrvand and E. Colin-Ramirez) independently screened the study titles and abstracts and selected potential studies. In case of ambiguity about the eligibility of an individual study based on title and abstract, the full-text article was reviewed. Any uncertainty or discrepancy was resolved upon further discussion and via input from J.A. Ezekowitz. This study is a meta-analysis and, as such, we are not required to seek approval from an institutional review board.

Table 1. Guideline Recommendations About Salt Restriction in Patients With HF

Guideline	Year	Sodium intake recommendation	Level of evidence
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand[4]	2018	<2 g/d	Not stated
Canadian Cardiovascular Society[5]	2017	2–3 g/d	Weak recommendation; low-quality evidence
American College of Cardiology/American Heart Association/Heart Failure Society of America[6]	2022	For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms.	C
Academy of Nutrition and Dietetics[7]	2018	2–3 g/d	Fair
Heart Failure Society of America[8]	2010	2–3 g/d; <2 g/d in severe HF	C
European Society of Cardiology[9]	2021	Avoiding excessive salt intake (>5 g/d)	Not stated
National Institute for Health and Care Excellence[10]	2018	Do not routinely advise people with HF to restrict their sodium consumption.	Not stated
		Reduce intake for people with high levels of salt consumption.	

HF indicates heart failure.

Data Extraction

After selecting the final set of included studies, 2 investigators (N. Sepehrvand and E. Colin-Ramirez) independently extracted data about study characteristics and patient populations into a predesigned electronic form. The discrepancies were resolved through discussion and with input from the third investigator (J.A. Ezekowitz). In case of missing data, we contacted the authors of the individual studies to access any potential unpublished data. Data were extracted for the following variables: study design, patient population (inpatients and outpatients), setting, HF type (HF with preserved and reduced ejection fraction [HFpEF and HFrEF]), exclusion criteria, sample size, intervention, co-interventions, comparator, studied outcomes, results; as well as age, sex, HF cause, and medications. Data were extracted specifically on the outcomes of mortality, hospitalization, composite outcome of death and hospitalization, NYHA class change, and change in the QoL.

Quality Assessment

Included RCTs were evaluated in terms of the risk of bias using the Cochrane Risk of Bias tool. The quality of evidence for each outcome was evaluated with the Grading of Recommendations Assessment, Development and Evaluation method,[16] exploring the 5 different Grading of Recommendations Assessment, Development and Evaluation domains including study limitations, consistency of effect, imprecision, indirectness, and publication bias. Study quality assessment was also done independently by N. Sepehrvand and E. Colin-Ramirez, and the discrepancies were resolved through discussion and via input from a third investigator (J.A. Ezekowitz).

Subgroup Analysis

We assessed the effect of salt or sodium restriction in different pre-specified subgroups including the inpatient versus outpatient settings, HFrEF versus overall HF or HFpEF groups, studies with dietary sodium <2000 or 2000 to 3000 mg/d in the intervention arm, with and without fluid restriction as a co-intervention, and with the duration of follow-up < or ≥6 months.

Sensitivity Analysis

In a sensitivity analysis, we explored the impact of including the 6 RCTs[17–22] that met the eligibility criteria but were excluded from the main analysis due to the use of co-interventions other than fluid restrictions (eg, hypertonic saline solutions or high dose of loop diuretics) and uncertainties about their implementation or reports. For missing data on outcomes, such as mortality or hospitalization, we explored different best-case and worst-case scenarios in the pooled analysis.

Statistical Analysis

We used random-effects models with the Mantel-Haenszel test to pool data on dichotomous outcomes such as all-cause mortality. Odds ratios (OR) and respective 95% CI were calculated for all categorical outcomes. For continuous variables, mean difference and 95% CI were reported. Heterogeneity across the studies was quantified using the I^2 statistic (I^2 >50% suggested substantial heterogeneity).[23] Publication bias was evaluated visually through Funnel plots or through Egger test in outcomes with at least 10 studies. Univariable meta-regressions were done to determine the impact of the study year, sample size, and follow-up time on outcome and heterogeneity. Review Manager version 5.0 and R version 4.1.2 were used for statistical analyses.

RESULTS

The results of the systematic search from inception to April 2, 2022, and the selection of studies according to the inclusion and exclusion criteria are shown in Figure 1. The study of Colin-Ramirez et al[24] was identified by reviewing the bibliography of the included studies. A total of 17 RCTs with 1683 participants were pooled in the meta-analysis (Table 2), while 6 RCTs were excluded from the main analysis but were included in a sensitivity analysis.

Fifteen RCTs of the included studies were parallel-designed RCTs, and the remaining 2 were cross-over RCTs.[24,28] The majority of the trials were from the outpatient setting studying patients with chronic HF.[24,26–32,34,36,38–40] However, 4 RCTs[25,33,35,37] investigated the effect of salt restriction in patients with acute decompensated HF in the inpatient setting. Nine studies included only patients with HFrEF,[24–30,32,38] Machado d'Almeida et

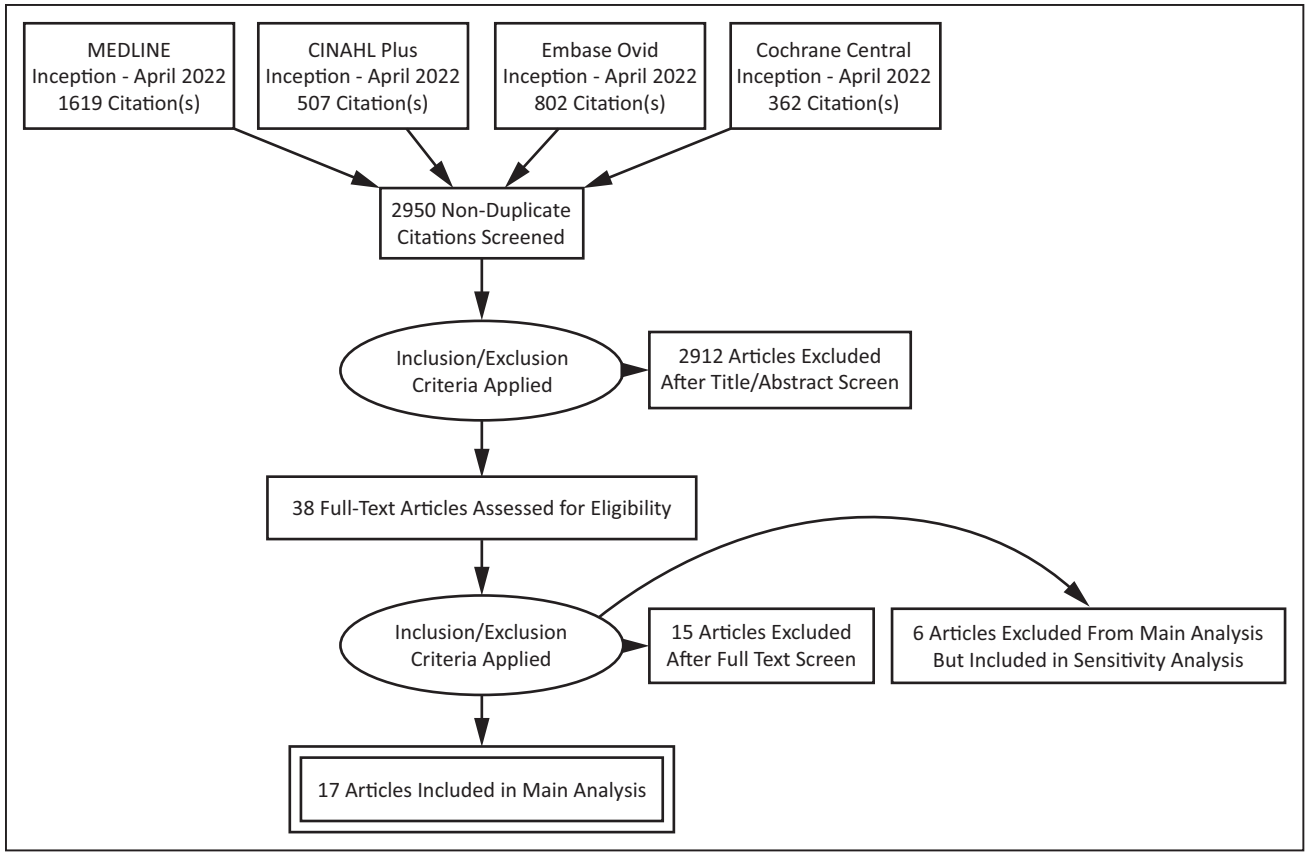

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
CINAHL indicates Cumulative Index to Nursing and Allied Health Literature; and Medline, Medical Literature Analysis and Retrieval System Online.

al[35] studied only patients with HFpEF, but others included patients with both HFrEF and HFpEF.[31,33,36,37,39,40] Ten studies were open-label, while there were 5 and 2 studies with single-blind[30–32,36,37] or double-blind[26,38] designs, respectively. Table 2 summarizes the characteristics of the included trials. Table 3 outlines the results of the included RCTs on the outcomes of death, hospitalization, and changes in NYHA class and QoL.

Patient characteristics of the participants (834 patients in the intervention group and 871 patients in the control group) of the 17 included RCTs are provided in Table S3. The mean age ranged from 52 to 74 years, and the trials included predominantly male patients (1069 patients, 64%). Included patients varied in terms of the HF cause, with 46% of patients in the pooled cohort being of ischemic origin. The frequency of comorbidities varied among the included studies, ranging from 28.0% to 98.4% for hypertension, 31.6% to 56.0% for diabetes, and 18.2% to 76.6% for ischemic heart disease. In 11 RCTs,[25,26,29,30,33–38,40] the salt intake was restricted to <2000 mg/d while others had dietary sodium intake at the range of 2000 to 3000 mg/d.[24,27,28,31,32,39] Six RCTs had fluid restriction as a co-intervention just in the intervention group,[24,27,31–33,35] while patients received fluid restriction in both arms in 3 studies.[25,30,37]

The assessment of the risk of bias is summarized in Figures S1 and S2. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation tool and was provided in Table S4. None of the outcomes were judged as having high certainty. All-cause mortality and HF-related hospitalizations were rated as moderate, and the rest of the studied outcomes were judged as having a low level of certainty.

All-Cause Mortality

Data on the outcome of all-cause mortality were available from 11 RCTs (Figure 2A).[24,26,32–40] Among 1492 patients, all-cause death occurred in 67 patients (31 patients [4.2%] in the sodium-restricted group and 36 patients [4.7%] in the control group). Sodium restriction did not reduce the risk of all-cause mortality (OR, 0.95 [95% CI, 0.58–1.58]). There was a low level of statistical heterogeneity among the included studies for the outcome of all-cause mortality (*P* value for χ^2=0.79; I^2=0%).

There was weak evidence suggesting potential heterogeneity in the all-cause mortality results driven by the year of publication (*P*=0.06; Figure S3). There was no evidence that study size or follow-up time was associated with outcome (*P*=0.13 and 0.57, respectively).

Table 2. Characteristics of the Included RCT

Study	Design	Patient population	Setting	HF type	Sample size	Intervention	Intervention, N	Duration of intervention	Fluid restriction	Comparator	Comparator, N
Cody et al[25]	Crossover RCT	Hospitalized patients with moderate to severe chronic HF	Inpatient	HFrEF	10	Very low sodium (230 mg/d)	10	14 d	Both arms at 2000 mL/d	Low sodium (2300 mg/d)	10
Kostis et al[26]	Parallel-designed RCT	Patients with chronic HF, HFrEF, and NYHA II–III	Outpatient	HFrEF	13	Combined nonpharmacologic intervention: sodium restriction (1200 mg/d) and weight reduction, graduated exercise training, and structured cognitive therapy	7	12 wk (84 d)	No	Placebo arm	6
Colin-Ramirez et al[27]	Pilot RCT	Adult patients with HF based on reduced systolic and diastolic function in echo	Outpatient	HFrEF	65	Sodium-restricted diet at 2000–2400 mg/d	30	6 mo	Intervention including fluid restriction to 1.5 L/d	Routine dietary advisories about decreased sodium and fluid intake but without any specific restriction	35
Alvelos et al[28]	Parallel-designed RCT	Adult patients with mild to moderate chronic stable HF with no exacerbations over the past 2 mo	Outpatient	HFrEF	24	Sodium restriction to 100 mmol/d (2300 mg/d)	12	15 d	No fluid restriction	Diet with usual salt intake	12
Damgaard et al[29]	Crossover RCT	Male patients with ADHF	Outpatient	HFrEF	12	Low sodium intake (70 mmol/d or 1610 mg/d)	12	1 wk	No fluid restriction	High sodium intake (250 mmol/d or 5750 mg/d)	12
Nakasato et al[30]	Single-blind RCT	Adult outpatients with mild to moderate HF (NYHA I–III) and LVEF ≤40% (past 6 mo)	Outpatient	HFrEF	50	Subgroup 2: Continue on 2 g of salt (800 mg sodium) per day for a week after a 1-wk run-in phase on low-salt diet	25	7 d	Both arms to maintain fluid intake at ≈1000 mL/d	Subgroup 1: To receive 6 g of salt (2400 mg of sodium) per day for a week after a 1-wk run-in phase on low-salt diet	25
Philipson et al[31]	Single-blind pilot RCT	Adult patients with stable HF, NYHA class II–IV, LV dysfunction; signs of fluid retention; 80 mg furosemide or equipotent doses of others diuretics for NYHA II or 40 mg for NYHA III–IV	Outpatient	HFrEF or HFpEF	30	Sodium-restricted diet of 2–3 g/d sodium (5–7.5 g/d salt) and fluid restriction to 1.5 L/d	17	12 wk (84 d)	Yes, in the intervention arm	General dietary recommendations from ESC HF guidelines delivered by dietitian or specialty-trained nurse	13
Colin-Ramirez et al[24]	Parallel-group RCT with blinded outcome assessors	Adult patients with HF based on reduced systolic and diastolic function in echo	Outpatient	HFrEF and HFpEF	203	Sodium-restricted (2000–2400 mg/d) and fluid-restricted (<1500 mL/d) diet	84	12 mo	Fluid restriction to <1500 mL/d in the IG	General nutritional recommendation	119
Philipson et al[32]	Single-blind multicentre RCT	Adult patients with stable HF, NYHA class II–IV, LV dysfunction; signs of fluid retention; on maximal tolerated doses of ACE inhibitor and BB, and 80 mg furosemide or equipotent doses of others diuretics for NYHA II or 40 mg for NYHA III–IV	Outpatient	HFrEF or HFpEF	97	Individualized salt and fluid restriction to reduce sodium intake to 2–3 g/d (5–7.5 g/d salt) to limit fluid intake to 1.5 L/d	49	12 wk (84 d)	1.5 L/d in the IG	Information given by the nurse-led HF clinics, eg, be aware not to drink too much and use salt with caution	48

(*Continued*)

Table 2. Continued

Study	Design	Patient population	Setting	HF type	Sample size	Intervention	Intervention, N	Duration of intervention	Fluid restriction	Comparator	Comparator, N
Aliti et al[33]	Parallel-group RCT with blinded outcome assessors	Adult patients hospitalized with ADHF, LVEF ≤45%, Boston criteria score ≥8 points, and LOS ≤36 h after hospital admission	Inpatient	HFrEF	75	Sodium restriction to 800 mg/d (2 g/d salt) and fluid restriction to 800 mL/d	38	7 d during hospital stay or until discharge in those with LOS <7 d.	Yes, in the intervention arm	Unrestricted sodium and fluid intake: 3000–5000 mg/d sodium (7.5–12.5 g/d salt) and >2500 mL of fluid	37
Colin-Ramirez et al[34]	Pilot RCT	Adult patients with HF, NYHA class II–III, and receiving GDMT	Outpatient	HFrEF and HFpEF	38	Low-sodium diet: 65 mmol/d or 1500 mg/d sodium (3.75 g/d salt)	19	180 d	Amount of fluid restriction not reported	Moderate intake: 100 mmol/d or 2300 mg/d sodium (5.75 g/d salt)	19
Machado d'Almeida et al[35]	Parallel-designed RCT with blinded outcome assessors	Patients admitted for decompensated HFpEF	Inpatient	HFpEF	53	Sodium and fluid restriction at 800 mg of sodium and 800 mL of fluid per day	30	7 d during hospital stay or until discharge in those with LOS <7 d	Yes, 800 mL/d in IG	Standard hospital diet; 4000 mg/d sodium (10 g of salt) and unlimited fluid intake	23
Hummel et al[36]	Single-blind multicentre RCT	Patients ≥55 y with history of hypertension, discharged from hospital with ADHF	Outpatient	HFrEF and HFpEF	66	Home-delivered sodium-restricted DASH diet food with 1500 mg/d sodium, 2100 Kcal, for 4 wk after hospital discharge in addition to the pamphlet "How to eat a low sodium diet" and phone calls from study staff every 2–3 wk	33	4 wk	No	Standard education pamphlet on "How to eat a low-sodium diet" and phone calls from study staff at 2–3 wk but without any specific prescription	33
Fabricio et al[37]	Single-blind RCT	Patients hospitalized with ADHF and randomized within 24 h of hospital admission	Inpatient	HFrEF and HFpEF	44	Low-sodium diet (3 g/d dietary salt, equal to 1200 mg/d sodium)	22	7 d	Both arms restricted to 1 L/d fluids	Normal-sodium diet (7 g/d salt equal to 2800 mg/d sodium)	22
Kalogeropoulos et al[38]	Double-blind Pilot RCT	Patients with HFrEF with recent hospitalization for HF within past 2 wk on optimal GDMT with SBP ≥100 mm Hg, who consume over 3000 mg daily of sodium based on 24-h urine sodium	Outpatient	HFrEF	27	Food with 1500 mg sodium content for 12 wk	12	12 wk (84 d)	No	Food with 3000 mg sodium content for 12 wk	15
Ivey-Miranda et al[39]	Double-blind RCT	Adult stable patients with chronic HFrEF on optimal treatment with both ACE inhibitor/ARB and BB, and SBP≥90 mm Hg	Outpatient	HFrEF	70	Sodium-restricted diet (2 g/d sodium)	37	20 wk	No	Diet with 3 g/d sodium	33
Ezekowitz et al[40]	Multinational open-label blinded end-point RCT	Adult patients with chronic HF (NYHA class II–III) receiving optimally tolerated GDMT	Outpatient	HFrEF and HFpEF	806	Low-sodium diet of <100 mmol (ie, 1500 mg) per day	397	12 mo	No	Usual care according to local guidelines	409

ACE indicates angiotensin-converting enzyme; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blockers; BB, β-blocker; DASH, Dietary Approaches to Stop Hypertension; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IG, intervention group; LOS, length of stay; LV, left ventricular; LVEF, left ventricular ejection fraction; N, number; NYHA, New York Heart Association; RCT, randomized controlled trial; and SBP, systolic blood pressure.

Table 3. Summary of Findings in the Included Randomized Controlled Trials

Study	Duration of F/U	Mortality	Hospitalization	Death/hospitalization	NYHA	HRQoL
Cody et al[25]	2 wk	NR	NR	NR	NR	NR
Kostis et al[26]	12 wk	1/6 died (meningococcal septicemia) in CG	NR	NR	NR	Nonpharmacologic measures resulted in improvement in mood indices, while placebo was associated with a trend towards worsening QoL.
Colin-Ramirez et al[26]	6 mo	NR	NR	NR	Baseline: IG: 18.5% class III, 22.2% class II, and 59.3% class I vs CG: 13.3% class III, 30% class II, and 56.7% class I; after 6 mo: IG: 7.4% class III, 18.5% class II, and 74.1% class I vs CG: 16.1% class III, 19.4% class II, and 64.5% class I; *P*=NS	Total HRQoL increased by 19.3±31.7% in the IG and by 3.2±18.4% in CG.
Alvelos et al[28]	15 d	NR	NR	NR	No difference in NYHA class change	NR
Damgaard et al[29]	1 wk	NR	NR	NR	NR	NR
Nakasato et al[30]	7 d	NR	NR		NR	Low-salt diet was associated with lower (ie, improved) MLHFQ scores.
Philipson et al[31]	3 mo	NR	NR		NR	HRQoL did not change due to intervention.
Colin-Ramirez et al[24]	12 mo	IG: 4 (4.7%), CG: 12 (10%)	CV hospitalization: IG: 10 (14.1%), CG: 23 (20.7%), *P*=0.17		NYHA improved significantly in both groups (*P*=NS)	NR
Philipson et al[32]	12 wk	IG: 1 (2.0%), CG: 1 (2.0%)	All-cause hospitalization: IG: 1 (2.0%), CG: 2 (4.1%)	NR	IG: NYHA I/II/III from 0/10/35 to 1/16/28, CG: NYHA I/II/III from 0/12/33 to 0/10/35, *P*=0.01	HRQoL did not change due to intervention (*P*=0.11)
Aliti et al[33]	30 d	Zero deaths during study period (0–7 d)	HF hospitalization: IG: 11 (29%), CG: 7 (19%)	NR	No difference in NYHA class at 30 d (IG: 2.16±0.9, CG: 1.89±0.8, *P*=0.16)	NR
Colin-Ramirez et al[34]	180 d (6 mo)	1 death in the CG.	NR	NR	No significant difference between arms in terms of NYHA class.	No difference in KCCQ at 6 mo between groups.
Machado d'Almeida et al[35]	30 d	IG: 2 patients (6.9%); CG: 2 patients (8.7%), *P*>0.99	All-cause hospitalization: IG: 12 patients (41.4%); CG: 10 patients (43.5%), *P*>0.99	NR	IG: NYHA I/II/III/IV from 0/2/15/13 to 0/5/13/5, CG: NYHA I/II/III/IV from 0/3/12/8 to 1/10/4/5, *P*=0.06 at 30-d F/U	NR
Hummel et al[36]	12 wk	No death within 30 d postdischarge. One death (3%) during 12 wk F/U in the CG.	At 12 wk, IG: 15 all-cause rehospitalization in 11 patients (33.3%), CG: 22 all-cause rehospitalization in 14 patients (42.4%), *P*=0.45; HF hospitalization: IG: 8 HFH in 7 patients (21.2%), CG: 18 HFH in 13 patients (39.4%), *P*=0.11	IG: 11 (33.3%), CG: 14 (42.4%)	NR	KCCQ OSS increased similarly between groups (*P*=0.38), but KCCQ CSS increase tended to be greater in the IG compared with CG (*P*=0.053).
Fabricio et al[37]	30 d	No in-hospital death, but 2 death (1 per arm) after discharge from hospital.	All-cause hospitalization: during the 30 d F/U, 31% of IG patients, and 33% of CG patients were readmitted (*P*=1.0)	NR	NR	NR
Kalogeropoulos et al[38]	12 wk postintervention F/U (24 wk in total)	There were no deaths.	All-cause and CV hospitalizations are the same: 5 patients (8 hospitalizations) in IG, and 4 patients (16 hospitalizations, 10 of which was only in 1 patient) in CG. HF hospitalization: IG: 2 HFH in 1 patient, CG: 7 HFH in 3 patients	IG: 5 (42%), CG: 4 (27%)	NR	KCCQ OSS and CSS improved in IG but did not change in CG.

(*Continued*)

Table 3. Continued

Study	Duration of F/U	Mortality	Hospitalization	Death/hospitalization	NYHA	HRQoL
Ivey-Miranda et al[39]	20 wk	14 patients experienced HF readmission and 1 patient died. Of the 15 events, 8 occurred in IG and 7 in CG.	HF hospitalization: 14 patients experienced HF readmission and 1 patient died. Out of the 15 events, 8 occurred in IG and 7 in CG.	IG: 8 (21.6%), CG: 7 (21.2%)	NR	No significant change in MLHFQ in the IG, but a trend for improvement in QoL in CG (P=0.052).
Ezekowitz et al[40]	12 mo postintervention	All-cause death occurred in 22 (6%) patients in IG and 17 (4%) in CG.	CV-related hospitalization occurred in 40 (10%) patients in IG and 51 (12%) patients in CG (HR, 0.82 [0.54–1.24]; P=0.36).	IG: 60 (15%), CG: 70 (17%)	Significant difference between groups in NYHA class at 12 mo, with the IG having greater likelihood of improving by 1 NYHA class than the CG (odds ratio, 0.59 [95% CI, 0.40–0.86]; P=0.0061)	Increases in KCCQ OSS, CSS and the physical limitation score were greater in IG than in CG between baseline and 12 mo.

CG indicates control group; CSS, clinical summary score; CV, cardiovascular; F/U, follow-up; HF, heart failure; HFH, HF hospitalization; HR, hazard ratio; HRQoL, health-related quality of life; IG, intervention group; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living With Heart Failure Questionnaire; NR, not reported; NS, not significant; NYHA, New York Heart Association; and OSS, overall summary score.

All-Cause Hospitalization

The outcome of all-cause hospitalization was reported in 5 RCTs.[32,35–38] Among 274 patients, all-cause hospitalization was reported in 69 patients (34 patients [24.2%] in the sodium-restricted group and 35 patients [26.1%] in the control group). Sodium restriction did not significantly reduce the risk of all-cause hospitalization (OR, 0.86 [95% CI, 0.48–1.57]; Figure S4). There was a low level of statistical heterogeneity among the included studies for the outcome of all-cause hospitalization (P value for χ^2=0.84; I^2=0%).

Cardiovascular Hospitalization

Cardiovascular-related hospitalizations were reported in 3 RCTs.[26,34,36] Among 1015 patients, cardiovascular-related hospitalization occurred in 133 patients (55 patients [11.4%] in the sodium-restricted group and 78 patients [14.5%] in the control group). Sodium restriction was not associated with a reduced risk of cardiovascular hospitalization (OR, 0.79 [95% CI, 0.54–1.15]; Figure 2B). There was a low level of statistical heterogeneity in the pooled analysis for cardiovascular-related hospitalization (P value for χ^2=0.47; I^2=0%).

HF-Related Hospitalization

HF-related hospitalization was only reported in 4 RCTs.[33,36,38,39] Among 238 patients, there were 56 patients with HF hospitalizations (26 patients [21.6%] in the sodium-restricted group and 30 patients [25.4%] in the control group). Sodium restriction did not reduce the risk of HF-related hospitalization (OR, 0.80 [95% CI, 0.39–1.64]) in the pooled analysis (Figure S5). In this analysis, there was a low level of heterogeneity (P value for χ^2=0.28; I^2=22%).

Composite of All-Cause Death or Hospitalization

Composite outcome of death or hospitalization was reported in 4 RCTs.[36,38–40] In the pooled cohort of 969 participants, the composite outcome occurred in 242 patients (110 patients [22.9%] in the sodium-restricted group and 132 patients [26.9%] in the control group). Sodium restriction was not associated with a significantly lower risk of the composite of death and hospitalization (OR, 0.81 [95% CI, 0.60–1.09]; Figure 2C). There was a low level of statistical heterogeneity in this pooled analysis (P value for χ^2=0.69; I^2=0%).

Change in NYHA Class

The change in NYHA class with salt restriction was reported in 8 RCTs.[24,27,28,32–35,40] The results of 5 trials,[24,27,28,33,34] accumulating 405 patients in total, showed no difference between arms in terms of the change of NYHA class from baseline to follow-up. The study of Machado d'Almeida et al[35] suggested a trend for the difference in NYHA class at 30-day follow-up (P=0.06). The studies of Philipson et al[32] and Ezekowitz et al[40] which included the majority of patients (903 patients, 66.3%) in the pooled cohort suggested an improvement in NYHA class with sodium restriction (Table 3).

Quality of Life

The study of Kostis et al[26] used mood indices as a measure of the QoL and showed nonpharmacologic measures in the intervention arm to be associated with improved mood indices, while there was a trend towards worsening QoL among controls. Colin-Ramirez et al[27] and Philipson et al[31,32] measured QoL using a non-specific measure, however, 2 and 4 RCTs, respectively, used the Minnesota Living with Heart Failure

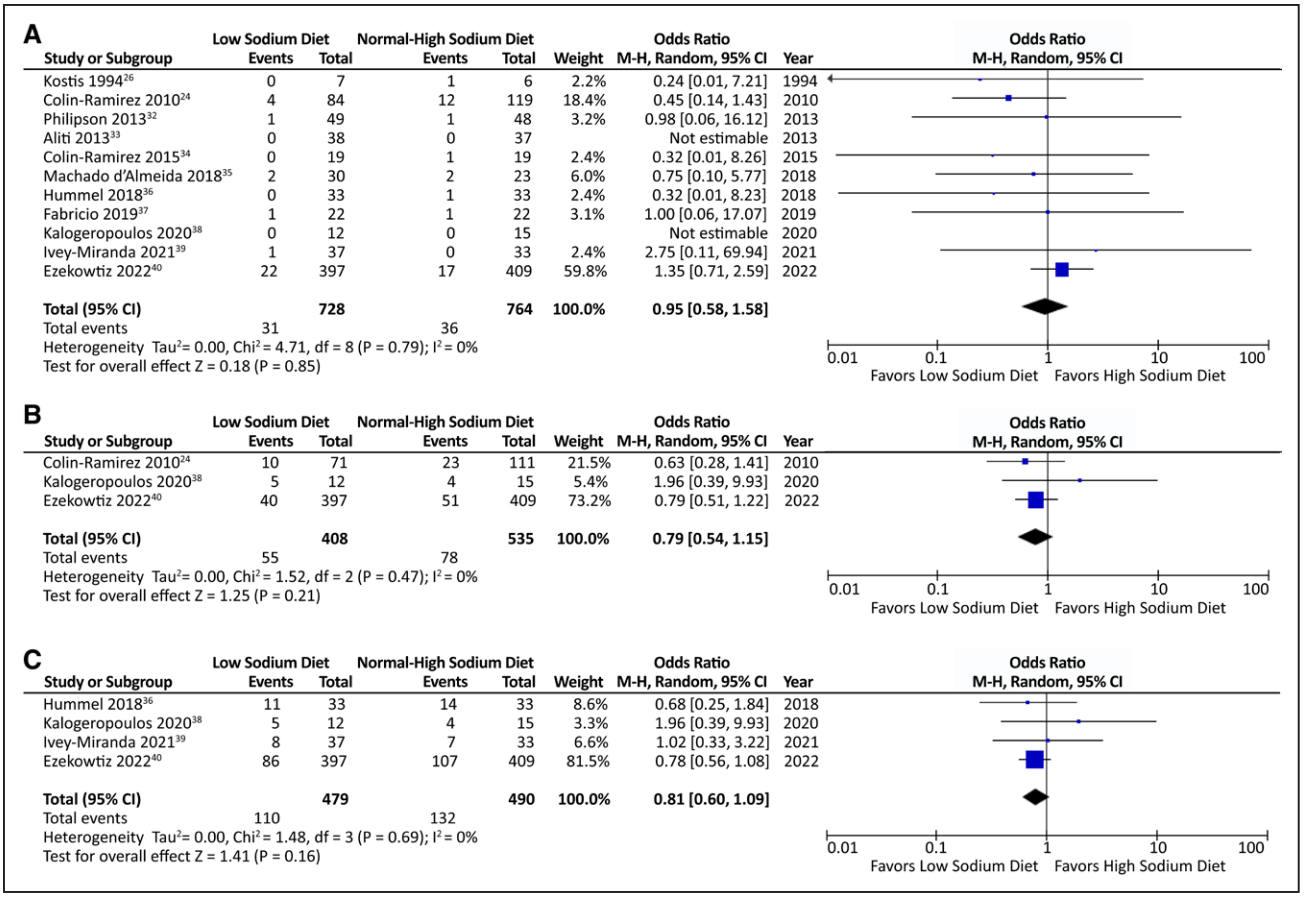

Figure 2. Forest plot of low-sodium vs normal-high–sodium diet for different outcomes.
A, All-cause mortality; **B**, cardiovascular hospitalization; and **C**, composite of all-cause death and hospitalization.

Questionnaire[30,39] and Kansas City Cardiomyopathy Questionnaire.[34,36,38,40] Six RCTs[26,29,30,32,36,39] showed improvement or trends for improvement in QoL measures with salt restriction, while 3 trials[31,32,34] showed no benefit of salt restriction on QoL and 1 study suggested a trend for improved Minnesota Living With Heart Failure Questionnaire in the control group but not the intervention group[39] (Table 3).

Subgroup Analysis

Similar outcome associations were found across studies with different HF classes (HFrEF versus HFpEF), study settings (outpatient versus inpatient), or follow-up periods (< or ≥6 months) in terms of all-cause mortality. Among the included studies, a sodium restriction to the range of 2000 to 3000 mg/d was associated with numerically lower risks of all-cause mortality (OR, 0.59 [95% CI, 0.21–1.65]), when compared with RCTs with sodium restriction to <2000 mg/d in the intervention arm (OR, 1.11 [95% CI, 0.62–1.97]). Similarly, the studies that had fluid restriction as a co-intervention showed a numerically lower risk of all-cause mortality compared with studies without fluid restriction as a co-intervention or those that had a fluid restriction in both study arms (Figures S6 through S11).

When pooling the existing data on the outcome of all-cause hospitalization, salt restriction was not associated with different risks of hospitalization in subgroups of studies of different HF subtypes (HFrEF versus HFpEF), studies with and without fluid restriction as co-intervention, different intensities of sodium restriction (<2000 or 2000–3000 mg/d sodium intake in the intervention arm), or those with < or ≥6 months follow-up period (Figures S12 through S16).

Sensitivity Analysis

In a sensitivity analysis, including 6 RCTs[17–22] that were excluded from the main analysis due to having co-interventions such as high-dose furosemide in both study arms beyond routine practice (Tables S5 through S7), 549 deaths occurred in a pooled cohort of 4185 patients from 16 trials, and sodium restriction was associated with a higher risk of all-cause mortality (OR, 1.92 [95% CI, 1.28–2.89]; I^2=43%; Figure S17).

Similarly, in a sensitivity pooled analysis of all eligible RCTs that reported any type of hospitalization,

hospitalization was reported in 1061 cases among the 4100 patients in the pooled analysis of 14 RCTs. Sodium restriction was associated with a higher risk of any hospitalization (OR, 1.93 [95% CI, 1.31–2.84]). However, the level of heterogeneity was high in this pooled analysis (*P* value for χ^2<0.001; I^2=75%; Figure S18).

Publication Bias Assessment

There was no publication bias using funnel plot for the outcomes studied in this meta-analysis (*P* value for Egger test =0.21 for all-cause mortality; Figure S19).

DISCUSSION

In this meta-analysis of 17 trials comprising 1683 adult patients with HF, we evaluated the most recent evidence stemming from RCTs assessing the effects of sodium restriction on clinical outcomes in HF. This work represents an updated meta-analysis of the effects of reduced sodium intake on clinical outcomes in patients with HF. We found that sodium restriction, regardless of the level of restriction, was not associated with a reduced or increased risk of all-cause mortality, hospitalizations (all-cause, cardiovascular-, or HF-related) or a composite outcome of death and hospitalization. Despite the inherent differences in the design and implementation among the included RCTs, the level of statistical heterogeneity was low in the pooled analysis for the above-mentioned outcomes.

In the sensitivity analysis, which included the 6 trials that were excluded from the main analysis due to uncertainties about their data integrity or applicability,[17–22] we found sodium restriction to be associated with a higher risk of mortality or hospitalization; however, moderate-to-high levels of heterogeneity were observed between studies included in those pooled analyses (I^2=43% for the outcome of all-cause death and 75% for any hospitalization).

This updated meta-analysis builds upon a previous systematic review by Mahtani et al,[15] which included 9 studies involving 479 participants and insufficient data on the primary outcomes of interest (cardiovascular-associated mortality, all-cause mortality, and adverse events, such as stroke and myocardial infarction), which precluded the conduct of a meta-analysis. Recently, the results of the GOURMET-HF (Geriatric Out of Hospital Randomized Meal Trial in Heart Failure),[36] SODIUM-HF (Study of Dietary Intervention Under 100 mmol in Heart Failure),[40] and PROHIBIT Sodium (Dietary Sodium Intake and Outcomes in Heart Failure),[38] among other trials significantly improved our understanding of the effects of this nonpharmacological intervention in patients with HF. SODIUM-HF is the largest RCT to date, testing the effects of sodium restriction in adult outpatients with HF, in which sodium intake <1500 mg/d was not associated with reduced all-cause mortality or hospitalizations.[40] This single trial contributed 59.8% and 73.2% of the total weight for the outcomes of all-cause mortality and cardiovascular hospitalization, respectively, in the current meta-analysis.[40]

There was a trend for a differential effect of sodium reduction on the outcome of all-cause mortality based on the intensity of sodium restriction. When the level of sodium restriction in the intervention arm was split at 2000 mg/d, a numerically higher risk of all-cause mortality was observed among trials with sodium restriction <2000 mg/d compared with those with a less strict level of restriction (2000–3000 mg/d). Although the difference was not significant, this observation generates a hypothesis that may require testing in future studies but suggests caution in implementing strict sodium restriction practices.

Baseline dietary sodium intake observed in both groups in SODIUM-HF trial as an international and multicenter study, suggested that the current usual care in HF leads to a dietary sodium intake between 2000 and 2300 mg/d.[40] The baseline dietary sodium intake may vary across different populations and countries around the world. Currently, the evidence does not support a beneficial effect or adverse effect of further dietary sodium restriction on the outcomes of mortality or hospitalization in patients with HF. However, it is important to note that the results of current meta-analysis may not be generalizable to populations with higher baseline sodium intake where stricter restriction might deliver differential clinical outcomes.

Among RCTs reporting the NYHA change, 2 RCTs accounted for two-thirds of the pooled cohort and showed improvement in NYHA class with salt restriction.[32,40] Others did not show any difference between groups with and without sodium restriction. Moreover, 6 RCTs showed improvement or trends for improvement in QoL measures with sodium restriction,[26,29,30,32,36,39] while 4 RCTs showed no benefit of salt restriction on QoL.[31,32,34,39] The data on the outcomes of the change in NYHA class or QoL was not suitable for meta-analysis and hence the findings were not definitive. Thus, further evidence would be warranted to support current practice in restricting sodium intake in patients with HF in the absence of consensus among HF clinical guidelines.

In the meta-regression analysis, there was a borderline association between earlier year of publication and the impact of sodium restriction on mortality reduction. This trend for association, although not statistically significant, may be explained by patients of earlier RCTs with limited medical therapies at their disposal being more prone to potential deleterious neurohormonal effects of high dietary sodium intake as opposed to current era patients with HF who are being treated routinely with inhibitors of renin-angiotensin-aldosterone system.

Our study has several limitations. First, not all of the trials included in this meta-analysis reported all outcomes,

thus, there were subgroups including just a few trials. Second, most of the included studies enrolled <100 participants, leading to a high contribution of SODIUM-HF trial to the results of the pooled analysis. Third, due to diverse levels of sodium restriction used across trials, it is not possible to attribute the lack of effects of dietary sodium reduction on clinical outcomes to any specific level of restriction; however, the subgroup analysis splitting dietary sodium restriction in the intervention arm at 2000 mg/d suggests a potentially differential effect of sodium restriction on all-cause mortality according to the intensity of restriction. Moreover, it should be noted that sodium restriction in particular, and nutritional interventions in general, are inherently challenging topics to study and analyze. It is hard to measure dietary sodium intake in a large population and dietary sodium and fluid intake may interact with the impact of HF medications or other dietary components. The findings of the meta-analysis could depend on factors such as length of follow-up or severity of HF in the included individual studies. Subgroups analyses in this study did not reveal significant heterogeneity in terms of effect in studies from outpatient or inpatient settings or those with differential follow-up periods. Although there was some disparity among the included studies in terms of the follow-up period and considering that the average follow-up period among studies was below 1 year, the meta-regression analysis did not reveal any impact of the duration of follow-up on the studied outcomes.

In conclusion, in this meta-analysis of 17 RCTs, sodium restriction was not associated with fewer deaths or hospitalizations in patients with HF, although sodium restriction might be associated with improvements in symptoms, as measured by NYHA class, or in QoL.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1–S19
Tables S1–S7

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