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ORIGINAL PAPER

Role of dietary sodium restriction in chronic heart failure: systematic review and meta-analysis

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Abstract

Background Dietary sodium restriction remains a guidelines-approved lifestyle recommendation for chronic heart failure (CHF) patients. However, its efficacy in clinical outcome improvement is dubious.

Objective The study evaluated whether dietary sodium restriction in CHF reduces clinical events.

Methods We performed a systematic review of the following databases: Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition, MEDLINE, Embase, Clinicaltrials.gov and Cochrane Library (trials) to find studies analysing the impact of sodium restriction in the adult CHF population. Both observational and interventional studies were included. Exclusion criteria included i.e.: sodium consumption assessment based only on natriuresis, in-hospital interventions or mixed interventions—e.g. sodium and fluid restriction in one arm only. The review was conducted following PRISMA guidelines. Meta-analysis was performed for the endpoints reported in at least 3 papers. Analyses were conducted in Review Manager (RevMan) Version 5.4.1.

Results Initially, we screened 9175 articles. Backward snowballing revealed 1050 additional articles. Eventually, 9 papers were evaluated in the meta-analysis. All-cause mortality, HF-related hospitalizations and the composite of mortality and hospitalisation were reported in 8, 6 and 3 articles, respectively. Sodium restriction was associated with a higher risk of the composite endpoint (OR 4.12 [95% CI 1.23–13.82]) and did not significantly affect the all-cause mortality (OR 1.38 [95% CI 0.76–2.49]) or HF hospitalisation (OR 1.63 [95% CI 0.69–3.88]).

Conclusions In a meta-analysis, sodium restriction in CHF patients worsened the prognosis in terms of a composite of mortality and hospitalizations and did not influence all-cause mortality and HF hospitalisation rate.

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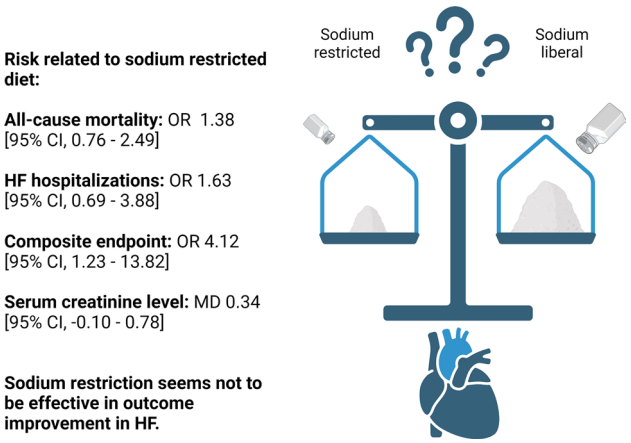
Graphical abstract



Keywords Heart failure · Sodium · Salt · NaCl

Introduction

For many years, sodium restriction has been recommended as a key dietary intervention for patients with heart failure (HF) [1]. This recommendation was based on the belief that a low-sodium diet would reduce fluid retention and decrease the risk of HF hospitalizations [2]. Whilst this assumption was based on the fact that in HF, water and sodium homeostasis are greatly disturbed, and any interference may lead to clinical deterioration. However, recent studies have cast doubt on the effectiveness of this intervention, with some suggesting that it may even be harmful [3].

One of the main criticisms of sodium restriction in the management of HF is that the evidence supporting its implementation is relatively weak and based on early experiments that involved assessing the pathological responses of HF patients to sodium loading [4]. Thus, these experiments may not accurately reflect the effects of long-term sodium restriction. On the other hand, the burden of pharmacological and non-pharmacological recommendations in HF is significant and often challenging to maintain in the long run [5–7].

Given these unclear or conflicting perspectives, there is a significant need to evaluate the effect of recommended low-sodium diet in HF. In our meta-analysis, we aim to provide a comprehensive evaluation of the existing evidence on the benefits and risks of sodium restriction in the management of HF.

Methods

Search strategy

Initially, we screened the following databases: Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition, MEDLINE, Embase, Clinicaltrials.gov and Cochrane Library (trials) for the relevant articles. No restrictions regarding the publication date were determined, screening and papers export were performed on 11.10.2022. The keywords differed slightly in different sources.

In EMBASE, Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition and Cochrane Library, keywords were as follows: ((diet*) OR (eat*) OR (ingestion) OR (feed) OR (micronutrient) OR (macronutrient) OR (intake*) OR (nutri*) OR (consump*)) AND ((heart failure) OR (ventricular dysfunction) OR (HF) OR (HFpEF) OR (HFrEF) OR (cardiomyopat*) OR (((cardia*) OR (myocardial)) AND ((failure) OR (insufficienc*)))) AND ((sodi*)

OR (salt)). In the CochraneLibrary, trials section was screened for suitable papers, and Cochrane Reviews were screened for the reviews available for the backward snowballing, but non-relevant reviews were identified. Searching in Clinicaltrials.gov included the following conditions: Condition or disease: ((heart failure) OR (ventricular dysfunction) OR (HF) OR (HFpEF) OR (HFrEF) OR (cardiomyopat*) OR (((cardia*) OR (myocardial)) AND ((failure) OR (insufficienc*)))) Other terms: ((diet*) OR (eat*) OR (ingestion) OR (feed) OR (micronutrient) OR (macronutrient) OR (intake*) OR (nutri*) OR (consump*)) OR ((sodi*) OR (salt)). Only studies with the status of completed, terminated or unknown were screened. Studies which analysed children were excluded from the search engine.

All the records ($n = 9175$) were exported into the Excel file, and duplicates were removed ($n = 395$); further, two independent reviewers (S.U., M.F.) screened the titles, abstracts and full texts.

In the second step, backward snowballing was performed by 2 reviewers (O.S. and M.G.). Both references of included articles and papers which cited them were screened for the relevant records. Reviews and editorials were also screened [1, 2, 8–10], and 1050 records were identified.

Eligibility criteria

Inclusion criteria were defined as: studies analysing the impact of dietary sodium restriction on HF patients' outcome, full-text, peer-reviewed articles written in English, the population of heart failure patients of age > 18 years, both interventional and observational studies, reporting of at least one of the endpoints of interest: all-cause, cardiovascular or HF-related mortality; all-cause, cardiovascular or HF-related hospitalisation, emergency department visit, and HF decompensation.

Exclusion criteria were as follows: studies analysing the amount of the added salt (not the total dietary sodium restriction), case reports or review articles, studies based on the animal models, mixed interventions, e.g. studies that limited both sodium and fluids only in the intervention arm, in-hospital intervention only and studies in which the time of the intervention was shorter than the follow-up time.

Studies which assessed the sodium consumption based only on the natriuresis were excluded, as it was shown that such a method of sodium consumption evaluation is unsatisfactory in the patients treated with loop diuretics [11] The review was performed following PRISMA guidelines [12] and was registered in PROSPERO (CRD42023391133).

Data collection and analysis

After the screening, data extraction was performed by 2 independent reviewers (K.F. and M.G.), and the discrepancies were solved by the discussion with the input of the third investigator (S.U.). Authors of the papers with missing data necessary for the quantitative analysis were contacted to obtain relevant information. Data regarding study design, inclusion and exclusion criteria, sample size, age and sex of participants, method of sodium consumption assessment, amount of sodium restriction, length of follow-up, mortality, HF hospitalisations, composite endpoint compounds and occurrence and serum creatinine levels were extracted. Studies with no events in both arms were not included in the meta-analysis [13].

We used random effect with the Mantel–Haenszel test to analyse categorical variables. The odds ratio and 95% confidence intervals (CI) were calculated for the outcomes. Continuous variables were assessed using the inverse variance method and random effects model. Heterogeneity was evaluated using I^2 ($I^2 > 50\%$ was considered significant heterogeneity). Meta-regression was performed to assess the impact of the year of publication on the outcomes assessed in at least 6 studies [14]. Funnel plots for the publication bias assessment were not performed due to the limited number of included studies [15]. Review Manager version 5.4.1 (The Cochrane Collaboration, 11–13 Cavendish Square, London, W1G 0AN United Kingdom) was used for the statistical analysis, and Biorender was used to create the figures.

Subgroup and sensitivity analysis

Trial-level subgroup analysis was performed to investigate the source of the heterogeneity. We assessed the effect in the following subgroups: follow-up longer and shorter than 1 year; heart failure with reduced ejection fraction (HFrEF) population only and merged HFrEF and heart failure with preserved ejection fraction (HFpEF); and sodium restriction below 2 g per day. Sensitivity analysis, which included randomised control trials and observational studies separately, was performed for the selected outcomes.

Risk of bias assessment

The risk of bias (ROB) in the selected studies was assessed using Cochrane-designed tools. Risk of Bias 2 and ROBIN-I were used for randomised trials and observational studies respectively [16, 17]. Two independent reviewers (S.U. and O.S.) performed a quality evaluation, and the discussion resolved all the discrepancies. The study was considered low risk when the ROB was assessed as a low risk in all the domains.

Grading the quality of evidence

The overall quality of the acquired evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [18]. Each outcome was assessed separately for randomised and observational studies. GradePRO GDT (McMaster University and Evidence Prime Inc.) was used to create a Summary of Findings and Certainty of Evidence table.

Results

The results of the search are displayed in Fig. 1. The research revealed 9 articles, including 2210 participants—1130 in the sodium-restricted (SR) and 1080 in the sodium-liberal (SL) group. Five studies were RCTs, 2 prospective cohort studies and 2 propensity score matching registry analyses. Patients were observed from 12 weeks to 3 years (mean follow-up time 15.77 months). Three studies included the HFrEF population exclusively, whilst 6 studies analysed the subjects regardless of the ejection fraction. In 5 studies, researchers restricted sodium consumption to 2 g per day or less, and 5 studies included only patients with accurately chosen NYHA class. Men constituted 64% of patients, and the mean age was 67 years. The characteristic of the included studies is described in Table 1.

Four parameters, i.e. all-cause mortality, HF hospitalisation, a composite of mortality and readmission and serum creatinine level, were reported in at least 3 studies; therefore, quantitative analysis of these features was performed. A summary of the findings is shown in Table 2. Forrest plots of the merged analyses are displayed in Fig. 2. Specific subgroup data with the accurate number of patients with events are available in the Supplementary material (Figure S1).

All-cause mortality

All-cause mortality was reported in 8 studies with 2140 participants. The death occurred in 121 (11.07%) in the SR group and 87 (8.31%) in the SL group. Dietary sodium restriction did not significantly affect mortality in HF patients (OR 1.38 [95% CI 0.76–2.49]). It was close to significance in the RCTs analysis, reaching (OR 2.30 [95% CI 0.98–5.41], $p = 0.06$). The effect remained neutral

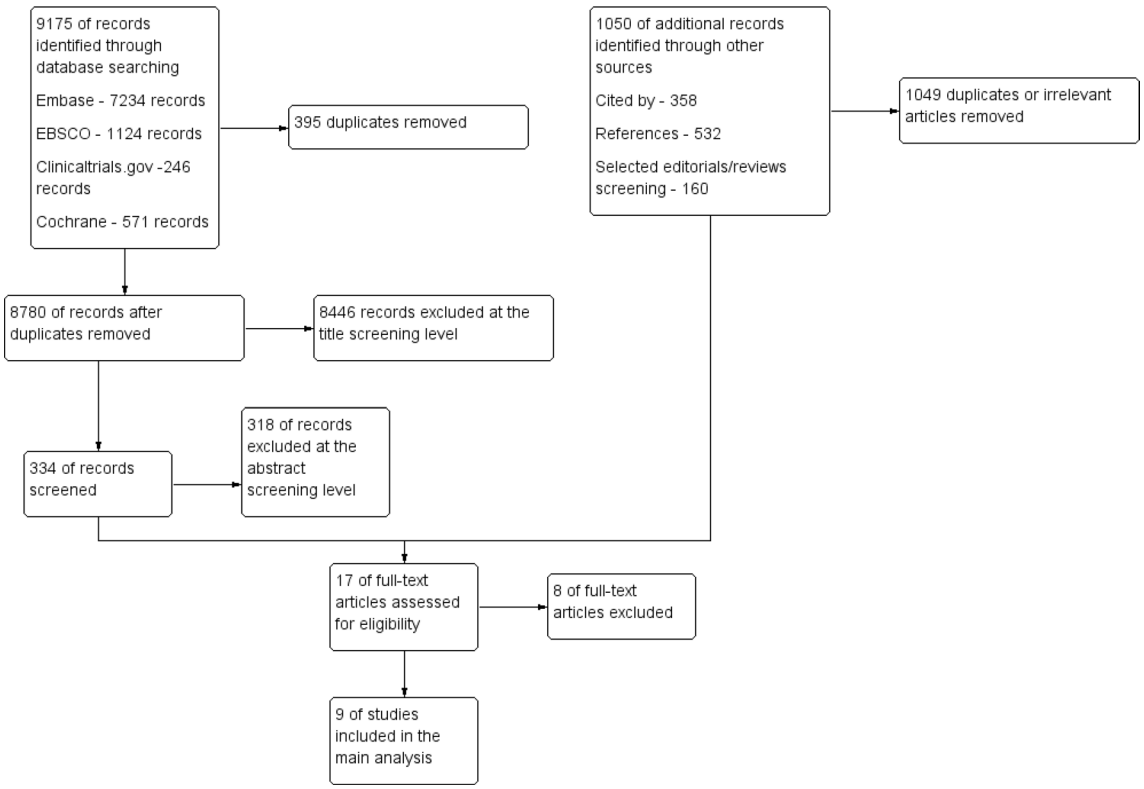


Fig. 1 Flowchart of the systematic review process. Excel files with the screened articles and exclusion reasons at every stage are available at request

Table 1 Characteristic of the included studies

Author	Study design	Population	Sample size	SR group, *n*	SL group, *n*	Males *n*, (%)	Mean age, years	Amount of sodium restriction	Control group recommendations	Sodium consumption assessment method
Ezekowitz et al. [3]	RCT	NYHA II–III, HFpEF and HFrEF	806	397	409	538 (66)	67 [58–74]	< 1500 mg of sodium/day	Usual care with general advice to restrict dietary sodium	3-day food record
Ivey-Miranda et al. [38]	RCT	NYHA I–II, HFrEF	70	37	33	47 (67)	60 ± 12	2000 mg of sodium/day	3000 mg of sodium/day	Food frequency questionnaire, 24-h food diary and 24-h urine collection
Senturk et al. [39]	Observational, registry PSM analysis	No specified NYHA, HFrEF	236	118	118	159 (67)	65 ± 11	Declaration of complying with SR	Declaration of not complying with SR	Patients self-assessment
Hummel et al. [40]	RCT	No specified NYHA, HFpEF and HFrEF	66	33	33	46 (70)	71 ± 8	1500 mg of sodium/day	Usual care with general advice to restrict dietary sodium	3-day food record, urinary sodium and potassium assessment, and meal delivery records
Doukky et al. [41]	Observational, registry PSM analysis	NYHA II–III, HFpEF and HFrEF	260	130	130	113 (44)	63.5 ± 13	< 2500 mg of sodium/day	> 2500 mg of sodium/day	Food frequency questionnaire
Song et al. [42]	Prospective, cohort study	No Specified NYHA, HFpEF and HFrEF	244	132	112	162 (66)	61 ± 12	< 3000 mg of sodium/day	> 3000 mg of sodium/day	4-day food record
Arcand et al. [43]	Prospective, cohort study	No Specified NYHA, HFrEF	123	82	41	94 (76)	60 ± 12	Low and middle sodium intake tertiles: < 2800 mg/day	High sodium intake tertile: ≥ 2800 mg/day	3-day food record
Parinello et al. [44]	RCT	NYHA II, HFrEF	173	87	86	105 (61)	73 ± 7	1800 mg of sodium/day	2800 mg of sodium/day	Food diary and telephone interview 1/week
Paterna et al. [45]	RCT	NYHA II, HFrEF	232	114	118	144 (62)	73 ± 8	1800 mg of sodium/day	2800 mg of sodium/day	Food diary and telephone interview 1/week

Per protocol data are shown—intended values of sodium restriction and the number of enrolled patients are displayed. Age is presented as mean ± standard deviation, except study by Ezekowitz et al.—median [interquartile range]

SR sodium restriction, *SL* sodium-liberal, *RCT* randomised controlled trials, *PSM* propensity score matching, *NYHA* New York heart association, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction

Table 2 Summary of findings of the included studies

Author	Duration of follow-up, months	Mortality *n*, (%)	HF hospitalisation *n*, (%)	Composite of death and hospitalisation *n*, (%)	Creatinine mg/dl, mean ± SD
Ezekowitz et al. [3]	12	SR 22 (6); SL 17 (4)	NR	NR	NR
Ivey-Miranda et al. [38]	5	NR	NR	SR 8 (21); SL 7 (21)	SR 1.16 ± 0.06; SL 1.20 SD 0.06
Senturk et al. [39]	20	SR 35 (10); SL 36 (31)	SR 70 (59); SL 87 (74)	NR	NR
Hummel et al. [40]	3	SR 0 (0); SL 1 (3)	SR 7 (21); SL 13 (39)	NR	SR 1.4 ± 0.4; SL 1.3 SD 0.5
Doukky et al. [41]	36	SR 24 (19); SL 14 (11)	SR 42 (32); SL 26 (20)	NR	NR
Song et al. [42]	12	SR 3 (2); SL 3 (3)	SR 14 (11); SL 8 (7)	NR	NR
Arcand et al. [43]	28	SR 2 (2); SL 6 (15)	NR	NR	NR
Parinello et al. [44]	12	SR 20 (23); SL 4 (5)	SR 44 (51); SL 12 (14)	SR 64 (73); SL 16 (19)	SR 2.1 ± 0.5; SL 1.45 SD 0.4
Paterna et al. [45]	6	SR 15 (13); SL 6 (5)	SR 30 (26); SL 9 (8)	SR 45 (39); SL 15 (13)	SR 2.1 ± 0.5; SL 1.45 SD 0.4

Mean follow-ups are presented in the observational studies

SR sodium-restricted, *SL* sodium-liberal, *NR* not reported, *SD* standard deviation

in subgroup and sensitivity analysis: (OR 0.87 [95% CI 0.39–1.96]) in observational studies, (OR 1.28 [95% CI 0.65–2.50]) and (OR 1.69 [95% CI 0.28–10.35]) in studies with > 1-year and < 1-year follow-up respectively, (OR 1.86 [95% CI 0.93–3.75]) in studies which restricted sodium consumption to 2 g per day, (OR 1.51 [95% CI 0.24–9.67]) and (OR 1.45 [95% CI 0.92–2.28]) in studies which included HFrEF only and in HFpEF and HFrEF respectively.

Meta-regression analysis showed no significant association between the year of the publication and the all-cause mortality ($\beta = -0.05$, 95% CI = −0.16 to 0.05, $p = 0.325$).

HF hospitalisations

HF-related hospitalisations occurrence was assessed in 6 studies with 1211 patients. The endpoint took place in 207 (33.71%) patients in SR and 155 (25.96%) in the SL population. Sodium restriction did not significantly affect the HF hospitalisations rate (OR 1.63 [95% CI 0.69–3.88]). The comparable results have been accomplished in the analysis of the following subgroups: RCTs (OR 2.36 [95% CI 0.54–10.24]); observational studies (OR 1.13 [95% CI 0.46–2.77]); follow-up longer (OR 1.74 [95% CI 0.61–4.95]) and shorter (OR 1.38 [95% CI 0.14–13.74]) than 1 year; sodium restriction equal or below 2 g/d (OR 2.14 [95% CI 0.68–6.77]); HFrEF analysis only (OR 2.38 [95% CI 0.45–12.66]) and merged HFpEF and HFrEF (OR 1.13 [95% CI 0.45–2.83]).

The meta-regression revealed a significant impact of the year of publication on the effect size regarding the HF hospitalisation occurrence ($\beta = -0.19$, 95% CI = −0.26 to −0.12, $p < 0.0001$).

Composite endpoint

The composite endpoint of all-cause mortality and hospitalisation was analysed in 3 papers (475 participants). The composite endpoint occurred in 117 (49.16%) patients in SR and 38 (16.04%) in SL cohorts. A diet with a restricted amount of administered sodium significantly increased the risk of death or hospitalisation (OR 4.12 [95% CI 1.23–13.82]). Due to the low number of studies, no subgroup analysis regarding this outcome was performed.

Serum creatinine level

Serum creatinine level at the end of the follow-up was reported in 4 studies (541 participants). The mean difference between the groups was estimated as 0.34 mg/dL [95% CI − 0.1 to 0.78]) suggesting that serum creatinine may be higher in the SR population. The results, however, did not reach statistical significance ($p = 0.13$).

Risk of bias and certainty of the evidence

The results of the ROB assessment are displayed in Fig. 3. The quality of evidence assessed by GRADE criteria for the observational studies was very low. The quality of the evidence in RCTs was: moderate for all-cause mortality, very low for HF hospitalisation and moderate for a composite of mortality and hospitalisations (Table 3).

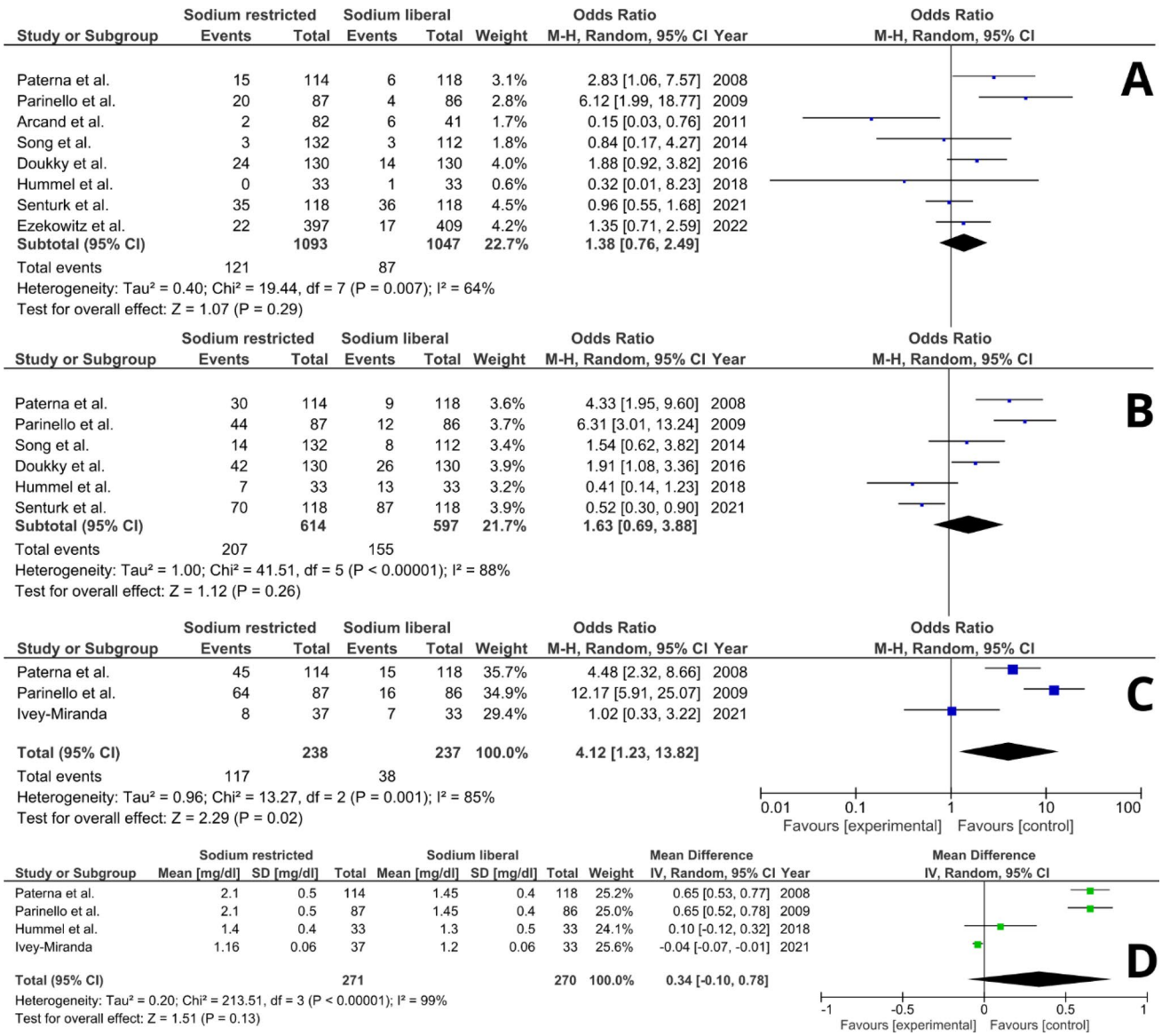


Fig. 2 Forrest plots of the sodium-restricted vs sodium-liberal diet for the analysed outcomes. Forrest plots of the subgroup analyses are available in Supplement Figure S1. **A** All-cause mortality; **B** HF hospitalisation; **C** composite of mortality and readmission; **D** serum creatinine level

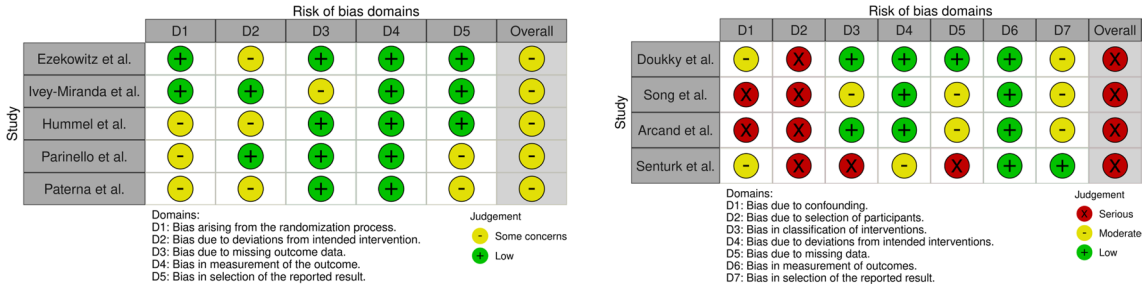


Fig. 3 Risk of bias (ROB) in the included studies. ROB was assessed separately for the randomised (left side) and observational studies (right side). Cochrane tools, i.e. risk of bias 2 for randomised trials and ROBINS-I for the observational studies, were used. Red colour marks high ROB, green low ROB. The yellow colour describes the risk as some concerns in randomised data and moderate in observational data

Table 3 Summary of findings and certainty of evidence table

Outcomes	No of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with regular diet	Risk difference with dietary sodium restriction
All-cause mortality—RCT only	1277 (4 RCTs)	⨁⨁⨁◯ Moderate[a]	OR 2.30 (0.98–5.41)	43 per 1000	51 more per 1000 (1 fewer to 154 more)
All-cause mortality—Observational studies	863 (4 observational studies)	⨁◯◯◯ Very low[b,c,d]	OR 0.87 (0.39–1.96)	147 per 1000	17 fewer per 1000 (84 fewer to 106 more)
Composite of all-cause mortality and hospitalisation	475 (3 RCTs)	⨁⨁⨁◯ Moderate[e]	OR 4.12 (1.23–13.82)	160 per 1000	280 more per 1000 (30 more to 565 more)
HF hospitalisation—RCT studies	471 (3 RCTs)	⨁◯◯◯ Very low[d,e]	OR 2.36 (0.54–10.24)	143 per 1000	140 more per 1000 (61 fewer to 488 more)
HF hospitalisation—Observational studies	740 (3 observational studies)	⨁◯◯◯ Very low[b,d,e]	OR 1.13 (0.46–2.77)	336 per 1000	28 more per 1000 (147 fewer to 248 more)

CI confidence interval, *OR* odds ratio

[a]Number of events does not meet the optimal information size of 400 events, 95% CI includes no effect and appreciable harm

[b]Some limitations for multiple criteria, mainly serious bias in the selection of participants into the study in all studies and serious bias due to confounding in half of the studies

[c]Substantial inconsistency that can be partially explained as a result of different cut off for the amount of sodium in sodium reduced diet as well as different participation of HFpEF

[d]The number of events does not meet the optimal information size of 400 events, 95% CI includes no effect and appreciable benefit and harm

[e]Considerable inconsistency that can be partialy explained as a result of different cut off for amount of sodium in sodium reduced diet as well as different participation of HFpEF

Discussion

In this interventional and observational data meta-analysis, we evaluated current evidence for dietary sodium restriction in the HF population. Our data showed that the sodium restriction does not provide benefit in terms of outcome improvement. Importantly, these results remained neutral regardless of the: type of study (RCT vs observational), left ventricular ejection fraction, duration of follow-up and amount of sodium restriction. Further, sodium restriction showed no benefit in any of the analysed outcomes. Its impact on all-cause mortality and HF hospitalisations was insignificant, whilst it was meaningful in terms of the composite of mortality and hospitalisation. Sodium restriction significantly increased the risk of the composite endpoint (OR 4.12 [95% CI 1.23–13.82], $p = 0.02$).

Noteworthy, our analysis is the first one to show the aggregated impact of sodium restriction on serum creatinine levels, which seems to be numerically higher in the SR group, without reaching statistical significance (+0.34 mg/dL [95% CI − 0.1 to 0.78], $p = 0.13$). This finding may be partly explained by the prognostic role the increased natriuresis plays in the decongestion process [19]. Further studies are warranted to elucidate the phenomenon comprehensively.

Current ESC guidelines mention the role of dietary sodium restriction in 2 parts. First, they recommend avoiding excessive salt intake < 5 mg/day. Importantly, they also highlight the gaps in the knowledge regarding the topic [6].

SODIUM-HF [3] was the most numerous RCT that analysed the effect of dietary sodium restriction in HF. Its results have considerably questioned the long-lasting, guidelines-supported paradigm. Following the trial, the authors prepared a meta-analysis of the existing evidence on that topic [8]. Collin-Ramirez et al. showed that the sodium restriction presented a neutral effect on the analysed endpoints, i.e. all-cause mortality (OR 0.95 [95% CI 0.58–1.58]), cardiovascular hospitalisation (OR 0.79 [95% CI 0.54–1.15]) and the composite of all-cause death and hospitalisation (OR 0.81 [95% CI 0.60–1.09]). Similar events were analysed in both of the meta-analyses. However, in our study, SR was associated with a slightly higher risk regarding all the outcomes, even reaching the statistical significance in the composite endpoint.

Some essential differences in the construction of studies may explain the differences and, therefore, require clarification. First, differences in inclusion criteria for our analysis resulted in a slightly larger number of patients (and events) being examined. Second, opposite to the authors' findings, we did not include studies that analysed salt and fluid restriction in one of the arms. Whilst the fluid restriction is also being questioned as a standard of care [20, 21], its conjunction with sodium restriction may confound the results, potentially contributing to the lower incidence of the endpoints

in the Colin–Ramirez study. Moreover, our meta-analysis comprises solely outpatient interventions. Finally, we have not included studies which based the sodium consumption assessment exclusively on natriuresis, as it was shown to be inappropriate in the patients on loop diuretics [11]. Although natriuresis is a marker of decongestive abilities and prognosis in acutely decompensated HF patients, its utility and interpretation in chronic HF are much more complicated and related to many uncontrollable factors, not just diet [22, 23]. Thus, the assumption that the population presenting higher natriuresis is the population with higher sodium consumption—the SL group—will favour it regarding the prognosis.

Given these, our meta-analysis was based on the different inclusion criteria and aimed to analyse the effect of the isolated sodium restriction. Our results complement the work mentioned above, providing further evidence for the SR ineffectiveness, which stemmed from the studies performed in a different setting (Fig. 4).

Omitting its possible harmful effect, the assumption that the sodium restriction in HF may be unjustified has profound clinical implications. HF patients receive a long list of recommendations, some of which are troublesome and inconvenient for the patients [5]. Presuming that the patients have the limited ability to cover all the physicians' advice, as we take care of the patient's compliance, we should focus on communicating and underlining indications with a reliable, evidence-based effect. In the same manner, as physicians should fight polipharmacy [24], they should try to eliminate unreasonable recommendations that may distract patient attention from the essential ones.

This review focuses on the role of dietary sodium consumption in the chronic HF population. The detailed description of the results of sodium studies in AHF is beyond the scope of this article, however, it requires a brief comment. Traditionally, both fluid and sodium net negative balance were considered therapeutic goals during the AHF therapy, and high urine sodium excretion is a marker of good diuretic response [25] and reflects neurohormonal activation in AHF [26]. Thus, intuitively increasing the sodium intake during AHF would be contraindicated [27]. Some recent data from trials [28] and metanalyses [29] questioned this paradigm showing the neutral-to-superior outcomes whilst using oral or intravenous sodium loading during decongestive therapy in AHF. Summarising the recent data from acute and chronic HF populations, which challenges the previous beliefs, it seems that the role of sodium in the pathophysiology of HF has not been fully understood.

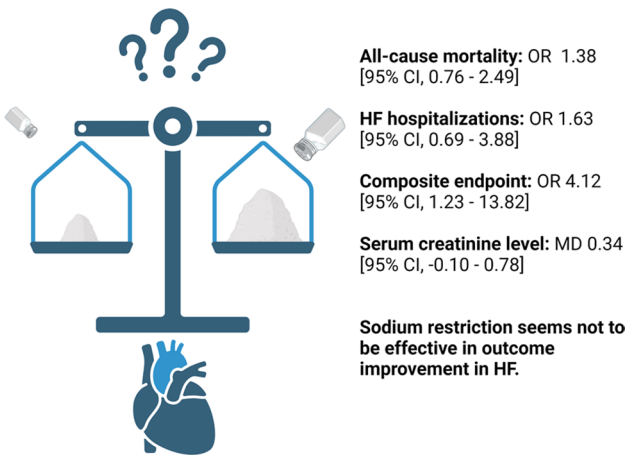


Fig. 4 Central illustration summarising most important findings. *OR* odds ratio, *HF* heart failure, *MD* mean difference

There are important differences regarding the outcome and efficacy of therapeutic interventions in HFrEF and HFpEF [6]. Our review included only the analysis HFrEF population or HFrEF and HFpEF due to the lack of data on HFpEF populations only. In both of the subgroups, sodium restriction did not present a significant effect on the analysed outcomes. However, the group of HFpEF and HFrEF seems to present numerically (but not statistically) lower risk associated with the restricted diet for heart failure hospitalisation OR 1.13 vs 2.38, in HFrEF and HFpEF vs HFrEF only, respectively. This seems coherent with the previous evidence. In SODIUM-HF, the most numerous RCT by now, the population with EF > 40% presented a lower risk of cumulative events (HR 0.82 vs 1.05 for EF > 40% vs EF < 40%, respectively) associated with sodium restriction diet [3]. Similarly, in the aforementioned meta-analysis of the RCTs, in the HFpEF population, dietary sodium restriction was associated with the lower risk of all-cause mortality (OR 0.75 vs 0.87 in HFpEF vs HFrEF, respectively) [30]. All of the above results were not statistically significant and are derived from the subgroup analyses of relatively small subpopulations with wide confidence intervals; thus, these should be treated rather as a weak signal than a definitive conclusion. Further studies, especially performed in the isolated HFpEF population, are warranted to analyse the differences between the role of dietary sodium in HFrEF and HFpEF.

We presume that these potential differences in prognosis may stem from the meaningful pathophysiological distinctions between HFpEF and HFrEF. HFpEF was shown to be associated with the increased burden of comorbidities [31], making this population highly heterogeneous compared to HFrEF.

Notably, the meta-regression showed an association between the year of the performed study and HF hospitalisation. It is an interesting finding, suggesting that the dietary sodium restriction may have been more harmful in the past than currently. We may only hypothesise that it may be caused by the advances in modern pharmacotherapy, especially by the wider use of RAA-affecting drugs and the more aggressive up-titration of its doses. Accurate elucidation of

this phenomenon would require further studies and a better understanding of the complexity of sodium handling in heart failure.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have recently emerged as the cornerstone of heart failure (HF) therapy [6]. The exact mechanism of their beneficial action remains unclear, and their pathophysiological effects are currently being intensively investigated. One of the proposed mechanisms for their positive impact on heart failure is their influence on sodium homeostasis [32]. SGLT2 has been demonstrated to enhance diuresis [33, 34] and reduce sodium concentrations in skin tissue [35]. However, the available data on dietary sodium intake is outdated in the context of widespread SGLT2 inhibitor use in HF patients. Consequently, it is currently impossible to assess the intervention's effect size based on the existing retrospective data. Further trials conducted in SGLT2-treated patient populations are necessary to evaluate its interaction with varying levels of dietary sodium intake.

Our study is not free from limitations. The scheduled analysis design, which included both interventional and observational studies, was, per se, associated with the higher ROB. Different scales are designed to assess the ROB in the observational and interventional studies [36, 37], which makes it difficult to compare the reliability of the included studies. Moreover, analysed studies were published between 2008 and 2022—during this period, 4 European and American guidelines were published. Patients' management, e.g. recommended pharmacotherapy, did change remarkably, which may impact the generalizability of the results. Further, the analysed studies presented considerable heterogeneity—they differed in terms of design, e.g. time of follow-up, included population, amount of sodium restriction and concomitant interventions. Finally, there was an inherent problem with blinding the participants and the personnel due to the nature of the studied, nutritional intervention.

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Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information. Excel files with the screened articles and exclusion reasons at every stage as well as Risk of Bias assessment tables are available at request.

Declarations

Conflict of interest Prof. Piotr Ponikowski has received personal fees for consultancy and Speakers Bureau from AstraZeneca, Boehringer Ingelheim, Vifor Pharma, Servier, Bayer, Bristol Myers Squibb, Respocardia, Berlin-Chemie, Cibiem, Novartis, and Renal Guard; other support for participation in clinical trials from Boehringer Ingelheim, Amgen, Vifor Pharma, Bayer, Bristol Myers Squibb, Cibiem, Novartis, and RenalGuard; and research grants to his institution from Vifor Pharma. All other authors have no conflicts of interest to declare that are relevant to the content of this article.

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