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SYSTEMATIC REVIEW

Efficiency of Hypertonic Saline in the Management of Decompensated Heart Failure: A Systematic Review and Meta-Analysis of Clinical Studies

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Abstract

Introduction Acute decompensated heart failure (ADHF), with an incidence of 1–2%, is a clinical syndrome with significant morbidity and mortality despite therapeutic advancements and ongoing clinical trials. A recent therapeutic approach to patients with ADHF includes combination therapy with hypertonic saline solution (HSS) and furosemide, based on the hypothesis that resistance to loop diuretics occurs because of achievement of plateau in water and sodium excretion in patients receiving long-term loop diuretic therapy.

Objective Our aim was to conduct a meta-analysis to evaluate the efficiency of combination HSS plus furosemide therapy in patients with ADHF in terms of mortality, readmissions, length of hospital stay, kidney function, urine output, body weight, and B-type natriuretic peptide (BNP).

Methods A total of 14 studies—four observational and ten randomized studies (total 3398 patients)—were included in the meta-analysis.

Results Our results demonstrate the superiority of combination HSS plus furosemide therapy over furosemide alone in terms of kidney function preservation (mean creatinine difference − 0.33 mg/dL; $P < 0.00001$), improved diuresis (mean difference [MD] 581.94 mL/24 h; $P < 0.00001$) and natriuresis (MD 57.19; $P < 0.00001$), weight loss (MD 0.99 kg; $P < 0.00001$), duration of hospital stay (MD − 2.72 days; $P < 0.00001$), readmissions (relative risk 0.63; $P = 0.01$), and mortality (relative risk 0.55; $P < 0.00001$). However, no difference in BNP levels was detected (MD 19.88 pg/mL; $P = 0.50$).

Conclusion Despite the heterogeneity and possible risk of bias among the studies, results appear promising on multiple aspects. A clear need exists for future randomized controlled trials investigating the role of combination HSS plus furosemide therapy to clarify these effects and their possible mechanisms.

Key Points

Hypertonic saline with furosemide therapy might be a promising therapy in heart failure.

Combination of hypertonic saline with furosemide decreases mortality and length of hospital stay.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40256-020-00453-7) contains supplementary material, which is available to authorized users.

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1 Introduction

The European Society of Cardiology defines congestive heart failure (CHF) as a clinical syndrome characterized by signs and symptoms of pulmonary and systemic congestion, including dyspnea, orthopnea, pretibial edema, hepatomegaly, and jugular venous distention, caused by cardiac dysfunction [1]. The prevalence rate of CHF is 1–2% and increases considerably with age, and the World Bank estimates that annual medical spending for treatment of CHF is $US108 billion [2, 3]. Patients with decompensated heart failure (HF) are more likely to have comorbid conditions, with valvular heart diseases (44%), atrial flutter or fibrillation (30%), diabetes mellitus (40%), and renal diseases (30%) being the most commonly encountered [4–7]. In-hospital and 1-year post-discharge mortality rates of hospitalized patients with decompensated HF are

high at 4–11% and 20–36%, respectively, in large-scale studies [8–10]. Intravenous loop diuretics and vasodilators are the most common therapeutic approach, whereas inotropic agents or vasopressors may be preferred in cases with low systolic blood pressure or features of cardiogenic shock [11]. Given the ongoing high mortality rates, novel therapeutic approaches, including levosimendan (a calcium-sensitizing agent), nesiritide (a recombinant human brain natriuretic peptide [BNP]), and istaroxime (stimulator of sarcoplasmic reticulum calcium adenosine triphosphatase isoform 2a), have been proposed as potential therapies [12]. Another novel approach is the combination of hypertonic saline solution (HSS) with furosemide. This is based on the hypothesis that resistance to loop diuretic occurs because of achievement of plateau in water and sodium excretion in patients receiving long-term loop diuretic therapy, which is referred as "chronic braking" therapy [13]. Another mechanism of diuretic resistance is the functional adaptation of the distal tubule regarding transporters or prevention of intravascular volume depletion [14–16]. Potential beneficial effects with HSS in clinical trials include improved cardiac biomarkers, weight loss, symptom resolution, increased urine output, and improved kidney function. However, results vary significantly among studies, and there exists a clear need to re-evaluate the evidence, taking into account the potential impacts on clinical practice.

In this meta-analysis, we aim to evaluate the efficiency of HSS plus furosemide therapy in patients with decompensated HF in terms of mortality, readmissions, length of hospital stay, kidney function, urine output, body weight, and BNP levels.

2 Methods

We conducted a literature review and meta-analysis according to the methods specified by the Cochrane Collaboration and Quality of Reporting of Meta-Analyses (QUOROM) [17]. We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide reporting of this study [18].

2.1 Literature Search

The literature search for this meta-analysis was performed up to 25 May 2020 and included three databases: Embase (Elsevier), the Cochrane Central Register of Controlled Trials (Wiley), and PubMed/MEDLINE Web of Science. The following terms and their combinations were used: acute heart failure, heart failure, decompensated heart failure, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, systolic heart failure, diastolic heart failure, pulmonary congestion, furosemide, hypertonic saline, saline, saline infusion, hypertonic saline infusion, loop diuretics, diuretics, treatment, and therapy. The titles and abstracts of each study were independently evaluated by two authors (S.C. and B.A.), with consensus reached after detailed examination of the study and discussion of conflicts with the third author. In addition, we hand searched journals, conference proceedings, and current awareness alerts without applying language restrictions.

After preliminary elimination of the studies by evaluation of the titles and abstracts, full texts were independently assessed by each author. Selected studies and references of the included studies were further evaluated.

2.2 Inclusion and Exclusion Criteria

All randomized controlled trials (RCTs) and observational studies with retrospective or prospective designs investigating the efficiency of HSS with furosemide infusion in patients with acute decompensated HF and published in a peer-reviewed journal in English before June 2020 were included in this meta-analysis. We excluded studies that were not considered original articles (i.e., systematic reviews, meta-analyses, editorials, and commentaries), studies with missing data or inadequate descriptions of outcomes, study types not listed in the inclusion criteria, studies lacking clear methodology (i.e., case reports, case series), and unpublished data.

Outcome measures in the meta-analyses included mortality; readmissions; length of hospital stay; kidney function, measured as serum creatinine value, urine output, and natriuresis; body weight, and BNP levels. Figure 1 shows the details of the study selection procedure.

2.3 Quality Assessment

The Newcastle–Ottawa Scale was utilized for the observational studies included in this meta-analyses. This scale includes three main criteria for evaluation: selection of study groups, comparability of groups, and assessment of outcomes. Nine stars indicates the highest-quality research. For RCTs, we assessed the risk of bias in the included studies by standard domains of the risk of bias tool developed by the Cochrane Collaboration [17]. Quality assessment of each study was mediated via consensus decision of the authors (S.C. and B.A.).

2.4 Statistical Analysis

We used a random-effects model for meta-analysis and expressed treatment effects as relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes

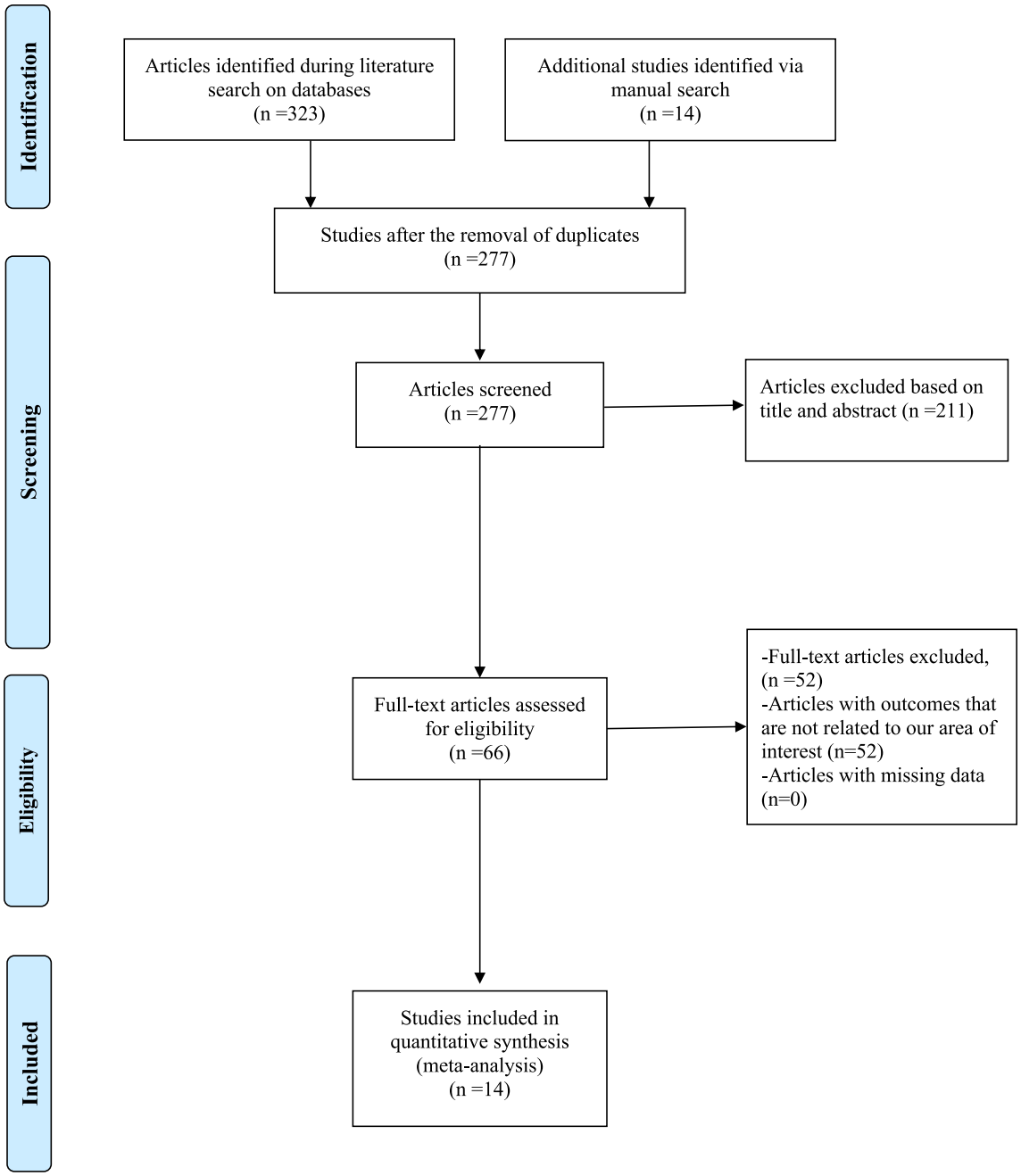

Fig. 1 Details of study selection process for the meta-analyses as shown by PRISMA flow chart

(readmissions, long-term mortality, in-hospital death) and as mean differences (MDs) for continuous outcomes with 95% CIs (kidney function, diuresis, and urinary sodium, BNP, body weight loss, length of hospital stay). We converted median and interquartile ranges to means and standard deviations and converted standard errors to standard deviations using standard formulas [19–21].

We used the I^2 statistic to assess for inconsistency across individual studies [22]. An $I^2 > 50\%$ indicated a large heterogeneity that was not explained by chance. If a sufficient number of studies were identified, subgroup analysis was used to explore possible sources of heterogeneity. All statistical analyses were performed using Review Manager version 5.3 (The Cochrane Collaboration 2012) [23].

3 Results

We included 14 studies (four observational [24–27] and ten randomized [28–37]) in our final analysis, with a total of 3398 included patients (minimum 32 [29], maximum 1927 [35]). The treatment arm consisted of HSS plus furosemide. The concentrations of the administered HSS were reported as follows: 1.4–4.6% [26, 30, 33–35], 1.7% [27, 31], 1.95% [36], 2.4% [28], 2.8% [37], 3% [24, 25, 32], and 7.5% [29]. None of the included studies reported the mean dosage of HSS. However, one study [25] reported a mean of 5.1 ± 2 doses of HSS, and another [24] reported a median of three doses of HSS. Only one study used carperitide for the control arm [27]; all other studies used furosemide alone. In addition, only one study [25] reported the administration of seven doses of metolazone during standard and experimental treatment. Four studies used high doses of furosemide [24, 26, 30, 33], with all other studies using conventional doses.

Only two of the included studies reported outcomes as changes per day of treatment [24, 25]; all others reported the outcomes as MDs between groups or between baseline and post-intervention values measured at different times across the study (24 h [31], 4 days [29], 5 days [28], 6 days [32], 8 days [26], and discharge [27, 30, 33–37]). When necessary, we calculated the MD between the pre- and post-intervention groups.

3.1 Outcome Measures Reporting

3.1.1 Kidney Function

Eleven studies (nine randomized [28–36] and two observational [24, 25]) evaluated the effect on renal function of adding HSS to furosemide. As shown in Fig. 2, the combined therapy preserved renal function, leading to an overall decrease of serum creatinine in the HSS plus furosemide arm from admission to discharge (MD − 0.33 mg/dL [95% CI − 0.42 to − 0.23]; $P < 0.00001$).

Given the increased heterogeneity ($\chi^2 = 291.17$; $I^2 = 97\%$; $P < 0.00001$), we also separately analyzed the effect of HSS treatment on renal function without the two studies reporting daily changes in serum creatinine. There was a trend for a further decrease in serum creatinine levels in the HSS + furosemide arm (MD − 0.45 mg/dL [95% CI − 0.51 to − 0.39]; $P < 0000.1$) (Fig. 1 in the electronic supplementary material). We also performed a separate analysis after removing studies that used high doses of furosemide [24, 30, 33]. The beneficial effect of the administration of HSS plus furosemide was slightly attenuated (MD − 0.25 mg/dL [95% CI − − 0.48 to − 0.03]; $P = 0.003$).

3.1.2 Diuresis and Urinary Sodium

To assess the efficacy of adding HSS to furosemide, we evaluated two outcomes: diuresis (mL/24 h) and urinary sodium (mEq/24 h). Seven RCTs [30–35, 37] and one observational study [24] reported daily diuresis in both arms, allowing us to calculate the MD between them. In both groups (1436 subjects treated with HSS plus furosemide and 1465 treated with furosemide), an increase in daily diuresis was observed, with 581 mL per 24 h higher volumes in the intervention group (MD 581.94 mL/24 h [95% CI 495.94–667.94]; $P < 0.00001$). When analyzing separately the studies that used conventional doses of furosemide, a further increase in daily diuresis was observed (MD 620.82 mL/24 h [95% CI 510.79–730.86]; $P < 0.00001$). Urinary sodium variation with treatment was reported in five randomized studies [30–33, 35]. HSS administration led to a significant increase in natriuresis (MD 57.19 [95% CI 47.56–66.82]; $P < 0.00001$) (Fig. 3). After removing the two studies that

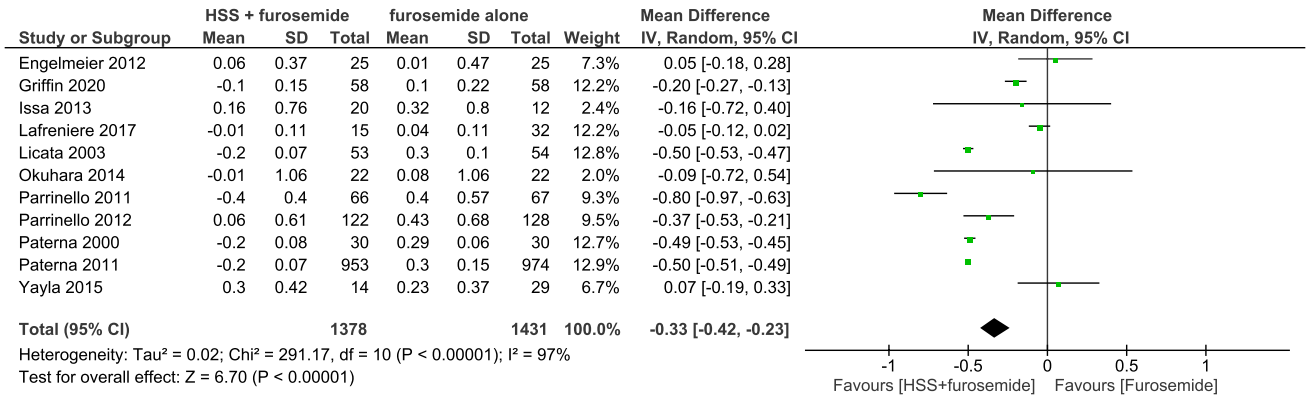

Fig. 2 Forest plot of the included studies for kidney function. *CI* confidence interval, *HSS* hypertonic saline solution, *IV* inverse variance, *SD* standard deviation

used high doses of furosemide [30, 33], a trend towards a smaller increase in natriuresis was observed (MD 46.9 [95% CI 41.14–52.66]; $P < 0.00001$).

3.1.3 B-Type Natriuretic Peptide

Variations in BNP levels were reported in four RCTs [29, 34, 35, 37] and one observational study [26] that included 1347 subjects treated with HSS and furosemide and 1276 subjects treated with furosemide alone. Four studies [26, 34, 35, 37] reported BNP values in pg/mL and showed a reduction in BNP levels in the HSS plus furosemide group. One study [29] did not mention the unit used to measure BNP and showed no change in BNP levels between the two groups. Overall, the meta-analysis did not find a significant difference between the two groups (MD 19.88 pg/mL [95% CI − 37.93 to 77.68]; $P = 0.50$) (Fig. 4).

3.1.4 Body Weight Loss

In total, 12 studies (nine RCTs [28–36] and three observational [24, 25, 27]) reported data for change in body weight. Overall, treatment with HSS led to more substantial weight loss than control (MD 0.99 kg [95% CI 0.59–1.39]; $P < 0.00001$) (Fig. 5). After excluding studies that used high doses of furosemide [24, 30, 33], there was a trend towards lower body weight loss (MD 0.96 kg [95% CI 0.32–1.6]; $P = 0.003$).

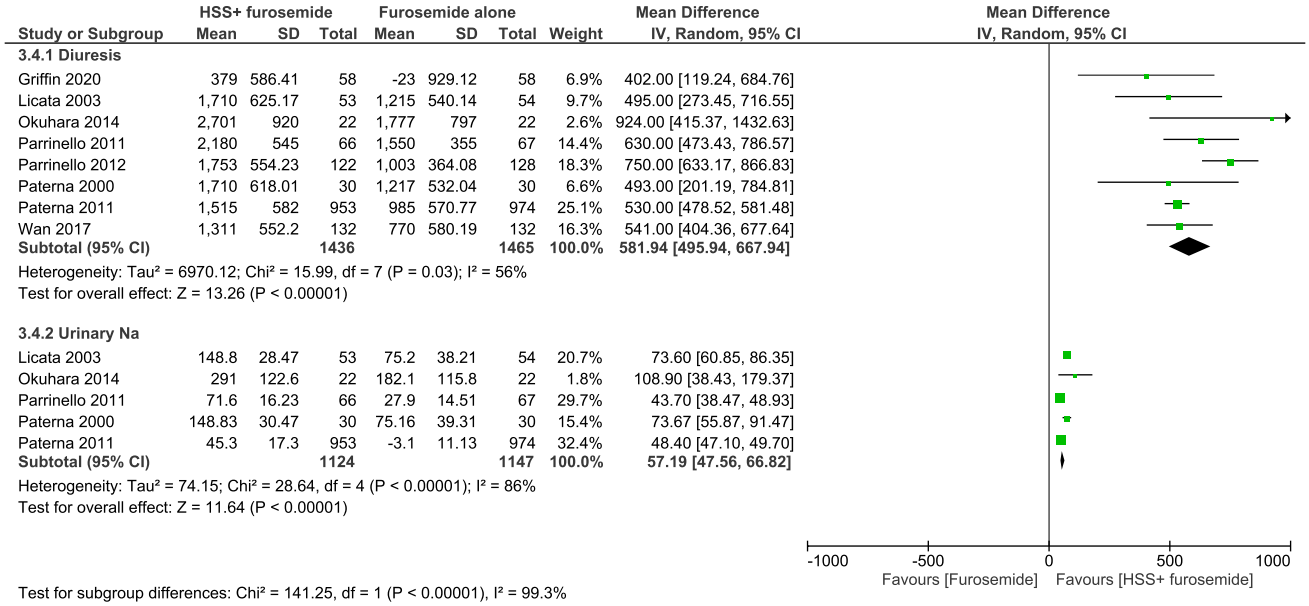

Fig. 3 Forest plot of the included studies for diuresis and natriuresis. *CI* confidence interval, *HSS* hypertonic saline solution, *IV* inverse variance, *SD* standard deviation

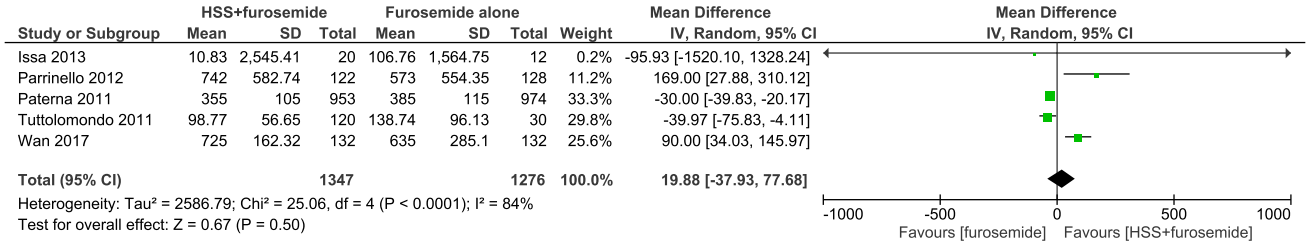

Fig. 4 Forest plot of the included studies for brain natriuretic peptide. *CI* confidence interval, *HSS* hypertonic saline solution, *IV* inverse variance, *SD* standard deviation

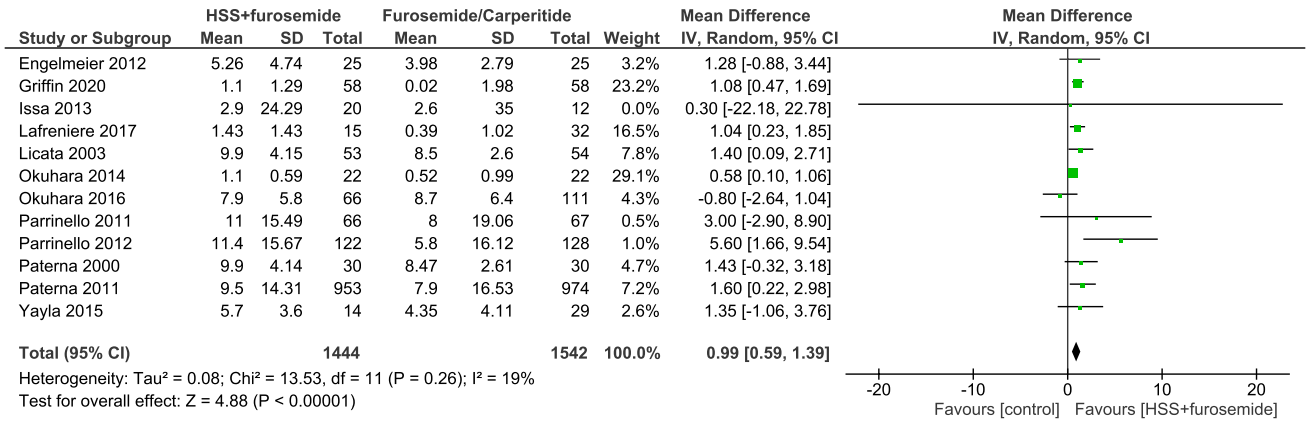

Fig. 5 Forest plot of the included studies for body weight loss. *CI* confidence interval, *HSS* hypertonic saline solution, *IV* inverse variance, *SD* standard deviation

3.1.5 Length of Hospital Stay

The length of hospital stay was reported in ten studies (eight RCTs [28, 30, 32–37] and two observational [26, 27]) as MDs between the HSS ($n = 1579$) and the control group ($n = 1580$). In two studies [26, 28], the length of hospitalization was higher in the HSS group (MD 0.12 days [95% CI − 2.15 to 2.39] and 0.36 days [95% CI − 0.52 to 1.24], respectively). Overall, treatment with HSS significantly reduced the length of hospital stay, by approximately 3 days (MD −2.72 days [95% CI − 3.59 to − 1.86]; $P < 0.00001$) (Fig. 6). After excluding studies that used high doses of furosemide [26, 30, 33], the length of hospital stay was further reduced in the HSS arm (MD − 3.13 days [95% CI − 4.18 to − 2.08]; $P < 0.00001$).

3.1.6 Readmissions

The number of readmissions was reported in four studies (three RCTs [30, 33, 35] and one observational study [27]). Notably, there were 210 events in the HSS-treated group (20.5%) and 400 events in the control group (37.03%). Thus, the use of HSS was associated with a reduction in the risk of readmission of 37% compared with the control arm (RR 0.63 [95% CI 0.44–0.9]; $P = 0.01$) (Fig. 7).

Excluding the study by Licata et al. [30] led to a loss of statistical significance (RR 0.62 [95% CI 0.32–1.18]; $P = 0.14$), as did excluding the study by Paterna et al. [35] (RR 0.65 [95% CI 0.33–1.25]; $P = 0.20$). Moreover, excluding studies that used high doses of furosemide [30, 33] resulted in no significant statistical difference between the two arms (RR 0.7 [95% CI 0.4–1.25]; $P = 0.23$).

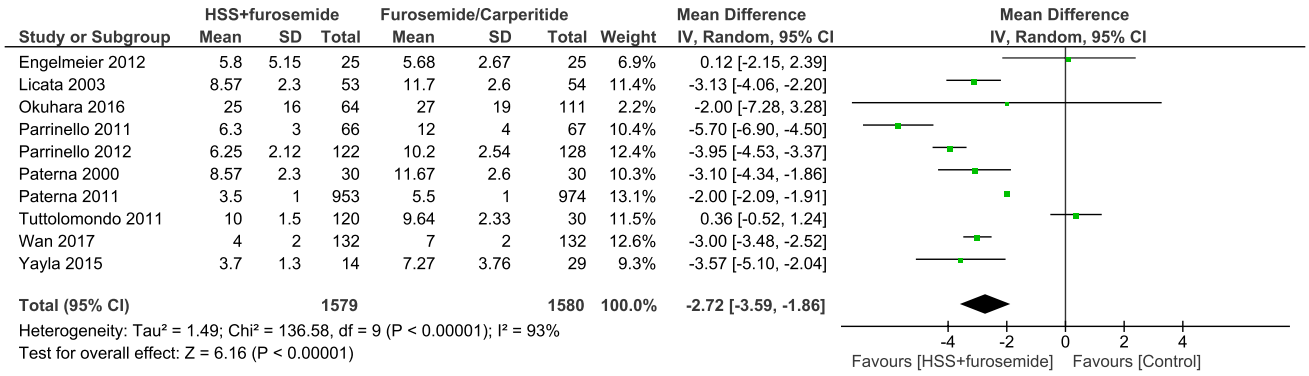

Fig. 6 Forest plot of the included studies for length of hospital stay. *CI* confidence interval, *HSS* hypertonic saline solution, *IV* inverse variance, *SD* standard deviation

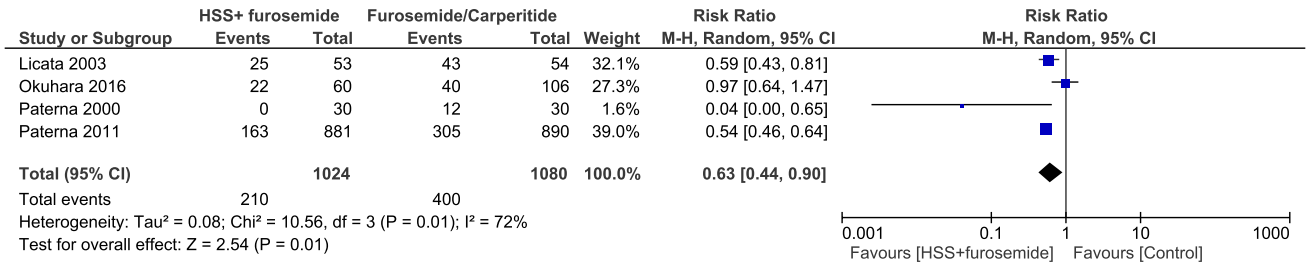

Fig. 7 Forest plot of the included studies for readmissions. *CI* confidence interval, *HSS* hypertonic saline solution, *M-H* Mantel–Haenszel

3.1.7 Mortality

Five studies (four randomized [30, 33, 35, 37] and one observational [27]) reported long-term mortality, and two studies (one RCT [29] and one observational [27]) reported in-hospital death. Overall, we performed the analysis in 2338 patients and found 174 deaths in the HSS group and 322 in the control group (15.19 vs. 26.99%, respectively). The risk of long-term mortality was 45% lower in patients treated with HSS than in controls (RR 0.55 [95% CI 0.47–0.65]; $P < 0.00001$). On the other hand, the risk of in-hospital death was 46% higher in the HSS arm, but data were available for only 207 patients (RR 1.46 [95% CI 0.70–3.07]; $P = 0.32$) (Fig. 8). The risk of long-term mortality was 40% lower in patients who were treated with HSS and conventional doses of furosemide (RR 0.60 [95% CI 0.43–0.89]; $P = 0.002$).

3.1.8 Risks of Bias

All trials had serious limitations because of a risk of bias in most of the domains evaluated. Most were at high risk of selection bias, and outcome assessors were not blinded in 80% of studies. Outcome reporting seemed to be selective in almost 50% of the included studies.

4 Discussion

Our meta-analysis, which included 14 studies and 3398 patients, indicated that treatment with HSS plus furosemide in patients with decompensated HF had positive effects on mortality, mean hospital stay, renal function, and readmissions.

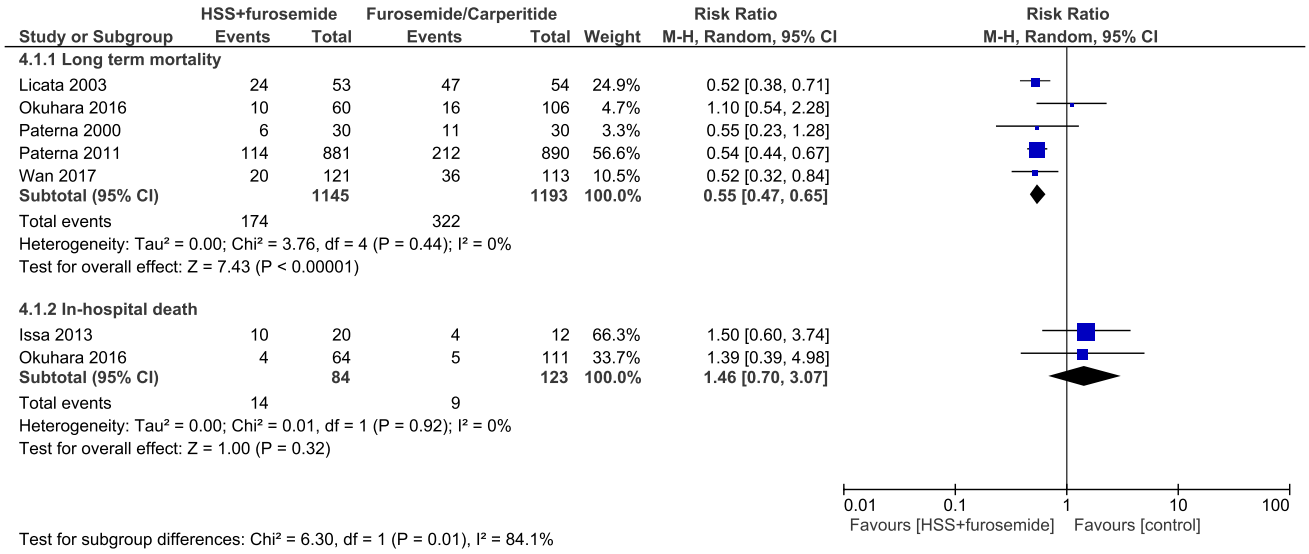

Fig. 8 Forest plot of the included studies for mortality. *CI* confidence interval, *HSS* hypertonic saline solution, *M-H* Mantel–Haenszel

Decompensated HF is a clinical condition with high morbidity and mortality that may develop in patients with or without preexisting cardiovascular comorbidities. Intravenous loop diuretics, including furosemide, are the most commonly administered medication in such cases. However, mortality rates remain relatively high. In this meta-analysis, we demonstrated that intravenous administration of HSS with furosemide in patients with acute decompensated HF led to shorter mean hospital stays, lower mortality rates, fewer readmissions, and significant improvements in serum creatinine levels, 24-h urine output, and weight loss compared with intravenous furosemide therapy alone. Although the exact mechanism of action of HSS is unclear, a few hypotheses have been generated. Furosemide reaches the intraluminal site of nephrons, where it exerts its function via active secretion from proximal tubules. Most patients with decompensated HF develop hypovolemia and decreased renal blood flow (RBF), which impairs the active secretion process [38]. Administration of HSS increases intraluminal furosemide concentrations, 24-h diuresis, urinary sodium levels, and urinary osmolarity [39]. Another aspect of reduced RBF is the over-activation of the tubuloglomerular feedback mechanism, which may be defined as vasomotor response to tubular osmolarity and sodium concentrations detected by macula densa cells [40]. For correction of such compensatory feedback mechanisms, HSS treatment as well as many other drugs that may attract extravascular volume towards intravascular compartments, such as mannitol and dextran, have been proposed [41, 42].

Additionally, reduced RBF and load of tubular volume and solute may cause a shift in renal plasma flow, which may be reversible via administration of HSS [43, 44]. The importance of that shift depends upon the presence of deep medullary nephrons with well-developed loop of Henle in medullary in contrast to cortical nephrons. Moreover, HSS caused a decrease in plasma renin activity and atrial natriuretic peptide levels [45].

Increased myocardial contractility with HSS may be another possible reason for the observed outcomes. Indeed, HSS improved myocardial contractility in experimental models [46]. It has also been shown that HSS improved cardiac contractile function during sepsis by preserving calcium handling [47].

HSS may also have anti-inflammatory actions, as evidenced by inhibition of neutrophil activation and infiltration in lungs [48]. Furthermore, HSS can ameliorate organ dysfunction in severe sepsis caused by cecal ligation and puncture, and this is mediated via its antioxidant and anti-inflammatory effects [49]. Anti-apoptotic actions of HSS have also been demonstrated [50]. Lastly, it has been hypothesized that HSS with furosemide attenuates the possible harmful effects of neuro-hormonal excitation that occurs in HF [15].

The results of this meta-analyses offer the potential for changes to management guidelines for decompensated HF. In addition to improvements in clinical outcomes, such as readmissions and mean length of hospital stay, HSS offers potential improvements in renal function, which is one of the primary poor predictive factors for adverse outcomes [51]. Baseline urine urea nitrogen/creatinine ratio, a prognostic factor in patients with HF, has been shown to be the strongest predictor of HSS treatment-related diuretic response [52]. A retrospective analysis of 58 diuretic therapy-refractory patients with decompensated HF demonstrated that administration of HSS improved serum creatinine levels, total urinary output, and body weight loss, a change that was statistically significant, without any significant pulmonary or neurological adverse effects [53]. This study is crucial as it provides further clinical evidence for the use of HSS. Additionally, HSS administration reduces serum levels of many proinflammatory cytokines, including tumor necrosis factor-α and interleukin (IL)-6 and IL-1β, providing evidence that HSS therapy may reverse the inflammatory response that develops in response to congestion, edema, and tissue injury [54]. An increasing level of scientific evidence favors the use of HSS in the management of decompensated HF. Nevertheless, comprehensive multicenter large-scale clinical trials are required to reach a definitive conclusion. Also, the possible role of confounding factors, including comorbidities frequently present in patients with HF, such as diabetes mellitus, renal diseases, and arrhythmia, should not be overlooked in study groups (Tables 1, 2).

We included 14 studies in this meta-analyses, with ten RCTs, which is considerably more than in previous meta-analyses. We also included more clinical and laboratory parameters in the qualitative analysis [40, 55]. Limitations of our study include the exclusion of severe renal disorders, which is a common comorbidity in patients with long-standing HF, possible variations in baseline serum electrolyte levels among participants, and possible bias associated with the high number of studies performed by the same research group. It should be noted that two of the included studies [30, 35] reported different long-term sodium intake regimens for the HSS and furosemide group and the control group (120 and 80 mmoL/day, respectively). It could be concluded that the long-term effects could be solely due to differences in sodium restriction. Other important limitations of our analysis include the use of different protocols for the

Table 1 General characteristics of the studies included in the meta-analyses

Study	Study design	Participant characteristics	Placebo group characteristics	Inclusion criteria	Exclusion criteria
Paterna et al. [33]	SB, RCT	*N* = 30 (19 males) Mean age: 73.57 ± 7.95 years SBP: 142 ± 23.8 mmHg HR: 82.7 ± 13.7 bpm EF: 30.3 ± 5.34% Na^+: 135.9 ± 6.8 mEq/L K^+: 4.4 ± 0.6 mEq/L Cr: 1.6 ± 0.05 mg/dL Albumin: 3.9 ± 0.5 mg/dL Uric acid: 6.3 ± 2.1 mg/dL	*N* = 30 (20 males) Mean age: 74.3 ± 5.86 years SBP: 145 ± 27.5 mmHg HR: 83.9 ± 15.5 bpm EF: 30.27 ± 3.26% Na^+: 134.7 ± 7.9 mEq/L K^+: 4.6 ± 0.9 mEq/L Cr: 1.65 ± 0.07 mg/dL Albumin: 4.1 ± 0.7 mg/dL Uric acid: 6.7 ± 2.6 mg/dL	NYHA class IV, ADHF and unresponsive to therapy EF < 35% SCr < 2 mg/dL BUN < 60 mg/dL Reduced urinary volume and low natriuresis	NA
Licata et al. [30]	SB, RCT	*N* = 53 (33 males) Etiology: 31 CAD, 12 HHD, 10 DCM Mean age: 74.7 ± 8 years SBP: 142 ± 22 mmHg DBP: 80 ± 13 mmHg EF: 30.4 ± 5% Na^+: 135.8 ± 7 mEq/L K^+: 4.4 ± 0.5 mEq/L Cr: 1.6 ± 0.05 mg/dL Albumin: 3.9 ± 0.5 mg/dL	*N* = 54 (35 males) Etiology: 31 CAD, 14 HHD, 9 DCM Mean age: 74.5 ± 6 years SBP: 145 ± 25 mmHg DBP: 82 ± 14 mmHg HR: 84 ± 15 bpm EF: 30.3 ± 3% Na^+: 134.8 ± 8 mEq/L K^+: 4.6 ± 0.7 mEq/L Cr: 1.65 ± 0.05 mg/dL Albumin: 4.1 ± 0.6 mg/dL	NYHA class IV, ADHF and unresponsive to standard therapy EF < 45%	NA
Parrinello et al. [32]	DB, RCT	*N* = 66 (42 males) Mean age: 75.6 ± 7 years Etiology: 32 CAD, 22 HHD, 12 DCM SBP: 135 ± 21 mmHg DBP: 80 ± 13 mmHg HR: 83 ± 12 bpm Na^+: 136 ± 6 mEq/L K^+: 4.4 ± 0.4 mEq/L Cr: 1.5 ± 0.3 mg/dL Albumin: 4.1 ± 0.6 mg/dL	*N* = 67 (44 males) Mean age: 76.3 ± 9 years Etiology: 35 CAD, 18 HHD, 14 DCM SBP: 133 ± 24 mmHg DBP: 81 ± 12 mmHg HR: 80 ± 12 bpm Na^+: 135 ± 4 mEq/L K^+: 4.2 ± 0.4 mEq/L Cr: 1.4 ± 0.5 mg/dL Albumin: 4.1 ± 0.3 mg/dL	NYHA class IV, ADHF unresponsive to therapy LVEF < 40% SCr < 2.0 mg/dL BUN < 60 mg/dL UO < 500 mL/day Low natriuresis (< 60 mEq/day)	Alcohol dependence; cardiac resynchronization therapy; comorbidities (i.e., ESRD, uncontrolled DM, cirrhosis, dementia, malignancy, edematous syndromes); patients experiencing adverse effects of ACEi/ARBs; unable to follow treatment protocol; unable to provide informed consent; use of NSAIDs
Tuttolomondo et al. [26]	DB, RCT	*N* = 120 (65 males) Mean age: 64 years Weight: 75 kg EF: 35% SBP: 145 mmHg DBP: 80 mmHg Na^+: 137.0 mEq/L K^+: 4.0 mEq/L Cr: 1.1 mg/dL	*N* = 30 (16 males) Mean age: 66 years Weight: 72 kg EF: 39% SBP: 140 mmHg DBP: 85 mmHg Na^+: 139.0 mEq/L K^+: 4.1 mEq/L Cr: 1.0 mg/dL	All patients with HF	Acute myocarditis; active pulmonary and liver disease, autoimmune disorders, infection, malignant disease, muscle disorder and renal insufficiency (Cr > 2.5 mg/dL), or hematological diseases; use of anti-inflammatory drugs

Table 1 (continued)

Study	Study design	Participant characteristics	Placebo group characteristics	Inclusion criteria	Exclusion criteria
Paterna et al. [35]	SB, RCT	*N* = 953 (601 males) Mean age: 74.7 ± 11 years Etiology: 61.9% CAD, 33.6% HHD, 4.4% DCM Therapy: 100% ACEi, 69.1% BB, 85% spironolactone, 11.2% digitalis	*N* = 974 (612 males) Mean age: 73.4 ± 13 years Etiology: 62.9% CAD, 32.4% HHD, 4.6% DCM Therapy: 100% ACEi, 69.7% BB, 84.7% spironolactone, 11.8% digitalis	NYHA class III, ADHF and unresponsive to standard therapy EF < 40% SCr < 2.5 mg/dL BUN < 60 mg/dL Reduced urinary volume	Comorbidities (i.e., cerebral vascular disease, dementia, malignancy, uncontrolled DM, severe hepatic disease); loss of follow-up; unable to follow treatment protocol; unable to provide informed consent
Engelmeier et al. [28]	DB, RCT	*N* = 25 Weight: 91.37 ± 17.64 kg BUN: 47.28 ± 27.25 mg/dL eGFR: 36.84 ± 12.94 mL/min	*N* = 25 Weight: 93.07 ± 25.10 kg BUN: 41.0 ± 19.18 mg/dL eGFR: 38.96 ± 12.44 mL/min	ADHF with advanced renal failure (eGFR < 60 mL/min/m^2)	NA
Parrinello et al. [34]	DB, RCT	*N* = 122 (72 males) Mean age: 74.9 ± 10.9 years Therapy: 100% ACEi/ARB, 45% BB	*N* = 126 (76 males) Mean age: 72 ± 8.4 years Therapy: 100% ACEi/ARB, 45% BB	NYHA class III–IV, ADHF and unresponsive to standard therapy EF < 45% BNP > 100 pg/mL	Acute coronary syndrome, pulmonary thromboembolism, cardiac tamponade, pericarditis, renal insufficiency (SCr > 2.5 mg/dL, BUN > 60 mg/dL); alcohol dependence; comorbidities (i.e., autoimmune disorders, cancer, uncontrolled DM, chronic liver diseases); dialysis; requirement for pacemaker; unable to provide informed consent
Issa et al. [29]	SC, DB, RCT	*N* = 20 (95% males) Mean age: 53.3 ± 13 years SBP: 103.2 ± 14.5 mmHg Na^+: 137.6 ± 3.5 mEq/L K^+: 4.3 ± 0.7 mEq/L Cr: 1.72 ± 0.47 mg/dL Therapy: 55% ACEi/ARB, 75% BB, 45% spironolactone, 70% hydralazine	*N* = 12 (58.3% males) Mean age: 41.5 ± 13.1 years SBP: 100 ± 16.5 mmHg Na^+: 135.7 ± 3.4 mEq/L K^+: 4.1 ± 0.5 mEq/L Cr: 1.58 ± 0.48 mg/dL Therapy: 66.7% ACEi/ARB, 83.3% BB, 41.7% spironolactone, 33.3% hydralazine	ADHF with EF < 40%, age > 18 years	Acute pulmonary embolism; alcohol abuse; any severe systemic disease expected to impair survival; cardiac surgery or angioplasty within 6 months before randomization; COPD; immunosuppressive therapy; malignant tumors; myocardial infarction or unstable angina within 6 months before randomization; patient refusal; pregnancy or childbearing potential; primary valvular disease; restrictive cardiomyopathy; SCr > 3.0 mg/dL; serum potassium > 5.5 mg/dL; signs of hypoperfusion; surgical interventions or infections in the last 30 days

Table 1 (continued)

Study	Study design	Participant characteristics	Placebo group characteristics	Inclusion criteria	Exclusion criteria
Okuhara et al. [31]	P, NB, RCT	*N* = 22 (16 males) Mean age: 71 ± 11 years Etiology: 12 CAD, 18 HHD, 10 AF Therapy: 55% ACEi/ARB, 50% BB, 14% thiazide diuretics, 45% aldosterone antagonists EF: 32% SBP: 122 mmHg DBP: 70 mmHg HR: 78 bpm Na^+: 138 mEq/L K^+: 4.5 mEq/L Cr: 1.56 mg/dL	*N* = 22 (14 males) Mean age: 73 ± 10 years Etiology: 11 CAD, 19 HHD, 11 AF Therapy: 77% ACEi/ARB, 82% BB, 18% thiazide diuretics, 36% aldosterone antagonists EF: 37% SBP: 130 mmHg DBP: 76 mmHg HR: 81 bpm Na^+: 140.5 mEq/L K^+: 4.1 mEq/L Cr: 1.45 mg/dL	NYHA class III/IV, ADHF and unresponsive to standard therapy SBP > 80 mmHg eGFR > 15 mL/min/1.73 m^2 Serum Na < 148 mmol/L	Acute coronary syndrome; comorbid endocrinological disorders (i.e., siADH); infections; use of inotropic agents, carperitide, hemodiafiltration, or noninvasive positive pressure ventilation
Yayla et al. [36]	SC, RCT	*N* = 14 (9 males) Mean age: 70.6 ± 8.2 years EF: 40.5 ± 16.9% Cr: 0.96 ± 0.29 mg/dL Na^+: 138.3 ± 5.0 mEq/L BUN: 22.1 ± 7.2 mg/dL NT-proBNP: 3979 ± 2576 Therapy: 71.4% ACEi/ARB, 78.6 BB, 14.3% aldosterone antagonist	Two control groups with various furosemide doses	Acute decompensated HF, serum pro-BNP > 300 pg/mL	IV diuretic use before admission to hospital; SBP < 90 mmHg; need for IV vasodilators or inotropic agents other than digoxin; suspicion of acute coronary syndromes; SCr > 2.0 mg/dL
Okuhara et al. [27]	SC, retro cohort study	*N* = 64 (49 males) Mean age: 73 ± 13 years BMI: 24.3 ± 5.2 kg/m^2 Hct: 35.4 ± 6.5 BUN: 30.7 ± 17.5 mg/dL Cr: 1.42 ± 0.76 mg/dL Na^+: 138 ± 4.5 mEq/L K^+: 3.66 ± 0.49 mEq/L EF: 39 ± 17% Therapy: 59.4% ACEi/ARB, 59.4% BB, 64.1% loop diuretics, 15.9% thiazide diuretics	*N* = 111 (75 males) Mean age: 72 ± 14 years BMI: 24.1 ± 5.0 kg/m^2 Hct: 36.4 ± 6.9 Cr: 1.46 ± 0.92 mg/dL BUN: 29.7 ± 18.5 mg/dL Na^+: 138 ± 5.3 mEq/L K^+: 4.3 ± 0.7 mEq/L EF: 40 ± 17% Therapy: 46.9% ACEi/ARB, 52.3% loop diuretics, 8.1% thiazide diuretics, 47.8% BB	NYHA class II/III/IV, aged > 20 years, ADHF SBP ≥ 80 mmHg	Acute pulmonary edema and no leg edema; acute coronary syndrome; carperitide therapy; death within 24 h of admission; need for invasive positive pressure ventilation and inotropic agents such as catecholamines and PDE III inhibitors at admission; need for surgery; renal failure requiring renal replacement therapy at admission

Table 1 (continued)

Study	Study design	Participant characteristics	Placebo group characteristics	Inclusion criteria	Exclusion criteria
Lafrenière et al. [25]	P, NR	*N* = 47 (68.1% males) Mean age: 77.6 ± 9.5 years BMI: 28.2 ± 7.2 kg/m^2 eGFR: 42.2 ± 22.3 mL/min Therapy: 59.6% ACEi/ARB, 83% BB, 6.4% hydralazine, 17% spironolactone	NA	Constant increase of body weight Orthostatic hypotension with increased diuretic doses Patients with ADHF aged > 18 years with congestion signs despite standard therapy Persistence of peripheral or pulmonary edema Poor responsiveness to treatment with furosemide Reduction of urine volume Worsening renal function because of increased diuretic doses	Absence of congestive symptoms and signs; baseline hypernatremia; hypertensive crisis
Wan et al. [37]	NB, RCT	*N* = 132 (53 males) Mean age: 60.62 ± 10.13 years Etiology: 51.52% CAD, 15.91% HHD, 14.39% RHD Therapy: 81.06% ACEi, 34.85% BB, 75.76% digitalis, 90.15% spironolactone	*N* = 132 (48 males) Mean age: 61.18 ± 10.05 years Etiology: 50.76% CAD, 15.91% HHD, 13.64% RHD Therapy: 89.39% ACEi, 43.94% BB, 79.55% digitalis, 93.18% spironolactone	NYHA class IV, ADHF and unresponsive to standard therapy EF < 40% SCr < 1.73 mg/dL BUN < 60 mg/dL UO < 500 mL/day	Age < 18 years; failure to follow prescribed diet; failure to follow treatment protocol; loss of follow-up; plasma albumin < 30 g/L; serious water or activity restrictions; severe systemic diseases
Griffin et al. [24]	Retro analysis	*N* = 58 (13 males) Mean age: 60 ± 11 years Medical history: 55% HTN, 36% DM, 45% CHD, 60% ICD, 25% LVAD Mean EF: 35 ± 22% 64% received inotropes	NA	ADHF with signs of diuretic resistance (rising SCr, hyponatremia, and stagnant urine output in the 72 h preceding therapy)	Patients who received HSS for other indication

ACEi angiotensin-converting enzyme inhibitor, *ADHF* acute decompensated heart failure, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *BB* β-blocker, *BMI* body mass index, *BNP* brain natriuretic peptide, *BUN* blood urea nitrogen, *CAD* coronary artery disease, *CHD* congestive heart disease, *COPD* chronic obstructive pulmonary disease, *Cr* creatinine, *DB* double-blind, *DBP* diastolic blood pressure, *DCM* dilated cardiomyopathy, *DM* diabetes mellitus, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *Hct* hemotocrit, *HF* heart failure, *HHD* hypertensive heart disease, *HR* heart rate, *HSS* hypertonic saline solution, *HTN* hypertension, *ICD* implantable cardioverter-defibrillator, *IV* intravenous, K^+ potassium, *LV* left ventricle, *LVAD* left ventricular assist device, *LVEF* left ventricular ejection fraction, *N* number, *NA* not applicable, Na^+ sodium, *NB* nonblind (open-label), *NR* nonrandomized, *NSAID* nonsteroidal anti-inflammatory drug, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *NYHA* New York Heart Association, *P* prospective, *PDE* phosphodiesterase, *RCT* randomized controlled trial, *Retro* retrospective, *RHD* rheumatic heart disease, *SB* single-blind, *SBP* systolic blood pressure, *SC* single center, *SCr* serum creatinine, *siADH* syndrome of inappropriate antidiuretic hormone secretion, *UO* urine output

Table 2 Treatment protocol and quality assessment of the studies included in the meta-analysis

Study	Treatment protocol	Primary outcome
Paterna et al. [33]	Intervention group: IV furosemide 500–1000 mg + HSS (150 mL of 1.4–4.6% NaCl) BID Control group: IV furosemide 500–1000 mg BID as bolus Duration: 6–12 days	Shorter hospitalization time (1.67 ± 1.8 vs. 8.57 ± 2.3 days; $P = 0.001$)
Licata et al. [30]	Intervention group: IV furosemide 500–1000 mg + HSS (150 mL of 1.4–4.6% NaCl) BID in 30 min Control group: IV furosemide 500–1000 mg BID as bolus Duration: 6–12 days	After mean follow-up of 31 ± 14 months Better survival (55 vs. 13%; $P = 0.001$) Lower readmissions ($P < 0.05$) and lower irreversible HF ($P < 0.05$) No difference in sudden death rates
Parrinello et al. [32]	Intervention group: IV furosemide 250 mg + HSS (150 mL 3.0% Na) BID in 20 min + light restriction of sodium (120 mmol Na^+) Control group: IV furosemide 250 mg + low-sodium diet (80 mmol Na^+) Duration: 6 days	Higher plasma Na^+ ($P < 0.0001$) and K^+ ($P < 0.001$) Higher urinary Na ($P < 0.0001$) Lower SCr ($P < 0.0001$) Higher GFR ($P < 0.0001$) Lower BW ($P < 0.033$), BNP ($P < 0.001$), PCWP ($P < 0.0001$) Shorter hospitalization ($P < 0.0001$)
Tuttolomondo et al. [26]	Intervention group: IV furosemide 125–1000 mg + HSS (150 mL of 1.4–4.6% NaCl) BID in 30 min Control group: IV furosemide 125–1000 mg BID as bolus Duration: 8 days	Significant improvement in ANP, BNP, TNF-α, IL-1β and IL-6 No difference in E-Selectin, *P*-Selectin, and IL-10
Paterna et al. [35]	Intervention group: IV furosemide 250 mg + HSS (150 mL) BID in 30 min + light restriction of sodium (120 mmol Na) + 1000 mL fluid intake Control group: IV furosemide 250 mg + low-Na^+ diet (80 mmol Na^+) + 1000 mL fluid intake Duration: 6 days	Lower hospitalization time ($P < 0.0001$) and lower rate of readmissions ($P < 0.0001$) and mortality ($P < 0.0001$)
Engelmeier et al. [28]	Intervention group: IV furosemide 250 mg + HSS (150 mL of 2.4% NaCl) BID in 30 min Control group: IV furosemide 80 mg + fluid (150 mL of 0.9% NaCl) BID in 30 min	Elevated BUN levels ($P < 0.006$)
Parrinello et al. [34]	Intervention group: IV furosemide 250 mg + HSS BID in 30 min Control group: IV furosemide 250 mg	Significant reduction in BW ($P < 0.001$), cardiac troponin I ($P < 0.0001$), BNP ($P < 0.0001$), and hospitalization time ($P < 0.0001$)
Issa et al. [29]	Intervention group: IV furosemide + HSS (100 mL of 7.5% NaCl) BID in 1 h Control group: IV furosemide + HSS (100 mL of 0.9% NaCl) BID in 1 h Duration: 3 days	Reduced SCr ($P = 0.01$). Higher urinary protein expression of AQP-2 ($P = 0.004$), UT-A1 ($P = 0.001$), and NHE3 ($P = 0.008$) No difference in serum Na^+-K^+, IL-6, TNF-α, and osmolarity
Okuhara et al. [31]	Intervention group: IV furosemide 40 mg + HSS (500 mL of 1.7% NaCl) OD Control group: IV furosemide 40 mg + 500 mL of 5% glucose solution OD	Higher BW loss ($P = 0.05$). Higher 24-h urinary volume ($P < 0.001$). Rapid relief of dyspnea and systemic venous congestion symptoms ($P = 0.01$)
Yayla et al. [36]	Intervention group: IV furosemide 160 mg + HSS (150 mL of 1.95% NaCl) BID in 30 min Control group: IV furosemide 80–160 mg BID	No change in SCr ($P = 0.08$) and BW reduction ($P = 0.66$). Shorter hospital stay ($P < 0.01$)
Okuhara et al. [27]	Intervention group: IV furosemide 40 mg/day + continuous HSS (1.7% NaCl and at the speed of 500 mL/24 h) Control group: carperitide	No differences in length of hospital stay ($P = 0.170$), re-hospitalization at 1 month ($P = 1.000$) or 1 year ($P = 0.907$) and 1-year all-cause mortality ($P = 0.724$)
Lafrenière et al. [25]	Intervention group: IV furosemide 250 mg + HSS (150 mL of 3% NaCl) BID Control group: IV furosemide 250 mg Duration: 2 days	Higher BW loss ($P = 0.0168$). Greater decline in SCr ($P = 0.008$)

Table 2 (continued)

Study	Treatment protocol	Primary outcome
Wan et al. [37]	Intervention group: IV furosemide 100 mg + HSS (100 mL) BID + severe water restriction (< 500 mL) Control group: IV furosemide 100 mg	Lower readmission rates ($P < 0.01$) and mortality ($P < 0.01$)
Griffin et al. [24]	Median dose of loop diuretic prior to HSS: furosemide 400 (200–875) mg equivalents/24 h HSS (150 mL of 3% NaCl) + high doses of loop diuretics Trends were assessed by comparing to baseline levels (24 h pre-HSS)	Higher urinary output: 489 ± 241 mL during day 1 ($P = 0.04$), 1019 ± 241 mL during day 2 ($P < 0.001$), and 921 ± 244 mL during day 3 ($P < 0.01$) vs. values at 24 h before treatment. Average BW decreased by 0.6 ± 0.5 kg at 24 h ($P = 0.23$), 2.0 ± 0.5 kg at 48 h ($P < 0.001$), and 3.1 ± 0.5 kg at 72 h ($P < 0.001$). Serum Na^+, chloride, Cr improved after HSS administration ($P < 0.001$ for all). No deterioration in respiratory status

ANP atrial natriuretic peptide, *AQP-2* aquaporin 2, *BID* twice daily, *BNP* brain natriuretic peptide, *BUN* blood urea nitrogen, *BW* bodyweight, *Cr* creatinine, *GFR* glomerular filtration rate, *HF* heart failure, *HSS* hypertonic saline solution, *IL* interleukin, *IV* intravenous, K^+ potassium, Na^+ sodium, *NaCl* sodium chloride, *NHE3* sodium–hydrogen exchanger 3, *OD* once daily, *PCWP* pulmonary capillary wedge pressure, *SCr* serum creatinine, *TNF* tumor necrosis factor, *UT-A1* urea transporter A1

administration of hypertonic saline solutions, the limited number of patients included, and the increased heterogeneity of the studies.

In conclusion, the intravenous administration of HSS with furosemide in patients with acute decompensated HF may result in shorter mean hospital stays, lower mortality rates, fewer readmissions, and significant improvements in serum creatinine levels, 24-h urine output, and weight loss compared with intravenous furosemide therapy alone.

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