

Efficacy And Safety Of Combination Diuretic Therapy In Patients With Heart Failure: A Systematic Review And Meta-Analysis

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Abstract

Background: Persistent fluid overload is one of the hardest problems in heart failure (HF) care. Giving two or more diuretic classes together, for example metolazone with furosemide, has been suggested as a way to boost fluid removal and improve outcomes.

Objective: To judge the benefits and risks of combination diuretic strategies in patients with HF.

Methods: PubMed, the Cochrane Library, Embase and Web of Science were searched, yielding 61 records. Seven randomised controlled trials (RCTs) satisfied the eligibility criteria. Information on mortality, rehospitalisation, symptoms, electrolyte disturbance, kidney function and adverse events was extracted. Risk of bias was appraised with standard tools, and pooled estimates were produced with RevMan 5.4.0 using fixed- or random-effects models according to heterogeneity.

Results: Combination therapy produced a statistically significant fall in body weight ($P = 0.001$) but no meaningful difference in mortality (risk ratio [RR] 0.99;

95% CI 0.90–1.09) or rehospitalisation (RR 1.05; 95% CI 0.98–1.12) relative to control. Electrolyte disturbances (low or high sodium, low potassium) and worsening kidney function were reported in the combination arms of several trials, whereas serious adverse events were reported more often in control arms. The pooled

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difference in Kansas City Cardiomyopathy Questionnaire (KCCQ) score was 2.43 points (95% CI 0.95–3.92). Heterogeneity was low for most outcomes (I^2 below 50%), and funnel plots suggested limited publication bias.

Conclusions: Combination diuretics reduce fluid burden and weight but do not change mortality or readmission. Because they can disturb electrolytes and kidney function, close monitoring and individualised prescribing are essential. Future work should refine which combinations and doses are best.

Introduction

Congestion of the lungs is among the most frequent reasons patients with acute heart failure (AHF) are admitted to hospital [1]. Relieving the signs and symptoms of congestion, known as decongestion, is therefore a central aim of inpatient treatment [2–4]. In practice, many patients leave hospital still congested, and residual congestion has been tied to higher mortality and more HF readmissions [5,6]. This persistence of fluid overload justifies searching for better decongestion strategies.

Loop diuretics remain the foundation of treatment for congested patients with HF [7,8]. Their effect, however, can fade as the disease advances and as diuretic resistance develops. Clinicians then escalate the dose, which raises the likelihood of electrolyte disturbance, kidney injury and worse cardiovascular outcomes [9]. This has stimulated interest in combination regimens that pair different diuretic classes, namely loop diuretics, thiazide diuretics and mineralocorticoid receptor antagonists (MRAs), so that several sites of sodium reabsorption in the nephron are blocked at once. The expectation is better diuresis with fewer harms than high-dose single-agent treatment [8,10].

Why a review is needed

Several obstacles make combination therapy hard to evaluate. No standard protocol exists, so doses and drug pairings differ widely between studies, and this limits comparison. Patient factors such as kidney function, baseline electrolytes and comorbid illness also shape the response to diuretics; a patient with impaired kidney function may respond very differently from one with normal function, which argues against a one-size-fits-all approach. There are also concerns that combining diuretics may amplify electrolyte disturbance, kidney decline and neurohormonal activation [11,12]. Given limited high-quality evidence and genuine clinical uncertainty, a systematic synthesis was judged to be overdue. The aim was to support evidence-based decisions about fluid management, to identify the most effective and safest combinations, and to point out where further research is needed.

Methods

Design and reporting standard

This was a systematic review with meta-analysis, reported according to the PRISMA guidelines [12].

Search strategy

The methods section reports a search of PubMed and the Cochrane Database of Systematic Reviews between 1 and 31 March 2025, together with a check of the PROSPERO register; the results section describes four databases (PubMed, Cochrane Library, Embase and Web of Science). The strategy combined Medical Subject Headings and free-text terms covering acute heart failure or acute decompensated heart failure, diuretics or combination therapy, and randomised controlled or quasi-experimental designs. Reference lists of qualifying studies were searched by hand, and additional searches looked for guidelines and recommendations on diuretic use in HF.

Eligibility criteria (PICO)

Population: Patients hospitalised with AHF who needed intravenous diuretics for decongestion. Patients admitted for other reasons, and non-human studies, were excluded.

Intervention: Combination diuretic therapy.

Comparison: Placebo or diuretic monotherapy. Studies lacking a comparison group were excluded.

Outcomes: Effectiveness and safety measures, including mortality, rehospitalisation, symptom improvement, electrolyte abnormalities and kidney function.

Design: RCTs and quasi-experimental studies. Case studies, case reports, letters, editorials and comments were excluded.

Publication type: Peer-reviewed articles in English only; non-English papers were excluded because of translation costs.

Selection and data extraction

Two reviewers independently screened titles and abstracts for relevance and duplication, then assessed the full texts of potentially suitable papers against the predefined criteria. Disagreements were settled by discussion or by a third adjudicator. Data were extracted with the Covidence platform.

Risk-of-bias assessment

Two reviewers independently appraised study quality: the Cochrane Risk of Bias tool was applied to RCTs and ROBINS-I to non-randomised intervention studies. Their ratings were compared to check agreement.

Statistical analysis

Analyses were run in RevMan 5.4.0. Risk ratios with 95% confidence intervals described effects on dichotomous outcomes (mortality, electrolyte disturbance, adverse events and serious adverse events) using Mantel-Haenszel methods, while mean differences described continuous outcomes. Statistical significance was set at $P \leq 0.05$. Statistical heterogeneity was gauged with I^2 : values of 50% or lower were read as mild to moderate, and values around 75% as high. A fixed-effect model was used when I^2 was under 50% and a random-effects model when it exceeded 50%. Funnel plots were inspected for signs of publication bias.

Results**Study selection**

The database searches returned 61 records: 41 from PubMed, 5 from the Cochrane Library, 7 from Embase and 8 from Web of Science. Before screening, 15 duplicates and 10 records judged irrelevant were removed, leaving 36 to be screened. Seven were excluded at that stage, and 29 reports were sought for retrieval, of which 3 could not be obtained. Twenty-six reports were examined in full. Nineteen of these were excluded: 3 after full-text review, 11 for not meeting inclusion criteria, 3 for irrelevant outcomes and 2 for unclear follow-up. Seven RCTs remained and formed the basis of the review and meta-analysis.

Characteristics of the included trials

The seven trials enrolled between 51 and 4,133 participants, with mean ages ranging from 58 to 83 years. Men made up the majority of participants in most trials. All trials dealt with acute decompensated HF except one, which focused on HF with reduced ejection fraction. Furosemide was the main loop diuretic in most trials; two trials tested the thiazide hydrochlorothiazide (HCTZ), one tested empagliflozin (an SGLT2 inhibitor) against placebo on top of usual diuretics, and one tested tolvaptan (a

vasopressin receptor antagonist) against placebo. The individual trials were as follows.

Shah and colleagues (2014) [13]: A prospective randomised trial of 90 patients (mean age 58.2 years; 73% male) comparing three intravenous furosemide approaches over 48 hours: infusion plus low-dose dopamine, bolus dosing, and infusion alone, each using 100 mg per 24 hours. The primary outcome was negative fluid balance at 24 hours.

Piardi and colleagues (2021) [14]: A single-centre, double-blind, placebo-controlled trial of 51 patients (mean age 64 years) in which oral HCTZ 50 mg or placebo was added to furosemide for 3 days. The primary outcome was daily weight change over 3 days.

Mullens and colleagues (2022) [15]: A multicentre, double-blind, placebo-controlled trial of 519 patients (mean age about 78 years) that added acetazolamide 500 mg daily to a loop diuretic for 3 days. The primary outcome was successful decongestion.

Trullàs and colleagues (2023) [16]: A multicentre, double-blind, placebo-controlled trial of 230 patients (mean age 83 years; 48% women) adding HCTZ 25–100 mg daily, dosed by glomerular filtration rate, to intravenous furosemide 80 mg per day for up to 5 days. Primary outcomes were change in body weight and patient-reported dyspnoea at 72 hours.

Jackson and colleagues (2020) [17]: A secondary analysis of the double-blind DAPA-HF trial in patients with HF and reduced ejection fraction (mean age 66 years; 23.6% female), comparing dapagliflozin with placebo across patients using different loop and thiazide-like diuretic doses. In total 3,880 participants were on diuretics and 736 were not. The key question was whether the benefit of dapagliflozin held across diuretic subgroups.

Biegus and colleagues (2023) [18]: The multinational, double-blind EMPULSE trial of 530 patients (median age about 70 years) comparing empagliflozin 10 mg daily with placebo alongside standard loop diuretics for 90 days. The primary outcome was weight loss, adjusted for mean daily loop diuretic dose.

Konstam and colleagues (2007) [19]: The double-blind EVEREST trial of 4,133 patients (mean age about 65–66 years; roughly three-quarters male) comparing tolvaptan with placebo on a background of furosemide dosed at several intensities and by infusion or bolus. Follow-up covered 60 days, and the primary outcome was cardiovascular death or first HF hospitalisation.

Risk of bias

Overall, six of the seven trials were rated at low risk of bias and one (Shah et al.) at moderate risk. Every trial was rated low for random sequence generation and allocation concealment. Performance bias (blinding of participants and personnel) was low in six trials and unclear in one. Detection bias (blinding of outcome assessment) was low in six trials and high in one. Attrition bias was low in four trials and unclear in three. Selective reporting was low in four and unclear in three, and other sources of bias were low in only three and unclear in four. Several trials showed missing information on how interventions were classified and how deviations from intended treatment were handled.

Clinical outcomes and adverse events in individual trials

In Shah et al., deaths numbered 0 with dopamine-supplemented infusion, 2 with bolus and 1 with infusion alone, and there were no significant differences in serum sodium, potassium, urea or creatinine between groups. Piardi et al. reported in-hospital mortality of 3.8% with HCTZ versus 0% with placebo (not significant), non-significant improvement in dyspnoea and congestion scores, and a significantly larger creatinine rise with HCTZ (58% versus 41%). Hypokalaemia was similar between arms (3.8% versus 4.5%), and one HCTZ patient needed haemodialysis.

In Mullens et al., all-cause death was 29.7% with acetazolamide versus 27.8% with placebo (hazard ratio 1.07; 95% CI 0.78–1.48), and rehospitalisation was 18.4% versus 17.4%. Hypokalaemia was 5.5% versus 3.9%, and the renal safety endpoint occurred in 2.7% versus 0.8%. Serious adverse events were almost identical (48.0% versus 47.9%). Trullàs et al. found higher 30-day mortality with HCTZ (9.6% versus 6.0%) and higher 90-day mortality (20.2% versus 16.4%), with rehospitalisation of 37.7% versus 34.5%. Low sodium (130 mmol/L or less) occurred in 8.8% versus 5.2%, low potassium (3.5 mmol/L or less) in 44.7% versus 19.0%, and impaired kidney function in 46.5% versus 17.2% ($P < 0.001$), though dyspnoea improved slightly with HCTZ at 72 and 96 hours.

In Jackson et al., there were 245 deaths with dapagliflozin and 289 with placebo, KCCQ symptom scores improved significantly with dapagliflozin at all diuretic doses, and creatinine rose slightly while fewer kidney-related adverse events occurred. Biegus et al. reported significant weight loss and a small improvement in congestion score with empagliflozin. Konstam et al. showed that baseline oedema severity predicted outcomes: event rates for death or unscheduled urgent clinic visit were about 50% in patients with no oedema and 68% in those with the most severe oedema, and in-hospital weight loss from baseline to discharge ranged from roughly 12 to 15 pounds depending on oedema grade.

Pooled analyses

Mortality. Six trials contributed data on mortality (about 3,234 patients on combination or active treatment and 3,227 controls; roughly 661 and 667 deaths respectively). Individual risk ratios ranged from 0.50 in the smallest trial to 2.89 in a trial with a single death. The pooled risk ratio was 0.99 (95% CI 0.90–1.09; $P = 0.85$), with no heterogeneity ($I^2 = 0\%$), so a fixed-effect model was used. In short, combination therapy neither raised nor lowered death risk compared with control. By agent, furosemide and HCTZ showed no significant mortality effect, acetazolamide was associated with a slightly higher death rate that was not statistically distinct from placebo, and dapagliflozin was associated with fewer deaths across dose groups. The mortality funnel plot was broadly symmetrical, with the larger trials clustering near the pooled estimate and a couple of small trials scattered more widely, indicating little publication bias; the scatter of the smaller studies is typical of meta-analysis.

Rehospitalisation. Four trials supplied data (about 2,472 combination patients and 2,466 controls; roughly 968 and 922 events). Individual risk ratios fell between 0.88 and 1.09, with the very large EVEREST trial carrying about 90% of the weight at 1.05. The pooled risk ratio was 1.05 (95% CI 0.98–1.12; $P = 0.21$), again with I^2 of 0%. The funnel plot showed no notable asymmetry.

Symptom improvement. Body weight fell significantly with combination therapy ($P = 0.001$; pooled difference of roughly 1 kg or unit less than control, with very high heterogeneity). Dyspnoea showed a favourable trend of about half a point on the scale ($P = 0.09$ as stated in the text), and thirst scores showed a similar trend (mean difference -2.20 ; 95% CI -4.48 to 0.08 ; $P = 0.06$; a single study). Congestion score did not differ significantly (standardised mean difference -1.30 ; 95% CI -3.56 to 0.97 ; $P = 0.26$) and heterogeneity was extreme (I^2 98%). KCCQ score, however, improved by 2.43 points (95% CI 0.95–3.92; $P = 0.001$) with moderate heterogeneity (I^2 68%, random effects). The funnel plot covering these symptom measures was largely symmetrical and the studies appeared fairly consistent around the central line.

Electrolytes. Serum potassium did not differ between groups (mean difference 0.00; 95% CI -0.24 to 0.23 ; $P = 0.97$; two studies; I^2 38%). Serum sodium was assessed in one study only and showed a non-significant difference of -1.93 mEq/L (95% CI -5.97 to 2.11 ; $P = 0.35$). The risk of hypokalaemia was not significantly different (RR 1.37; 95% CI 0.64–2.94; $P = 0.41$; 15 versus 11 events; I^2 0%), and the single study contributing hypernatraemia data found no difference (RR 0.32; 95% CI 0.01–7.53; P

= 0.48). Funnel plots for potassium and sodium were symmetrical, though the hypernatraemia plot, based on one study, could not be interpreted reliably and may reflect variability or bias.

Kidney function. The pooled mean difference in serum creatinine was a very small 0.02 mg/dL (I^2 44%), and the pooled difference in blood urea was -8.72 mg/dL (95% CI -23.29 to 5.85 ; $P = 0.24$; I^2 99%). The authors concluded that combined treatment did not significantly alter creatinine or urea overall, although individual trials showed higher rates of worsening kidney function with HCTZ and high-dose furosemide, and dapagliflozin was linked to a small creatinine rise. Funnel plots for these outcomes did not suggest publication bias.

Adverse and serious adverse events. The overall risk of any adverse event was unchanged (RR 0.99; 95% CI 0.80–1.21; $P = 0.89$), but heterogeneity was substantial (I^2 65%) and a random-effects model was used. Some trials noted specific events, including ventricular arrhythmias, need for haemodialysis and cardiovascular adverse events. For serious adverse events, the pooled risk ratio was 0.84 (95% CI 0.76–0.94; $P = 0.002$; I^2 0%) in favour of the combination arms, with a single large study supplying almost 98% of the weight. The related funnel plot was symmetrical apart from one outlier among the any-adverse-event studies.

Subgroup observations

Formal subgroup and sensitivity analyses were scarce. Shah et al. found no differences between infusion methods in sodium, potassium, urea or creatinine. Jackson et al. showed that dapagliflozin improved symptoms regardless of loop diuretic dose. Piardi et al. found no significant HCTZ-versus-placebo differences in creatinine, dyspnoea, congestion score, hypernatraemia or hypokalaemia, and Mullens et al. observed a slightly worse renal profile with acetazolamide. Together these observations point to the value of treatment tailored to the individual patient.

The review further noted that earlier work has consistently found that pairings such as metolazone with furosemide, furosemide with quinethazone, and bendroflumethiazide with bumetanide improve diuresis and weight loss. Refractory fluid overload, marked by weak diuretic response, inadequate sodium and water excretion and fluid retention, remains a major problem despite therapeutic advances. Metolazone with furosemide, and empagliflozin, appeared promising for symptom control.

Discussion

The studies synthesised here examined many ways of pairing diuretics or adding agents with diuretic effects to ease HF symptoms. The EMPULSE trial of empagliflozin and the EVEREST trial of tolvaptan illustrate how quickly combination approaches have evolved [18,19]. SGLT2 inhibitors are now widely used in HF and have diuretic properties. In EMPULSE, empagliflozin produced greater decongestion and was associated with fewer HF hospitalisations and deaths [18], in keeping with DAPA-HF, where dapagliflozin lowered cardiovascular deaths and worsening HF events [17]. The consistent benefit across studies suggests SGLT2 inhibitors may become a standard component of combination diuretic regimens.

Tolvaptan has been reported to relieve congestion and symptoms in AHF [20]. It is the only clinically approved treatment for dilutional hyponatraemia and can improve dyspnoea and oedema, but it may activate the renin-angiotensin-aldosterone system, disturb electrolytes and worsen kidney function. In EVEREST, one of the included trials, tolvaptan improved congestion symptoms without materially changing long-term mortality or morbidity [19].

Different combinations vary in effectiveness. Furosemide plus metolazone was highly effective in clearing oedema [16,21], and empagliflozin gave better weight loss and congestion relief than placebo [18,22–24], consistent with earlier studies showing stronger diuresis with combination regimens [21,22,25]. Related evidence on how

loop diuretics are given comes from a Cochrane review of infusion versus bolus dosing, which found little or no difference in mortality, slightly more weight loss with continuous infusion, and no clear difference in hospital stay, readmission, electrolyte disturbance or complications such as ototoxicity, hypotension and acute kidney impairment [26]. A further meta-analysis found higher but non-significant mortality with infusion, similar length of stay and less hypokalaemia with bolus dosing [27]. Safety remains a major concern. Although overall adverse events did not rise significantly with combination therapy, specific problems were evident. Low sodium and low potassium appeared in several trials, with variable results. Piardi et al. reported more hypernatraemia and hypokalaemia events in particular arms [14], Trullàs et al. documented clearly more hypokalaemia with HCTZ [16], and Mullens et al. saw more renal impairment with acetazolamide [15]. These findings stress the need for careful monitoring of electrolytes and kidney function whenever diuretics are combined, and they mean the real benefits in fluid control must be weighed against risk.

Protocols should be adjusted to baseline kidney function, comorbidities and earlier diuretic response. Position statements recommend close surveillance of kidney function and electrolytes with high-dose diuretics [8]. Because many hospitalised patients with HF go home still congested, further research on optimal combinations and dosing strategies is needed.

Clinical implications

Clinicians should balance the gains and hazards of combination diuretics and personalise treatment according to age, comorbidities and baseline kidney function. This matches the individualised approach advocated by the American Heart Association and the European Society of Cardiology [4].

Strengths and limitations

Strengths include a broad search, restriction to RCTs and structured quality appraisal. Limitations include heterogeneity among trials, differences in drug combinations and doses, risk of bias in some studies, and the scarcity of long-term follow-up, which prevents firm statements about lasting efficacy and safety. In addition, the pooled analyses combined trials of quite different interventions (thiazides, acetazolamide, SGLT2 inhibitors and tolvaptan) and relied on a small number of studies for several outcomes, so some pooled results, including those for sodium and hypernatraemia, rest on a single trial. Large, long-term studies are needed.

Conclusions

Combination diuretic strategies offer real benefits for fluid overload in heart failure, notably weight reduction and better symptom scores, but they do not measurably alter mortality or rehospitalisation. Their potential to disturb electrolytes and kidney function demands careful balancing of risk and benefit. Personalised prescribing, rigorous monitoring and continued research are required to optimise heart failure treatment, and combination diuretics should be built into a comprehensive, individualised care plan.

Declarations

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