Prata *et al. Critical Care* (2025) 29:474
https://doi.org/10.1186/s13054-025-05707-x

Critical Care

REVIEW Open Access

Protocolized natriuresis-guided diuretic therapy in acute heart failure: a systematic review and meta-analysis

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Abstract

Background Volume overload is the primary pathophysiological mechanism underlying signs and symptoms in acute heart failure (AHF). However, evidence-based strategies for optimal loop diuretic dosing and monitoring remain limited. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of natriuresis-guided protocols for titrating diuretic therapy in patients with AHF.

Methods We searched Cochrane, PubMed, and Embase databases for studies that compared natriuresis-guided diuretic therapy versus standard management in patients with AHF from their inception until June 2025. We computed pooled risk ratio (RR) for binary outcomes, and for continuous outcomes, we calculated either pooled mean difference (MD) or geometric mean ratio (GMR) derived from differences in log-means, all with 95% confidence intervals (CIs). Data from the studies were pooled using R version 4.4.1. Risk of bias was assessed using RoB 2 and ROBINS-I tools. We also performed a sensitivity analysis restricted to randomized controlled trials (RCTs).

Results Three RCTs and two observational studies were included, encompassing 933 patients, of which 404 (43%) were in the natriuresis-guided therapy group. Protocolized therapy significantly increased natriuresis (GMR: 1.30; 95% CI: 1.14 to 1.49) and diuresis (GMR: 1.21; 95% CI: 1.09 to 1.35) after 48 h. No significant differences were observed in weight loss, length of hospital stay, heart failure rehospitalization, or all-cause mortality. Protocolized therapy was associated with a lower risk of doubling serum creatinine (RR: 0.52; 95% CI: 0.28 to 0.98), without increasing the risk of hypokalemia or hypotension. Two RCTs were deemed at "low" risk of bias by the RoB 2 tool, while Bayat et al. was rated as having "some concerns." For studies assessed using the ROBINS-I tool, the ENACT-HF study presented a "moderate" risk of bias, and Pellegrino et al. a "serious" risk. Nevertheless, our sensitivity analysis, limited to RCTs, confirmed our findings for all efficacy and safety endpoints.

Conclusion In this meta-analysis of patients with AHF, protocolized natriuresis-guided therapy was safe and associated with improved diuresis and natriuresis after 48 h, as well as a reduced risk of acute kidney injury. While the short-term safety and efficacy are promising, further large RCTs are needed to evaluate the effects on clinical endpoints in diverse healthcare settings and patients worldwide.

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Keywords Acute Heart failure, Natriuresis, Urinary sodium, Diuresis, Diuretics, Protocolized-therapy

Introduction

Acute heart failure (AHF) is one of the leading causes of hospitalization worldwide [1]. Volume overload plays an important role in these admissions, being the primary cause of a patients signs and symptoms [2]. The American Heart Association/American College of Cardiology (AHA/ACC) [3] and European Society of Cardiology (ESC) guidelines [4] classify the use of loop diuretics in the acute and chronic management of congestion as class 1 A of recommendation. However, the optimal dose and monitoring strategy of loop diuretics to maximize diuresis in AHF remain controversial.

Traditional but imprecise methods of monitoring diuresis, such as weight changes, may overestimate fluid loss, leading to residual volume overload [5]. This has been associated with increased rehospitalization and mortality rates among heart failure (HF) patients [6]. A recent ESC consensus statement [5] highlights that the primary goal of therapy in AHF is to achieve complete decongestion and restore euvolemic state. In this context, urinary sodium measurement has emerged as a potential tool to optimize diuretic therapy, especially within the first 24 h. ESC proposed measurement of urinary sodium two hours after the initial diuretic dose, with a result > 50 mmol indicating an effective dose of loop diuretics.

Most evidence supporting the use of urinary sodium to guide diuresis comes from non-randomized studies or small randomized controlled trials (RCTs) [7–11], lacking sufficient power to establish definitive clinical benefits. Therefore, we aimed to perform a systematic review and meta-analysis to evaluate the efficacy and safety of natriuresis-guided diuretic therapy compared to standard management in patients with AHF.

Methods

This systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines [12] and the Cochrane Collaboration Handbook for Systematic Reviews of Interventions guidelines [13], reported in Supplementary Methods 1. The prospective meta-analysis has been registered on the PROSPERO in June, 2025, under protocol CRD420251079475.

Eligibility criteria

Studies considered for inclusion in our meta-analysis were required to meet all of the following criteria: (1) RCTs or observational studies; (2) patients with AHF; (3) evaluation of protocolized natriuresis-guided diuretic therapy; and (4) comparison of the protocolized approach versus standard of care (SOC). We excluded studies that (1) were conference or congress abstracts, (2) were published in non-English languages, (3) had overlapping patient populations, (4) lacked a SOC comparison group, and (5) were case series or case reports. The eligibility criteria for each study are described in Supplementary Table 1.

Search strategy and data extraction

PubMed, Embase, and Cochrane databases were systematically searched from inception to June 2025. The references from all included studies, systematic reviews, and meta-analyses were also searched manually for additional studies. The full search strategy is reported in Supplementary Methods 2. Independently and using a double-blinded approach, six authors (A.P., A.C., A.P., W.N., P.S., J.F.), working in pairs, reviewed the main reports and supplementary materials and extracted relevant information from the included trials. An additional author (L.G.P.) was responsible for resolving any discrepancies through deliberation.

Endpoints and sensitivity analysis

We extracted data for a pooled analysis on the following outcomes to evaluate protocolized natriuresis-guided diuretic therapy. Efficacy endpoints included: (1) natriuresis after 2 days, (2) weight change after 2 days, (3) diuresis after 2 days, (4) length of hospital stay, (5) HF rehospitalization, and (6) all-cause mortality at follow-up. For safety outcomes, we extracted data for: (7) hypokalemia, (8) hypotension, and (9) doubling of serum creatinine from baseline. We performed a sensitivity analysis restricted to RCTs for all included outcomes. If the included studies did not provide means and standard deviations, we estimated their values using the reported medians and ranges, based on methods described by Luo et al. and Wan et al. [14, 15].

Quality assessment

Four independent authors conducted the risk of bias assessment (A.P., A.P., P.S., W.F.). Risk of bias in selected randomized trials was assessed using the Cochrane Revised tool to assess Risk of Bias in Randomized trials (RoB 2) [16], evaluating five domains for each outcome of the selected studies: (i) bias in the randomization process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing data; (iv) bias in outcome measurement; and (v) bias in the selection of the reported results. Risk of bias in non-randomized studies was assessed using the Cochrane Risk of Bias tool for

Non-randomized Studies (ROBINS-I) [17], evaluating seven domains for each outcome of the selected studies: (i) bias due to confounding; (ii) bias in selection of participants; (iii) bias in classification of interventions; (iv) bias due to deviations from intended interventions; (v) bias due to missing data; (vi) bias in measurement of outcomes; and (vii) bias in selection of the reported results. The overall risk of bias assessment for each specific trial outcome was derived from individual domain judgments. Disagreements were resolved through consensus after discussing the reasons for the discrepancy.

Statistical analysis

We computed pooled risk ratios (RRs) and mean differences (MDs) for binary and continuous outcomes, respectively, with 95% confidence intervals (CIs). Heterogeneity was examined using the I^2 statistic. The between-study variance (τ^2) in our random-effects models was estimated using Restricted Maximum Likelihood estimation. We used a random-effects model for all meta-analyses. R (R Foundation for Statistical Computing, Vienna, Austria) version 4.4.1 was used for statistical analyses using the "meta" package [18]. For the outcomes of length of hospital stay, diuresis after 48 h, and natriuresis after 48 h, most trials presented these results as arithmetic means and standard deviations, while the ENACT-HF trial [9] reported these outcomes as geometric means (GMs) with 95% CIs. To enable pooling of these data for meta-analysis, all estimates were standardized to the same scale. We employed the methodology described by Higgins et al. [19] for this conversion. For studies reporting arithmetic means and standard deviations, these values were converted to log-scale means and their corresponding standard errors. For the ENACT-HF study, the reported GMs and CIs were log-transformed to derive the means and standard errors on the log scale. Following this standardization, all studies were pooled in the meta-analysis using the MD as the effect measure. Calculations were performed on the log scale, and these results were then reported as difference in log-means and their corresponding geometric mean ratio (GMR).

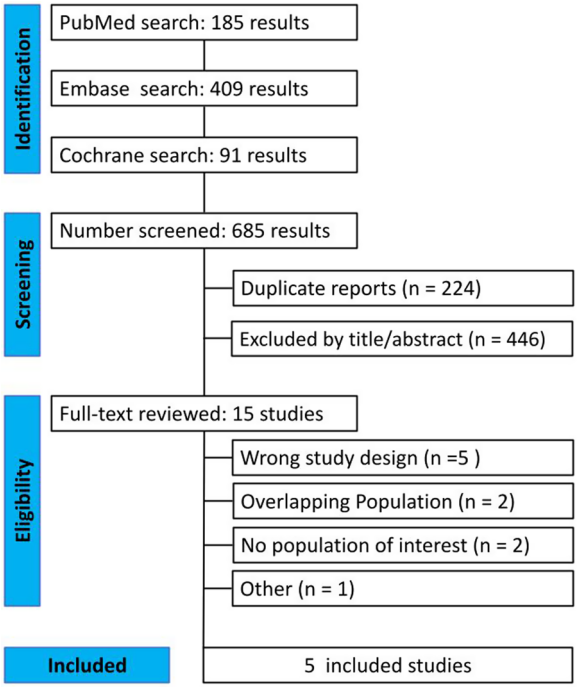

Fig. 1 PRISMA Flow Diagram. PRISMA flow diagram of study screening and selection

Results

Study selection and characteristics

A systematic search yielded 185 articles, of which 15 were selected for full-text review (Fig. 1). Ultimately, three RCTs and two observational studies met the inclusion criteria, comprising a total of 933 patients, of whom 404 underwent protocolized natriuresis-guided diuretic therapy. Detailed study designs and additional characteristics are provided in Table 1. Overall, the mean age was 73 years, with an average left ventricular ejection fraction (LVEF) of 41.1% and 36% female representation. The detailed characteristics of each studys natriuresis-guided diuretic protocols are presented in Table 2.

Efficacy endpoints

The pooled difference in log-means for natriuresis after 2 days was 0.26 (95% CI: 0.13 to 0.40; $p < 0.001$; $I^2 = 70.2\%$; Fig. 2A), corresponding to a GMR of 1.30 (95% CI: 1.14 to 1.49), indicating a 30% higher GM with protocolized therapy compared to SOC. Similarly, the pooled difference in log-means for diuresis after 2 days was 0.19 (95% CI: 0.09 to 0.30; $p < 0.001$; $I^2 = 70.9\%$; Fig. 2B), corresponding to a GMR of 1.21 (95% CI: 1.09 to 1.35), indicating a 21% higher GM with the protocolized approach.

There were no significant differences between protocolized natriuresis-guided and standard diuretic therapy regarding weight change after 2 days (MD: – 1.61 kg; 95% CI: – 4.06 kg to 0.84 kg; $p = 0.20$; $I^2 = 96.4\%$; Supplementary Fig. 1 A), length of hospital stay (MD: – 0.03; 95% CI: – 0.16 to 0.10; $p = 0.61$; $I^2 = 49.4\%$; Supplementary Fig. 1B), HF rehospitalization after hospital discharge (RR: 0.91; 95% CI: 0.61 to 1.35; $p = 0.64$; $I^2 = 0\%$; Fig. 3A), and all-cause mortality after hospital discharge (RR: 0.96; 95% CI: 0.64 to 1.44; $p = 0.83$; $I^2 = 0\%$; Fig. 3B).

Safety endpoints

Protocolized therapy was associated with a lower risk of doubling serum creatinine from baseline (RR: 0.52; 95% CI: 0.28 to 0.98; $p = 0.04$; $I^2 = 0\%$; Fig. 4A), with no significant differences in the risk of hypokalemia (RR: 0.97; 95% CI: 0.57 to 1.63; $p = 0.90$; $I^2 = 42.2\%$; Fig. 4B)

Table 1 Baseline characteristics of included studies

Study, year		PUSH AHF, 2023	ENACT-HF, 2024	EASY HF, 2024	Bayat et al., 2024	Pellegrino et al., 2023
Study design		Prospective, open-labelled RCT	Prospective, open-labelled Non randomized trial	Prospective, open-labelled RCT	Prospective, open-labelled RCT	Prospective cohort
Recruitment Period		February 2021—November 2022	October 2019—December 2022	March 2022—August 2023	October 2021—August 2022	September 2021—December 2022
Number of patients, n	Intervention*	150	147	30	30	47
	Control**	160	254	30	30	55
Age, years	Intervention*	74 [66–82]	69 (14)	80.4(8.4)	66.4 (16.9)	79.3 [73.6; 85]
	Control**	74 [65–81.2]	70 (13)	78.9(7.2)	73.2 (16.3)	80.3 [73.5; 83.9]
Female[a]	Intervention*	61 (41)	55 (37.4)	10 (33.3)	9 (30)	18 (38,3)
	Control**	77 (48)	96 (37.8)	5 (16.7)	8 (27)	23 (41.8)
BMI (Kg M2)[a]	Intervention*	27.3 [24.5–30.4]	29.2 (5.5)	28.7 [24.9–33.5]	-	24.5 [21.3; 28.1]
	Control**	28 [23.5–31.5]	29.7 (7.1)	27.5 [24.3–33.8]	-	23.3 [20.3; 28.8]
NYHA Class[a]	Intervention*	II: 5 (3) III 39 (26) IV 106 (71)	-	II: 1 (3.3) III: 16 (53.3) IV:13 (43.3)	II: 2 (3); III: 51 (85); IV: 7 (12)	III—IV: 25 (53.2)
	Control**	II: 11 (7) III: 29 (18) IV: 120 (75)	-	II: 3 (10.0) III: 11 (36.7) IV: 16 (53.3)	II: 0 (0); III: 26 (87); IV: 4 (13)	III—IV: 41 (74.6)
New-onset HF[a]	Intervention*	66 (44)	-	13 (43)	9 (30)	-
	Control**	69 (43)	-	9 (30)	8 (27)	-
Diabetes[a]	Intervention*	52 (34.7)	77 (52.4)	14 (46.7)	8 (27)	14 (29.8)
	Control**	66 (41)	110 (43.3)	9 (30)	13 (43)	18 (32.7)
Hypertension[a]	Intervention*	93 (62)	105 (71.4)	22 (73.3)	18 (60)	37 (78.7)
	Control**	102 (64)	192 (75.6)	22 (73.3)	21 (70)	39 (70.9)
Ischemic cause of HF[a]	Intervention*	56 (37)	65 (44.2)	-	9 (30)	-
	Control**	55 (34)	89 (35.0)	-	11 (37)	-
CKD[a]	Intervention*	28 (59.6)	74 (50.3)	-	15 (50)	-
	Control**	31 (56.4)	127 (50.0)	-	14 (47)	-
Systolic blood pressure[o]	Intervention*	128 [110–150]	124 (21)	125 (18)	-	120 [110; 130]
	Control**	127.5 [113.5–147]	127 (23)	133 (29)	-	124 [115; 140]
Sodium (mmol/l)[a]	Intervention*	137 [133–140]	138 (6)	139.8 (3.9)	138.7 (3.5)	140 [138; 142]
	Control**	137 [134–140]	138 (5)	139.3 (3.6)	140.4 (3.5)	140 [137; 142]
Potassium (mmol/l)[o]	Intervention*	4.3 [4.0–4.7]	4.3 (0.7)	4.1 (0.6)	-	3.8(0.1)
	Control**	4.3 [3.9–4.7]	4.2 (0.6)	4.1 (0.7)	-	3.9(0.1)
Creatinine (mg/dl)[o]	Intervention*	1.06 [0.84–1.50]	1.3 (1.0–1.8)	1.39 (0.48)	129.1 (56.4)	1.33 [1.07; 1.65]
	Control**	1.06 [0.79–1.50]	1.3 (1.0–1.8)	1.37 (0.41)	110.2 (40.4)	1.21 [0.99; 1.72]
eGFR (ml min 1,73 m2)[o]	Intervention*	54 [35–72]	48 [32–71]	49.8 (19.2)	-	48.9(22.5)
	Control**	53 [34.8–73.2]	50 [32–74]	51.0 (17.7)	-	50(21.7)
NT-proBNP (pg/l)[o]	Intervention*	4,390 [2,554–8,226]	6137 [3266–11394]	5077 [2654–12 150]	-	-
	Control**	4,947 [2,607–9,809]	5750 [3010–12685]	4532 [2651–7333]	-	-
LVEF (%)[o]	Intervention*	35 [25–53]	37 (14)	39.1 (15.9)	40.3 (14.4)	42 [32; 58]
	Control**	38 [28–48]	40 (16)	46.8 (14.3)	42.2 (16.5)	50 [30; 55]

*Natriuresis guided diuretic therapy

**Standard of care

[o]Mean or median (SD), (range),[IQR]

[a]Number (%)

AHF: Acute Heart Failure; BMI: Body Mass Index; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; HF: Heart Failure; LVEF: Left Ventricular Ejection Fraction; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; RCT: Randomized Controlled Trial

Table 2 Diuretic protocols definition

Study (Year)	Initial Diuretic Regimen	Dose Adjustment and Escalation	Combination Therapy
PUSH AHF (2023) [11]	**Bumetanide** is the preferred agent. For patients on outpatient loop diuretics with preserved renal function (eGFR ≥ 60 mL/min/1.73m^2), the starting IV dose equals the total daily outpatient dose given as a bolus, followed by twice-daily dosing. If renal function is impaired, the initial IV dose is double the outpatient dose, also continued twice daily. Diuretic-naïve patients receive 1 mg IV bumetanide if renal function is preserved, or 2 mg if impaired, both followed by twice-daily dosing. The maximum bolus dose is 5 mg bumetanide	Spot urinary sodium is assessed at 2 h after the initial loop diuretic dose using a urinary catheter when available. If the urinary sodium is < 70 mmol/L, an additional bolus of loop diuretic is administered, doubling the previous dose, with a maximum of 5 mg of bumetanide. If 5 mg was already given as the initial dose, this dose is repeated. The maintenance dose is adjusted to twice daily at the new bolus level. A second urinary sodium and urine output assessment occurs at 6 h. If urinary sodium remains < 70 mmol/L and/or diuresis is < 150 mL/h, and the patient remains congested, another dose of loop diuretic is given (doubling the previous dose, max 5 mg bumetanide), and the maintenance dose is again adjusted accordingly	If a patient has received two doses of 5 mg bumetanide with inadequate natriuresis or diuresis at two consecutive time points, **hydrochlorothiazide** 25 mg is added once daily. Patients already on combination diuretics at admission may escalate to second-step combination therapy with **acetazolamide** or an **SGLT2i**. If the patient used a thiazide but not a loop diuretic at admission, the thiazide is discontinued, and combination therapy with hydrochlorothiazide and a loop diuretic is initiated The treatment algorithm continues for up to 48 h, with natriuresis and diuresis evaluations every 12 h after 24 h. Additional diuretic doses are only administered if the patient remains congested. Combination diuretic therapy is discontinued once the patient achieves euvolemia or in cases of significant electrolyte imbalance or renal function deterioration without signs of congestion
ENACT-HF (2024) [9]	Patients received an intravenous loop diuretic bolus equivalent to twice their home oral dose, or 40 mg IV **furosemide** if diuretic-naïve	A spot urinary sodium sample was collected 2 h after the first dose, and urine output was measured over 6 h. If urinary sodium was < 50 mmol/L or urine output was < 100 mL/h, the dose was doubled, up to a maximum of 200 mg IV furosemide. Similar dose escalation strategies were applied if 24-h urine output remained < 3 L on the second day. After the initial 48 h, further management was left to the treating physician	If no adequate response was achieved at the highest dose, an oral **thiazide diuretic**(e.g., hydrochlorothiazide) was added
EASY HF (2024) [8]	The protocol begins with an initial dose of IV diuretics, followed by a 24-h urine collection	Urine sodium (Na +) is measured at specific intervals (2–4 h, 8–10 h, 14–16 h, and 20–22 h). If Na^+ is ≥ 70 mmol/L, the initial response is considered adequate; if < 70 mmol/L, diuretic dose is doubled (2X IV), then possibly quadrupled (4X IV), or even octupled (8X IV), depending on response. After 24 h, total urine volume is assessed, volumes ≥ 3L are considered satisfactory, while volumes < 3L prompt further escalation of diuretic therapy. The diuretic dose could be doubled, then possibly quadrupled, or even octupled	Not specified
Bayat et al., (2024) [7]	Diuretic-naïve patients received an initial IV bolus of 40 mg furosemide, while patients already on oral furosemide received their usual oral dose as an IV bolus, effectively doubling the dose	Spot urinary sodium (UNa) was measured within 6 h of the first intravenous (IV) loop diuretic dose and then every 6 h for the first 48 h. If UNa was < 50 mmol/L, the IV diuretic dose was doubled, with up to four dose escalations allowed during the 48-h period. The bolus was given twice daily, with a maximum of 80 mg twice a day. Patients requiring higher doses were switched to a continuous IV infusion, with the rate increased by 5 mg/h up to a maximum of 25 mg/h. UNa results were available within one hour of collection, enabling timely dose adjustments	Not specified

Table 2 (continued)

Study (Year)	Initial Diuretic Regimen	Dose Adjustment and Escalation	Combination Therapy
Pellegrino et al., (2023) [10, 21]	The Yale Diuretic Pathway (YDP) is initiated with a default starting dose of 2 mg **bumetanide**. The YDP algorithm allows another 2 possible sodium goals, 230 mmol and 500 mmol/day, equivalent to urine output goals of 3 and 5 l, respectively. Dosing and evaluation occur at 9:00 am, 3:00 pm, 9:00 pm, and 9:00 am the next day. The physician can also specify a starting dose, a goal sodium output (default 370 mmol of sodium, equivalent to ~4 l of urine output with a urine Na ~90 mmol/l), and "hold parameters" if an increase in creatinine (default 0.5 mg/dl increase) and systolic blood pressure (default 90 mm Hg)	Spot urine sodium and creatinine are obtained 1 to 2 h after loop diuretic administration. The EPIC system automatically calculates the predicted sodium output and the recommended next dose. The next days morning dose can be between 2 and 12.5 mg bumetanide (administered as IV piggyback infusion over 1 h) based on the YDP algorithm	The coadministration of a **thiazide-like diuretic** is prohibited while patients are on the YDP. An oral potassium sliding scale and twice-daily metabolic panel is included as default in the order set

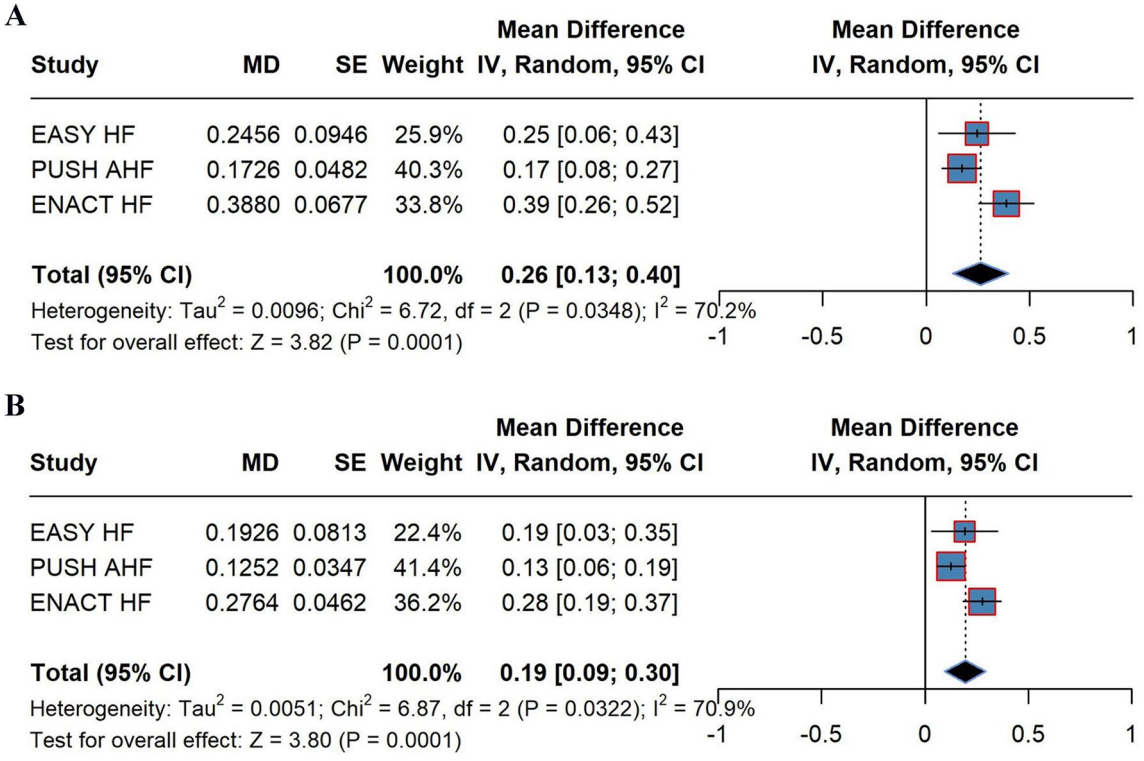

Fig. 2 Pooled analyses of natriuresis and diuresis after 2 days. (**a**) Natriuresis after 2 days. Natriuresis-guided diuretic therapy led to a statistically significant increase in natriuresis after 2 days compared to standard care. *CI: Confidence Interval; IV: Inverse Variance; MD: Mean Difference; SE: Standard Error.* (**b**) Diuresis after 2 days. Natriuresis-guided diuretic therapy led to a statistically significant increase in diuresis after 2 days compared to standard care. *CI: Confidence Interval; IV: Inverse Variance; MD: Mean Difference; SE: Standard Error*

or hypotension (RR: 1.06; 95% CI: 0.50 to 2.27; p = 0.88; I^2 = 22.8%; Fig. 4C).

Sensitivity analysis

Our sensitivity analysis, limited to RCTs, for all efficacy and safety endpoints confirmed our findings, as reported in Supplementary Figs. 2–5.

Quality assessment

Two RCTs [8, 11] were considered at "low" risk of bias, while Bayat et al. [7] was rated as having "some concerns" according to the RoB 2 tool, as detailed in Supplementary Table 2A. Regarding the ROBINS-I tool, the ENACT-HF study [9] was considered at "moderate" risk of bias, whereas Pellegrino et al. [10] was rated as "serious" risk

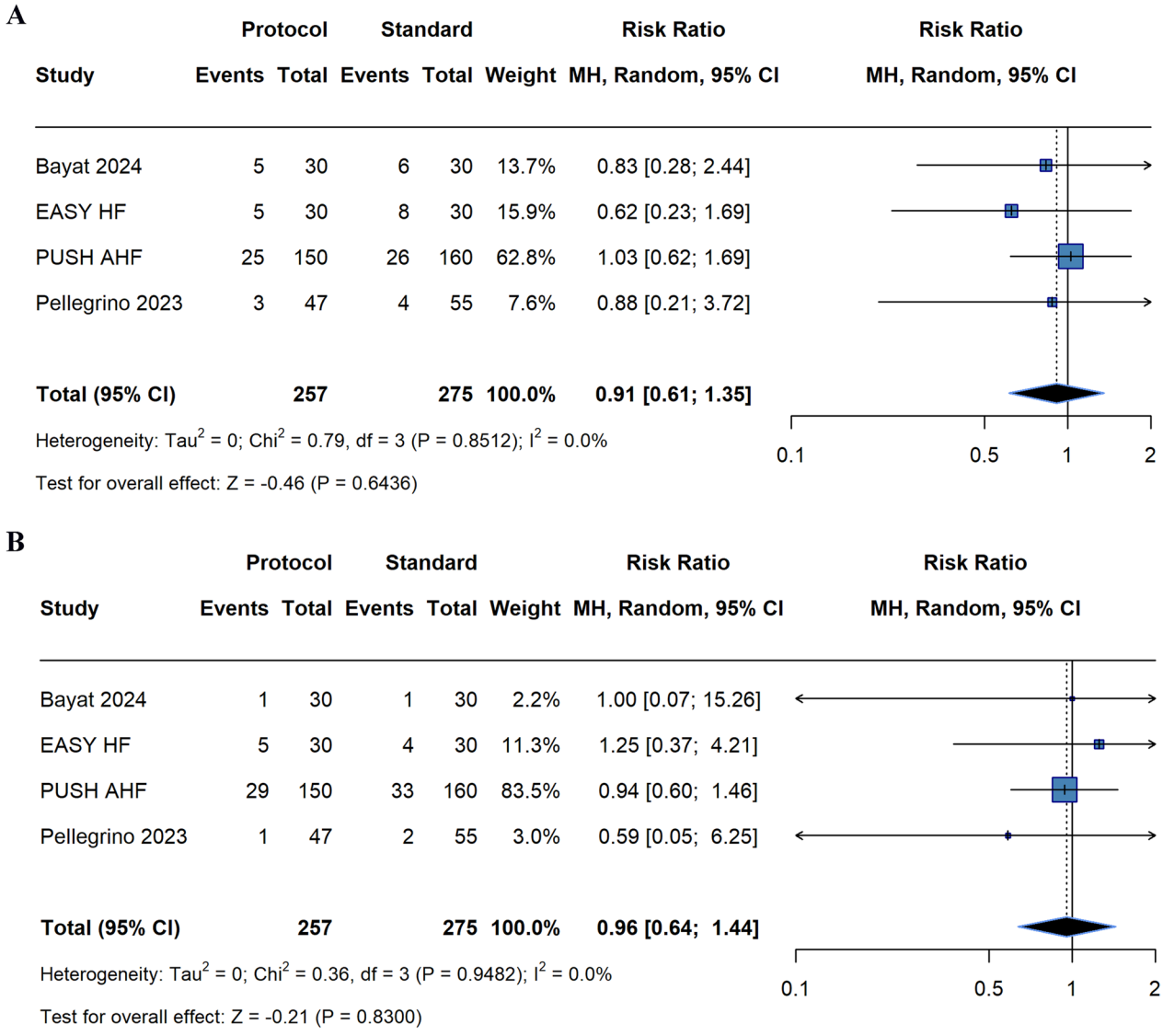

Fig. 3 Pooled analyses of heart failure hospitalization and all-cause mortality. (**a**) Hospitalization for Heart Failure. Natriuresis guided diuretic therapy did not show a statistically significant reduction in heart failure rehospitalization compared to standard care therapy. *CI: Confidence Interval; MH: Mantel–Haenszel; RR: Risk Ratio.* (**b**) All-cause mortality. Natriuresis guided diuretic therapy did not show a statistically significant reduction in all cause mortality compared to standard care. *CI: Confidence Interval; MH: Mantel–Haenszel; RR: Risk Ratio*

of bias according to the ROBINS-I tool, as detailed in Supplementary Table 2B.

Discussion

In this systematic review and meta-analysis of 3 RCTs and 2 observational studies encompassing 933 patients with AHF, we compared natriuresis-guided diuretic therapy with SOC. Our main findings were: (1) protocolized diuretic therapy significantly increased natriuresis and diuresis after 2 days with a trend toward greater weight loss; (2) no significant differences were observed between groups in length of hospital stay, all-cause mortality, or HF rehospitalization; and (3) protocolized therapy demonstrated a favorable safety profile, with no increased risk of hypokalemia or hypotension and a reduced incidence of serum creatinine doubling.

Management of fluid overload is the key goal during AHF. Loop diuretics are the number one recommended therapy by American and European guidelines [3, 4]. However, one-third of the patients with AHF are diuretic-resistant and need an increased medication dose to have an efficient diuresis. Previous monitoring tools have low accuracy in determining an appropriate treatment and rely on clinical signs and measurements that often take longer to obtain [20, 21]. Sodium natriuresis has emerged as an early tool to determine diuresis and individualize treatment for each patient. Nevertheless, its efficacy and

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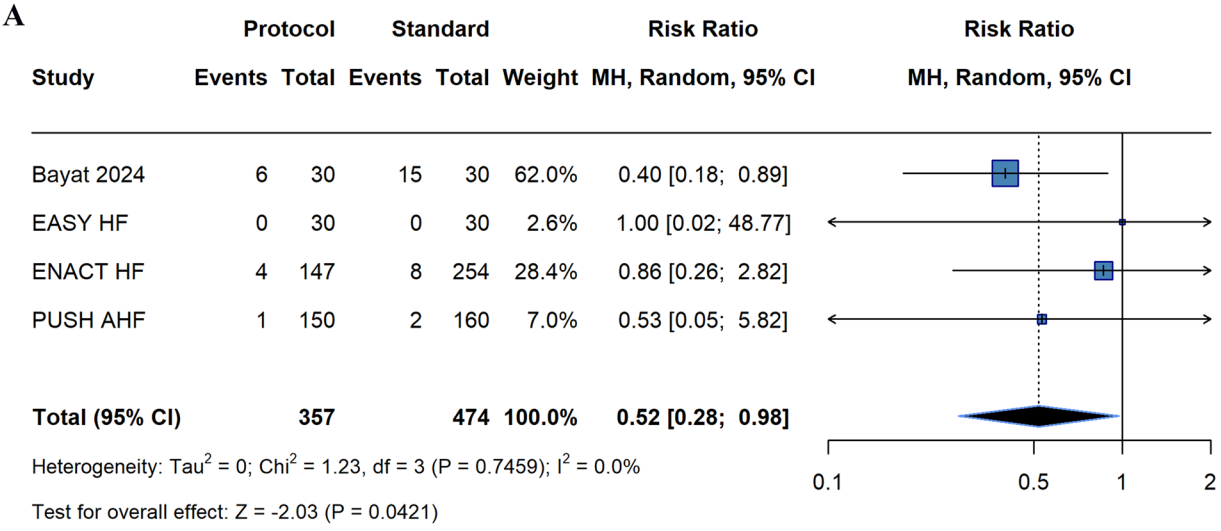

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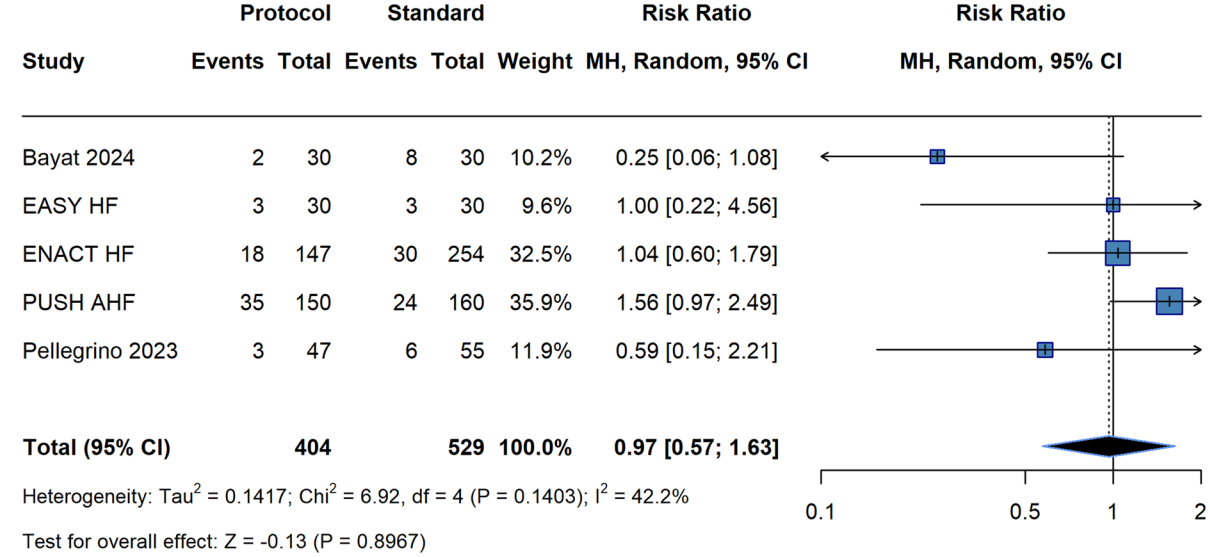

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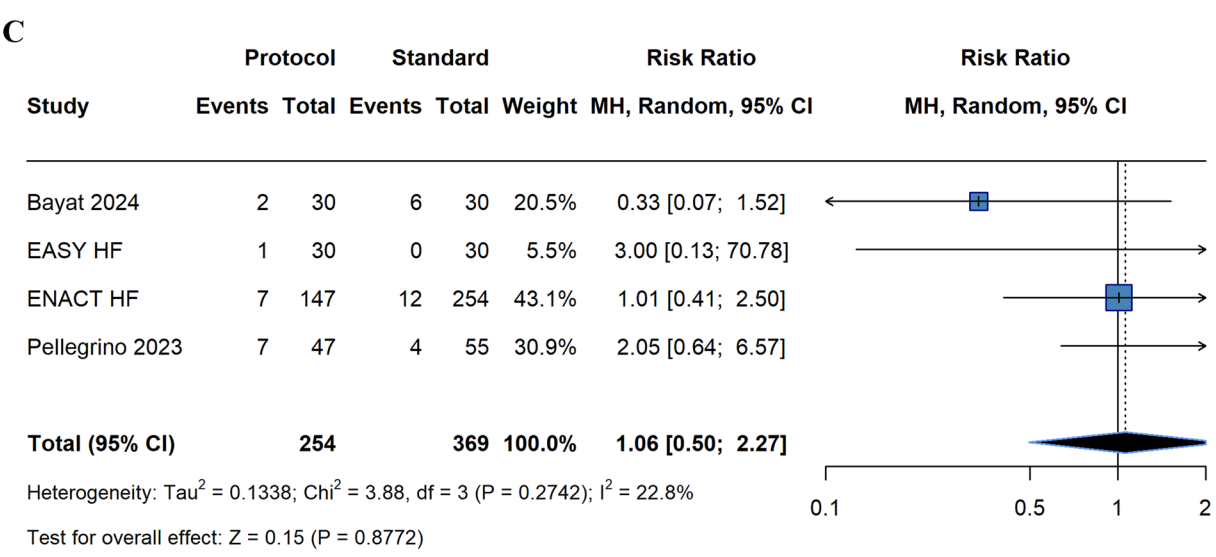

Fig. 4 (See legend on next page.)

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Fig. 4 Pooled analyses of safety outcomes. (**a**) Doubling serum creatinine from baseline. Natriuresis guided diuretic therapy showed statistically significant reduction in doubling of serum creatinine compared to standard care diuretic therapy. *Confidence Interval; MH: Mantel–Haenszel; RR: Risk Ratio.* (**b**) Hypokalemia. Natriuresis-guided diuretic therapy did not lead to a statistically significant difference in hypokalemia incidence compared to standard care. *CI: Confidence Interval; MH: Mantel–Haenszel; RR: Risk Ratio* (**c**) Hypotension. Natriuresis-guided diuretic therapy did not lead to a statistically significant difference in hypotension incidence compared to standard care. *CI: Confidence Interval; MH: Mantel–Haenszel; RR: Risk Ratio*

efficiency in clinical practice remain uncertain compared to standard management.

Natriuresis is one of the most important outcomes to assess during loop diuretic therapy, as a positive sodium balance is associated with higher mortality rates [22]. Our pooled analysis demonstrated a 30% higher GM of natriuresis in patients under the protocol after 48 h. Diuresis showed a similar trend, with a 21% higher GM of urinary volume in the intervention group. This may be explained by the higher doses of loop diuretics [8] administered in patients under the protocol compared to those in SOC, as the dose was individually adjusted according to urinary sodium. This approach appears particularly beneficial for patients with previous use of loop diuretics, as they tend to demonstrate greater resistance to diuretics [21]. However, the EASY-HF and PUSH-AHF trials were composed primarily of diuretic-naive patients, and also demonstrated an improved natriuresis when using the protocol, with no significant difference between diuretic-naive and previously treated with diuretics. Moreover, the PUSH-AHF [9] showed that differences in natriuresis and diuresis between the intervention and control groups were most pronounced during the first 24 h, likely due to protocol cessation after 36 h. These findings suggest that protocol-guided diuretic therapy may be effective in rapidly identifying and adjusting to the optimal loop diuretic dose, increasing diuresis and natriuresis using an individualized approach.

The rationale behind measurement of urinary sodium is its direct correlation with activation of the renin–angiotensin–aldosterone system (RAAS) [23]. During AHF there is decreased intravascular volume, which activates RAAS, increasing urinary and sodium retention [23]. Loop diuretics act by inhibiting the Na–K-2Cl cotransporter in the thick ascending limb, acutely increasing natriuresis and diuresis. Measurement of urinary sodium allows real-time assessment of the kidney's excretory pattern and the patient's response to diuretics. Moreover, another useful tool is the urinary Na/Cl ratio. Chloride and sodium are reabsorbed together, and abnormalities in chloride are associated with worse outcomes in AHF [22]. A disproportionate reduction in chloride compared to sodium in urine may enhance activation of RAAS further promoting sodium and water retention. Monitoring both ions can help identify maladaptation to loop diuretic therapy and guide its dosage.

Despite the significant increase in natriuresis and diuresis observed with the protocol-guided therapy, our analysis did not demonstrate a statistically significant difference in the incidence of HF rehospitalization ($p = 0.64$) or all-cause mortality ($p = 0.83$) after hospital discharge. This finding aligns with the results from the randomized PUSH-AHF trial, which enrolled 310 patients with symptomatic AHF and similarly showed no effect of natriuresis-guided therapy on the combined endpoint of all-cause mortality and HF rehospitalization. As the protocol is more effective in the 48 h of implementation, a long-term benefit may not be expected. The initiation of Guideline-Directed Medical Therapy for chronic HF in patients hospitalized for decompensated HF could be more effective in decreasing mortality rates, as suggested by randomized data [4, 24, 25]. Therefore, improving long-term clinical outcomes, especially for outpatients who were previously hospitalized for AHF, remains a significant challenge. It is important to recognize that the included studies evaluated short-term interventions, had short follow-up periods, and were not designed to detect differences in long-term outcomes.

Because the primary therapeutic goal during the acute phase of AHF management is effective decongestion, it is important to recognize how decongestion was defined across trials. In ENACT-HF, decongestion was evaluated using the ADVOR congestion score. EASY-HF employed natriuresis/diuresis endpoints and the achievement of complete decongestion (defined as no more than trace edema and absence of ascites or pleural effusion at 48 h). Bayat et al. applied the EVEREST clinical congestion score, while Pellegrino et al. used a $> 30\%$ reduction in BNP levels from admission to discharge as a biochemical marker of decongestion. While EASY-HF, ENACT-HF, and Pellegrino et al. demonstrated a non-significant trend towards improved congestion in the natriuresis-guided therapy group, Bayat et al. reported a significantly greater reduction in the clinical congestion score from admission to 48 h with natriuresis-guided therapy. This observed variability in definitions and outcomes consequently introduces heterogeneity and complicates cross-trial comparisons. Therefore, future studies should aim to standardize decongestion endpoints to enable more reliable evaluation and synthesis of evidence.

Despite an increased dose of loop diuretics in the intervention group, there were no safety concerns regarding renal function. Our analysis demonstrated a significant reduction in the doubling of serum creatinine from baseline for patients managed with the protocol-guided approach (RR: 0.52; 95% CI: 0.28 to 0.98; $p = 0.04$). This

finding underscores a remarkable benefit of protocol-guided therapy, particularly considering that worsening renal function during aggressive diuresis has historically been a major concern in AHF management, often leading to the de-escalation of diuretic therapy [26]. The observed improvement in renal function may be attributed to the higher rates of natriuresis and diuresis achieved by the protocol, due to the individualized, goal-directed nature of the protocol, which ensures that the patient receives the minimum diuretic dose that is effective for achieving decongestion, rather than a fixed high dose. The protocol avoids sub-therapeutic dosing that can lead to persistent congestion and worsening renal function. This mechanism is hypothesized to involve the reduction of systemic and renal venous congestion, thereby leading to improved renal perfusion and functional glomerular filtration rate [27]. Moreover, the protocol-guided natriuresis therapy proved safe. Rates of hypotension and hypokalemia were similar between intervention and SOC groups, indicating no increased risk of hemodynamic instability or electrolyte abnormalities. Emerging technologies, including real-time urinary biomarker analysis and artificial intelligence-based fluid status prediction, may complement natriuresis-guided protocols and further refine diuretic management in AHF [28].

Our meta-analysis demonstrated the safety of protocolized guided-diuretic therapy in both diuretic-naive patients and those previously treated with diuretics; however, it was unable to determine the effect on clinical outcomes. Given the limited number of studies included, these findings underscore the need for large RCTs studying a standard natriuresis-guided diuretic therapy that is based on the pathophysiology involved in AHF [29] to evaluate the true effect of this intervention on both short- and long-term clinical outcomes. A protocolized guided-diuretic therapy could facilitate the applicability of optimal guideline-based treatment for AHF patients across different healthcare settings, including secondary and tertiary hospitals, regardless of whether they currently have structured protocols in place. However, widespread implementation may be challenged by the need for frequent urinary sodium assessments, laboratory capacity, and clinician adherence to protocols. Future cost-effectiveness analyses and implementation studies will be important to evaluate the real-world feasibility of these strategies [30].

Risk-of-bias assessments using RoB 2 for randomized trials and ROBINS-I for non-randomized studies indicated a low risk of bias for most RCTs, contrasting with a moderate-to-serious risk for observational studies. While such discrepancies often reduce confidence in findings drawn from non-randomized data, we addressed this potential limitation directly. To ensure robustness, our subanalysis limited to only RCTs confirmed our findings across all evaluated outcomes.

It is worth noting that heterogeneity in natriuresis-guided protocols across studies may limit the generalizability of our findings, as detailed in Table 2. Our initial analysis showed a high degree of variability, a problem that was largely resolved when we restricted the analysis to only RCTs. This indicates that the non-randomized designs of some studies were the primary driver of the heterogeneity. Beyond study design, the protocols varied significantly in their approach to diuretic titration, tools used for measurement, and metrics used to define decongestion. The included studies also featured differences in patient populations, notably the inclusion of only diuretic-naive patients in the Bayat et al. study [7], which contrasts with the mixed populations in other trials. This distinction is critical, as diuretic-naive patients are more likely to respond favorably to a standard diuretic regimen. Future studies should aim to standardize sodium measurement timing, cut-offs, and diuretic titration algorithms to enhance reproducibility and clinical applicability [31]. It is possible that specific subgroups, such as patients with baseline diuretic resistance or cardiorenal syndrome, may derive greater long-term benefit from individualized natriuresis-guided therapy. Future trials should consider stratified analyses in these populations [6].

This study has limitations that temper the interpretation and generalizability of its findings. First, our meta-analysis was primarily composed of small, single-center RCTs, including only 36% women participants. The ENACT-HF [9] was the only multicenter study, including patients from 4 different continents, while the other 3 studies were conducted in Europe and Oceania. Second, individual patient data were not available, limiting the depth of analysis. Third, publication bias could not be assessed due to the low number of studies. Nevertheless, the potential for publication bias remains, as studies with negative findings may be underrepresented in the literature. This possibility should be considered when interpreting the pooled estimates. Finally, the studies employed heterogeneous natriuresis-guided diuretic protocols and featured relatively short follow-up periods. These factors highlight the critical need for larger, multicenter RCTs with standardized protocols to confirm and expand upon our results.

Conclusion

Overall, this systematic review and meta-analysis provides evidence supporting the safety and effectiveness of protocolized guided-diuretic therapy in the management of AHF. Protocolized diuretic therapy significantly improved diuresis and natriuresis after 48 h and reduced acute kidney injury. While the short-term

safety and efficacy are promising, further large RCTs are needed to evaluate the effects on clinical endpoints in diverse healthcare settings and patients worldwide. As the landscape of AHF treatment evolves, protocolized guided-diuretic therapy may offer a way to facilitate the implementation of optimal diuretic therapy for AHF patients across different clinical scenarios.

Abbreviations

AHF	Acute heart failure
AHA	American Heart Association
ACC	American College of Cardiology
ESC	European Society of Cardiology
HF	Heart Failure
RCT	Randomized controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SOC	Standard of care
RoB 2	Cochrane Revised tool to assess Risk of Bias in Randomized trials
ROBINS-I	Cochrane Risk of Bias tool for Non-randomized Studies
RR	Risk ratio
MD	Mean difference
CI	Confidence interval
GM	Geometric mean
GMR	Geometric mean ratio
RAAS	Renin–angiotensin–aldosterone system

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05707-x.

Additional file1

Acknowledgements
Not applicable.

Author contributions
A.A.P.1 and L.G.P. were responsible for the conceptualization and design of the study. A.A.P.1 and A.A.P.2. conducted the literature search and triage of the studies. Data extraction was performed by A.A.P.1, A.A.P.2, A.C.C.C., P.G.S., J.M.F., and W.F.N. A.A.P.1 performed the statistical analysis. A.A.P.2 and A.C.C.C. prepared Tables 1 and 2. J.M.F., P.G.S., and W.F.N. organized the study plan, appendix, and figures. All authors contributed to the interpretation of the results and wrote the main manuscript text. A.A.P.1 and L.G.P. reviewed the manuscript and made necessary adjustments.

Funding
Not applicable. This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethical approval and consent to participate
Not applicable. This study did not involve human participants, animal subjects, or any data requiring ethical approval.

Consent for publication
Not applicable.

Competing interests
All authors report no relationships that could be construed as a conflict of interest. and take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Received: 10 August 2025 / Accepted: 3 October 2025
Published online: 05 November 2025

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