REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220583

Comparison of continuous loop diuretic versus bolus injection regimens in patients with heart failure: a comprehensive meta-analysis of the literature

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INTRODUCTION

Heart failure (HF) is a challenging clinical syndrome and the leading cause of morbidity and mortality worldwide[1]. In decompensated HF patients, diuretic administration is a crucial and first-line therapeutic option for reducing fluid overload by diuresis[1]. Optimizing the loop diuretic dose is essential to produce a high proportion of loop diuretic transport in the proximal renal tubule, enabling it to optimally function on a Na^+-K^+-2Cl cotransporter on the luminal surface of the thick ascending limb of the loop of Henle[2]. Theoretically, continuous infusion of a loop diuretic may be preferable to intermittent bolus injection treatment in terms of length of hospital stay, weight loss, and urine output[3]. Possible underlying reasons may include that continuous infusion of a loop diuretic may ensure better urine output and less neurohormonal stimulation due to the constant delivery rate of the loop diuretics to the tubule, resulting in less alteration in intravascular volume and fewer occurrences of adverse side effects[3]. Despite the fact that most randomized controlled trials (RCTs) supported a continuous infusion in regard to diuretic efficiency, there is no convincing evidence in the present literature to indicate that continuous infusion of a loop diuretic is preferable to bolus injection treatment or vice versa[1,4]. As a result, we intended to perform a meta-analysis of RCTs that evaluated these two treatment options in HF patients.

METHODS

Data collection

We followed the recommended reporting items for systematic reviews and meta-analyses guidelines to report our results. Since the investigation was a meta-analysis, neither ethics committee approval nor patient informed consent was needed. First, we reviewed PubMed, Scopus, Google Scholar, and Cochrane libraries for relevant studies utilizing keywords such as "randomized controlled," "heart failure," "diuretic," and "continuous," "bolus," and "comparison." When all abstracts were reviewed, 39 studies remained out of 395 prospective investigations. Following an examination of the entire texts of the remaining articles, 21 studies were removed because they were duplicated and irrelevant, included meta-analyses, or had inaccurate results. Finally, the remaining 18 papers were subjected to our meta-analysis (Table 1).

Study evaluation

Two authors thoroughly reviewed the studies' applicability and bias probability. The studies were selected based on the following criteria: (1) prospective, randomized studies comparing intravenous (IV) continuous infusion of a loop diuretic to IV bolus injection of diuretics treatment in decompensated HF patients; (2) studies with at least in-hospital follow-up duration; (3) studies with the clinical outcomes, such as urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, estimated glomerular filtration (eGFR) change, and mortality; and (4) only furosemide treatment was used as the main diuretic regimen. Due to the possibility of selection bias, studies with a retrospective or observational design were not included in this meta-analysis. Finally, our meta-analysis excluded papers in which the effect size and standard error could not be calculated. All studies were evaluated using a modified Jadad scale with respect to study quality[5]. To assess the risk of bias, we used the Rob2 risk of bias tool as advised in the Cochrane Handbook for Systematic Reviews of Interventions (Supplementary 1)[6].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 02, 2022. Accepted on July 08, 2022.

Table 1. Characteristics of studies in the meta-analysis.

Study	Year	Country	Age	Patient population	Dose of diuretics	Duration of interventions (day)	Study design	Total sample size	Bolus group sample size	Continuous group sample size	End-points	Modified Jadad Scale
Makhoul et al[7].	1997	Israel	NA	NA	Bolus: 324 (110.8) mg tid, continuous: 329 (186.7) mg/24 h	24 h	RCT	20	10	10	Urine output	5
Allen et al.[8]	2010	USA	59.5 (14.9)	LVEF: 35 (19%), NYHA II-IV	Bolus: 162 (48) mg bid, continuous: 162 (52) mg/24 h	48 h	RCT	41	21	20	Change in creatinine, urine output, weight loss, length of hospital stay	6
Thomson et al.[9]	2010	USA	53.5 (23.2)	LVEF: 26.3 (13.6%), NYHA III-IV	Bolus: 172 (97) mg, continuous: 197 (148) mg/24 h	100 h	RCT	56	30	26	Change in creatinine, urine output, weight loss, length of hospital stay	6
Felker et al.[10]	2011	USA	66 (13.6)	LVEF: 35 (18%)	Bolus: 162 (52) mg bid, continuous: 162 (48) mg/24 h	72 h	RCT	308	156	152	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	8
Palazzuoli et al.[11]	2015	Italy	71.9 (7.5)	LVEF: 35 (9%)	Bolus: 160 (80) mg, continuous: 170 (70)	112 h	RCT	58	28	30	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	6
Llorens et al.[12]	2014	Spain	82 (9)	LVEF: <35 in 50% patients, NYHA I-IV	Bolus: 80 mg qid, continuous: 240 mg/10 h	24 h	RCT	73	37	36	Change in creatinine, urine output	6.5
Shah et al.[13]	2014	India	59.3 (7.5)	LVEF: 33% (SD not available)	Bolus: 100 mg bid, continuous: 100 mg/24 h	48 h	RCT	60	30	30	Change in creatinine, urine output	5.5
Yayla et al.[14]	2015	Turkey	68.4 (11.7)	LVEF: 42.9 (13.1)	Bolus: 160 mg bid, continuous: 160 mg/24 h	48 h	RCT	29	14	15	Change in creatinine, urine output, weight loss, length of hospital stay	8
Aaser et al.[15]	1997	Norway	54 (3)	LVEF: 24 (5)	Bolus: 145 (80) mg bid, continuous: 145 (80) mg/24 h	24 h	RCT	8	4	4	Urine output, sodium excretion	3
Dormans et al.[16]	1996	Netherlands	71 (11)	LVEF: NA	Bolus: 690 mg (250–2,000) bid, continuous: 690 (250–2000)/8 h	24 h	RCT	40	20	20	Urine output, sodium excretion	4
Shree et al.[17]	2020	India	66 (11.5)	LVEF: <40%, NYHA II-IV	Bolus: 120 mg tid, continuous: 2–3 mg/h	48 h	RCT	56	28	28	Urine output, length of hospital stay	4
Sager et al.[18]	2020	Sweden	82.4 (3.1)	LVEF: NA, NYHA III-IV	Bolus: 20–100 mg, Continuous: 100–500 mg/4–10 h	NA	RCT	40	20	20	Weight loss, change in creatinine, mortality	4
Zheng et al.[3]	2021	China	66.4 (8.2)	LVEF: 57.4 (11), NYHA III-IV	Bolus: 200 mg, Continuous: 160 mg	72 h	RCT	81	39	42	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	7
Lahav et al.[19]	1992	Israel	74.1 (SD not available)	NYHA III-IV	Bolus: 90–120 mg tid, 60–80 mg/24 h	48 h	RCT	18	9	9	Urine output, sodium excretion	4
Malkiwodeyar et al.[20]	2017	India	55.9 (SD not available)	LVEF: 33.3%	Bolus: 100 mg tid, continuous: 100 mg	24 h	RCT	50	25	25	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	6
Ragab et al.[21]	2018	Egypt	NA	NYHA III-IV	Bolus: 120 mg tid, continuous: 5 mg/h	24 h	RCT	40	20	20	Weight loss, mortality	5
Wang et al.[22]	2016	China	NA	NA	Bolus: 188 (64) mg, continuous: 197 (59) mg	52 h	RCT	70	35	35	Weight loss, length of hospital stay	5
Sharma et al.[23]	2018	USA	65.3 (11.6)	HFpEF	Bolus: 80 mg bid, continuous: 80 mg/24 h	72 h	RCT	42	19	23	Urine output, weight loss, length of hospital stay, mortality	7.5
Frea et al.[24]	2020	Italy	60.9 (11.9)	LVEF: <30%	Bolus: 120/240 mg bid, continuous: 120/240 mg 24 h	72 h	RCT	80	40	40	Urine output, weight loss	7

NA: non-applicable; RCT: randomized controlled trial; LVEF: left-ventricular ejection fraction; NYHA: New York Heart Association Functional Classification; bid: twice a day; tid: three times a day; qid: four times a day.

Clinical end points

The major end points evaluated in this meta-analysis were urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, eGFR change, and mortality.

Statistical analysis

This meta-analysis was carried out using the R software version 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). For analyses of pooled risk ratio and standardized mean difference (SMD) with 95% confidence intervals, a "meta" package containing "metabin" and "metacont" was utilized. The Higgins I^2 and Cochran's Q tests were used to analyze study heterogeneity. In the case of moderate to high heterogeneity (I^2>25%), the random-effect model was used to predict a pooled effect size, while the fixed-effect model was utilized in the case of low heterogeneity (I^2<25%). To determine publication bias, Egger's regression test was chosen. A funnel plot was also utilized to detect any potential publication bias among publications. To identify the likelihood of the underlying source of between-study heterogeneity, outlier and influential analyses were conducted. After the outlier or influential study was eliminated, the pooled effect size was recalculated. A p-value of 0.05 was used to determine statistical significance (two-tailed tests).

RESULTS

The meta-analysis examined 18 RCTs[3,7-24] with a total of 1,178 individuals (Table 1). The continuous infusion group (CG) had higher urine output than the bolus injection group (BG) (SMD=0.78 [0.11; 1.44], p<0.01) (Figure 1). The Eggers regression test was statistically meaningful for the pooled effect size for urine output (p<0.05), and I^2 was calculated as 87%, implying publication bias. A funnel plot revealed that the studies by "Dormans et al." and "Zheng et al." might have publication bias. Furthermore, these studies were also identified as outliers and influential articles. As a result, we eliminated these papers and repeated the pooled effect size for urine output. The overall heterogeneity dropped to 0%, and the CG still had higher urine output than the BG (SMD=0.40 [0.20; 0.61], p<0.01). In the subgroup analysis of urine output, the difference was significant between groups for 24-h urine output (p<0.01), whereas it was not significant between compared groups for 72 h (p=0.21). The CG actually had higher weight loss than the BG (SMD=0.39 [0.13; 0.65], p<0.01) (Figure 1). For weight loss, the study by "Zheng et al." was detected as might to be an outlier study and to have publication bias. So, the random-effect model was recalculated after removing this study, and the CG had still higher weight loss than the BG (SMD=0.24 [0.14; 0.34], p<0.01). The CG excreted more sodium than the BG (SMD=0.61 [-0.73; 1.94], p<0.01) (Figure 1). However, there was high heterogeneity between studies regarding the results for sodium excretion. As the study by "Zheng et al." was suspected to have high bias according to the Rob2 bias assessment, we removed this study from the pooled effect for urinary sodium excretion, which indicated a nonsignificant difference between groups (p=0.29). Finally, there were no significant differences in terms of in-hospital duration, variations in serum creatinine, eGFR rates, and mortality rates between groups (Figure 2).

DISCUSSION

This meta-analysis showed that HF patients who received a continuous diuretic regimen had higher urine output and weight loss compared to a bolus regimen. There was no change between groups in terms of hospital stay, change in serum creatinine, eGFR, and mortality. The issue of sodium excretion should be examined in future meta-analyses with more recent studies.

The main therapy goal for congestive HF is fluid removal, resulting in decreased congestion and reduced afterload. This objective would enhance hemodynamics and improve HF symptoms, as well as prevent rehospitalizations and mortality[25]. Loop diuretics, especially furosemide, are mainly used for this purpose via inhibiting salt and chloride reabsorption by acting on the Na^+-K^+-2Cl cotransporter in the thick ascending limb of the Henle loop[4]. The use of loop diuretics was recommended with a class IC indication in the recent guideline[1]. However, the decision of using continuous versus bolus diuretic therapy has been left to the physician's discretion. Bolus therapy has the advantage of convenience of preparation and administration compared to continuous therapy. Unfortunately, it might not be able to achieve sufficient concentration to block sodium reabsorption[26].

The comparison of continuous diuretic therapy with a bolus regimen has been evaluated in RCTs and meta-analyses. This meta-analysis was more comprehensive than previous ones by including 17 RCTs. Amer et al. reported similar findings with this report that the continuous group had higher urine output and weight loss with no difference in the duration of hospital stay[27]. However, they had a higher heterogeneity due to the study populations of RCTs included in their meta-analysis. Chan et al. found significant differences between groups with respect to urine output and weight loss, which was in accordance with our study[28]. Kuriyama et al. showed significant differences between the continuous and bolus regimens

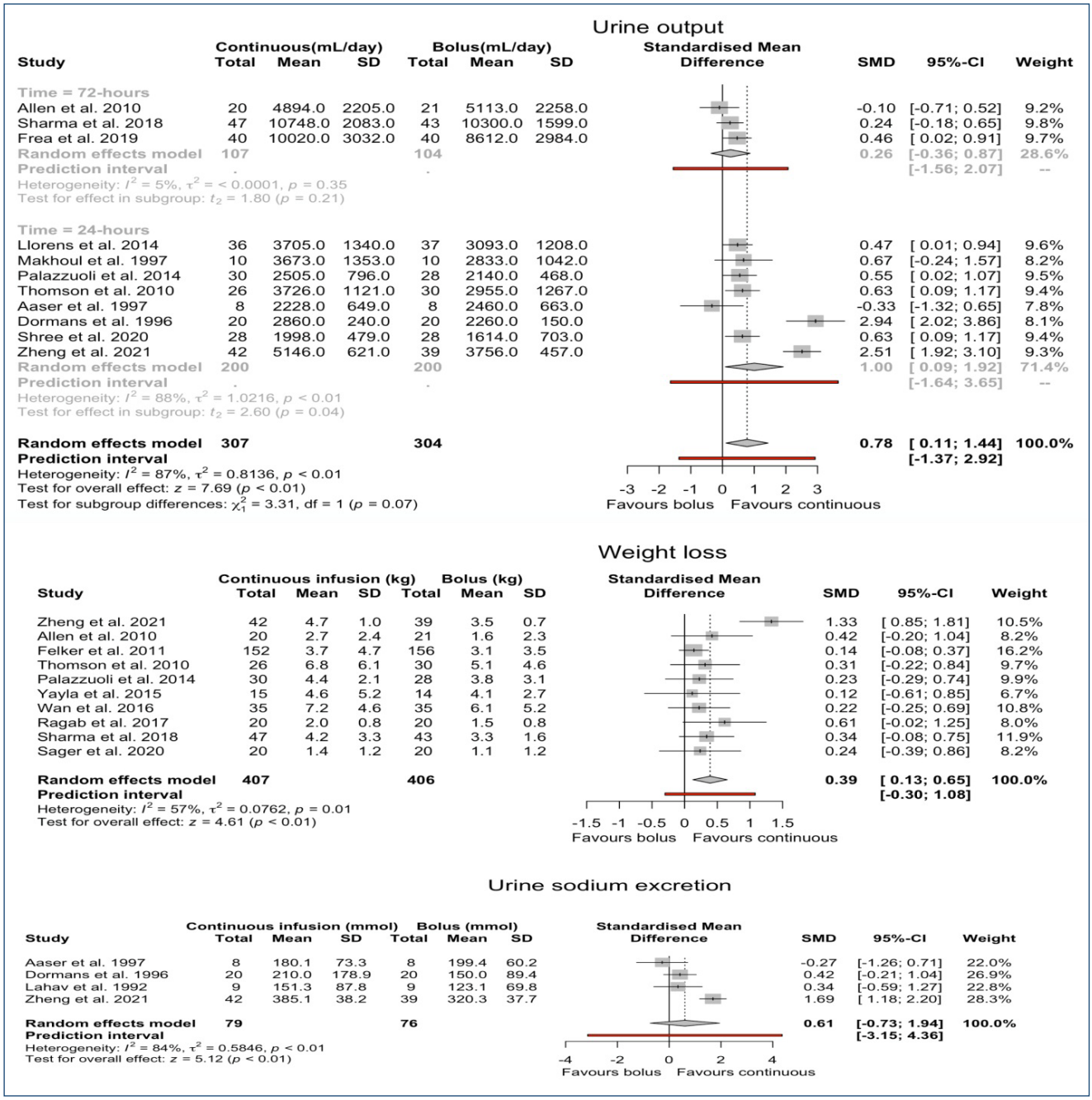

Figure 1. Forest plots of urine output, weight loss, and urine sodium excretion.

for urine output and weight loss but not for mortality, with similar findings reported in the current meta-analysis[29]. In a recent review, Shastri et al. did not find a difference between treatment regimens regarding mortality, length of hospital stay, and weight loss[30]. Compared to our study, fewer studies and sample size seem to have led to these results. Finally, Wu et al. conducted a meta-analysis and could not find a difference between continuous and bolus therapy groups[4]. The fact that some of the studies in the meta-analysis used torasemide instead of furosemide in the treatment and some of them were examined in all intensive care patients may also have contributed to these results. We included only studies that consisted of HF patients and used furosemide as a therapeutic agent in our meta-analysis.

There was high heterogeneity between studies in our meta-analysis. Most of them had an acceptable quality as

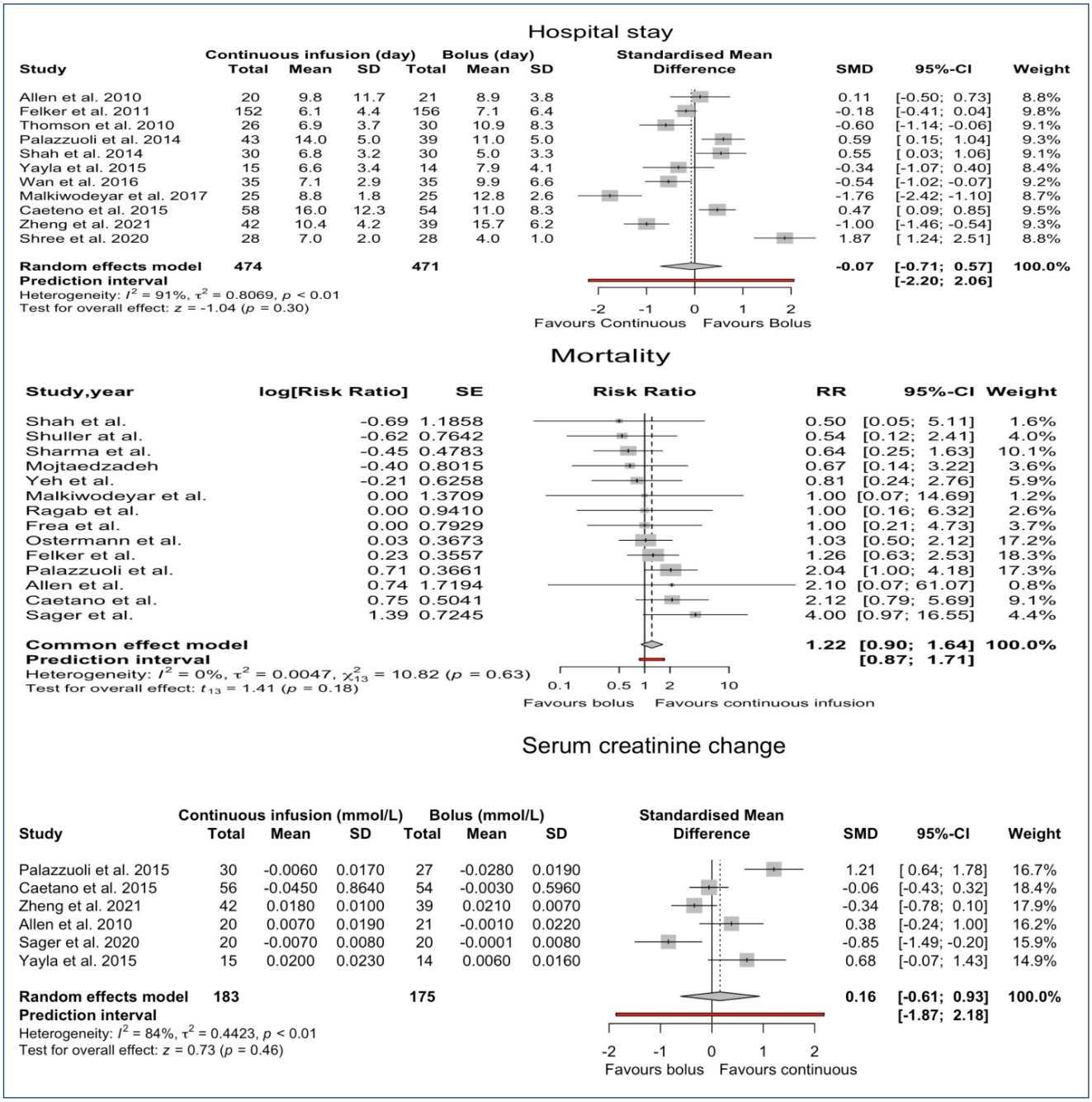

Figure 2. Forest plots of urine hospital stay, mortality, and serum creatinine change.

evaluated using the modified Jadad scale. Four studies were more likely to have a bias as assessed with Rob2[3,7,12,17]. Blinding is an important factor for avoiding bias in RCTs. Only 7 of 18 RCTs were designed in blinded study design[10-12,14,23,24], in which 3 of them reported blinding methods[14,23,24]. Another contributing factor that led to high heterogeneity in our meta-analysis might be the lack of a wash-out period in RCTs with a cross-over design[9,15,16,19]. Additionally, most studies in this meta-analysis did not explain which statistical analyses were used to detect differences between groups in detail, for accounting loss follow-up, missing data, or analyses were conducted on an intention-to-treat versus per-protocol basis in the presence of nonadherence. It has been suggested that, on a per-protocol basis, the groups should be balanced with and adjusted for nonadherence[31]. Finally, furosemide was used in all RCTs as a diuretic agent, but the differences between the

diuretic doses for both regimens of studies might have contributed to the existence of heterogeneity.

Limitations

This review had some limitations due to variances in basal characteristics of populations, various diuretic doses, and administration schedules, and using a concomitant medication, which were all the typical limitations of RCTs. Although the rate of mortality did not differ between compared groups, the mortality was calculated based on the risk ratio. So, it should be better to adjust for covariates and time. Unfortunately, none of the studies presented an adjusted hazard ratio for in-hospital mortality. Further meta-analyses with more RCTs might provide more information for the decision to use a continuous versus bolus diuretic regimen in HF patients.

CONCLUSION

The continuous diuretic infusion had a higher diuretic effect and weight loss than the bolus diuretic regimen, without affecting serum creatinine, eGFR, and mortality in HF patients.

AUTHORS' CONTRIBUTIONS

FŞ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **TC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726. https://doi.org/10.1093/eurheartj/ehab368
2. Verbrugge FH, Mullens W, Tang WH. Management of cardio-renal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med. 2016;18(12):11. https://doi.org/10.1007/s11936-015-0436-4
3. Zheng Z, Jiang X, Chen J, He D, Xie X, Lu Y. Continuous versus intermittent use of furosemide in patients with heart failure and moderate chronic renal dysfunction. ESC Heart Fail. 2021;8(3):2070-8. https://doi.org/10.1002/ehf2.13286
4. Wu MY, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, et al. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. J Crit Care. 2014;29(1):2-9. https://doi.org/10.1016/j.jcrc.2013.10.009
5. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. https://doi.org/10.1016/0197-2456(95)00134-4.
6. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2020;12(1):55-61. https://doi.org/10.1002/jrsm.1411
7. Makhoul N, Riad T, Friedstrom S, Zveibil FR. Frusemide in pulmonary oedema: continuous versus intermittent. Clin Intensive Care. 1997;8(6):273-6. https://doi.org/10.3109/tcic.8.6.273.276
8. Allen LA, Turer AT, DeWald T, Stough WG, Cotter G, O'Connor CM. Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. Am J Cardiol. 2010;105(12):1794-7. https://doi.org/10.1016/j.amjcard.2010.01.355
9. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. J Card Fail. 2010;16(3):188-93. https://doi.org/10.1016/j.cardfail.2009.11.005
10. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805. https://doi.org/10.1056/NEJMoa1005419
11. Palazzuoli A, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, et al. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. Crit Care. 2014;18(3):R134. https://doi.org/10.1186/cc13952
12. Llorens P, Miró Ò, Herrero P, Martín-Sánchez FJ, Jacob J, Valero A, et al. Clinical effects and safety of different strategies for administering intravenous diuretics in acutely decompensated heart failure: a randomised clinical trial. Emerg Med J. 2014;31(9):706-13. https://doi.org/10.1136/emermed-2013-202526
13. Shah RA, Subban V, Lakshmanan A, Narayanan S, Udhayakumaran K, Pakshirajan B, et al. A prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure. Indian Heart J. 2014;66(3):309-16. https://doi.org/10.1016/j.ihj.2014.03.006
14. Yayla Ç, Akyel A, Canpolat U, Gayretli Yayla K, Eyiol A, Akboğa MK, et al. Comparison of three diuretic treatment strategies for patients with acute decompensated heart failure. Herz. 2015;40(8):1115-20. https://doi.org/10.1007/s00059-015-4327-y
15. Aaser E, Gullestad L, Tølløfsrud S, Lundberg J, Hall C, Djøseland O, et al. Effect of bolus injection versus continuous infusion of furosemide on diuresis and neurohormonal activation in patients with severe congestive heart failure. Scand J Clin Lab Invest. 1997;57(4):361-7. https://doi.org/10.3109/00365519709099409
16. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28(2):376-82. https://doi.org/10.1016/0735-1097(96)00161-1
17. Shree JD, Daniel CJ, Marsh C, Daniel JS, Lavanya S. A study on continuous infusion versus intermittent bolus dosing of furosemide in hospitalized heart failure patients. Res J Pharm Technol. 2021;14(5):2814-8. https://doi.org/10.52711/0974-360X.2021.00496

18. Sager R, Lindstedt I, Edvinsson L, Edvinsson ML. Increased mortality in elderly heart failure patients receiving infusion of furosemide compared to elderly heart failure patients receiving bolus injection. J Geriatr Cardiol. 2020;17(6):359-64. https://doi.org/10.11909/j.issn.1671-5411.2020.06.009
19. Lahav M, Regev A, Ra'anani P, Theodor E. Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. Chest. 1992;102(3):725-31. https://doi.org/10.1378/chest.102.3.725
20. Malkiwodeyar PK, Hiregoudar N, Kabade D, Hasabi I. Continuous versus bolus dosing of furosemide in the treatment of patients with acute decompensated heart failure. Sch J Applied Med Sci. 2017;5(9B):3551-6. https://doi.org/10.21276/sjams.2017.5.9.17
21. Ragab D, Taema KM, Farouk W, Saad M. Continuous infusion of furosemide versus intermittent boluses in acute decompensated heart failure: effect on thoracic fluid content. Egypt Heart J. 2018;70(2):65-70. https://doi.org/10.1016/j.ehj.2017.12.005
22. Wang YTB, Xue L. A comparative study of continuous and intermittent administration of furosemide in acute decompensated heart failure. J Clin Med. 2016;3:8154-5.
23. Sharma K, Vaishnav J, Kalathiya R, Hu JR, Miller J, Shah N, et al. Randomized evaluation of heart failure with preserved ejection fraction patients with acute heart failure and dopamine: the ROPA-DOP trial. JACC Heart Fail. 2018;6(10):859-70. https://doi.org/10.1016/j.jchf.2018.04.008
24. Frea S, Pidello S, Volpe A, Canavosio FG, Galluzzo A, Bovolo V, et al. Diuretic treatment in high-risk acute decompensation of advanced chronic heart failure-bolus intermittent vs. continuous infusion of furosemide: a randomized controlled trial. Clin Res Cardiol. 2020;109(4):417-25. https://doi.org/10.1007/s00392-019-01521-y
25. Herzog E, Varley C, Kukin M. Pathway for the management of acute heart failure. Crit Pathw Cardiol. 2005;4(1):37-42. https://doi.org/10.1097/01.hpc.0000154606.55424.fc
26. Brater DC. Diuretic resistance: mechanisms and therapeutic strategies. Cardiology. 1994;84(Suppl. 2):57-67. https://doi.org/10.1159/000176458
27. Amer M, Adomaityte J, Qayyum R. Continuous infusion versus intermittent bolus furosemide in ADHF: an updated meta-analysis of randomized control trials. J Hosp Med. 2012;7(3):270-5. https://doi.org/10.1002/jhm.991
28. Chan JSK, Kot TKM, Ng M, Harky A. Continuous infusion versus intermittent boluses of furosemide in acute heart failure: a systematic review and meta-analysis. J Card Fail. 2020;26(9):786-93. https://doi.org/10.1016/j.cardfail.2019.11.013
29. Kuriyama A, Urushidani S. Continuous versus intermittent administration of furosemide in acute decompensated heart failure: a systematic review and meta-analysis. Heart Fail Rev. 2019;24(1):31-9. https://doi.org/10.1007/s10741-018-9727-7
30. Shastri P, Burmeister C, Tomcho J, Patel M, Elzanaty A, Bhuta S, et al. Continuous infusion versus intermittent bolus furosemide for acute decompensated heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2021;77:616. https://doi.org/10.1016/S0735-1097(21)01975-6
31. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med. 2017;377(14):1391-8. https://doi.org/10.1056/NEJMsm1605385