




# Advanced heart failure: parenteral diuretics for breathlessness and peripheral oedema – systematic review

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## ABSTRACT

**Background** Advanced heart failure patients suffer with breathlessness and peripheral oedema, which are frequently treated with parenteral diuretics despite limited evidence.

**Aim** To analyse the effectiveness of parenteral diuretics on breathlessness and peripheral oedema in advanced heart failure patients.

**Methods** We searched Embase, MEDLINE(R), PsycINFO, CINAHL and CENTRAL from their respective inceptions to 2021, and performed handsearching, citation searching and grey literature search; limited to English publications. Selection criteria included parenteral (intravenous/subcutaneous) diuretic administration in advanced heart failure patients (New York Heart Association class III–IV). Two authors independently assessed articles for inclusion; one author extracted data. Data were synthesised through narrative synthesis or meta-analysed as appropriate.

**Results** 4646 records were screened; 6 trials (384 participants) were included. All were randomised controlled trials (RCTs) comparing intravenous continuous furosemide infusion (CFI) versus intravenous bolus furosemide infusion (BFI). Improvement in breathlessness and peripheral oedema (two studies,  $n=161$ , OR 2.80, 95% CI 1.45 to 5.40;  $I^2=0\%$ ), and increase in urine output (four studies,  $n=234$ , mean difference, MD 344.76, 95% CI 132.87 to 556.64;  $I^2=44\%$ ), were statistically significant in favour of CFI. Significantly lower serum potassium was found in BFI compared with CFI (three studies,  $n=194$ , MD  $-0.20$ , 95% CI  $-0.38$  to  $-0.01$ ;  $I^2=0\%$ ). There was no difference between CFI and BFI on reduction in weight, renal function or length of hospital stay.

**Conclusions** CFI appears to improve congestion in advanced heart failure patients in the short term. Available data came from small trials. Larger, prospective RCTs are recommended to address the evidence gap.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intravenous diuretics are widely used in the management of acute heart failure decompensation. Parenteral diuretics have the potential to prevent/treat symptoms of advanced heart failure and in turn better meet the palliative care requirements of this patient population.

## WHAT THIS STUDY ADDS

⇒ The evidence that is available suggests that intravenous furosemide, particularly administered as a continuous infusion, improves congestion status in advanced heart failure patients in the short term. It is unclear to what extent parenteral diuretics are able to improve breathlessness and peripheral oedema specifically in advanced heart failure, and therefore, its effectiveness as a treatment in this patient population.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review has highlighted an evidence gap. Future studies should determine the effectiveness of parenteral diuretics to improve breathlessness and peripheral oedema in advanced heart failure patients in order to understand where, to whom and in what context, they should be administered. These studies should be undertaken in the advanced heart failure population, focus on the administration of subcutaneous diuretics and use appropriate palliative care outcome measures and validated tools to do so.

## INTRODUCTION

The prevalence of heart failure in the developed world is 1%–2%; this increases to over 10% in those over the age of 70.<sup>1–4</sup> With an ageing population<sup>5</sup> and continued improvement in cardiovascular

interventions,<sup>6</sup> this is predicted to continue to increase.<sup>7,8</sup>

It is widely recognised that the management of acute decompensation of heart failure involves intravenous diuretics and inpatient admission to re-establish euvolaemia.<sup>9</sup> In 2018, the National Institute for Health and Care Excellence highlighted the use of parenteral diuretics in patients with heart failure as an area recommended for further research.<sup>10</sup> A number of palliative care and cardiology societies, including the European Association for Palliative Care and the European Society of Cardiology, have come to an agreement that patients with advanced heart failure should have access to palliative care.<sup>11–13</sup> There are currently no systematic reviews that examine the use of parenteral diuretics on the improvement of symptom burden in advanced heart failure patients specifically. Other similar recent reviews either focus on diuretic administration in non-advanced heart failure populations<sup>14–17</sup> or parenteral diuretic administration in the outpatient setting exclusively.<sup>18</sup> These reviews outline the potential benefits of parenteral diuretics to prevent unnecessary hospitalisation, improve the symptoms and signs of heart failure (namely breathlessness and peripheral oedema) and in turn better meet the palliative care requirements of these patients.

In this systematic review, we (1) identify and describe the relevant studies and evidence reporting on the effectiveness of either intravenous or subcutaneous (SC) diuretics to improve symptom control in patients with advanced heart failure; (2) critically appraise the clinical effectiveness of parenteral diuretics on palliative care relevant outcomes; (3) determine any side effects or safety issues with this intervention in this population group and (4) highlight areas where evidence is lacking and in turn determine the scope for future research in these areas.

## METHODS

### Study design

This systematic review was conducted using the approach described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>19</sup>

### Eligibility criteria

#### Population

The updated 2018 Heart Failure Association of the European Society of Cardiology criteria for defining advanced heart failure was applied to identify the target population.<sup>20</sup> Participants with other comorbidities were not excluded.

#### Intervention

The administration of either intravenous or SC diuretics to relieve breathlessness or peripheral oedema due to advanced heart failure. Diuretics may be administered in any setting whether this be in a hospital, hospice

or in the community. The diuretic intervention being investigated must be administered via a specified route and the intervention must be a single diuretic and not a combination.

### Comparators

Included studies required a comparator group, which could involve any of the following: (1) alternative route/method of diuretic administration, including either oral or parenteral diuretic administration, (2) alternative dose of diuretic therapy, (3) alternative type of diuretic, including any class of diuretic therapy or (4) standard care.

### Outcomes

The reported outcomes included in this review are as follows: improvement in breathlessness and peripheral oedema, reduction in body weight, increase in urine output, deterioration in renal function, serious adverse events, length of hospital stay, improvement in New York Heart Association (NYHA) class, reduction in thoracic fluid content (TFC).

### Study design

Randomised controlled trials (RCTs), quasi-experimental studies and observational studies were to be included in order to obtain all high-quality evidence to answer the specified research question. Qualitative studies, case reports, conference abstracts, editorials and non-English studies were excluded.

### Data extraction

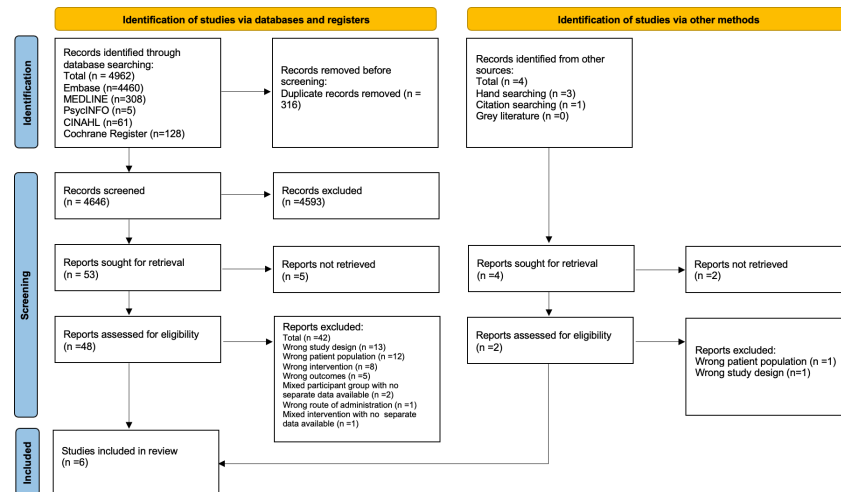
Full details of the search and data extraction can be found in online supplemental appendices A and B, respectively. The search was completed on 10 November 2021. We contacted study authors for additional information where necessary.

### Study risk of bias assessment

The risk of bias assessment was undertaken by the study author (AH) using V.2 of the Cochrane risk-of-bias tool for randomised trials (RoB2).<sup>21</sup> The risk of bias for each domain was considered as low, high or some concerns. All studies were included regardless of score.

### Synthesis methods

The synthesis of results was performed using the framework based on the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews.<sup>22</sup> A descriptive summary of included studies is provided. Where appropriate, we carried out meta-analysis using Review Manager (RevMan, V.5.4.1).<sup>23</sup> If data allowed for meta-analysis, we used the  $I^2$  statistic, the  $\chi^2$  test and a visual inspection of the forest plots to assess for heterogeneity. A fixed or random effects meta-analysis was undertaken depending on the  $I^2$  statistic and the  $p$  value for the  $\chi^2$  test (a random effects model was used if



**Figure 1** PRISMA flow chart to illustrate the flow of studies through the review and the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

$p < 0.10$  and/or  $I^2 > 50\%$ ). For most of the primary and secondary outcomes, we expressed the pooled effect as mean difference for continuous furosemide infusion (CFI) compared with bolus furosemide infusion (BFI) with the exception of freedom from congestion and acute kidney injury (AKI) (measured by number of patients with elevated serum creatinine during treatment period) which we expressed as ORs.

## RESULTS

The screening process identified six eligible studies and the PRISMA flow chart (figure 1) illustrates the flow of studies through the selection process. An overview of the main characteristics of the included studies can be seen in table 1 and online supplemental appendix C.

### Study characteristics

#### Design

All included studies were RCTs with a parallel design, of which three were pilot studies,<sup>24–26</sup> and one was double blinded and used a double-dummy design.<sup>27</sup> The rest were all open labels.

#### Sample sizes

A total of 384 participants were included across the 6 studies within this review, with a range of sample sizes from 40 to 94 and a range in the length of recruitment time from 6 to 43 months.

#### Location

The studies within this review were undertaken in six different countries. Two of the studies recruited from cardiac care units,<sup>24 27</sup> two from intensive care units<sup>25 28</sup> and two from tertiary care general medicine units.<sup>26 29</sup>

#### Sample characteristics

The exclusion criteria within the included studies comprised of participants with recent myocardial infarction,<sup>24 25 27 28</sup> end-stage renal disease,<sup>24 27–29</sup>

participants requiring renal replacement therapy<sup>24 25 28 29</sup> and those who had received more than two intravenous doses of diuretics or any continuous infusion of diuretics before randomisation.<sup>24 26</sup> The mean age of participants ranged from 55 to 73 years, with just one of the studies reporting a statistically significant difference in the mean age between study arms.<sup>28</sup> One study also reported a median age of 54.5 years. When analysing the gender distribution, there were more males recruited proportionally into each of the six included studies. Across all studies, the total percentage of participants that were male was 67.5% and female 32.4%, with the notable outlier being the Frea *et al*<sup>27</sup> study, where 90% of participants were male. All studies provided information with regards to heart failure classification by reporting participants' NYHA class and left ventricular ejection fraction (LVEF). Thirty-eight per cent of all participants classified as NYHA class III and the other 62% classified as NYHA class IV. The mean LVEF across the study samples was 34.8%. Persistently high N-terminal pro B-type natriuretic peptide (NT-pro-BNP) values can be used as a marker of severe cardiac dysfunction and were reported in four out of the six studies.<sup>24 27–29</sup>

#### Continuous diuretic infusion

The six studies all compared intravenous CFI to BFI, with only Frea *et al*<sup>27</sup> specifically designing their study to assess for superiority in the continuous infusion over the bolus infusion. There was considerable variability in what constituted a CFI from one study to the next, with variability in dose, titration and length of infusion time. Frea *et al*<sup>27</sup> and Zheng *et al*<sup>29</sup> both set specific daily furosemide doses, with participants either receiving a high or low dose depending on the participant's renal function. In comparison, Jaya Shree *et al*<sup>28</sup> and Ragab *et al*<sup>25</sup> set hourly infusion rates, with Thomson *et al*<sup>26</sup> and Palazzuoli *et al*<sup>24</sup> not setting any

Table 1 Study characteristics											
Author, year, country	Study design	Study location	Intervention	Comparator	Intervention group		Comparator group				
					Sample size	Mean age (years)	NYHA class	Sample size	Mean age (years)	NYHA class	Risk of bias
Frea 2020, Germany <sup>27</sup>	RCT	Cardiac care unit	IV furosemide continuous infusion, 120 mg/day or 240 mg/day	IV furosemide bolus every 12 hours, 120 mg/day or 240 mg/day	n=40	63.0±13	IV: 40 (100%)	n=40	58.7±10	IV 40 (100%)	Low
Jaya Shree, 2021, India <sup>28</sup>	RCT	Intensive care unit	Continuous IV furosemide infusion, initial rate 2–3 mg/hour	IV furosemide bolus, initial dose 40 mg every 8 hours	n=28	69±9	III: 11 (39.2%) IV: 17 (60.7%)	n=28	63±13	III: 16 (57.1%) IV: 12 (42.8%)	High
Palazzuoli, 2015, Italy <sup>24</sup>	RCT	Cardiac care unit	Continuous IV furosemide infusion for 72–120 hour. Mean dose 188±70 mg/day.	IV furosemide bolus twice-daily for 3–5 days. Mean dose 170±80 mg/day.	n=30	71±7	III: 4 (13%) IV: 27 (90%)	n=28	73±8	III: 5 (18%) IV: 22 (79%)	Low
Ragab, 2018, Egypt <sup>25</sup>	RCT	Critical care unit	Continuous IV furosemide infusion, initial rate 5 mg/hour.	IV furosemide bolus, initial dose 40 mg every 8 hour.	n=20	53.5	III: 5 (25%) IV: 15 (75%)	n=20	57	III: 8 (40%) IV: 12 (60%)	High
Thomson <i>et al</i> , 2010, USA <sup>26</sup>	RCT	Tertiary care medical centre	Continuous IV furosemide infusion, mean 197±48 mg/day. Mean duration of administration was 86.4±50.5 hour	Intermittent infusion of furosemide. The mean daily dose of furosemide was 172±97 mg. The mean duration of administration was 12.5±73 hour	n=26	56.4	III: 10 (38%) IV: 9 (35%) Not reported: 7 (27%)	n=30	54.6	III: 11 (37%) IV: 11 (37%) Not reported: 7 (23)	Some Concerns
Zheng, 2021, China <sup>29</sup>	RCT	Tertiary care medical centre	IV continuous furosemide infusion over 6 hours, 160 mg/day or 200 mg/day depending on eGFR.	IV furosemide bolus once daily, 160 mg/day or 200 mg/day depending on eGFR.	n=47	65.53±7.84	III: 32 (76.19%) IV: 10 (23.81%)	n=47	67.38±8.57	III: 33 (84.62%) IV: 6 (15.38%)	Some Concerns
eGFR, estimated glomerular filtration rate; IV, intravenous; NYHA, New York Heart Association; RCT, randomised controlled trial											

specific daily dose. Furthermore, four of the studies allowed for dose escalation and subsequent titration of furosemide as guided by clinical response.<sup>24–26 28</sup>

#### Bolus diuretic infusion

Similarly, there was significant variation as to how a BFI was defined within the included studies, with variability in dose, titration and number of bolus infusions per 24 hours. The frequency of bolus infusions of furosemide per 24 hours differed between studies, with two studies administering a bolus infusion every 8 hours,<sup>25 28</sup> two studies every 12 hours,<sup>24 27</sup> one study every 24 hours<sup>29</sup> and one study did not report the frequency of bolus administration.<sup>26</sup>

#### Risk of bias in included studies

A risk of bias assessment was undertaken using RoB2 and an overview of the results of this assessment can be found in [table 1](#) and online supplemental appendix D. Additionally, the complete risk of bias assessment containing the response options and detailed comments for each set of signalling questions is presented in online supplemental appendix E.

#### Results of individual studies and results of synthesis

##### Primary outcomes

##### Breathlessness and peripheral oedema

Two of the studies reported on participant breathlessness and peripheral oedema, both of which used two outcome measurement tools to do so.<sup>27 29</sup> Freedom from congestion at 72 hours was used in both of these studies. Zheng *et al*<sup>29</sup> also assessed the degree of dyspnoea of study participants by using the 0–10 modified Borg's scale, which is a recommended measure for breathlessness in advanced disease.<sup>30</sup> In addition to measuring freedom from congestion, Frea *et al*<sup>27</sup> assessed for treatment failure, which they defined as persistent participant congestion, with a wet score of greater than 12 at 72 hours.

As illustrated in [figure 2](#), pooled data from the two studies that reported freedom from congestion at 72 hours with 161 patients showed that CFI led to a significant improvement compared with bolus infusion (OR 2.80, 95% CI 1.45 to 5.40;  $I^2=0\%$ ).

Zheng *et al* also reported that participants receiving a CFI had reduced dyspnoea scores at 48 hours, ( $4.29 \pm 1.23$  vs  $5.97 \pm 1.56$ ,  $p=0.02$ ) which continued over the next 24 hours ( $1.15 \pm 0.35$  vs  $2.66 \pm 0.83$ ,

$p=0.003$ ).<sup>29</sup> Frea *et al* reported a higher incidence of treatment failure in the BFI group in comparison to the CFI group (38% vs 15%,  $p=0.02$ ).<sup>27</sup> Across both studies, there were statistically significant differences in favour of CFI over BFI on breathlessness and peripheral oedema outcomes.

##### Reduction in body weight

Five of the studies provided information on participant weight loss from the time of enrolment to treatment termination.<sup>24–27 29</sup> This outcome measure was used as acute changes in body weight are a proxy marker for fluid balance and congestion status.<sup>31</sup> Three studies reported data that could be pooled together in a meta-analysis, and found no statistically significant reduction in body weight at longest follow-up (see [figure 3](#)).

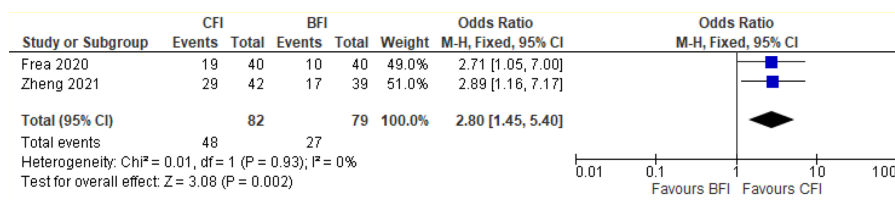
Three studies (Frea *et al*,<sup>27</sup> Ragab *et al*,<sup>25</sup> Jaya Shree *et al*<sup>28</sup>) could not be pooled in the meta-analysis. Jaya Shree *et al*<sup>28</sup> did not report on this outcome while Ragab *et al*<sup>25</sup> reported reduction in median body weight and Frea *et al*<sup>27</sup> reported only weight loss normalised for amount of furosemide received.

Ragab *et al*<sup>25</sup> found a statistically significant reduction in median body weight in the CFI arm after 24 hours, compared with the BFI arm (2 (1.5–2.5) kg vs 1.5 (1–2) kg,  $p=0.03$ ), but not at 48 hours (2 (1.1–2.5) kg vs 2 (1.5–2) kg,  $p=0.4$ ). Zheng *et al*<sup>29</sup> reported a greater reduction in mean body weight in the CFI group at 48 hours ( $3.46 \pm 0.63$  kg vs  $2.36 \pm 0.57$  kg,  $p=0.03$ ) and 72 hours ( $4.72 \pm 1.01$  kg vs  $3.53 \pm 0.73$  kg,  $p=0.02$ ). Frea *et al*<sup>27</sup> reported a statistically significant result of greater weight loss in the CFI group at 72 hours ( $1 \pm 0.7$  vs  $0.6 \pm 0.6$  kg/40 mg furosemide/72 hours,  $p<0.01$ ).

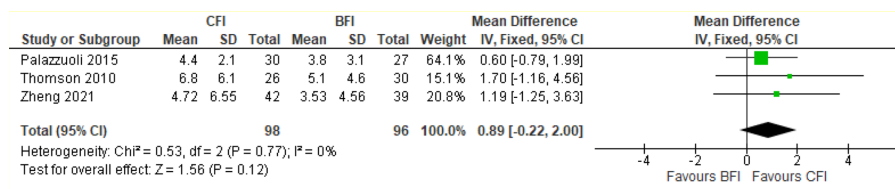
##### Urine output

Urine output was assessed in all studies within this review, as an objective way of assessing diuretic effectiveness. As shown in [figure 4](#), four of the studies reported data from 234 patients that could be pooled in a meta-analysis and found that participants receiving CFI compared with BFI had a statistically significantly greater urine output at 24 hours (mean difference 344.76, 95% CI 132.87 to 556.64;  $I^2=44\%$ ).

The study by Ragab *et al*<sup>25</sup> could not be included in the meta-analysis as it reported only median urine output, while Zheng *et al*<sup>29</sup> did not report usable



**Figure 2** Meta-analysis of CFI versus BFI on freedom from congestion at 72 hours. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.



**Figure 3** Meta-analysis of CFI versus BFI on body weight at longest follow-up. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.

data at 24 hours. We contacted the authors of Zheng *et al*<sup>29</sup> but had not received a response at the time of submission for publication. In Ragab *et al*<sup>25</sup> difference in median urine output between the continuous and bolus groups during the first 24 hours ( $p=0.08$ ), second 24 hours ( $p=0.08$ ) and third 24 hours ( $p=0.1$ ) was not significantly different. Zheng *et al*<sup>29</sup> reported no difference between groups at 24 hours ( $p=0.12$ ), but urine output in favour of the continuous group compared with the bolus group at 48 hours ( $p=0.01$ ) and 72 hours (5145.98 (SE: 621.37) mL vs 3755.95 (SE: 456.93),  $p=0.007$ ). Thomson *et al*<sup>26</sup> further reported mean net urine output in 24 hours (nUOP/24 hours), net daily urine output normalised for amount of furosemide received (nUOP/mg furosemide) and total daily urine output normalised for amount of furosemide received (tUOP/mg furosemide). There was no statistically significant difference between the groups in nUOP/24 hours ( $p=0.086$ ) and nUOP/mg furosemide ( $p=0.178$ ). The tUOP/mg furosemide favoured the continuous group with a mean daily tUOP of 38 (SD 31) mL/mg of furosemide vs 22 (SD 13) mL/mg in the BFI group ( $p=0.021$ ). Freja *et al*<sup>27</sup> also reported total urinary output in favour of the continuous group compared with the bolus group after 72 hours (10020 (SD 3032) mL vs 8612 (SD 2984) mL,  $p=0.04$ ). Jaya Shree *et al*<sup>28</sup> reported no significant difference between the two groups at 24, 48 and 72 hours after admission, but no data were provided in the study.

#### Secondary outcomes

##### Renal function

Renal function was reported in all six of the studies in a number of different ways. This is an important outcome measure to report when investigating loop diuretics, as their use can lead to excessive diuresis and subsequent AKI. The prevalence of AKI was reported in five of the studies.<sup>24–27 29</sup> Figure 5 shows the pooled data from the five studies with 314 participants showed

no statistically significant difference in the odds of AKI between those that received CFI and those that had BFI (OR 1.27, 95% CI 0.74 to 2.17;  $I^2=0\%$ ).

All the studies reported on serum creatinine levels but only four could be pooled together in a meta-analysis (figure 6). Data from 274 participants showed no significant difference between both groups (mean difference 0.22, 95% CI  $-0.04$  to  $0.48$ ;  $I^2=78\%$ ).

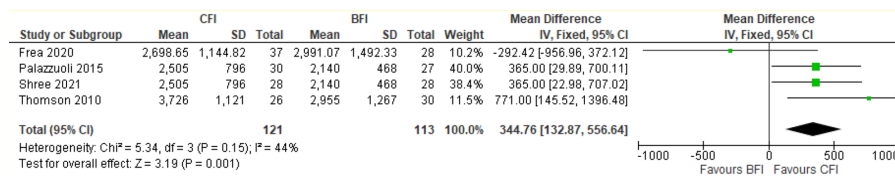
One study by Ragab *et al*<sup>25</sup> reported their data in different units, while Thomson *et al*<sup>26</sup> only presented the mean values without the SD or standard errors. Ragab *et al*<sup>25</sup> reported a statistically significant elevation after 48 hours in the median serum creatinine values in the CFI group compared with the BFI group ( $0.2$  ( $0.1$  to  $0.5$ ) mg % vs  $0$  ( $-0.1$  to  $0.2$ ) mg %,  $p=0.009$ ). By contrast, Thomson *et al*<sup>26</sup> reported a significant difference in favour of the CFI group compared with the BFI ( $p=0.035$ ).

The final marker of renal function that was assessed was the estimated glomerular filtration rate, with three studies reporting on this outcome.<sup>24 27 28</sup> Only Palazzuoli *et al*<sup>24</sup> reported a significant difference between intervention groups, with the analysis demonstrating a reduced renal function in the continuous infusion group compared with the bolus group.

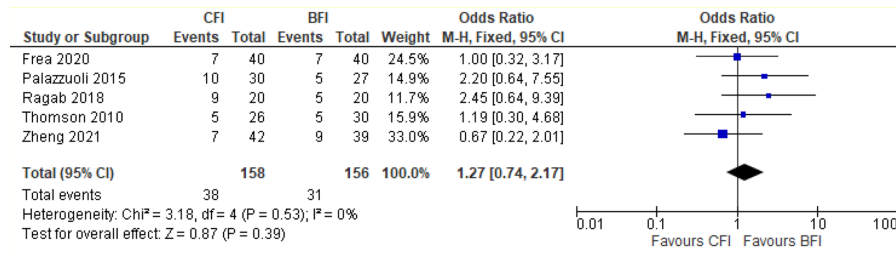
##### Serious adverse events

Serious adverse events were reported in five of the studies.<sup>24–26 28 29</sup> All five of these studies reported electrolyte disturbances,<sup>24–26 28 29</sup> with hyponatraemia and hypokalaemia considered to be common side effects of loop diuretics.<sup>32</sup> Pooled data (figure 7) from three studies with 194 patients showed no difference between the CFI and the BFI group on serum sodium levels (mean difference 0.15, 95% CI  $-1.97$  to  $2.27$ ;  $I^2=0\%$ ).

Three studies (Freja *et al*,<sup>27</sup> Ragab *et al*,<sup>25</sup> Thomson *et al*<sup>26</sup>) could not be included in the meta-analysis.



**Figure 4** Meta-analysis of CFI versus BFI on urine output at 24 hours. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.



**Figure 5** Meta-analysis of CFI versus BFI on acute kidney injury (measured by number of patients with elevated serum creatinine during treatment period). BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.

Thomson *et al*<sup>26</sup> did not report on serum sodium while Frea *et al*<sup>27</sup> reported that serum sodium was not different between the two groups but no data was reported. Ragab *et al*<sup>25</sup> presented median serum sodium values during the first 24 hours and found that no significant difference between the treatment groups. Serum sodium reduced by 0 (−1 to 1) mEq/L in the CFI group and increased by 1 (−2 to 1) mEq/L in the BFI group ( $p=0.5$ ).

Three studies with 194 patients reported data that could be pooled together on serum potassium (figure 8) and found a significantly lower serum potassium in the BFI group compared with the CFI group (mean difference −0.20, 95% CI −0.38 to −0.01;  $I^2=0\%$ ).

Data from three studies (Frea *et al*,<sup>27</sup> Ragab *et al*,<sup>25</sup> Thomson *et al*<sup>26</sup>) could not be pooled regarding serum potassium. Frea *et al*<sup>27</sup> did not report on serum potassium. Ragab *et al*<sup>25</sup> reported median serum potassium levels during the first 24 hours and found no significant difference between the CFI and BFI group ((0.1 (0.1 to 0.5) vs 0.1 (−0.3 to 0.3) mEq/L,  $p=0.2$ ). Ragab *et al*<sup>27</sup> further showed that after 48 hours of treatment, hypokalaemia occurred in eight participants receiving CFI, compared with just one receiving BFI ( $p=0.02$ ). Thomson *et al*<sup>26</sup> reported no difference in potassium replacement between the CFI and BFI group ( $p=0.86$ ).

The need for additional treatments during the intervention period was documented as an outcome in two of the included studies, with varying additional treatments administered in these studies. Palazzuoli *et al*<sup>24</sup> described how a higher frequency of participants receiving the continuous infusion required additional hypertonic saline solutions (40% vs 19 %,  $p<0.01$ ) and dobutamine infusions (50% vs 26 %,  $p<0.01$ ) in comparison to the bolus group. Another serious adverse event reported in two of the studies was

hypotension,<sup>26 29</sup> with both studies reporting a non-significant result between the two study arms in terms of hypotension prevalence. The last serious adverse event which was only reported in the Zheng *et al*<sup>29</sup> study was the prevalence of tinnitus, with only a small percentage of participants affected and no significant differences emerging between groups.

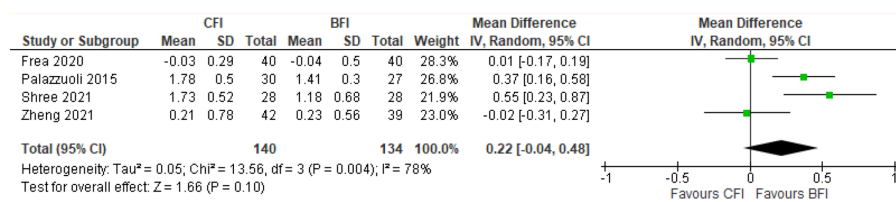
#### Length of hospital stay

Length of hospitalisation was reported in five of the included studies,<sup>24–26 28 29</sup> with Ragab *et al*<sup>25</sup> and Jaya Shree *et al*<sup>28</sup> specifically reporting on the length of stay in ICU, and the other three studies documenting the total length of hospital stay. Pooled data from the three studies with 194 patients showed no statistically significant difference in the length of hospital stay between the continuous group and the bolus group (mean difference −1.09, 95% CI −7.05 to 4.86;  $I^2=82\%$ ), as shown in figure 9.

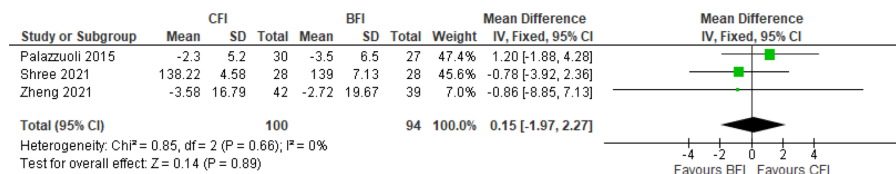
Data from Ragab *et al*<sup>25</sup> and Jaya Shree *et al*<sup>28</sup> could not be pooled in a meta-analysis. Ragab *et al*<sup>25</sup> presented their data as range while Jaya Shree *et al*<sup>28</sup> presented median length of stay in ICU. There was no significant difference between the continuous group and the bolus in Ragab *et al*<sup>25</sup> ( $p=0.7$ ), while Jaya Shree *et al*<sup>28</sup> reported an increase in ICU length of stay but did not state if this was statistically significant or not. These results showed no clear consensus with regards to whether a CFI or a BFI resulted in a reduced length of hospital stay.

#### NYHA classification

Improvement in NYHA class from enrolment to treatment termination was an outcome measured in two of the studies, both showing an improvement in both intervention groups but no statistically significant



**Figure 6** Meta-analysis of CFI versus BFI on serum creatinine levels. Zheng *et al* presented mean and SE for creatinine as  $\mu\text{mol/L}$ . This was converted to  $\text{mg/dL}$  in this meta-analysis. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.



**Figure 7** Meta-analysis of CFI versus BFI on serum sodium. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.

difference between groups.<sup>25 28</sup> Ragab *et al*<sup>25</sup> found the NYHA class was unimproved during the first 24 hours in five patients from the CFI group and six patients in the BFI group, and an improvement by 1° (eg, from NYHA IV to III or from NYHA III–II) in 15 and 14 patients from the continuous and bolus groups respectively ( $p=0.7$ ). Similar results were demonstrated during the second day of treatment, with improvement by 1° in 15 and 14 patients from the continuous and bolus groups, respectively ( $p=0.6$ ). Shree *et al*<sup>28</sup> did not report the number of patients with improvement in NYHA class; therefore, data cannot be pooled for this outcome.

#### Thoracic fluid content

Ragab *et al*<sup>25</sup> was the only study to measure the reduction in TFC. The study reports that in both intervention groups the TFC was significantly reduced after 24 hours of furosemide treatment compared with enrolment. The decrease in TFC during the first 24 hours was significantly greater in the CFI group, compared with the BFI group (10 (6.3–14.5)/kΩ vs 7 (3.3–9.8)/kΩ,  $p=0.02$ ), which continued over the next 24 hours as well.

#### Summary of results

A number of outcome measures were used in the studies and have been summarised in [table 2](#). See online supplemental appendix C for full results.

## DISCUSSION

### Summary

Parental diuretics are used clinically in the management of advanced heart failure patients despite a lack of evidence in palliative care literature.<sup>9 13 33–35</sup> This review, therefore, aimed to analyse the available evidence regarding the effectiveness of parenteral diuretics on breathlessness and peripheral oedema in this population.

Six studies were identified, all of which compared continuous against bolus intravenous furosemide infusion. Only two assessed participant breathlessness

and peripheral oedema directly, using three different outcome measurement tools to do so. Other studies used more objective proxy measures of congestion, such as reduction in body weight, increased urine output and decreased TFC, which are commonplace in heart failure research.<sup>36</sup>

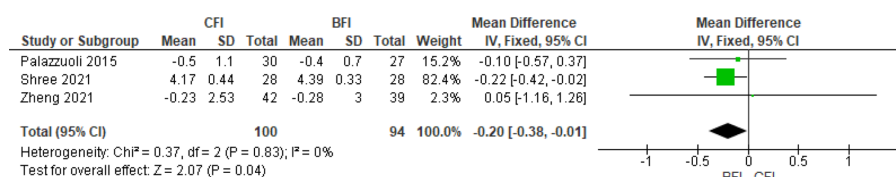
There was variance in results across the studies. The one outcome in which there was no variance was that of breathlessness and peripheral oedema, which was assessed in two studies. Meta analysis of this outcome, reported as freedom from congestion, found statistically significant results in favour of the continuous intravenous furosemide infusion intervention. Of the two studies, one had a low overall risk of bias score and the other had some concerns. It must also be stated that the bolus infusion also showed outcome improvement, particularly in outcomes corresponding to diuresis. There was no difference between continuous and bolus infusions on reduction in weight, renal function and length of hospital stay.

Safety issues which were highlighted include AKI, electrolyte disturbance, hypotension and tinnitus, all of which are known side effects of diuretics. There were no statistically significant differences in incidence of AKI between continuous and bolus administration of furosemide.

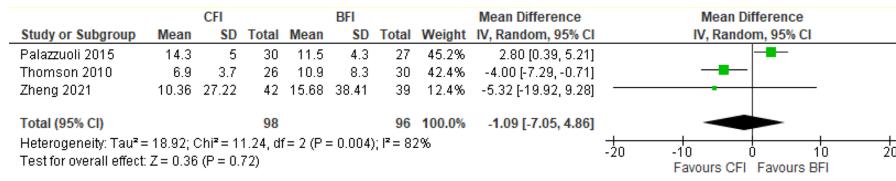
The systematic review process revealed a paucity of evidence, with only six small studies meeting inclusion criteria and no studies comparing parental diuretics to other interventions such as diuretics administered via alternative routes, opioids or non-pharmacological treatments.

### General interpretation

It has been shown that it is extremely difficult to recruit advanced heart failure patients into research studies, which has led to a lack of research in this population group.<sup>37</sup> This is due to a number of different factors, such as the varying terminology used to describe heart failure progression, a lack of prognostic certainty, ethical concerns due to patient vulnerability and



**Figure 8** Meta-analysis of CFI versus BFI on serum potassium. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.



**Figure 9** Meta-analysis of CFI versus BFI on length of hospital stay. BFI, bolus furosemide infusion; CFI, continuous furosemide infusion.

increased attrition rates due to symptom burden and high mortality rates.<sup>38–40</sup> This is at least part of the reason why so few high-quality studies with sufficiently advanced patients were included in this review. This difficulty with recruitment appears to have been an issue in a number of studies, with multiple studies reporting small sample sizes as part of their limitations.<sup>24–26 29</sup> Four of the studies report being underpowered,<sup>25 26 28 29</sup> with only two studies demonstrating power and sample size estimation,<sup>24 27</sup> and the other studies not indicating how the sample sizes were determined, therefore, increasing the risk of wrongly failing to reject the null hypothesis.

A true representation of the population of advanced heart failure patients with palliative care requirements may not have been completely captured within this review, due to discrepancies in age, gender, study setting and disease severity of the included participants. This, therefore, suggests there may be an element of selection bias across all studies. First, the mean age of participants within the studies ranged from 55 to 73 years, with only one of the included studies having a mean age above the age of 70. This is notably lower than what would be expected in the developed world, where both the incidence and prevalence of heart failure increases with age, with an average age of diagnosis at 77.<sup>10</sup> Across all of the studies, the total percentage of participants that were female was 32.4% and male 67.5%, with one outlying study reporting that 90% of participants were male.<sup>27</sup> This particular study found no statistically significant difference in gender distribution between study arms and there was no reasoning or detail as to why such a high proportion of males were recruited into the study, even though there is a similar overall lifetime risk of heart failure among men and women.<sup>41</sup>

The six included studies all compared the effectiveness of continuous intravenous furosemide infusion to bolus intravenous furosemide infusion. Therefore, in this review, there are no studies in which diuretics were administered via the SC route, despite a body of evidence suggesting this is an advantageous route of administration in end of life patients.<sup>14</sup> The reason for the exclusion of these studies was due to either inappropriate study design, for example, case series,<sup>42–45</sup> or insufficient disease severity,<sup>46</sup> which further highlights the paucity of high-quality evidence answering this research question. In terms of the other outcomes

reported, there does not appear to be a method of administration that is significantly better than the other. These findings are replicated in two other systematic reviews and meta-analyses that compared these two interventions in non-advanced heart failure populations.<sup>15 16</sup>

In order to assess the ability of parenteral diuretics to improve breathlessness and peripheral oedema, it is essential to measure subjective severity. First, only two of the studies actually assessed participant breathlessness and peripheral oedema directly, using three different outcome measurement tools to do so. The predominant way of assessing intervention effectiveness was by measuring improvements in congestion through a reduction in body weight, increased urine output and reduced TFC. These outcome measures, although more objective, do not provide any information on whether a patient's symptom burden has improved throughout the study. It has been shown that these proxy measures cannot be assumed to demonstrate improvements in breathlessness and peripheral oedema, with a reduction in body weight not necessarily correlating with reduced intravascular volume and an improvement in a patient's signs and symptoms.<sup>47</sup> This, therefore, means there is insufficient use of validated tools to measure breathlessness and peripheral oedema, which makes interpretation of these results more difficult and less reliable.

### Strengths and limitations

Using rigorous methods, this systematic review has identified and analysed the available evidence, with only RCTs meeting the set criteria. RCTs have increased internal validity and are the best study design for assessing the efficacy and effectiveness of new interventions.<sup>48 49</sup> This, therefore, means the evidence included within this review is of higher quality and lower bias. A number of relevant but uncontrolled case series were not included, which has therefore prevented this study type to significantly influence this review.<sup>42–45</sup>

All six of the studies, although performed in advanced heart failure patients, are focused on outcomes more relevant to cardiology than palliative care. This is shown by the outcome measures used, with all studies measuring the diuretic effect of intravenous furosemide, but only two studies measuring breathlessness and peripheral oedema specifically, and no studies using any other palliative care relevant outcome

**Table 2** Outcome measures used in studies and summary of results

Outcome	Outcome measure	Study author	Summary of results
Breathlessness and peripheral oedema	Freedom from congestion	Frea <i>et al</i> , Zheng <i>et al</i> <sup>27 29</sup>	Pooled data from 161 patients showed improvement in favour of CFI for freedom from congestion (OR 2.80, 95% CI 1.45 to 5.40; $I^2=0\%$ ). Improvement in both groups with statistically significant difference in favour of CFI in both studies was also reported for the other outcomes.
	Borg's scale	Zheng <i>et al</i> <sup>29</sup>	
	Treatment failure using wet score	Frea <i>et al</i> <sup>27</sup>	
Reduction in body weight	Weight loss from the time of enrolment to treatment termination	Frea <i>et al</i> , Ragab <i>et al</i> , Thomson <i>et al</i> , Zheng <i>et al</i> , Palazzuoli <i>et al</i> <sup>24–27 29</sup>	Pooled data from three studies with 194 patients showed no significant difference between groups (MD 0.89, 95% CI –0.22 to 2.00, $I^2=0\%$ ).
Urine output	Total urinary output	Frea <i>et al</i> <sup>27</sup>	Pooled data from four studies with 234 patients found that participants receiving CFI compared with BFI had a significantly greater urine output at 24 hours (MD 344.76, 95% CI 132.87 to 556.64; $I^2=44\%$ )
	Mean total daily urinary output	Thomson <i>et al</i> , Palazzuoli <i>et al</i> , Jaya Shree <i>et al</i> <sup>24 26 28</sup>	
	Hourly urine output for every kg of body weight	Ragab <i>et al</i> <sup>25</sup>	
	Total net urinary output	Zheng <i>et al</i> <sup>29</sup>	
	Net daily urinary output	Thomson <i>et al</i> <sup>26</sup>	
	Net daily urinary output normalised for amount of furosemide received	Thomson <i>et al</i> <sup>26</sup>	
	Total daily urinary output normalised for amount of furosemide received	Thomson <i>et al</i> <sup>26</sup>	
Renal Function	Increase in prevalence of acute kidney injury	Frea <i>et al</i> , Ragab <i>et al</i> , Thomson <i>et al</i> , Zheng <i>et al</i> , Palazzuoli <i>et al</i> <sup>24–27 29</sup>	Pooled data from five studies with 314 participants demonstrated no significant difference between groups in the odds of AKI measured by number of patients with elevated serum creatinine during treatment period (OR 1.27, 95% CI 0.74 to 2.17; $I^2=0\%$ ). Pooled data from 274 participants showed no significant difference in serum creatinine levels between both groups (MD 0.22, 95% CI –0.04 to 0.48; $I^2=78\%$ ). Three reported on the estimated glomerular filtration rate, <sup>24 27 28</sup> but only Palazzuoli <i>et al</i> <sup>24</sup> reported significantly greater prevalence in the CFI group.
	Increase in serum creatinine	Frea <i>et al</i> , Ragab <i>et al</i> , Zheng <i>et al</i> , Palazzuoli <i>et al</i> , Jaya Shree <i>et al</i> <sup>24 25 27–29</sup>	
	Decrease in glomerular filtration rate	Frea <i>et al</i> , Palazzuoli <i>et al</i> , Jaya Shree <i>et al</i> <sup>24 27 28</sup>	
	Decrease in serum creatinine clearance	Ragab <i>et al</i> <sup>25</sup>	
Serious adverse events	Electrolyte disturbances	Ragab <i>et al</i> , Thomson <i>et al</i> , Zheng <i>et al</i> , Palazzuoli <i>et al</i> , Jaya Shree <i>et al</i> <sup>24–26 28 29</sup>	Pooled data from three studies with 194 patients showed no difference between CFI and BFI on serum sodium levels (Mean Difference 0.15, 95% CI –1.97 to 2.27; $I^2=0\%$ ). Three studies with 194 patients found a significantly lower serum potassium in the BFI group compared with the CFI group (Mean Difference –0.20, 95% CI –0.38 to –0.01; $I^2=0\%$ ).
	Prevalence of hypokalaemia	Ragab <i>et al</i> , Zheng <i>et al</i> <sup>25 29</sup>	
	Need for additional treatments during the intervention period	Palazzuoli <i>et al</i> , Thomson <i>et al</i> <sup>24 26</sup>	
	Increased Rehospitalisation and mortality	Palazzuoli <i>et al</i> <sup>24</sup>	
	Prevalence of Significant hypotension	Thomson <i>et al</i> , Zheng <i>et al</i> <sup>26 29</sup>	
	Tinnitus	Zheng <i>et al</i> <sup>29</sup>	
Length of hospital stay	Increase in length of hospital stay	Thomson <i>et al</i> , Zheng <i>et al</i> , Palazzuoli <i>et al</i> <sup>24 26 29</sup>	Five of the six included studies reported outcomes related to length of hospital stay. Pooled data from three studies with 194 patients showed no significant difference in the length of hospital stay between both groups (MD –1.09, 95% CI –7.05 to 4.86; $I^2=82\%$ ).
	Increase in length of ICU stay	Ragab <i>et al</i> , Jaya Shree <i>et al</i> <sup>25 28</sup>	
New York Heart Association (NYHA) Classification	Improvement in NYHA Class	Ragab <i>et al</i> , Jaya Shree <i>et al</i> <sup>25 28</sup>	Improvement in both groups. A meta-analysis was not possible due to insufficient data.
Thoracic Fluid Content (TFC)	Decrease in TFC	Ragab <i>et al</i> <sup>25</sup>	Improvement in both groups.

AKI, acute kidney injury; BFI, bolus furosemide infusion; CFI, continuous furosemide infusion; ICU, intensive care unit; MD, mean difference.

measure. This demonstrates that the research question could have been answered more effectively had more appropriate outcome measures been consistently used across all studies. In particular, the use of a patient

reported, multidimensional tool to measure breathlessness and peripheral oedema, as recommended.<sup>50</sup> Outcomes were also assessed at 72 hours, with no further follow-up, meaning the effectiveness after this

time period is not reported. Furthermore, all of the included studies had small numbers of participants and were exclusively undertaken in secondary and tertiary care, with no studies in primary or community care.

### Implications and recommendations

There is a general consensus that a palliative care approach should be introduced and integrated early into the treatment of patients with heart failure, in order to optimise the care provided and maximise patient outcomes.<sup>51–53</sup> This integration between cardiology and palliative care is not particularly present when considering the current evidence base for parenteral diuretics to improve breathlessness and peripheral oedema in advanced heart failure patients. The cardiology-focused research, as included in this review, is more robust; however, it does not focus specifically on measuring palliative care relevant outcomes, despite these patients being classified as having palliative care needs. This is exemplified by the included studies in this review, which measure the short-term diuretic effects of parenteral diuretics in acutely decompensated heart failure, with less focus on measuring more chronic symptoms/signs and the subsequent effects on quality of life.

Due to a lack of funding and difficulty in recruiting advanced heart failure patients into prospective RCTs, there is a lack of robust evidence in the palliative care literature answering this research question.<sup>37 54</sup> This is epitomised by the fact that no studies investigating SC diuretics to improve breathlessness and peripheral oedema in advanced heart failure patients met the inclusion criteria for this review. This is despite a high level of research interest in this treatment over a number of years, as well as its use in palliative care clinical practice at this moment in time. This review has highlighted an evidence gap, as there are no high-quality studies that specifically determine whether parenteral diuretics improve breathlessness and peripheral oedema in advanced heart failure patients, by assessing appropriate outcome measures and using validated tools to do so. This gap needs to be filled with high-quality evidence answering the following key research questions:

- ▶ Do SC diuretics improve breathlessness and peripheral oedema in advanced heart failure patients?
- ▶ What is the most appropriate dose, route and setting for the administration of parenteral diuretics in advanced heart failure patients?
- ▶ Which advanced heart failure patients are most likely to benefit from parenteral diuretics, particularly in terms of symptom burden and stage and severity of disease?
- ▶ How to effectively recruit a more representative advanced heart failure population into research studies?
- ▶ Which validated tools are the most appropriate to assess breathlessness and peripheral oedema in advanced heart failure patients, and how can these tools become more commonplace in heart failure research?

As outlined, a number of research questions have been developed from the findings in this review, and one that should certainly be prioritised is whether SC diuretics are an appropriate and effective treatment. This treatment has significant potential to be effective in advanced heart failure patients, and therefore, a trial should be prioritised for a number of reasons. First, this review found that a continuous infusion of intravenous diuretics has a greater effect on breathlessness and peripheral oedema than a bolus infusion. Based on this information, a hypothesis can be made that administering diuretics continuously via the SC route would be effective. Administering medications via this route has a number of benefits to patients with palliative care requirements.<sup>55 56</sup> This treatment is also used in clinical practice without a strong evidence base,<sup>57</sup> and using interventions without a sufficient evidence is not advisable, as demonstrated by the experiences in the replacement of the Liverpool Care Pathway.<sup>58</sup> It is important to establish the efficacy, effectiveness and safety of parenteral diuretics in advanced heart failure patients before models of care are designed and implemented around these interventions. This, therefore, highlights the urgency of these research recommendations.

### CONCLUSION

This review demonstrates that a continuous intravenous infusion of furosemide leads to improvement in breathlessness and peripheral oedema and an increase in urine output, as compared with a bolus intravenous infusion of furosemide in the short term. Advanced heart failure patients with palliative care requirements may therefore benefit from a continuous infusion of intravenous furosemide. There were no studies included in this review that investigated the administration of diuretics via the SC route, which means the safety and effectiveness of diuretics via this route of administration are not reported. Due to a lack of available relevant evidence in the included studies, it is not certain what the most appropriate dose, route and setting for the administration of parenteral diuretics should be. As well as this, it is not possible to extrapolate which advanced heart failure patients with palliative care requirements are most likely to benefit from this treatment. Therefore, sufficiently powered RCTs are necessary to confirm or reject the findings of this review. Future trials should measure breathlessness and peripheral oedema using validated tools, alongside palliative care relevant outcomes in advanced heart failure patients, to demonstrate safety, effectiveness and appropriateness of parenteral diuretics as a viable treatment option.

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#### REFERENCES

- Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;93:1137–46.
- Redfield MM, Jacobsen SJ, Burnett JC, *et al.* Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194–202.
- Bleumink GS, Knetsch AM, Sturkenboom MCJM, *et al.* Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure the Rotterdam study. *Eur Heart J* 2004;25:1614–9.
- Ceja F, Fonseca C, Mota T, *et al.* Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* 2002;4:531–9.
- Bone AE, Gomes B, Etkind SN, *et al.* What is the impact of population ageing on the future provision of end-of-life care? Population-based projections of place of death. *Palliat Med* 2018;32:329–36.
- Jones NR, Roalfe AK, Adoki I, *et al.* Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019;21:1306–25.
- Groenewegen A, Rutten FH, Mosterd A, *et al.* Epidemiology of heart failure. *Eur J Heart Fail* 2020;22:1342–56.
- Guha K, McDonagh T. Heart failure epidemiology: European perspective. *Curr Cardiol Rev* 2013;9:123–7.
- McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
- National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: diagnosis and management, 2018. Available: <https://www.nice.org.uk/guidance/ng106/resources/chronic-heart-failure-in-adults-diagnosis-and-management-pdf-66141541311685> [Accessed 25 Nov 2021].
- Jaarsma T, Beattie JM, Ryder M, *et al.* Palliative care in heart failure: a position statement from the palliative care workshop of the heart failure association of the European Society of cardiology. *Eur J Heart Fail* 2009;11:433–43.
- Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200.
- Sobanski PZ, Alt-Epping B, Currow DC, *et al.* Palliative care for people living with heart failure: European association for palliative care Task force expert position statement. *Cardiovasc Res* 2020;116:12–27.
- Afari ME, Aoun J, Khare S, *et al.* Subcutaneous furosemide for the treatment of heart failure: a state-of-the-art review. *Heart Fail Rev* 2019;24:309–13.
- Chan JSK, Kot TKM, Ng M, *et al.* Continuous infusion versus intermittent boluses of furosemide in acute heart failure: a systematic review and meta-analysis. *J Card Fail* 2020;26:786–93.
- Ng KT, Yap JLL. Continuous infusion vs. intermittent bolus injection of furosemide in acute decompensated heart failure: systematic review and meta-analysis of randomised controlled trials. *Anaesthesia* 2018;73:238–47.
- Faris RF, Flather M, Purcell H, *et al.* Diuretics for heart failure. *Cochrane Database Syst Rev* 2012:CD003838.
- Wierda E, Dickhoff C, Handoko ML, *et al.* Outpatient treatment of worsening heart failure with intravenous and subcutaneous diuretics: a systematic review of the literature. *ESC Heart Fail* 2020;7:892–902.
- Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- Crespo-Leiro MG, Metra M, Lund LH, *et al.* Advanced heart failure: a position statement of the heart failure association of the European Society of cardiology. *Eur J Heart Fail* 2018;20:1505–35.
- Higgins JPT, Savović J, Page MJ, *et al.* Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for systematic reviews of interventions version 6.2*. Cochrane, 2021. [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook)
- Popay J, Roberts H, Sowden A, *et al.* *Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme*, 2006.
- RevMan. [Computer program], Nordic Cochrane Centre, Cochrane Manager 5 (RevMan 5). Version 5.4.1. Copenhagen: Nordic Cochrane Centre, Cochrane, 2020.
- Palazzuoli A, Pellegrini M, Franci B, *et al.* Short and long-term effects of continuous versus intermittent loop diuretics treatment in acute heart failure with renal dysfunction. *Intern Emerg Med* 2015;10:41–9.
- Ragab D, Taema KM, Farouk W, *et al.* Continuous infusion of furosemide versus intermittent boluses in acute decompensated heart failure: effect on thoracic fluid content. *Egypt Heart J* 2018;70:65–70.
- Thomson MR, Nappi JM, Dunn SP, *et al.* Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail* 2010;16:188–93.
- Freja S, Pidello S, Volpe A, *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;109:417–25.
- Jaya Shree D, Daniel CJ, Marsh C, *et al.* A study on continuous infusion versus intermittent bolus dosing of furosemide in hospitalized heart failure patients. *Research Journal of Pharmacy and Technology* 2021;14:2814–8.
- Zheng Z, Jiang X, Chen J, *et al.* Continuous versus intermittent use of furosemide in patients with heart failure and moderate chronic renal dysfunction. *ESC Heart Fail* 2021;8:2070–8.

- 30 Bausewein C, Farquhar M, Booth S, *et al.* Measurement of breathlessness in advanced disease: a systematic review. *Respir Med* 2007;101:399–410.
- 31 Gheorghiade M, Follath F, Ponikowski P, *et al.* Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure Committee of the heart failure association of the European Society of cardiology and endorsed by the European Society of intensive care medicine. *Eur J Heart Fail* 2010;12:423–33.
- 32 Oh SW, Han SY. Loop diuretics in clinical practice. *Electrolyte Blood Press* 2015;13:17–21.
- 33 Johnson M. *Heart failure and palliative care: a team approach*. 2nd ed. Taylor & Francis Group, 2017.
- 34 Guideline for the administration of subcutaneous furosemide in the community setting, 2017. Available: <http://www.yorkandscotlandformulary.nhs.uk/docs/BNF/02/Guidelines%20for%20subcutaneous%20Furosemide%20in%20the%20community.pdf> [Accessed 01 Jan 2021].
- 35 Guidance for the use of subcutaneous furosemide by continuous infusion for heart failure in community settings. Available: <https://www.heartfailurehubscotland.co.uk/wp-content/uploads/2016/04/NHS-Highlands-SC-furosemide-policy3.pdf> [Accessed 01 Jan 2021].
- 36 Heart Failure Society Of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail* 2006;12:10–38.
- 37 Kane PM, Murtagh FEM, Ryan KR, *et al.* Strategies to address the shortcomings of commonly used advanced chronic heart failure descriptors to improve recruitment in palliative care research: a parallel mixed-methods feasibility study. *Palliat Med* 2018;32:517–24.
- 38 Fitzsimons D, Strachan PH. Overcoming the challenges of conducting research with people who have advanced heart failure and palliative care needs. *Eur J Cardiovasc Nurs* 2012;11:248–54.
- 39 Zambroski CH, Buck H, Garrison CM, *et al.* Lessons from the field: challenges in accruing hospice heart failure patients to intervention research. *J Cardiovasc Nurs* 2014;29:91–7.
- 40 Goodlin SJ, Quill TE, Arnold RM. Communication and decision-making about prognosis in heart failure care. *J Card Fail* 2008;14:106–13.
- 41 Lam CSP, Arnott C, Beale AL, *et al.* Sex differences in heart failure. *Eur Heart J* 2019;40:3859–68.
- 42 Brown A, Westley K, Robson J, *et al.* Furosemide in end-stage heart failure: community subcutaneous infusions. *BMJ Support Palliat Care* 2022;12:e763–6.
- 43 Birch F, Boam E, Parsons S, *et al.* Subcutaneous furosemide in advanced heart failure: service improvement project. *BMJ Support Palliat Care* 2023;13:112–6.
- 44 Zacharias H, Raw J, Nunn A, *et al.* Is there a role for subcutaneous furosemide in the community and hospice management of end-stage heart failure? *Palliat Med* 2011;25:658–63.
- 45 Civera J, de la Espriella R, Heredia R, *et al.* Efficacy and safety of subcutaneous infusion of Non-formulated furosemide in patients with worsening heart failure: a real-world study. *J Cardiovasc Transl Res* 2022;15:644–52.
- 46 Sica DA, Muntendam P, Myers RL, *et al.* Subcutaneous furosemide in heart failure: pharmacokinetic characteristics of a newly buffered solution. *JACC Basic Transl Sci* 2018;3:25–34.
- 47 Konstam MA, Gheorghiade M, Burnett JC, *et al.* Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the Everest outcome trial. *JAMA* 2007;297:1319–31.
- 48 Murad MH, Asi N, Alsawas M, *et al.* New evidence pyramid. *Evid Based Med* 2016;21:125–7.
- 49 Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J* 2003;20:164–8.
- 50 Johnson MJ, Oxberry SG, Cleland JGF, *et al.* Measurement of breathlessness in clinical trials in patients with chronic heart failure: the need for a standardized approach: a systematic review. *Eur J Heart Fail* 2010;12:137–47.
- 51 Hill L, Prager Geller T, Baruah R, *et al.* Integration of a palliative approach into heart failure care: a European Society of cardiology heart failure association position paper. *Eur J Heart Fail* 2020;22:2327–39.
- 52 Kavalieratos D, Gelfman LP, Tycon LE, *et al.* Palliative Care in Heart Failure: Rationale, Evidence, and Future Priorities. *J Am Coll Cardiol* 2017;70:1919–30.
- 53 Hauptman PJ, Havranek EP. Integrating palliative care into heart failure care. *Arch Intern Med* 2005;165:374–8.
- 54 Sleeman KE, Gomes B, Higginson IJ. Research into end-of-life cancer care--investment is needed. *Lancet* 2012;379:519.
- 55 Bartz L, Klein C, Seifert A, *et al.* Subcutaneous administration of drugs in palliative care: results of a systematic observational study. *J Pain Symptom Manage* 2014;48:540–7.
- 56 Centre for Palliative Care Research and Education Queensland Health. Management of subcutaneous infusions in palliative care, 2010. Available: [https://www.health.qld.gov.au/\\_\\_data/assets/pdf\\_file/0026/152909/modules.pdf](https://www.health.qld.gov.au/__data/assets/pdf_file/0026/152909/modules.pdf) [Accessed 01 Jan 2021].
- 57 Beattie JM, Johnson MJ. Subcutaneous furosemide in advanced heart failure: has clinical practice run ahead of the evidence base? *BMJ Support Palliat Care* 2012;2:5–6.
- 58 Sleeman KE, Collis E. The Liverpool care pathway: a cautionary tale. *BMJ* 2013;347:f4779.