

## REVIEWS

# Continuous Infusion Versus Intermittent Bolus Furosemide in ADHF: An Updated Meta-Analysis of Randomized Control Trials

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**OBJECTIVE:** Administering intermittent boluses of furosemide to patients with acute decompensated heart failure (ADHF) often leads to unfavorable hemodynamic changes. Continuous infusion may induce similar or greater diuresis without adverse hemodynamic consequences. We conducted a systemic review and meta-analysis of randomized clinical trials that compared the effects of continuous infusion and intermittent bolus of furosemide in patients hospitalized with ADHF.

**METHODS:** We searched PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials databases from their inception until March 2011. Two investigators independently abstracted data on study characteristics, quality, and selected outcomes. Differences between investigators were resolved by mutual consensus. Comparisons were reported as the weighted mean difference (WMDs).

**RESULTS:** Ten trials involving a total of 564 patients were included. When administered as a continuous infusion,

furosemide resulted in greater diuresis (WMD,  $-240.54$  mL/24 hours/100 mg furosemide; 95% confidence interval [CI],  $-462.42$  to  $-18.66$ ) and reduction in total body weight (WMD,  $-0.78$  kg; 95% CI,  $-1.54$  to  $-0.03$ ), than when administered in intermittent boluses. Urinary sodium excretion (WMD,  $-20.26$  mmol/24 hours; 95% CI,  $-60.48$  to  $19.96$ ) and duration of hospital stay (WMD,  $0.99$  days; 95% CI,  $-2.08$  to  $4.06$ ) were not different between the 2 groups.

**CONCLUSION:** This meta-analysis showed statistical support for administering furosemide as a continuous infusion for greater diuresis and reduction in total body weight in patients hospitalized with ADHF. With the exception of greater diuresis, available data are homogenous for the reported outcomes but lack information on clinical endpoints. Larger studies are needed to provide robust recommendations for clinical practice. *Journal of Hospital Medicine* 2012;7:270–275. © 2011 Society of Hospital Medicine.

Acute decompensated heart failure (ADHF) is the most common cause of hospitalization among adults in the United States and is associated with high morbidity and mortality.<sup>1</sup> The estimated direct and indirect cost of ADHF management in the United States was \$40 billion in 2010.<sup>1</sup> There are approximately 5.7 million patients with heart failure in the United States with an annual mortality rate of 300,000 deaths per year.<sup>2</sup> The Healthcare Cost and Utilization Project reported 1.1 million hospital admissions, an average hospital stay of 5.5 days, and 4% in-hospital mortality for patients with heart failure in 2004.<sup>3</sup>

Intravenous administration of loop diuretics is the mainstay of treatment of volume overload in patients hospitalized with ADHF.<sup>4</sup> However, when adminis-

tered as intermittent bolus injections, loop diuretics usually lead to rapid intravascular volume changes,<sup>5</sup> significant electrolyte abnormalities,<sup>6,7</sup> renal dysfunction,<sup>8,9</sup> and undesired neurohormonal activity.<sup>10,11</sup> Compared with intermittent bolus injections, continuous infusion of loop diuretics may induce a more sustained and greater diuresis and fewer electrolyte abnormalities.<sup>12–16</sup> Several studies of limited duration have compared the effectiveness of the 2 routes of intravenous administration of loop diuretics; however, the results of these studies are contradictory.<sup>13,14,17,18</sup> In a meta-analysis, Salvador et al<sup>19</sup> compared the effectiveness of continuous infusion and intermittent bolus injections of loop diuretics. The authors reported greater diuresis (measured as 24-hour urinary output) in patients receiving continuous infusion of loop diuretics. However, the meta-analysis included studies that examined loop diuretics other than furosemide,<sup>20</sup> allowed concomitant use of hypertonic saline infusions,<sup>21</sup> and included patients with pulmonary edema from noncardiogenic causes.<sup>22</sup>

Furosemide is one of the most commonly used loop diuretics.<sup>23</sup> The current literature lacks a systematic review and meta-analysis comparing the effectiveness of continuous infusion and intermittent bolus

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furosemide therapy among nonsurgical, hemodynamically stable, hospitalized patients with ADHF. In addition, several important randomized trials published in recent years comparing the effectiveness of the 2 routes of intravenous furosemide delivery warrant<sup>17,24–27</sup> systematic review, because the last published meta-analysis (by Salvador et al<sup>19</sup>) was in 2005.

We therefore conducted a systematic review and meta-analysis of randomized controlled trials that compared the effects of continuous infusion and intermittent bolus of furosemide in patients hospitalized with ADHF.

## METHODS

### Study Selection

We searched the PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials electronic databases systematically from their inception through March 2011 using the search terms *lasix*, *furosemide*, *diuretic*, *congestive heart failure*, *infusion*, and *bolus*. The electronic database search was supplemented by hand-searching bibliographies of the retrieved articles. Two investigators independently reviewed all retrieved articles for their eligibility based on predefined criteria. Disagreement on study selection was resolved by mutual consensus and by the involvement of a third investigator. All selected studies were assessed for content validity.

We included both crossover and parallel-arm randomized control trials. Studies were included if patients were randomized to intermittent bolus or continuous infusion of furosemide, and data were reported on 24-hour urinary volume, total body weight loss, 24-hour urinary sodium excretion, and duration of hospital stay. Randomized control trials that included patients with cardiogenic shock requiring concomitant vasopressor therapy, renal failure with or without hemodialysis, and loop diuretics other than furosemide were excluded. The primary authors of the included studies were contacted if the results of the selected outcomes either were not reported or required further clarification. A flow diagram was produced following guidelines from The Quality of Reporting of Meta-analyses (QUOROM) group<sup>28</sup> to provide information on randomized clinical trial identification for the final inclusion in the meta-analysis.

### Data Extraction

Data on study design, participant characteristics, methods, intervention, and selected outcomes were independently extracted by 2 investigators. Interobserver agreement for full study selection was calculated using an unweighted kappa statistic. A chi-square test ( $\chi^2$ ) and  $I^2$  statistic were used to report the percentage of variability in the effect estimates across studies.

## Quality Assessment

The quality of included trials was assessed using a validated scale developed by Jadad et al<sup>29</sup> that assigns a score from 0 to 5, with a higher score indicating higher quality. Two investigators independently evaluated studies on 3 parameters: randomization, blinding, and dropouts. The third investigator helped resolve discordant assessments. We assessed publication bias visually by examining the symmetry of funnel plots and statistically using Begg<sup>30</sup> and Egger<sup>31</sup> tests.

## Data Synthesis and Analysis

For the reported outcomes, we recorded the mean difference between the groups and measures of dispersion. If a mean difference was not reported, we calculated point estimates by using the mean difference from baseline for each group. If a mean difference from baseline was not reported, we calculated point estimates using the baseline and final value for each group. If a measure of dispersion was not reported for the between-group difference, we calculated it by using the sum of the variance for the mean difference from baseline in each group. If no measure of dispersion was reported for the mean difference from baseline for each group, we calculated variance by using the standard deviation of the baseline and final values, and assumed a correlation between the baseline and final values of 0.5.

Urinary volume was measured in milliliters per 24 hours per 100 mg furosemide to compare the diuretic effect between the 2 routes of intravenous administration. Total body weight loss was measured in kilograms. Urinary sodium was measured in millimoles per 24 hours, and duration of hospital stay was measured in days.

Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for all prespecified outcomes using Review Manager (RevMan) Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. We pooled results from individual studies using a random-effects model. Statistical significance was set at  $P \leq 0.05$  using a 2-tailed Z-test. Sensitivity analyses were conducted by omitting one study at a time for all outcomes.

## RESULTS

### Study Selection

We identified 104 studies using the previously stated search terms. Following QUOROM guidelines, ten randomized clinical trials, enrolling a total of 564 patients, fulfilled the inclusion criteria (Figure 1). The interobserver agreement (unweighted kappa statistic) between investigators for study selection was 0.75.

### Study Characteristics

The majority of patients were male (60%) with a mean age of 62.8 years (range 54 - 74.1 years). The

duration of follow-up while on furosemide in both arms ranged from twelve hours<sup>24</sup> to six days<sup>13</sup> (Table 1). We found significant variability in dose, frequency, and duration of treatment across studies for both routes of intravenous furosemide administration (Table 2). Four of 10 studies were crossover trials<sup>13,14,18,32</sup> and the rest were parallel-arm trials. Randomization to 1 of the 2 treatment groups was reported in all 4 crossover trials.

**Outcomes**

Data on 24-hour urinary volume were reported in all 10 studies. We found that the continuous infusion of

furosemide was associated with a statistically significant increase in 24-hour urinary output compared with intermittent bolus injections (WMD, -240.54 mL/24 hours/100 mg furosemide; 95% CI, -462.42 to -18.66;  $P = 0.03$ ). There was evidence of statistically significant heterogeneity between the studies for the outcome of 24-hour urinary volume ( $I^2 = 89\%$ ;  $\chi^2 = 93.11$ ;  $P < 0.001$ ) (Figure 2). The magnitude of statistical heterogeneity decreased ( $I^2 = 53\%$ ;  $\chi^2 = 19.11$ ;  $P = 0.02$ ) but remained significant after removing a study by Ostermann et al.<sup>26</sup>

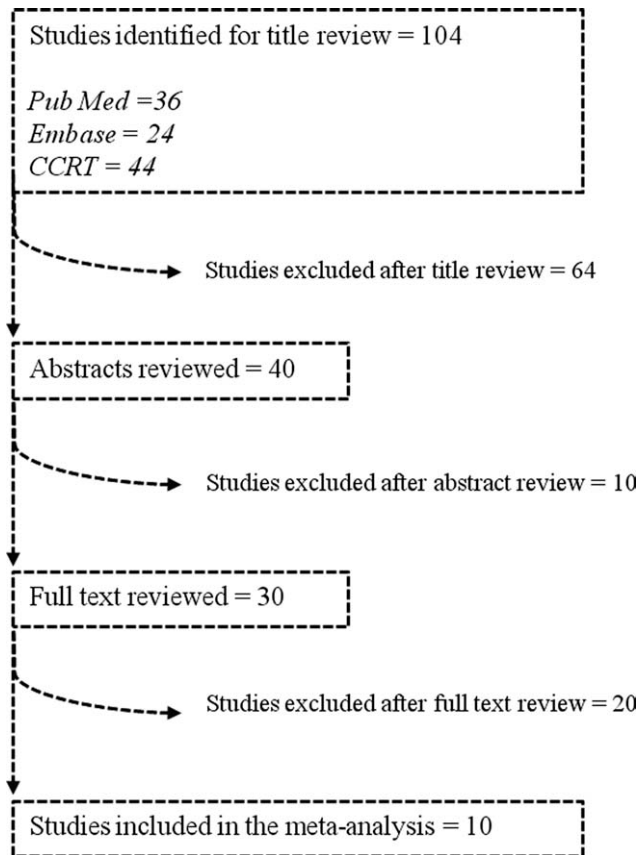
Data on total body weight loss was reported in 3 parallel trials. Patients treated with a continuous infusion of furosemide had statistically greater changes in total body weight (WMD, -0.78 kg; 95% CI, -1.54 to -0.03;  $P = 0.04$ ) when compared with patients receiving bolus injections of furosemide. Data for total body weight loss were collected at 72 hours of treatment in 2 trials<sup>17,27</sup> and was reported for the duration of the entire study by Thomson et al.<sup>25</sup> There was no statistical evidence of heterogeneity between the studies for total body weight loss ( $I^2 = 0\%$ ;  $\chi^2 = 0.66$ ;  $P = 0.72$ ) (Figure 3).

Data on 24-hour urinary sodium excretion was reported for 57 patients in the 4 crossover studies. A continuous infusion of furosemide was associated with a statistically insignificant increase in 24-hour urinary sodium (WMD, -20.26 mmol/24 hours; 95% CI, -60.48 to 19.96;  $P = 0.32$ ). There was no statistical evidence of heterogeneity between studies for 24-hour urinary sodium excretion ( $I^2 = 0\%$ ;  $\chi^2 = 2.76$ ;  $P = 0.60$ ) (Figure 2).

Duration of hospital stay was reported in 3 parallel trials. Patients receiving intermittent injections of bolus furosemide had longer hospital stays (WMD, 0.99 days; 95% CI, -2.08 to 4.06;  $P = 0.53$ ), but this difference was not statistically significant. There was no evidence of heterogeneity between the studies for the duration of hospital stay ( $I^2 = 64\%$ ;  $\chi^2 = 5.51$ ;  $P = 0.06$ ) (Figure 3).

**Risk of Bias and Sensitivity Analysis**

Individual quality assessment scores based on a scoring system developed by Jadad et al<sup>29</sup> for included trials are reported (Table 1). Randomization was



**FIG. 1.** Quality of Reporting of Meta-analysis (QUOROM) flow chart. CCRT: The Cochrane Central Register of Controlled Trials.

**TABLE 1.** Characteristics of Studies Included in the Meta-analysis

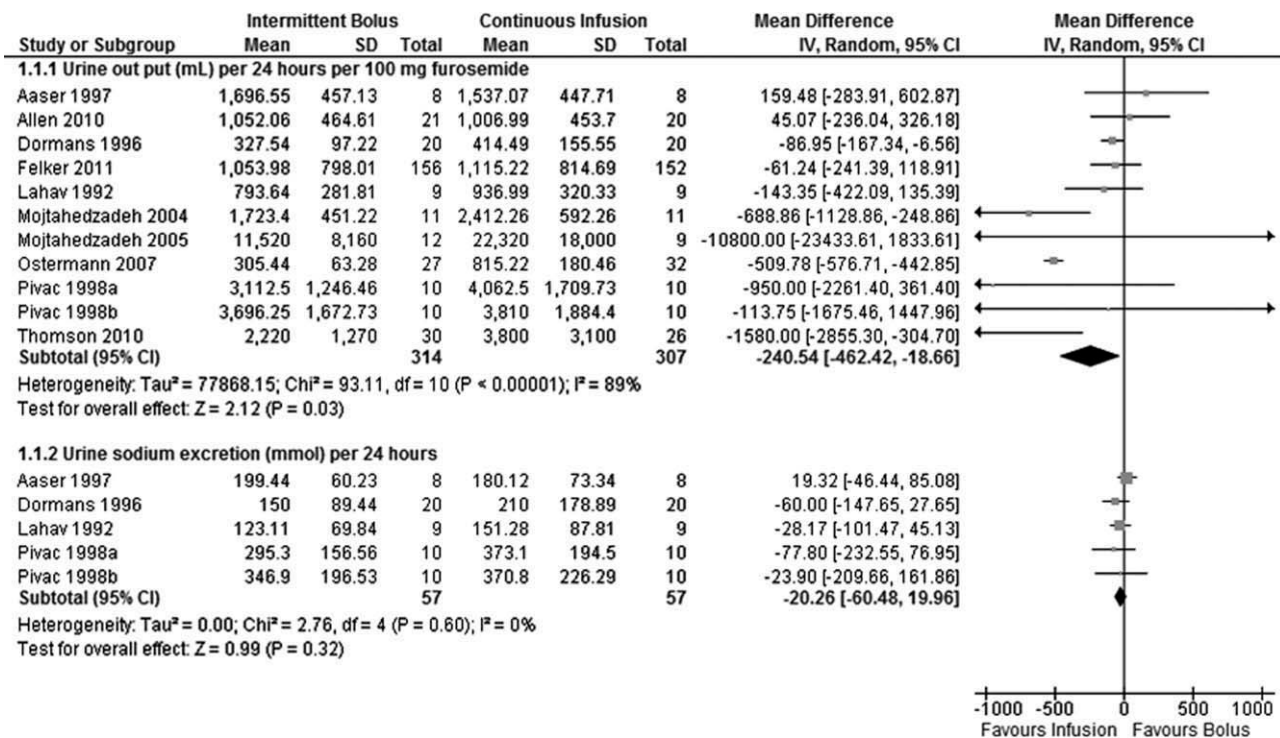
Study	Study Design*	Total (N)	Mean Age (years)	Male (n)	Duration on Furosemide (days)	Country of Study	NYHA Class	Jadad Quality Score
Aaser et al <sup>18</sup>	CO	8	54	6	2	Norway	III-IV	1
Allen et al <sup>17</sup>	PA	41	61	26	2	USA	NR	3
Dormans et al <sup>13</sup>	CO	20	71	13	6	Netherlands	III-IV	1
Felker et al <sup>27</sup>	PA	308	66	226	3	USA	NR	4
Lahav et al <sup>14</sup>	CO	9	74.1	5	4	Israel	III-IV	1
Mojtahedzadeh et al <sup>33</sup>	PA	22	NR	NR	1.5	Iran	NR	2
Mojtahedzadeh et al <sup>24</sup>	PA	21	56.5	11	0.5	Iran	NR	2
Ostermann et al <sup>26</sup>	PA	59	64	31	2	UK/Canada	NR	3
Pivac et al <sup>32</sup>	CO	20	62.2	9	3	Croatia	III	1
Thomson et al <sup>25</sup>	PA	56	56.4	32	3.5-4.6	USA	III-IV	3

Abbreviations: CO, crossover; NR, not reported; NYHA, New York Heart Association; PA, parallel-arm.  
\* Randomized control trials.

**TABLE 2.** Furosemide Dosing from Studies Included in the Meta-analysis

Study	Furosemide Dose (Mean ± SD)		Additional Comments
	Intermittent Bolus	Continuous Infusion	
Aaser et al <sup>18</sup>	145 ± 80 mg bid	145 ± 80 mg/24 hr	Furosemide dose was same as usual daily oral dose
Allen et al <sup>17</sup>	162 ± 48 mg bid	162 ± 52 mg/24 hr	Dose was determined by attending physician after enrolment
Dormans et al <sup>13</sup>	Single bolus of continuous dose	690 mg/8 hr (250–2000 mg)	Patients received additional single oral doses of furosemide on first and second day
Felker et al <sup>27</sup>	134 ± 53 mg/day	127 ± 50 mg/day	Treatment was continued for up to 72 hours; at 48 hours, the treating physician had the option of adjusting the diuretic dose on the basis of clinical response
Lahav et al <sup>14</sup>	30–40 mg/8 hr	60–80 mg/24 hr	Continuous group received 30–40 mg bolus furosemide as loading dose
Mojtahedzadeh et al <sup>33</sup>	320 mg/dose	0.75 mg/kg/hr	All patients received 20 mg of furosemide as initial bolus in both arms
Mojtahedzadeh et al <sup>24</sup>	20 mg initial, then doubled every 3 hr*	0.1 mg/kg/hr (total 250 mg)	Both regimens were titrated for a goal net fluid balance of at least 1 mL/kg/hr
Ostermann et al <sup>26</sup>	0.6–5.14/kg/dose	0.4–0.6 mg/kg/hr	Predefined algorithms aiming for minimum hourly urine output was used in both arms
Pivac et al <sup>32</sup>	40 mg bid	40 mg bid	Goal was to increase urine output to at least 50% from baseline or a minimum of 1 mL/kg/hr
Thomson et al <sup>25</sup>	172 ± 97 mg	197 ± 148 mg/day	The mean duration of study drug administration was shorter by approximately 1 day in the continuous group

Abbreviations: bid, twice a day; SD, standard deviation. \*The maximum amount per dose was 320 mg.



**FIG. 2.** Mean differences in 24-hour urinary volume (mL) and urinary sodium excretion (mmol) in patients treated with intermittent bolus and continuous infusion of furosemide.

reported by all studies, but the explicit methodology of randomization was defined in only 4 studies.<sup>17,25–27</sup> Allocation concealment was defined in 1 study.<sup>26</sup> Dropouts were reported in 4 studies.<sup>24–26,33</sup> Adherence to intervention per study protocol was not reported in any of the selected studies. Three studies mentioned intention to treat.<sup>25,26</sup> Sensitivity analyses demonstrated that the direction of the mean estimates did not change for any of the 4 outcomes when individual studies were excluded.

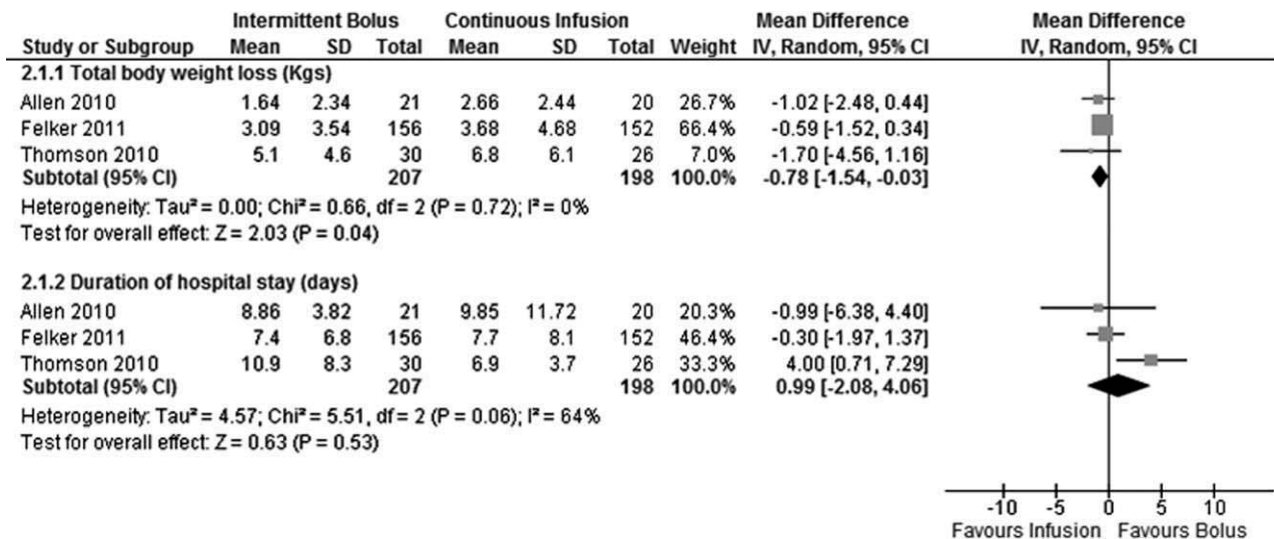
**DISCUSSION**

Our meta-analysis of 10 randomized, controlled clinical trials found that continuous infusion of furosemide results in significantly greater diuresis and reduction

in total body weight than intermittent boluses in patients hospitalized with ADHF. No statistical differences were observed in urinary sodium excretion or the duration of hospital stay between the 2 routes of intravenous furosemide administration. The data on greater diuresis from the available clinical trials was widely heterogeneous that may limit the merits of assessment of greater diuresis between the 2 methods of intravenous furosemide administration. In addition, data on clinical outcomes such as rates of rehospitalization, cardiovascular, and all-cause mortality were not reported in the studies selected for this meta-analysis.

The mean effective dose of loop diuretics administered as intermittent boluses varies widely<sup>5</sup> and





**FIG. 3.** Mean differences in total body weight loss (kg) and duration of hospital stay (days) in patients treated with intermittent bolus and continuous infusion of furosemide.

quickly dissipates to a level that fails to block Na<sup>+</sup> reabsorption in renal tubules.<sup>34</sup> Additionally, the effectiveness of loop diuretics is limited by the rebound in sodium reabsorption during periods of subtherapeutic renal tubular concentration because of their short half-life.<sup>4,6,35</sup> It is possible that the ineffectiveness of subtherapeutic tubular filtrate levels of loop diuretics toward the end of a dosing interval when administered as a bolus is responsible for their unsustained diuretic effects. Bolus injections of furosemide have been associated with diuretic tolerance, reduced short-term natriuresis, and a probable rise in plasma aldosterone levels in the settings of salt restriction.<sup>36</sup> Data from physiological studies suggest that greater diuresis, which also results in weight loss with continuous infusion of loop diuretics, is due to the minimal variation in the mean effective dose of drug in the renal tubules.<sup>12-16</sup> By preventing subtherapeutic tubular dose concentrations, continuous infusion may limit rebound resorption helping to improve symptoms of ADHF.<sup>4</sup>

Our study has several limitations. First, we examined only surrogate endpoints. Second, we included crossover trials<sup>13,14,18,32</sup> in the analysis, and the variation in the washout periods of these trials may have affected the reported outcomes. The study by Aaser et al<sup>18</sup> lacked a washout period because the authors were concerned for the hemodynamic stability of diuretic-dependent ADHF patients. Lahav et al<sup>14</sup> reported a washout period of 3 hours, while Dormans et al<sup>13</sup> and Pivac et al<sup>32</sup> did not report the duration of washout periods. Finally, we excluded studies that enrolled postsurgical patients and patients with pulmonary edema from noncardiac causes. As a result, the generalizability of our findings is limited to relatively stable ADHF patients hospitalized because of medical, dietary, or pharmacological noncompliance. We re-

stricted our analysis to studies using furosemide therapy only. By excluding trials using loop diuretics other than furosemide and trials reporting concomitant use of vasopressors or hypertonic saline in the study population, we are confident in the assessment of the isolated effects of furosemide for either route of its intravenous administration in patients hospitalized with ADHF.

The continuous infusion of furosemide has been well tolerated in most instances.<sup>13,25-27,32</sup> Thomson et al<sup>25</sup> found no difference on the incidence of significant hemodynamic changes or need for renal replacement therapy between the 2 groups. Similarly, Ostermann et al<sup>26</sup> reported no significant differences in heart rate and mean arterial pressures changes from two treatment groups. In addition, Felker et al<sup>27</sup> and Pivac et al<sup>32</sup> found no differences in the proportion of serious adverse effects between the 2 routes of intravenous furosemide administration.

In the absence of information on clinical endpoints such as rehospitalization, all-cause mortality, and cardiovascular mortality, this meta-analysis could not settle the issue to provide definitive recommendations for treatment guidelines to use either route of intravenous furosemide in ADHF patients. However, it is important to note that despite different study populations, our finding of greater diuresis with continuous infusion of furosemide is consistent with results reported by Salvador et al.<sup>19</sup> Given the higher prevalence, mortality, and significant cost related with ADHF management in the United States, we support the use of furosemide as a continuous infusion to ensure limited but established benefits, such as greater diuresis and reduction in total body weight. This approach seems reasonable, especially when the safety profiles between the 2 treatment groups are not different.<sup>25-27,32</sup> However, the benefits on surrogate outcomes cannot be

overstressed due to lack of information on the cost-effectiveness of furosemide or other loop diuretics administered as a continuous infusion.

## CONCLUSIONS

We report a systematic review and meta-analysis comparing the effectiveness of 2 routes of intravenous furosemide administration in patients with ADHF. We found that continuous infusion of furosemide results in greater diuresis and greater reduction in total body weight. With the exception of greater diuresis, available data are homogenous for the reported outcomes in this meta-analysis. Due to lack of information on clinical endpoints and cost-effectiveness from currently available data, robust recommendations for clinical practice guidelines cannot be made at this time. Randomized controlled trials measuring hard clinical endpoints in larger patient populations may add stronger evidence to settle this issue in future. Further studies comparing cost-effectiveness related with continuous infusion of furosemide may provide critical information to establish it as the preferred route over intermittent bolus injection in clinical practice.

Disclosure: The authors have no conflicts of interest to report.

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