

# Efficacy of Intravenous Furosemide Versus a Novel, pH-Neutral Furosemide Formulation Administered Subcutaneously in Outpatients With Worsening Heart Failure

Nisha A. Gilotra, MD,<sup>a</sup> Oluseyi Princewill, MD,<sup>b</sup> Bonnie Marino, RN,<sup>a</sup> Ike S. Okwuosa, MD,<sup>a</sup> Jessica Chasler, PHARM.D,<sup>a</sup> Johana Almansa, DNP,<sup>a</sup> Abby Cummings, CRNP,<sup>a</sup> Parker Rhodes, MS,<sup>a</sup> Julianne Chambers, RN,<sup>a</sup> Kimberly Cuomo, CRNP,<sup>a</sup> Stuart D. Russell, MD<sup>a</sup>

## ABSTRACT

**OBJECTIVES** This study sought to determine the efficacy and safety of a novel, pH-neutral formulation of furosemide administered subcutaneously (SC) for treatment of acute decompensated heart failure (HF).

**BACKGROUND** Congestion requiring intravenous (IV) administration of a diuretic agent is the main reason patients with HF present for acute medical care.

**METHODS** Outpatients presenting with decompensated HF were randomized to receive a single SC or IV dose of furosemide. Primary outcome was 6-h urine output, and secondary outcomes were weight change, natriuresis, and adverse events.

**RESULTS** Forty-one patients were randomized: 19 were treated with IV (mean dose: 123 ± 47 mg) and 21 with SC furosemide (fixed dose of 80 mg over 5 h). The 6-h urine output in the IV group was not significantly different from that in the SC furosemide group (median IV: 1,425 ml; interquartile range [IQR]: 1,075 to 1,950 ml; vs. median SC: 1,350 ml; IQR: 900 to 1,900 ml; p = 0.84). Additionally, mean weight loss was not significantly different (−1.5 ± 1.1 kg in the IV group vs. −1.5 ± 1.2 kg in the SC group; p = 0.95). Hourly urine output was significantly higher in the IV group at hour 2 (425 ml in the IV group vs. 250 ml in the SC group; p = 0.02) and higher in the SC group at hour 6 (125 ml, IV group vs. 325 ml, SC group; p = 0.005). Natriuresis was higher in the SC group (IV: 7.3 ± 35.3 mEq/L vs. SC: 32.8 ± 43.6 mEq/L; p = 0.05). There was no worsening renal function, ototoxicity, or skin irritation with either formulation. Thirty-day hospitalization rates were similar.

**CONCLUSIONS** In this phase II trial, we did not identify significant differences between urine output obtained with pH-neutral furosemide administered SC and that obtained by IV. This method of decongestion may allow treatment at home and reduced HF resources and warrants further investigation. (Sub-Q Versus IV Furosemide in Acute Heart Failure; [NCT02579057](https://doi.org/10.1016/j.jchf.2017.10.001)) (J Am Coll Cardiol HF 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

The heart failure (HF) syndrome is characterized in many patients by a vicious cycle of recurrent congestion (1). This syndrome results in high use of health care resources, with more than 1 million hospitalizations for HF annually

and a 25% 30-day readmission rate (2). Diuretic agents remain the mainstay treatment of both chronic and acute decompensated heart failure (ADHF) (3). The loop diuretic furosemide was first introduced more than 50 years ago. In its oral formulation,

From the <sup>a</sup>Division of Cardiology, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland; and the <sup>b</sup>MedStar Cardiology Associates, MedStar Heart and Vascular Institute, Olney, Maryland. This investigation was supported by scPharmaceuticals. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 19, 2017; revised manuscript received October 3, 2017; accepted October 4, 2017.

**ABBREVIATIONS  
AND ACRONYMS****ADHF** = acute decompensated heart failure**HF** = heart failure**IV** = intravenous**NYHA** = New York Heart Association**SC** = subcutaneous

furosemide has a peak onset of action within 1 to 2 h, which then wanes; however, particularly in the setting of worsening edema of the gut, oral absorption can be quite erratic (4). Therefore, in these situations, patients may require intravenous (IV) diuretic therapy, often resulting in HF hospitalization. In fact, nearly 90% of patients with ADHF are treated with IV loop diuretics (5). With the rising cost of HF hospitalization (6), novel strategies are being used worldwide to keep HF patients out of the hospital. In 2012, we established the Johns Hopkins Heart Failure Bridge Clinic (HFBC), an outpatient HF disease management program with the ability to administer IV diuretics. In 2016, we administered IV furosemide 441 times. Other studies have shown that such a strategy is safe and results in significant urine output (7). However, this therapy still requires a clinic visit, use of resources, patient inconvenience, and peripheral IV catheter placement.

Furosemide for injection (or furosemide USP) has an alkaline pH ranging from 8.0 to 9.3, thus limiting the ability to administer the drug subcutaneously (SC) due to discomfort upon injection and local skin irritation (8). A novel, buffered, pH-neutral formulation of furosemide was developed for SC administration (scFurosemide, product SCP-101, scPharmaceuticals, Lexington, Massachusetts) with the aim of developing an alternative to IV furosemide that could ultimately be used by patients outside the acute care setting. scFurosemide injection (80 mg/0 ml) is administered by SC infusion, with 30 mg delivered in the first hour and 12.5 mg/h delivered for the subsequent 4 h for a total dose of 80 mg. The SC infusion has been demonstrated to be well tolerated and can achieve therapeutic drug levels in stable chronic HF subjects (9). We sought to study the efficacy and safety of scFurosemide administered SC in patients with worsening HF requiring IV diuresis in the outpatient clinic.

**METHODS**

**STUDY DESIGN.** This was a randomized proof-of-concept pilot study.

**STUDY PARTICIPANTS.** Adult outpatients who presented to the HFBC with a history of HF treatment of least 3 months or HF hospitalization within 60 days and who were identified by providers as requiring IV diuresis for worsening HF were eligible for the study. Patients were categorized as New York Heart Association functional classes II to IV with signs and/or symptoms of volume overload. Exclusion criteria were as follows: patients presenting with signs or

symptoms where chance of hospitalization was high, such as myocardial ischemia, uncontrolled arrhythmia, infection, fever  $>101^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ), hemodynamic instability (systolic blood pressure  $\leq 80$  mm Hg, symptomatic hypotension, diastolic blood pressure  $\geq 120$  mm Hg, or evidence of hypertensive urgency or emergency), respiratory compromise, mental status changes, acute kidney injury defined as  $>25\%$  increase in serum creatinine from baseline, hypokalemia defined as serum potassium  $<4.0$  mmol/l, patients receiving experimental medication therapy or currently participating in another cardiovascular research study, presence of or need for urinary bladder catheterization, urinary tract abnormality or disorder interfering with urination, or allergy to loop diuretics. Subjects were enrolled from February 2016 to April 2017, and all participants provided written informed consent. Patients could only be enrolled in the study once during the study period. The study was approved by the Johns Hopkins Institutional Review Board.

**RANDOMIZATION AND TREATMENT ADMINISTRATION.**

Subjects were randomly assigned, in a 1:1 ratio, to receive a single dose of IV furosemide or scFurosemide. Randomization was performed using block-stratified assignments by using a computerized pseudorandom number generator by the Johns Hopkins Hospital Investigational Drug Service, which dispensed study drug and was blinded to clinical outcomes. All subjects underwent examinations for baseline vital signs, weight, and laboratory testing (including serum sodium, potassium, creatinine, pro-B-type natriuretic peptide [proBNP] and urinary sodium concentrations). All laboratory testing occurred at the Johns Hopkins core laboratory. Subjects randomized to IV therapy underwent usual care, with placement of peripheral IV catheter and administration of diuretic agent as an IV bolus. Dose was calculated based on the subject's outpatient oral dose, typically with a 1:1 conversion, with a maximum IV dose of 160 mg. The SC group received 80 mg of scFurosemide administered over 5 h (30 mg in the first hour, followed by 12.5 mg/h for 4 h) by using an infusion pump system (Perfusor space infusion pump, B. Braun Medical, Bethlehem, Pennsylvania) and a standard commercial infusion set. Subjects also received potassium or magnesium supplementation according to standard of care protocol in the diuresis clinic. Subjects vital signs (blood pressure and heart rate) and urine output were monitored for 6 h. Subjects urinated in a pre-specified container with marked milliliter measurements, either at bedside or in a restroom facility located in the clinic room itself. Urine output was measured and recorded by a clinic

staff member on an hourly basis over the 6-h study observation period. During diuretic administration, all patients underwent a 100-ml fluid consumption restriction. At 6 h, patients' weight measurements and laboratory testing were repeated. They were monitored for side effects and adverse events, including access site discomfort (burning, itching, pain, and rash), ototoxicity, change in renal function and potassium concentrations, and symptoms of positional lightheadedness. Subjects were then discharged from the clinic, and were followed for clinical events for 30 days.

**ENDPOINTS.** The primary outcome was volume of urine output at 6 h. Secondary outcomes included weight change, hourly urine output, natriuresis, frequency of adverse events, and 30-day hospitalization rate. A follow-up telephone call and medical chart review were performed at 1, 7, and 30 days to assess for side effects, further IV diuretic needs, and hospitalization.

**SAMPLE SIZE.** Based on experience in the clinic, we estimated the 6-h urine output to be approximately 1,200 ml in the IV group. We considered a difference in urine output of 500 ml to be clinically significant. Using a SD of 500 ml, we estimated we would need approximately 20 patients in each group to have 80% power to detect a clinically significant difference in 6-h urine output between the IV and SC groups.

**STATISTICAL METHODS.** The Shapiro-Wilk test was used to determine data distribution. Parametric continuous variables are given as mean  $\pm$  SD, and nonparametric continuous variables are reported as medians and interquartile ranges. Comparisons were made using the Student *t* or Wilcoxon rank sum tests. Categorical variables are presented as percentages and were compared using the chi-squared test. The pre-specified threshold for significance was a *p* value  $<0.05$ . All statistical analyses were performed using STATA version 13 software (Stata Corp., College Station, Texas).

## RESULTS

Forty-one patients were enrolled in the study. One patient was a screen failure after randomization and prior to receiving study drug due to lack of need for IV diuretic on reassessment. Twenty-one patients received SC furosemide, and 19 patients received IV furosemide. The mean IV dose administered was  $123 \pm 47$  mg, with 58% of subjects receiving the maximum dose of 160 mg.

Baseline characteristics are described in [Table 1](#). Study subjects were average  $57 \pm 13$  years of age, 55%

**TABLE 1** Baseline Characteristics and Pre-Diuresis Assessment

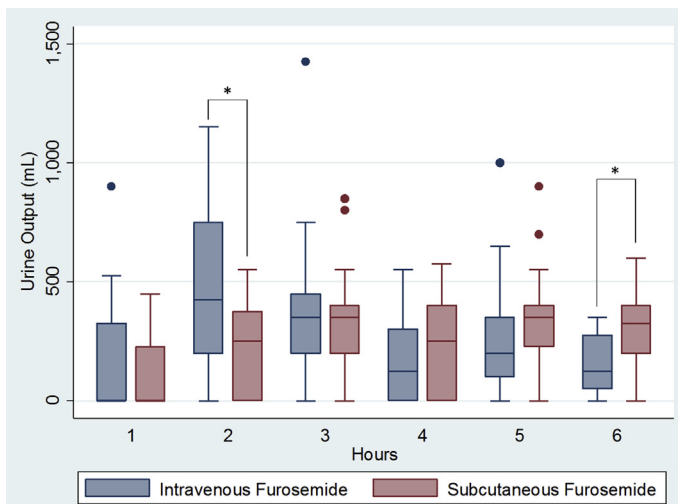
	IV n = 19	SC n = 21	Total N = 40
Age, yrs	54 $\pm$ 13	59 $\pm$ 13	57 $\pm$ 13
Females	9 (47)	13 (62)	22 (55)
Race			
White	5 (26)	8 (38)	13 (33)
Black	14 (74)	12 (57)	26 (65)
Asian	0 (0)	1 (5%)	1 (2.5)
Body mass index, kg/m <sup>2</sup>	39.7 $\pm$ 11.2	37.8 $\pm$ 11.3	38.7 $\pm$ 11.2
Comorbidities (%)			
Atrial fibrillation	6 (32)	7 (33)	13 (33)
Coronary artery disease	8 (42)	6 (29)	14 (35)
Diabetes mellitus	12 (63)	7 (33)	19 (48)
Chronic kidney disease	9 (47)	11 (52)	20 (50)
Chronic obstructive pulmonary disease	4 (21)	4 (19)	8 (20)
Hypertension	12 (63)	18 (86)	30 (75)
Left ventricular ejection fraction, % (median IQR)	20 (20-55)	25 (15-55)	25 (15-55)
Heart failure with preserved ejection fraction	5 (26)	8 (38)	13 (33)
Amyloid	2 (11)	0 (0)	2 (5)
Furosemide daily dose, mg	228 $\pm$ 174	261 $\pm$ 164	246 $\pm$ 167
Beta-blocker	15 (79)	16 (76)	31 (78)
ACE-inhibitor/ARB	10 (53)	13 (62)	23 (58)
Aldosterone antagonist	7 (37)	8 (38)	15 (38)
New York Heart Association functional class			
II	7 (37)	5 (24)	12 (30)
III	11 (58)	13 (62)	24 (60)
IV	1 (5)	3 (14)	4 (10)
Systolic blood pressure, mm Hg	118 $\pm$ 21	124 $\pm$ 26	121 $\pm$ 24
Diastolic blood pressure, mm Hg	68 $\pm$ 13	72 $\pm$ 14	70 $\pm$ 14
Heart rate, beats/min	86 $\pm$ 16	83 $\pm$ 16	85 $\pm$ 16
S <sub>3</sub> heart sound	2 (11)	0 (0)	2 (5)
Jugular venous distention*	12/16 (75)	17/19 (90)	29/35 (83)
Rales/diminished breath sounds	5 (26)	12 (57)	17 (43)
Lower extremity edema	16 (84)	18 (86)	34 (85)
Dyspnea on exertion	18 (95)	21 (100)	39 (98)
Orthopnea/paroxysmal nocturnal dyspnea	9 (47)	12 (57)	21 (53)
Fatigue	8 (42)	8 (38)	16 (40)
Serum sodium, mmol/l	139 (137-142)	139 (137-140)	139 (137-142)
Creatinine, mg/dl	1.2 (0.9-1.6)	1.3 (0.9-1.7)	1.3 (0.9-1.7)
Glomerular filtration rate, ml/min/1.73 m <sup>2</sup> †	67 $\pm$ 32	57 $\pm$ 21	62 $\pm$ 53
proBNP, pg/dl	1,556 (198-3,449)	1,545 (501-3,123)	1,551 (435-3,278)

Values are mean  $\pm$  SD, n (%), or median (IQR). \*Presence or absence of jugular venous distention reported in 16 and 19 subjects in the IV and SC groups, respectively. †Calculated using the Modification of Diet in Renal Disease Study equation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; IQR = interquartile range; IV = intravenous; proBNP = pro-B-type natriuretic peptide; SC = subcutaneous.

were female; and the average body mass index was  $38.7 \pm 11.2$  kg/m<sup>2</sup>. The mean home oral furosemide daily dose was  $246 \pm 167$  mg. No meaningful baseline clinical differences were observed between IV and SC groups ([Table 1](#)).

After study drug administration, median 6-h urine output in the IV group was not significantly

**FIGURE 1** Hourly Urine Output With Diuresis

Boxes show the median hourly urine output in intravenous (blue) and subcutaneous (red) furosemide groups as shown by the line inside the box. Box limits depict the interquartile range. \* $p < 0.05$ , using Wilcoxon rank sum test comparing intravenous with subcutaneous furosemide.

different than that in the SC group (IV: 1,425 ml; IQR: 1,075 to 1,950 ml vs. 1,350 ml in the SC group; IQR: 900 to 1,900 ml;  $p = 0.84$ ). Mean urine output in the IV group also did not differ significantly from that in the SC group (IV: 1,636 ml; 95% confidence interval [CI]: 1,182 to 2,089 ml vs. SC: 1,514 ml; 95% CI: 1,182 to 1,847 ml; mean difference between groups: 121 ml; 95% CI: -415 to 658 ml;  $p = 0.649$ ). Maximum 6-h urine output was 4,325 ml in the IV group and 3,200 ml in the SC group. Hourly urine output was significantly lower in the SC group at hour 2 (IV: 425 ml vs. SC: 250 ml;  $p = 0.02$ ) and higher in the SC group at hour 6 (IV: 125 ml vs. SC: 325 ml;  $p = 0.005$ ) (Figure 1).

Weight loss between the 2 groups was not significantly different (IV:  $-1.5 \pm 1.1$  kg vs. SC:  $-1.5 \pm 1.2$  kg;  $p = 0.95$ ). There was a trend toward increased natriuresis, as measured by change in urinary sodium concentration, in the SC group (IV:  $7.3 \pm 35.3$  mEq/l; vs. SC:  $32.8 \pm 43.6$  mEq/l;  $p = 0.05$ ). Serum creatinine concentration decreased post-diuresis to a similar extent in both groups (IV:  $-0.07 \pm 0.14$  mEq/l vs. SC:  $-0.05 \pm 0.16$  mEq/dl;  $p = 0.70$ ). Although the percent change in baseline proBNP concentration decreased in the IV group ( $-2 \pm 14$  mEq/l) and increased in the SC group ( $+3.5 \pm 13$  mEq/l), the difference was not statistically significant ( $p = 0.21$ ).

There were no events of worsening renal function, severe electrolyte disturbances, arrhythmia, ototoxicity, or skin irritation with either formulation. There

was 1 case of mild hypokalemia in the SC group, in which the pre-diuresis serum potassium concentration of 4.1 mEq/l fell to 3.3 mEq/l.

At 1-, 7- and 30-day follow ups, no patients in the SC group reported delayed skin irritation or pain at infusion site after leaving the clinic. There was a 42% ( $n = 8$  of 19 subjects) 30-day hospitalization rate in the IV group compared with a 52% ( $n = 11$  of 21 subjects) 30-day hospitalization rate in the SC group ( $p = 0.55$ ). Within 7 days of study drug administration, 6 subjects in the IV group and 10 in the SC group ( $p = 0.35$ ) required repeat IV diuretic administration in the clinic or emergency department or were admitted.

## DISCUSSION

There have been limited advancements in diuretic therapy in decompensated HF, despite diuretics serving as the mainstay for relief of congestion for several decades. This is the first study to examine the efficacy of a novel SC formulation of the loop diuretic furosemide administered by 5-h fixed-dose infusion in patients presenting with worsening HF in the outpatient setting. We found that the 80-mg 5-h infusion of scFurosemide achieved diuresis and weight change similar to and effectively as that of IV furosemide at an average 50% higher dose, without any differences in adverse events.

The biphasic diuretic administration regimen used in this study was designed to achieve maximum diuretic efficiency, that is, milliliters of urine output per milligram of drug. We were initially concerned that using only 80 mg of SC furosemide would be an insufficient amount of furosemide as many of our patients were receiving higher oral doses. The 80-mg dose is a fixed dose determined by tolerability studies of the volume of drug that can be infused and by pharmacokinetic studies showing a sustained therapeutic drug level. Despite the fact that the IV group received a greater average dose of furosemide, there were no differences in urine output volume at 6 h. Buckley et al. (7) administered a total IV bolus dose of 260 mg of furosemide followed by an infusion strategy to a similar patient population and demonstrated a median urine output of 1,045 ml over the course of a clinic visit. Based on our current study, 80 mg SC furosemide administered in this biphasic regimen is clearly an efficacious dose for HF patients with acute volume overload.

The efficacy of the lower SC dose is in part due to its better bioavailability, in addition to the slow infusion design. In a small study of healthy volunteers, low-dose SC furosemide (20 mg) produced both

diuretic ( $1,430 \pm 504$  ml vs.  $459 \pm 279$  ml urine output;  $p < 0.05$ ) and natriuretic ( $134 \pm 31$  mEq/l vs.  $29 \pm 17$  mEq/l urine sodium;  $p < 0.05$ ) effects compared with placebo (8). A study using a continuous SC infusion by using an elastomeric pump for 4 to 5 days demonstrated a significant weight change from baseline of 79.4 kg to 77.3 kg (10). Prior studies of oral furosemide have demonstrated low bioavailability (72%) with wide variability within individual patients (11). Using the SC formulation studied and administered at the same doses as in the current study, scFurosemide has been shown to achieve therapeutic plasma levels within 30 min of administration as well as nearly 100% bioavailability (9). In comparison, the mean bioavailability of the oral formulation was 61% of the SC formulation. Compared with both oral and IV formulations in pharmacokinetic studies, the SC groups avoided peak concentrations and demonstrated a constant rate of absorption (9). In our study, subjects in the scFurosemide group had more robust hourly urine output later in the 6-h observation window than that in the IV group. This difference may reflect the more consistent drug level attained by SC formulation than that in the early peak seen with bolus IV administration. It is also possible that the SC group would have had ongoing diuresis and greater total urine output over a longer window of time (8 to 12 h), given the later peak in urine output in the SC group seen in this study. Additionally, despite the average body mass index of  $38.7 \pm 11.2$  kg/m<sup>2</sup> in our study subjects, the SC group had an equally robust urinary and a greater natriuretic response than that in the IV group. This further emphasizes the efficacy of the SC route of administration. Further study is needed to assess the delayed (previous 6-h) effects of SC furosemide.

Prior formulations of SC furosemide have been limited by the alkaline pH, allowing only low-volume injection and causing frequent administration site burning and stinging (8,12). Alternative strategies to administration of the SC formulation have been the use of an elastomeric pump; however, that too has limitations as it requires catheter placement and continuous infusion and has been complicated by frequent site reactions including abscess formation (10,12). In an attempt to address some of these hurdles to SC administration of furosemide, the scFurosemide used in this study was developed with a physiologic pH of 7.4 and the ability to administer it through an infusion pump. Notably, there were no skin administration site reactions or patient reports of discomfort acutely or at follow-up. This new mode of furosemide administration therefore seems to have

eliminated prior concerns of skin irritation and infusion intolerance.

Acute HF is a burgeoning epidemic and accounts for more than 1 million hospitalizations annually in the United States (2). Additionally, 25% of patients hospitalized with HF are readmitted within 30 days of discharge (13). HF health care costs are expected to approach \$70 billion by 2030 (6). The main driver for these HF presentations is congestion that necessitates IV diuretic therapy in a hospital or clinic setting with a certified health care professional. Therefore, the potential use of SC rather than IV furosemide in the management of volume overload has significant clinical implications by shifting treatment outside the hospital setting.

Already, SC medications are used in patients under palliative or hospice care, to avoid venous access and improve patient comfort. Small retrospective case series have demonstrated the efficacy of SC administration of furosemide in end-stage HF patients to relieve dyspnea and congestion in home or hospice settings (14-16). Our study expands the possibility of applying this novel treatment strategy in patients with less advanced HF presenting to the outpatient clinic with an acute decompensation, who can be treated and discharged home without an admission. Ultimately, the goal would be to send patients home with SC furosemide or to prescribe the medication without the patient having to come in to the clinic or hospital. The current need for patients to present to a clinical setting naturally delays diuretic administration, and it has recently been demonstrated that earlier administration of diuretics in the emergency department is associated with improved outcomes in cases of worsening HF (17). The furosemide formulation in this study is being developed to be administered through a wearable SC drug delivery infusor (i.e., a patch pump) for use outside the acute care setting. This strategy's safety and impact on use of resources warrants future investigation.

**STUDY LIMITATIONS.** It was a small, single-center study carried out at an urban tertiary care center, thus potentially limiting generalizability. However, it is the largest study of its nature, assessing the SC administration of furosemide in patients with ADHF, and the first study to evaluate a novel, pH-neutral formulation of furosemide in patients with volume overload presenting to an outpatient HF clinic. Additionally, this was a high-risk outpatient HF cohort, in which nearly half the patients required hospitalization during study follow-up. This likely speaks to the population treated in the HFBC but also

to study design, which required subjects to remain in clinic for 6 h, thus limiting participant enrollment perhaps to those patients who are seen frequently for IV diuresis and are, therefore, at higher risk for future diuresis need or hospitalization. Although the longer administration time of the SC formulation may be seen as a barrier to widespread use, the benefit of 5-h administration is the maximization of diuretic efficiency, which allows a more steady-state concentration and prolonged diuresis, as we demonstrate.

## CONCLUSIONS

This study, the first in outpatients with worsening HF, demonstrated clinical efficacy and safety of SC administration of furosemide that was comparable to that of IV furosemide. We describe the first clinical comparison between the fixed dose of a novel, pH-neutral formulation of furosemide and our standard regimen, which involved IV administration of a dose that was approximately 50% higher. The findings of this study corroborate the design premise that a higher diuretic efficiency can be achieved by slower infusion compared to that of the IV bolus. Additionally, these results have significant implications for the outpatient management of HF. Future

investigation is required to assess home self-administration of scFurosemide and its potential effects on HF hospitalization reduction.

**ACKNOWLEDGMENT** The authors thank Kenneth Shermock, PharmD, PhD (Johns Hopkins School of Public Health) for reviewing the manuscript.

**ADDRESS FOR CORRESPONDENCE:** Dr. Nisha A. Gilotra, Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, 600 North Wolfe Street, Carnegie Building, Suite 568c, Baltimore, Maryland, 21287. E-mail: [naggarw2@jhmi.edu](mailto:naggarw2@jhmi.edu).

## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

In patients with worsening HF, fixed-dose SC administration of scFurosemide resulted in diuresis that was similar to bolus dose IV furosemide.

**TRANSLATIONAL OUTLOOK:** Future studies are needed to assess the use of scFurosemide at home and the impact of such an intervention on outcomes in patients with HF.

## REFERENCES

- Gheorghide M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: An essential target of evaluation and treatment. *Am J Med* 2006;119:53-10.
- Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;133:447-54.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2013;62:e147-239.
- Gottlieb SS, Khatta M, Wentworth D, Roffman D, Fisher ML, Kramer WG. The effects of diuresis on the pharmacokinetics of the loop diuretics furosemide and torsemide in patients with heart failure. *Am J Med* 1998;104:533-8.
- Peacock WF, Costanzo MR, De Marco T, et al. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology* 2009;113:12-9.
- Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606-19.
- Buckley LF, Carter DM, Matta L, et al. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. *J Am Coll Cardiol HF* 2016;4:1-8.
- Verma AK, da Silva JH, Kuhl DR. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. *Ann Pharmacother* 2004;38:544-9.
- Sica DD, Muntendam P, Myers RL, et al. Subcutaneous furosemide in heart failure: pharmacokinetic characteristics of a newly buffered solution. *JACC Basic Transl Sci* 2017. In press.
- Zatarain-Nicolás E, López-Díaz J, de la Fuente-Galán L, García-Pardo H, Recio-Platero A, San Román-Calvar JA. Subcutaneous infusion of furosemide administered by elastomeric pumps for decompensated heart failure treatment: initial experience. *Rev Esp Cardiol* 2013;66:1002-4.
- Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clinical Pharmacol Ther* 1995;57:601-9.
- Goenaga MA, Millet M, Sanchez E, Garde C, Carrera JA, Arzellus E. Subcutaneous furosemide. *Ann Pharmacother* 2004;38:1751.
- Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009;360:1418-28.
- Farless LB, Steil N, Williams BR, Bailey FA. Intermittent subcutaneous furosemide: parenteral diuretic rescue for hospice patients with congestive heart failure resistant to oral diuretic. *Am J Hosp Palliat Care* 2013;30:791-2.
- Galindo-Ocana J, Romero-Mena J, Castillo-Ferrando JR, Aguilera-Gonzalez C, Bernabeu-Wittel M, Ollero-Baturone M. Subcutaneous furosemide as palliative treatment in patients with advanced and terminal-phase heart failure. *BMJ Support Palliat Care* 2013;3:7-9.
- Zacharias H, Raw J, Nunn A, Parsons S, Johnson M. Is there a role for subcutaneous furosemide in the community and hospice management of end-stage heart failure? *Palliat Med* 2011;25:658-63.
- Matsue Y, Damman K, Voors AA, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;69:3042-51.

**KEY WORDS** congestion, disease management, diuretic, drug delivery, subcutaneous