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Review Article

From Oral to Subcutaneous Furosemide: The Road to Novel Opportunities to Manage Congestion

Garima Dahiya, MD [a], Daniel Bensimhon, MD [b], Matthew M. Goodwin, PharmD [c], John F. Mohr, PharmD [c], Tamas Alexy, MD, PhD [a,*]

[a] Division of Cardiology, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA
[b] Division of Cardiovascular Medicine, Cone Health, Greensboro, North Carolina, USA
[c] Clinical Development and Medical Affairs, scPharmaceuticals, Burlington, Massachusetts, USA

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ABSTRACT

The steadily rising prevalence of heart failure (HF) and the associated increase in health care expenditures represent a significant burden for patients, caregivers, and society. Ambulatory management of worsening congestion is a complex undertaking that requires diuretic escalation, yet clinical success is often hindered by the progressively declining bioavailability of oral agents. Once beyond a threshold, patients with acute on chronic HF often require hospital admission for intravenous diuresis. A novel, pH neutral formulation of furosemide that is administered by a biphasic drug delivery profile (80 mg total over 5 hours) via an automated, on-body infusor was designed to overcome these limitations. Early studies have shown that it has equivalent bioavailability with comparable diuresis and natriuresis to the intravenous formulation, leads to significant decongestion, and improvement in quality of life. It was shown to be safe and is well tolerated by patients. Although there is one ongoing clinical trial, available data have demonstrated the potential to shift hospital-administered, intravenous diuresis to the outpatient setting. Reduction in the need for recurrent hospital admissions would be highly desirable by most patients with chronic HF and would lead to a significant reduction in health care expenditures. In this article, we describe the rationale and evolution of this novel PH neutral formulation of furosemide administered subcutaneously, summarize its pharmacokinetic and pharmacodynamic profiles, and review emerging clinical trials demonstrating its clinical safety, efficacy, and potential to reduce health care expenditures.

ABBREVIATIONS

ED, emergency department; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; QOL, quality of life; SC, subcutaneous.

Introduction

Heart failure (HF) is a highly heterogenous clinical syndrome that represents a significant public health burden. It is estimated that more than 6.2 million individuals aged >18 years were affected in 2018 within the United States alone and its prevalence is expected to increase beyond 8 million by 2030.[1] By the same year, the annual expenditures attributed to HF-related health care delivery are estimated to reach $70 billion.[2,3] A significant proportion of this cost is encountered in the setting of repeated and often prolonged hospital admissions, as patients enter the later stages of the disease process.[4,5] HF is a phenotypically progressive disease, wherein structural or functional maladaptation and neurohormonal activation leads to a perpetuating cascade of myocardial remodeling, altered ventricular geometry, and worsening cardiac contractility or relaxation.[6] The resultant elevation in cardiac filling pressures leads to typical signs and symptoms of HF and, ultimately, hospitalization to administer decongestive therapies.[7] In the setting of an aging population, increasing frailty, and growing burden of comorbidities, there has been an alarming rise in the prevalence of admissions for decompensated HF in the United States and across Europe.[8,9] Not only does this have a profound negative impact on patient life expectancy and quality of life (QOL), but it also poses a significant burden in the health care system. Especially in the setting of limited bed availability plaguing hospital systems in the post-COVID era, it is critical to develop novel tools

* Address correspondence to: Tamas Alexy, MD, PhD, Division of Cardiology, Department of Medicine, University of Minnesota, 420 Delaware St SE, MMC 508, Minneapolis, MN 55455.
E-mail address: alexy001@umn.edu (T. Alexy).

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and strategies to address this unfavorable trend and increasingly shift HF care delivery to the outpatient setting.

The presenting symptoms for most patients with HF are related to congestion and include dyspnea, orthopnea, bendopnea, reduced exercise tolerance, lower extremity edema, abdominal bloating, and weight gain.[10] Accordingly, the fundamental aspect of ambulatory congestion management is to address volume overload through diuretic augmentation and titration to improve symptoms and to reduce the need for hospital admission. However, the strategy often fails due to various factors or their combination, such as the unpredictable, reduced, and highly variable oral bioavailability of furosemide especially with worsening intestinal edema, and impaired drug secretion into the renal tubules.[11-13] Sequential nephron blockade with the addition of a thiazide agent may be effective temporarily; however, the combination increases the risk for renal dysfunction, severe electrolyte disturbances (which can predispose to life-threatening arrhythmias), and gout.[14,15] At this stage, patients with acute decompensated HF will typically require hospital admission for parenteral diuretic therapy. This is not only associated with worse clinical outcomes but also impacts the patients'/caregivers' QOL and drives up health care costs significantly.[2,4,5,10] Therefore, there is a critical need to find alternative solutions to hospital-based decongestion. Several large health care systems across the United States have established outpatient centers for intravenous (IV) diuretic administration. Although this strategy has been shown to decrease HF hospitalizations, its generalizability is limited because of the extensive supporting infrastructure requirements and the need for dedicated health care professionals to oversee patient care.[16-19] In addition, research has shown that congested patients who received only a single dose of IV diuretic in an outpatient HF clinic still had a 30-day readmission rate >40%.[20]

Subcutaneous (SC) furosemide is a novel, pH neutral formulation of the well-established diuretic that can be self-administered and circumvents many of the limitations associated with oral administration. It has the potential to fill a large, unmet gap in the ambulatory management of patients with congestion. In this review, we explore the evolution, pharmacokinetics, pharmacodynamics, and safety profile of the novel SC furosemide formulation and review the clinical evidence available to date supporting its use in HF patients with congestion.

Mechanism of Action and Routes of Furosemide Administration

Furosemide is a potent loop diuretic that was first approved by the Food and Drug Administration for medical use in 1966. It is an organic anion that binds to plasma proteins with high affinity, limiting its volume of distribution.[11,21] Furosemide reaches the lumen of the renal proximal convoluted tubule from the circulation through the combination of glomerular filtration and active secretion facilitated by organic anion transporters.[11,22] It acts by inhibiting the sodium-potassium-chloride cotransporters (Na^+-K^+-2 Cl^-) in the thick ascending limb of the loop of Henle and macula densa.[11,22] This results in excessive excretion of sodium, chloride, magnesium, and calcium, along with water.[11,23]

Various formulations of furosemide are currently approved for the management of patients with HF and fluid retention, including oral, intramuscular, and IV. Although oral administration is the only currently feasible option at home, the development of venous congestion and impaired renal perfusion in the setting of worsening HF leads to reduced and highly variable bioavailability ranging between 10% and 90%, with a mean of 50%.[10,11] The ensuing reduced peak plasma concentration adversely impacts the steep dose-response curve and, therefore, clinical efficacy. The resultant relative diuretic resistance often mandates IV administration to achieve appropriate diuresis and clinical improvement.

Alternative loop diuretics, such as oral bumetanide and torsemide, consistently have almost complete bioavailability (80%-100%) compared with IV formulations and reach peak serum concentration more rapidly than furosemide.[12] In addition, the absorption of these agents is significantly less affected by food intake or intestinal edema, a common phenomenon associated with congestion.[10,15] Consequently, bumetanide and torsemide have more predictable diuretic and natriuretic effect than furosemide, often making them the preferred agents for patients with recurrent HF exacerbations.[10,24]

Chronic loop diuretic therapy may lead to the "*braking phenomenon*," a significant reduction in their efficacy due to enhanced sodium reabsorption in the distal renal tubules caused by hypertrophy and hyperplasia of the epithelial cells.[15] This may potentially negate the intended therapeutic effect of the diuretic prompting dose escalation, switching to an alternative agent, or addition of a thiazide to achieve sequential nephron blockade.[10,15] However, side effects, such as severe electrolyte derangements, are increasingly common with such interventions and often limit safe outpatient management. In addition, a ceiling effect is often reached with the administration of oral agents that may only be circumvented by changing the mode of drug delivery to the IV or SC route.

Challenges With Subcutaneously Delivered Traditional Furosemide

Given the logistical challenges associated with IV diuresis, such as the need for emergency department (ED)/infusion center visit or hospital admission, SC drug delivery has been attempted as an alternative mode of therapy. The diuretic efficacy of subcutaneously administered furosemide was first evaluated in healthy volunteers in a single-center, double-blind, randomized, cross-over pilot study in 2004.[25] Twenty milligram of furosemide (2 mL) or equal volume of 0.9% NaCl was given SC by investigators, and voided urine volume, urine sodium concentration, and effect onset time were compared. The differences in all end points were statistically significant ($p < 0.05$), suggesting that SC furosemide administration is feasible and efficacious.[25] However, participants noted transient injection site burning, pain, and skin irritation related to the alkaline pH of the parenteral solution (pH: 8.0-9.3).[25]

Over the ensuing decade, multiple retrospective cohort studies assessed the diuretic efficacy of furosemide administered SC in patients with HF.[26-31] The target populations were primarily those with end-stage disease to maximize time spent at home and to prevent "revolving door"–style prolonged hospital admissions. For instance, Zacharias et al. evaluated the impact of continuous SC furosemide infusion in 32 patients with end-stage HF (43 total episodes of severe congestion) on improving volume status, weight loss, and preventing hospitalizations. The study was run as a multidisciplinary team approach between cardiology and palliative care services.[26] The total daily dose of furosemide ranged from 40 mg to 240 mg and was given for a median of 10 days. The vast majority of patients (93%) were able to avoid hospitalization and showed improvement in fluid status/weight (70%), and symptoms were well controlled in all 15 dying patients.[26] However, the incidence of mild infusion site reactions was reported at 23%.

In another study, Birch et al.[27] administered furosemide as continuous SC infusion to manage 130 episodes of decompensation among 116 patients with advanced HF. The average total daily dose delivered was 125 mg (40-300 mg) for an average of 10 days (1-49 days). Treatment goal was achieved in 91.5%, with resultant improvement in self-reported dyspnea and weight loss. Adverse events, including localized skin irritation and infection, occurred at a rate of 24%.

Overall, these studies established the clinical efficacy of furosemide delivered SC for the management of patients with decompensated HF. Although the relatively high frequency of side effects related to alkaline pH rendered this approach unfavorable, it paved the way for the development of a novel furosemide formulation using a pH-neutral buffered solution.

Furoscix: A Novel Furosemide Formulation and On-Body Infusor Combination

Aiming to overcome injection site side effects during SC administration while maintaining clinical efficacy, a pH neutral formulation of

furosemide was recently developed. Furoscix (scPharmaceuticals, Burlington, MA, USA) is a single-use, drug-device combination product consisting of the following: (1) 80 mg furosemide reconstituted in 10 mL buffered solution containing tromethamine at a physiological pH of approximately 7.4 (7.2-7.6); (2) external, on-body, preprogrammed SC delivery system (Figure 1). The device is applied to the abdominal skin using medical grade adhesives, and on pressing the blue activation button, a 6-mm-long, 27-gauge needle automatically deploys, and drug administration is initiated. The device infuses 80 mg of furosemide subcutaneously in a biphasic delivery profile over 5 hours: 30 mg given over the initial 60 minutes, followed by 12.5 mg/h for the subsequent 4 hours. On removal of the device after the infusion is complete, a safety latch covers the needle to protect against accidental needle sticks.

Pharmacokinetics and Pharmacodynamics of the Novel, pH Neutral Furosemide Formulation

Sica et al.[32] performed the first-in-man, proof-of-concept *Furopharm-HF* study (Furosemide Pharmacodynamics and Pharmacokinetics after Subcutaneous or Oral Administration) in 2015 to compare the pharmacodynamic and pharmacokinetic profiles of the pH neutral furosemide solution administered SC and oral furosemide. Ten individuals with chronic HF were initially randomized 1:1 to Furoscix vs. 80 mg oral furosemide dose. After a 14-day washout period, participants crossed over to the alternate group. All individuals achieved therapeutic plasma levels (>250 ng/mL) within 30 minutes of SC infusion initiation, which was maintained above 1000 ng/mL during the plateau phase (60-300 minutes). In contrast, peak furosemide concentration was recorded at 60 minutes after oral administration with significant reduction in bioavailability and interindividual variation compared with SC, primarily because of the differences in intestinal absorption. Diuretic response was slightly more profound with SC infusion.

In a second *PK/PD study*, 16 subjects with chronic HF were randomized 1:1 to IV furosemide (40 mg bolus dose followed by a second 40 mg bolus dose 2 hours later) vs. Furoscix 80 mg over 5 hours.[32] Participants crossed over to the alternate group after a 7-day washout period. SC administration resulted in complete, 99.6% furosemide bioavailability compared with the IV dosing. Consistent with the prior study, therapeutic plasma levels were reached within 30 minutes of initiation and were maintained throughout the 5 hours of continuous infusion. Clinically, SC furosemide achieved equivalent natriuresis and diuresis compared with the IV formulation, both during the 0 to 8 hours period and the 0 to 24 hours interval. Furoscix was well tolerated overall in the studies. There were no reports of associated pain, but 9 subjects described slight or minimal erythema, and 1 experienced well-defined erythema. Six subjects experienced minimal swelling at the SC infusion site likely related to the adhesive. All skin reactions resolved spontaneously shortly after completing the prescribed dose.

In a *phase II trial*, Gilotra et al.[20] assessed the safety and efficacy of Furoscix among patients with decompensated HF in the outpatient setting. Forty individuals were randomized 1:1 to receive a single injection of IV furosemide (n = 19) with a maximum dose up to 160 mg (mean dose: 123 ± 47 mg) or Furoscix (n = 21) using the standard biphasic dosing pattern (30 mg within the first 60 minutes and an additional 50 mg over 4 hours). The diuretic response between the 2 groups was similar over 6 hours, but natriuresis was higher in those receiving the SC infusion ($p = 0.05$). There was no adverse impact on renal function, ototoxicity, skin erythema, pain, or infusion site irritation. One subject in the SC group experienced mild hypokalemia with the serum potassium decreasing from 4.1 mEq/L to 3.3 mEq/L post-Furoscix dose. The rate of 30-day hospitalization was also similar between the groups (42% with IV vs. 52% with SC; $p = 0.55$).[20]

The multicenter, investigator-initiated *SUB-Q-HF study* (Subcutaneous Furosemide in Acute Decompensated Heart Failure; NCT02877095) was conducted at 5 experienced centers within the Heart Failure Network.[33] It consisted of 2 pilot studies assessing the safety and efficacy of Furoscix in a population with acutely decompensated HF. The first pilot enrolled 20 hospitalized individuals who were treated with Furoscix for 48 hours once or twice a day (80 mg furosemide delivered SC using the biphasic pattern over 5 hours) instead of an IV loop diuretic. The diuresis prompted a mean urine output of 5.3 L, weight loss of 1.35 kg, and significant improvement in congestion. The subsequent outpatient pilot enrolled 20 individuals who were discharged within 24 hours from the hospital with diuresis continued at home for up to 7 days using the Furoscix. Patients noted improvement in HF symptoms with minimal decline in weight at day 7. These studies demonstrated that Furoscix provided decongestion both in the inpatient setting and post-hospitalization with infrequent and mild side effects.

The previously mentioned studies have established the safety and clinical efficacy of the pH neutral furosemide solution administered SC and paved the way for further clinical studies.

Paradigm Shift in HF Care

There has been an alarming uptrend in HF hospitalizations in the United States and Europe in recent years.[8,9] According to the American Heart Association's projections from the Medical Expenditure Panel Survey (MEPS 2004-2008), up to 80% of the direct costs associated with HF cares will be attributed to hospitalizations by 2030 unless there is a paradigm shift in current practices.[2,3] Shifting patient management from the inpatient to outpatient "interceptive" therapies for decongestion has the potential to ease this economic burden and to improve patient-centered outcomes.[34] Multiple clinical trials have been completed, and 1 additional study is ongoing that provide insights into the role Furoscix can play in achieving these ambitious goals (Table 1). These studies aim to establish the impact of Furoscix on symptom burden, HF hospitalizations/ED visits, and health care–related expenditures while administering the product in the home setting to patients with worsening congestion.

The recently completed *FREEDOM-HF* (Furoscix Real-World Evaluation for Decreasing Hospital Admissions in Heart Failure; NCT03458325) was a prospective, multicenter, open-label, case–control study of patients with acute on chronic HF who presented to the ED with worsening congestion despite background oral diuretic therapy. Twenty-four adults

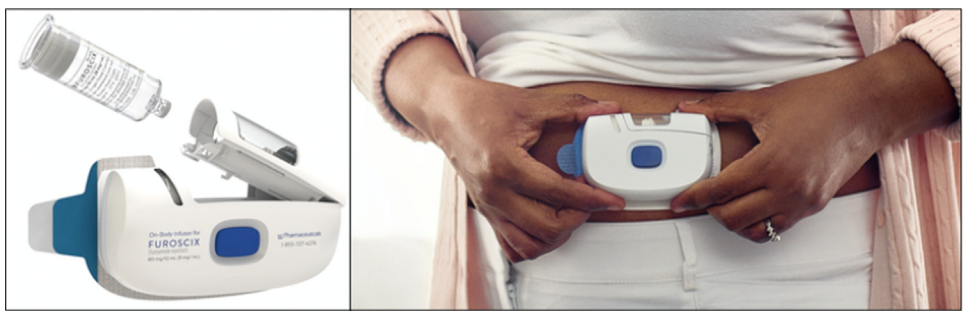

Figure 1. Furoscix drug-device combination product.

Table 1
Pharmacokinetics, clinical efficacy and adverse event profile of subcutaneous furosemide

Clinical study	Authors	Type of study	Population	Study arms	Results	Adverse events
FUROPHARM-HF	Sica et al.[32]	Prospective, randomized, cross-over PK/PD study	Chronic HF patients with fluid overload (n = 10)	PO vs. SC furosemide	Mean plasma concentration of 916 ng/mL after 30 min and mean plateau concentration (hours 1-5) of 2129 ng/mL with SC furosemide. Highly variable PK with PO dosing, oral bioavailability of 61% vs. SC Lasix	None reported
N/A	Sica et al.[32]	Prospective, randomized, cross-over PK/PD study	Chronic HF patients with fluid overload (n = 16)	IV vs. SC furosemide	99.6% bioavailability of SC furosemide vs. IV dosing. Comparable natriuresis (SC: 286 mmol vs. IV: 307 mmol) and diuresis (SC: 2663 ± 1021 mL vs. IV: 2718 ± 654 mL) at 0-8 h and at 0-24 h (SC: 3614 ± 1045 mL vs. IV: 3672 ± 740 mL)	No infusion site pain. Nine patients developed slight or minimal erythema and 1 well-defined erythema. Six with minimal swelling at the infusion site likely related to adhesive
N/A	Gilotra et al.[20]	Prospective, single-center, randomized clinical study	Outpatients with acute decompensated HF (n = 40)	IV furosemide (n = 19) vs. SC furosemide (n = 21)	Comparable diuretic effect (SC: 1514 mL vs. IV: 1636 mL), natriuresis (SC: 32.8 ± 43.6 mEq/L vs. IV: 7.3 ± 35.3 mEq/L), and weight change at 6 h (SC: 1.5 ± 1.2 kg vs. IV: 1.5 ± 1.1 kg). Similar 30-d hospitalization rates	No worsening renal function, arrhythmia, ototoxicity, or skin irritation with either formulation. A single case of hypokalemia in SC group (4.1 mEq/L to 3.3 mEq/L)
FREEDOM-HF	Bensimhon et al. (unpublished study)	Prospective, multicenter, matched comparative, open-label study	Patients with acute on chronic HF presenting to the ER with worsening congestion despite oral diuretics (n = 24)	SC furosemide (n = 24) vs. patients with acute decompensated HF admitted for IV diuresis (n = 66 identified from IBM MarketScan database)	Significant reduction in HF-related ($16,995) and overall health care costs with SC furosemide. Reduction in natriuretic peptide levels and improvement in KCCQ scores at day 30 vs. baseline with SC furosemide	Infusion site bruising (29%), infusion site pain (29%), and dizziness (12.5%), all mild in severity
AT HOME-HF (ongoing trial: NCT04593823)	N/A	Phase 2 prospective, multicenter, randomized open-label study	Patients with acute on chronic HF presenting to the heart failure clinic with worsening congestion (n = 51)	2:1 randomization. SC furosemide (n = 34) vs. uptitrating PO diuretics (TAU; n = 17)	Trial ongoing. Composite primary endpoint: CV death, HF hospitalizations, unscheduled ED/clinic visits, and change in NT-proBNP using Finkelstein-Schoenfeld method. Secondary endpoints: change in NYHA functional class, composite congestion score, 5-point and 7-point dyspnea score, ReDS measurement, KCCQ-12 score, visual analog score, and 6-min walking distance	TBD

Abbreviations: CV, cardiovascular; ER, emergency department; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; PK/PD, pharmacokinetic/pharmacodynamic; SC, subcutaneous.

with New York Heart Association (NYHA) Class II-III symptoms, stable vital signs, and creatinine within 0.5 mg/dL of baseline were discharged home with Furoscix to be used over 30 days. The following outcomes were monitored: (1) HF hospitalizations/ED/clinic visits; (2) change in circulating natriuretic peptide levels; and (3) improvement in QOL as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ-12) scores. In addition, overall and HF-attributable health care expenditures were derived and compared with 66 matched controls admitted with congestion and requiring IV diuresis for <72 hours. The detailed results of the trial are currently under publication, but Furoscix use was associated with a significant reduction in overall and HF-related health care costs as presented at the 2021 Annual Scientific Meeting of the Heart Failure Society of America. In addition, a profound decline in circulating natriuretic peptide levels was documented, and the median KCCQ-12 score increased significantly by day 30. There were no major adverse events in the treatment group. These preliminary results suggest that Furoscix, when used in the home setting, leads to significant cost savings by reducing the need for hospital admissions.

The *AT HOME-HF* (Avoiding Treatment in the Hospital With Furoscix for the Management of Congestion in Heart Failure; NCT04593823) trial is ongoing. It is a multicenter, randomized, open-label, controlled study evaluating the safety and effectiveness of Furoscix among patients with chronic HF who develop signs and symptoms of acute congestion requiring diuretic dose titration outside of the acute care setting. Fifty-one patients will be randomly assigned in a 2:1 ratio to either receive Furoscix or continue medical management. The primary combined composite endpoint consists of (1) cardiovascular death, (2) HF hospitalizations, (3) urgent ED/clinic visit for worsening HF symptoms, and (4) percent change in NT-proBNP at day 7 from baseline using the Finkelstein-Schoenfeld Win ratio. In addition, the change in NYHA functional class, composite congestion score, 5-point current dyspnea score, 7-point dyspnea score, KCCQ-12 score, visual analog score, ReDS lung fluid measurement (Sensible Medical, Netanya, Israel), and 6-minute walking test will be compared between the groups at 7 and 30 days. Laboratory parameters and adverse events will also be assessed.

These ongoing trials are of critical importance for patients with chronic HF and have the potential to further establish Furoscix as a safe and effective treatment alternative to hospital admission for IV diuresis while significantly reducing health care costs.

The Potential Benefits of Furoscix in the Era of COVID-19

Similar to most other disease states, HF care delivery was significantly impacted by the COVID-19 pandemic. Although the number of admissions for acute decompensated HF decreased substantially after March 26, 2020, a concomitant increase in mortality was documented among those requiring hospitalization.[35,36] Potential reasons for the increased mortality include delayed clinical presentation associated with end-organ dysfunction, more advanced symptoms, and higher NYHA functional class at the time of medical contact, as well as limited hospital capacity because of the clinical burden posed by the large number of individuals infected with SARS-CoV-2.[36,37] Patients with congestion were likely managed in the outpatient setting for too long with augmented oral diuretics or discharged prematurely before reaching euvolemia to increase bed availability.[38] Amplification of health inequity due to socioeconomic disparities triggered by the pandemic has also impacted HF cares.[39] Consequently, reconfiguration of HF management pathways came into focus with one of the aims to intensify ambulatory services to reduce hospital admissions. The novel subcutaneously delivered formulation of furosemide has the potential to fill this gap.

Intersection of Furoscix and Palliative Care

Chronic HF and congestion lead to a marked impairment in QOL, which parallels worsening NYHA functional class and the stage of the disease.[40,41] Recurrent, often prolonged hospitalizations further exacerbate the physical and emotional symptoms caused by the disease process, especially toward the end of life. Most patients with advanced HF would opt to spend more time at home or with family rather than on the hospital ward if appropriate symptom control could be achieved. This is especially true for dyspnea, one of the most distressing symptoms of congestion.[10] As detailed previously, SC administration of traditional furosemide has been reported in the palliative care setting with great clinical efficacy; however, injection site complications were frequent, limiting its widespread adoption.[26-28] The novel, pH neutral formulation of furosemide combined with an automated on-body infusor has the potential to overcome these challenges. Studies suggest that it is safe, has similar efficacy to IV formulation and leads to rapid symptomatic relief and improvement in QOL. Consequently, it has the potential to become the treatment of choice for patients with end-stage HF for out-of-hospital palliation.

Conclusion

The novel, pH neutral formulation of furosemide developed for SC administration via a preprogrammed, single-use on-body infusor (Furoscix) has the potential to address a large, unmet gap in ambulatory HF management and to transform the care of patients with chronic HF. Pharmacokinetic, pharmacodynamic, and proof-of-concept studies have demonstrated that it can be administered safely in settings outside of the hospital. It provides good symptomatic control by reducing congestion, and its clinical efficacy is equivalent to the IV alternative. By allowing for more effective and earlier home care for HF patients, it has the potential to profoundly reduce hospital admissions as well as emergency room and urgent care visits, leading to a significant cost savings to the health care system. One clinical trial is currently ongoing (AT HOME-HF), and the FREEDOM-HF trial has recently been completed; the results have been presented at the 2021 Annual Scientific Meeting of the Heart Failure Society of America. Additional data are highly anticipated and will further inform the widespread outpatient applicability of Furoscix.

ORCIDs

Garima Dahiya https://orcid.org/0000-0003-1925-7722
Tamas Alexy https://orcid.org/0000-0001-8381-6299

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References

1 Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743. https://doi.org/10.1161/CIR.0000000000000950
2 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;6:606-619.
3 Heidenreich PA, Fonarow GC, Opsha Y, et al. Economic issues in heart failure in the United States. *J Card Fail*. 2022;28:453-466.
4 Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovasc Disord*. 2018;18:74.
5 Kilgore M, Patel HK, Kielhorn A, et al. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. *Risk Manag Healthc Policy*. 2017;10:63-70.
6 Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112:3958-3968.
7 Parrinello G, Greene SJ, Torres D, et al. Water and sodium in heart failure: a spotlight on congestion. *Heart Fail Rev*. 2015;20:13-24.
8 Bonilla Palomas JL, Anguita-Sanchez MP, Elola FJ, et al. Trends in hospitalization and in-hospital mortality of patients with heart failure in Spain. A population-based study (2003–2015). *Eur Heart J*. 2020;41, ehaa946.1187.
9 Salah HM, Minhas AMK, Khan MS, et al. Trends in hospitalizations for heart failure, acute myocardial infarction, and stroke in the United States from 2004 to 2018. *Am Heart J*. 2022;243:103-109.
10 Mullens W, Damman K, Harjola V-P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology: diuretics in heart failure. *Eur J Heart Fail*. 2019;21:137-155.
11 Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med*. 2017;377:1964-1975.
12 Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther*. 1995;57:601-609.
13 Shah N, Madanieh R, Alkan M, et al. A perspective on diuretic resistance in chronic congestive heart failure. *Ther Adv Cardiovasc Dis*. 2017;11:271-278.
14 Brisco-Bacik MA, ter Maaten JM, Houser SR, et al. Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis. *J Am Heart Assoc*. 2018;7(18), e009149. https://doi.org/10.1161/JAHA.118.009149
15 Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol*. 2010;56:1527-1534.
16 Schipper JE, Domingo GR, Dickson VV, et al. Implementation of tailored intravenous heart failure therapy in a non-dedicated outpatient infusion center. *J Card Fail*. 2012;18:S104.
17 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. *JACC Heart Fail*. 2016;4:1-8.
18 Makadia S, Simmons T, Augustine S, et al. The diuresis clinic: a new paradigm for the treatment of mild decompensated heart failure. *Am J Med*. 2015;128:527-531.
19 Hamo CE, Abdelmoneim SS, Han SY, et al. OUTpatient intravenous LASix trial in reducing hospitalization for acute decompensated heart failure (OUTLAST). *PLoS One*. 2021;16, e0253014.
20 Gilotra NA, Princewill O, Marino B, et al. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. *JACC Heart Fail*. 2018;6:65-70.
21 Andreasen F, Mikkelsen E. Distribution, elimination and effect of furosemide in normal subjects and in patients with heart failure. *Eur J Clin Pharmacol*. 1977;12:15-22.
22 Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol*. 2002;13:798-805.
23 Ellison DH. Clinical pharmacology in diuretic use. *Clin J Am Soc Nephrol*. 2019;14:1248-1257.
24 Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. *J Am Coll Cardiol*. 2012;59:2145-2153.
25 Verma AK, da Silva JH, Kuhl DR. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. *Ann Pharmacother*. 2004;38:544-549.
26 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;25:658-663.
27 Birch F, Boam E, Parsons S, et al. Subcutaneous furosemide in advanced heart failure: service improvement project. *BMJ Support Palliat Care*. 2021. bmjspcare-2020-002803.

28 Brown A, Westley K, Robson J, et al. Furosemide in end-stage heart failure: community subcutaneous infusions. *BMJ Support Palliat Care*. 2020. bmjspcare-2019-002158.
29 Austin J, Hockey D, Williams WR, et al. Assessing parenteral diuretic treatment of decompensated heart failure in the community. *Br J Community Nurs*. 2013;18:528-534.
30 Lozano Bahamonde A, Escolar Pérez V, Echebarria Chousa A, et al. Subcutaneous furosemide in patients with refractory heart failure. *Rev Esp Cardiol (Engl Ed)*. 2019; 72:500-502.
31 Galindo-Ocaña J, Romero-Mena J, Castillo-Ferrando JR, et al. Subcutaneous furosemide as palliative treatment in patients with advanced and terminal-phase heart failure. *BMJ Support Palliat Care*. 2013;3:7-9.
32 Sica DA, Muntendam P, Myers RL, et al. Subcutaneous furosemide in heart failure. *JACC Basic Transl Sci*. 2018;3:25-34.
33 Felker GM, Redfield MM, Mentz RJ, et al. Subcutaneous furosemide in the treatment of patients with decompensated heart failure: data from the sub-Q pilot studies. *J Card Fail*. 2019;25:S75.
34 Greene SJ, Mentz RJ, Felker GM. Outpatient worsening heart failure as a target for therapy: a review. *JAMA Cardiol*. 2018;3:252.
35 Hall ME, Vaduganathan M, Khan MS, et al. Reductions in heart failure hospitalizations during the COVID-19 pandemic. *J Card Fail*. 2020;26:462-463.
36 Cannatà A, Bromage DI, Rind IA, et al. Temporal trends in decompensated heart failure and outcomes during COVID -19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail*. 2020;22:2219-2224.
37 Kubica J, Ostrowska M, Stolarek W, et al. Impact of COVID-19 pandemic on acute heart failure admissions and mortality: a multicentre study (COV-HF-SIRIO 6 study). *ESC Heart Fail*. 2022;9:721-728.
38 Shoaib A, Van Spall HGC, Wu J, et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes*. 2021;7:378-387.
39 Yancy CW. COVID-19 and African Americans. *JAMA*. 2020;323:1891.
40 Heo S, Lennie TA, Okoli C, et al. Quality of life in patients with heart failure: ask the patients. *Heart Lung*. 2009;38:100-108.
41 Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart*. 2002;87:235-241.