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Research Article

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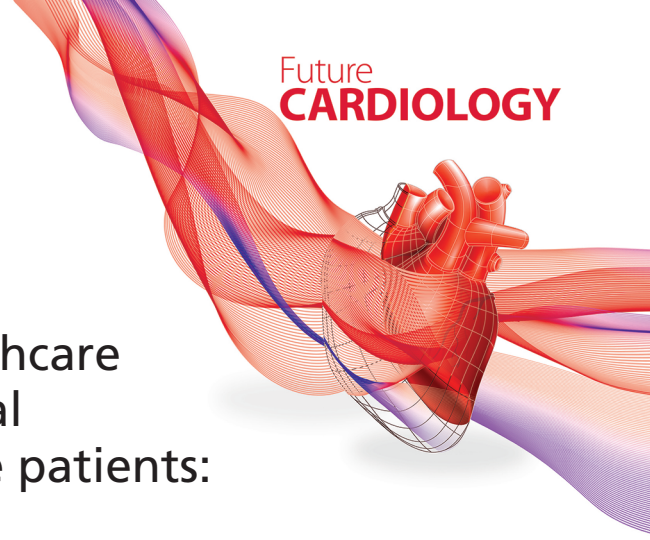

Future CARDIOLOGY

Reduced heart failure-related healthcare costs with Furoscix versus in-hospital intravenous diuresis in heart failure patients: the FREEDOM-HF study

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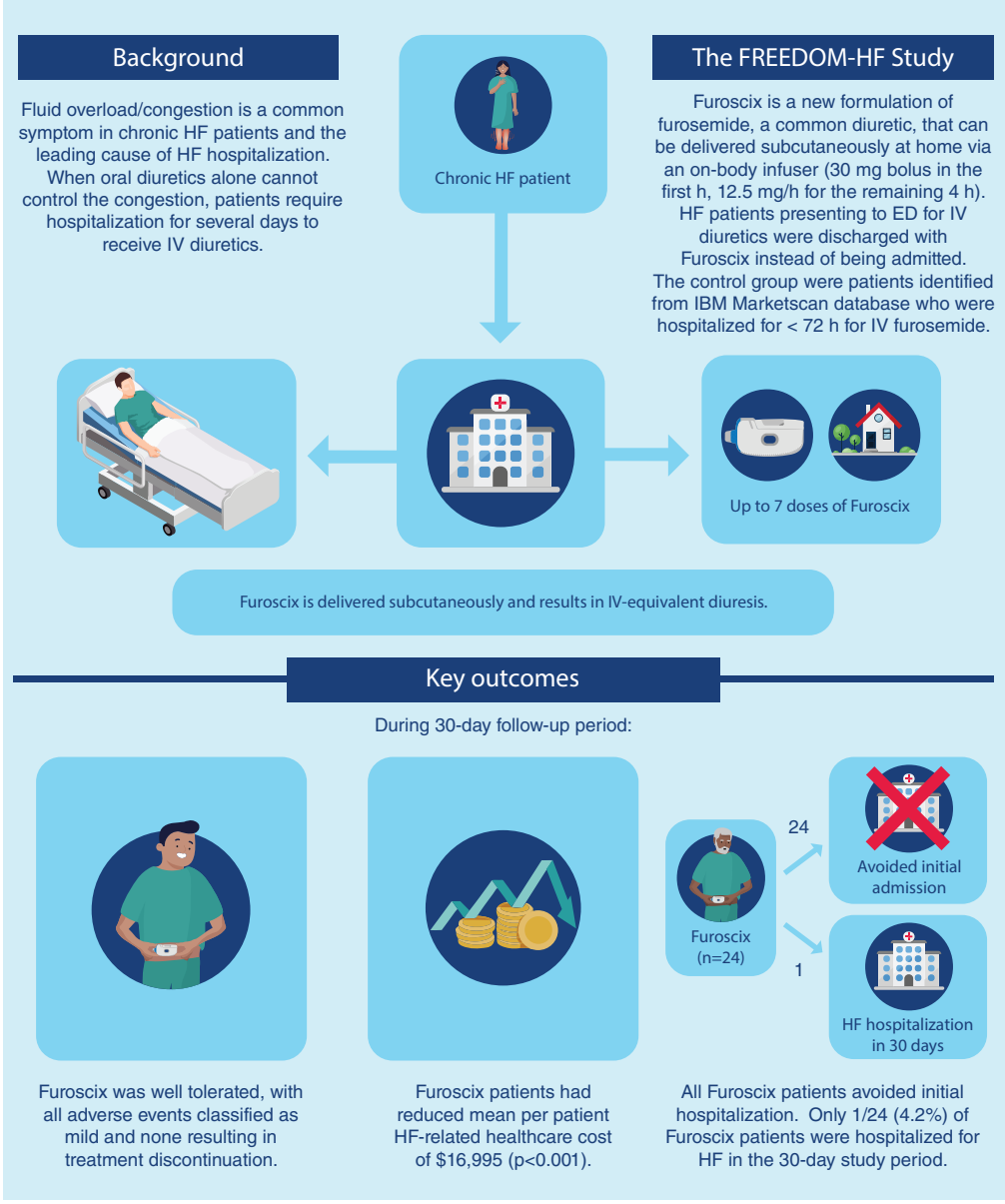
Aim: Compare heart failure (HF) costs of Furoscix use at home compared with inpatient intravenous (IV) diuresis. **Patients & methods:** Prospective, case control study of chronic HF patients presenting to emergency department (ED) with worsening congestion discharged to receive Furoscix 80 mg/10 ml 5-h subcutaneous infusion for ≤7 days. 30-day HF-related costs in Furoscix group derived from commercial claims database compared with matched historical patients hospitalized for <72 h. **Results:** Of 24 Furoscix patients, 1 (4.2%) was hospitalized in 30-day period. 66 control patients identified and were well-matched for age, sex, ejection fraction (EF), renal function and other comorbidities. Furoscix patients had reduced mean per patient HF-related healthcare cost of $16,995 ($p < 0.001$). **Conclusion:** Furoscix use was associated with significant reductions in 30-day HF-related healthcare costs versus matched hospitalized controls.

Plain language summary: reduced heart failure costs with subcutaneous Furoscix at home versus in-hospital intravenous diuretics:
What is this article about? In heart failure (HF), the heart cannot pump as well as it should. This causes blood to back up in the vessels that return blood to the heart. Fluid leaks from these vessels and collects in vital organs such as the lungs. This fluid build-up is called congestion. Congestion causes symptoms such as shortness of breath, tiredness and leg swelling. Furoscix is a prescription medicine, a diuretic, that treats congestion. Diuretics help get rid of extra fluid by increasing urination. Congestion is usually managed with oral diuretics, but sometimes congestion cannot be controlled by oral diuretics and patients may have to spend several days at a clinic or hospital to receive diuretics given through a vein (intravenous or iv.). Furoscix is a new formulation of furosemide, a common diuretic, and is delivered into the skin (subcutaneous) by a self-administered pump instead of through an iv. **Our investigation aimed to answer two questions** Can Furoscix be given to patients at home instead of in the hospital with iv. diuretics? Is there a cost savings to using Furoscix? Instead of being admitted to the hospital for iv. diuretics, HF patients with worsening congestion who came to the emergency department were sent home to receive Furoscix 80 mg/10 ml 5-h subcutaneous infusion for ≤7 days. 30-day costs related to HF in these patients were compared with costs from similar group of patients previously hospitalized for iv. diuretics. **What were the results & what do they mean?** In patients who needed to be admitted to the hospital for iv. diuretics, Furoscix given at home instead reduced congestion and resulted in significant cost savings. Patients with heart failure, who are not getting relief with oral diuretics, can be treated with Furoscix at home without having to be admitted to the hospital for iv. diuretics. Use of Furoscix instead of iv. furosemide can save money to the healthcare system.

Future Medicine

Tweetable abstract: Compared with a historical matched cohort of patients admitted to hospital for ≤72 h to receive intravenous furosemide, use of Furoscix at home resulted in a per patient reduction in heart failure-related costs of $16,995.

Graphical abstract:



Clinical Trial Registration: NCT03458325 (ClinicalTrials.gov)

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Keywords: congestion • diuretics • emergency department • Furosemide • heart failure • subcutaneous

The prevalence of chronic heart failure (HF) continues to rise in the USA, with more than 8 million Americans projected to be affected by 2030. Management of this growing HF population creates a significant economic and logistic burden to the healthcare system. Most of these costs are driven by hospital admissions and the frequent need for readmission [1–3]. Currently in the USA, nearly 25% of patients discharged after an admission for HF are readmitted in 30 days and over 40% are admitted within 90 days [4].

Symptoms related to lung and peripheral congestion are the primary reason patients with chronic HF seek medical attention [5,6]. While increasing the patient's daily dose of oral loop diuretic or adding a thiazide diuretic remain the cornerstone for managing outpatient worsening of chronic HF, these interventions can be ineffective in a significant proportion of decompensated HF patients due to reduced diuretic absorption. Therefore, parenteral diuretics are necessary. However, intravenous (IV) diuretic administration typically requires hospitalization, an emergency department (ED) visit or access to a specialized infusion center [5,7,8].

Given comorbidities and the high symptom burden of HF patients, approximately 90% of patients presenting to the ED with signs and symptoms of worsening congestion are admitted to the hospital. However, based on previous studies it is estimated that 50% of these ED admissions are potentially avoidable if safe and effective decongestion could be achieved, thus avoiding an unnecessary hospitalization [9,10]. Furthermore, 66% of patients hospitalized with HFrEF do not have treatment escalated beyond initial iv. diuretics [11]. Avoiding hospitalizations solely for iv. diuretics would not only free up highly desired inpatient bed capacity but would also reduce the cost burden to society. A recent study reported a potential $667 million cost savings if 10% of HF admissions were targeted and 60% were successfully shifted from the inpatient to outpatient setting [12]. In addition, home decongestion could improve patient/caregiver satisfaction and quality of life.

Furoscix® is a recently approved pH neutral formulation of furosemide 80 mg/10 ml, administered by subcutaneous infusion via a single-use, wearable, drug-delivery system. The device component in Furoscix (Infusor) is a compact, ethylene oxide (EtO) sterilized, electromechanical (battery powered, micro-processor controlled), on-body subcutaneous delivery system based on the SmartDose® Gen II 10 ml (West Pharmaceutical Services). The Infusor includes a prefilled furosemide cartridge, has visual and audible feedback, and is attached to the skin via an integrated medical-grade adhesive patch. Furosemide is delivered over 5 h using a biphasic profile (30 mg during the first hour, 12.5 mg/h over the subsequent 4 h).

In a study evaluating the pharmacokinetics/pharmacodynamics (PK/PD) of Furoscix in a HF population, subcutaneous infusion demonstrated 99.6% bioavailability relative to an 80 mg dose of iv. furosemide with comparable diuresis and natriuresis [13]. A subsequent study in an outpatient HF infusion clinic setting found that the diuretic effect of 80 mg Furoscix administered over 5 h was comparable to a mean dose of 123 mg iv. furosemide [14].

The objectives of this study were to evaluate differences in healthcare resource utilization costs for patients treated with Furoscix outside the hospital compared with patients who received iv. furosemide for ≤72 h in the hospital setting, and to evaluate safety, quality of life and patient satisfaction for patients who received Furoscix outside the hospital setting.

Methods

Study design & patient population

Furoscix Real-World Evaluation for Decreasing Hospital Admissions in Heart Failure (FREEDOM-HF) was a prospective, multicenter, open-label, case-control study that evaluated the safety and HF-related healthcare costs of using Furoscix for low to moderate-risk HF patients presenting to the ED with signs and symptoms of congestion and managed at home. Patients were followed for 30 days after ED discharge and financial savings were derived from claims data using matched historical controls (Figure 1). The study was reviewed and approved by an Institutional Review Board and was conducted in full compliance with the Declaration of Helsinki and the guidelines set forth by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

Patients were eligible to receive Furoscix if they were 18–80 years old, had chronic HF (New York Heart Association [NYHA] class II-III), were on background oral diuretic therapy (40–160 mg furosemide equivalent daily), and presented to the ED with signs and symptoms directly related to worsening congestion defined as 1 or more of the following: elevated jugular venous distension, worsening pitting edema, abdominal fullness/distension, pulmonary edema on chest x-ray or pulmonary rales. The decision for hospital admission was made by the ED physician. After initial ED evaluation and treatment (i.e., at the time of the care transition decision to leave the ED), eligible patients had to be clinically stable, defined as meeting all the following criteria: oxygen saturation ≥90% on room air with exertion, respiratory rate <24 breaths per min, resting heart rate <100 beats per min and systolic blood pressure >100 mmHg. Patients with a complicating comorbid condition that required immediate hospitalization or anticipated hospitalization within 30 days, local abdominal skin abnormalities that prevented Furoscix application, pregnancy, estimated creatinine clearance (CrCl) <30 ml/min and those with creatinine level ≥0.5 mg/dl above baseline were excluded.

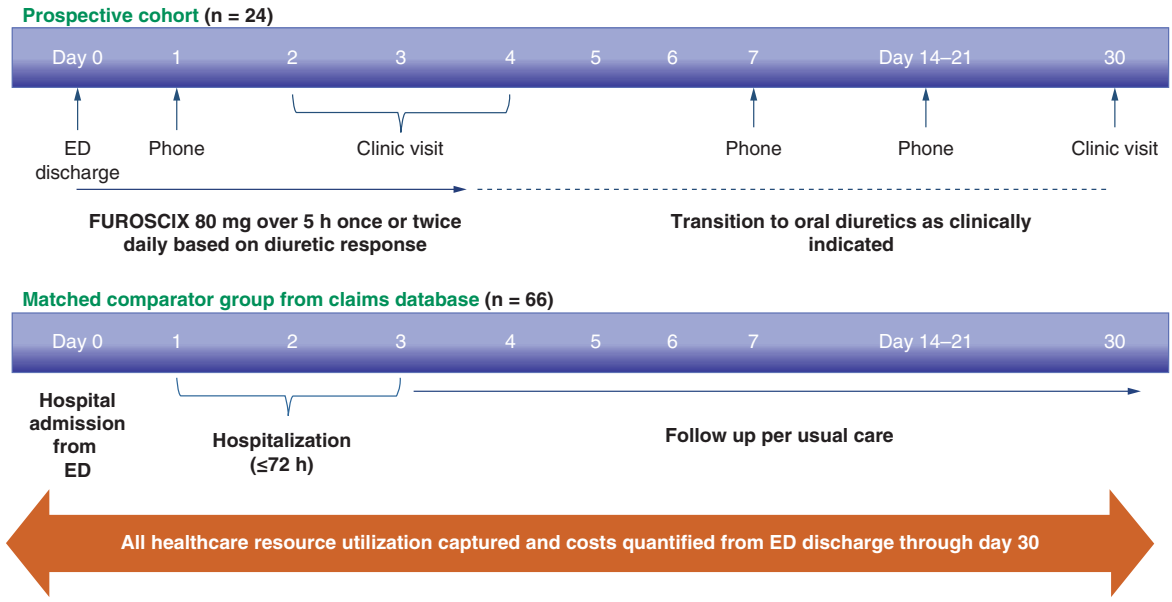

Figure 1. FREEDOM-HF study design.
ED: Emergency department.

Furoscix 80 mg via subcutaneous infusion could be administered once or twice daily up to a maximum of 7 doses, based on the individual investigator's estimated volume of diuresis required to transition the patient back to their oral diuretic maintenance therapy. Patients were seen in the HF clinic between days 2–4 and on day 30 and received phone calls from the research staff on day 7 and between day 14–21. Patients with worsening congestion after transition back to oral loop diuretics could receive additional doses of Furoscix as determined by investigators.

Historical control group patients were identified from the IBM® MarketScan® Commercial Claims and Medicare Supplemental Database from 2018–2019. Inclusion criteria consisted of inpatient claims coded with a HF (ICD-9/ICD-10) diagnostic code in the primary position, worsening HF as defined by one of the HF DRGs (291, 292, 293), 3 days or less hospital length of stay, ED service category visit, age ≥18 years, continuous enrollment for 1 year before and 3 months after index date, and first qualifying claim defined as the index date. Patients with chronic kidney disease (CKD) stage IV/V, those not on background oral loop diuretic therapy within 90 days of index visit, and those with complicating conditions during the hospital admission such as renal failure, dialysis, myocardial infarction or pneumonia were excluded from the comparator group.

Cohort matching

Control patients were matched based on having a 1–3 day hospitalization for HF and the following seven predetermined variables: age, sex, left ventricular ejection fraction, history of CKD, HF hospitalization within the prior 6 months, presence of chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) [15].

Derivation of 30-day HF-related costs

Healthcare resources for both groups were derived from the IBM® MarketScan® Commercial Claims and Medicare Supplemental Database. Cost benchmarks were derived from the final control population that met the inclusion/exclusion criteria, and costs were applied to the Furoscix and control patients based on individual utilization (Table 1). The cost of Furoscix was not included in the analysis as pricing was not known at the time of study completion.

The costs associated with the claims for hospitalizations, ED visits and clinic visits were evaluated during the 30-day period following the index ED visit. These costs included the actual reimbursements paid by health plans plus any patient cost sharing in the form of deductibles, copayments and coinsurance. To estimate HF-related costs, only claims with a primary diagnosis of HF were included. The cost for hospitalization during the 30-day follow-up were calculated as the mean cost per day. Each cost variable was summed over the 30-day period for each patient then the total 30-day hospitalization cost was divided by total length of stay. Clinic and ED visit costs were

Table 1. Cost benchmarks.

Cost variable	Cost benchmark: mean (SD)
Cost of index hospitalization for control group	
Length of stay = 1	$12,477.97 (8397.44)
Length of stay = 2	$15,181.96 (10,971.97)
Length of stay = 3	$17,691.73 (12,033.46)
HF-related 30-day costs	
Hospitalization (cost/day)	$10,884.08 (22,874.64)
Clinic visit (cost/visit)	$180.16 (204.14)
Emergency department visit	$1,194.70 (1770.19)
All-cause 30-day costs	
Hospitalization (cost/day)	$10,132.77 (14,880.06)
Clinic visit	$223.51 (308.45)
Emergency department visit	$1,331.14 (1596.83)
**All costs are in 2020 USD*	

HF: Heart failure; SD: Standard deviation.

calculated as the mean cost per visit per patient during the 30-day follow-up time. To obtain the visit cost for each patient, the total 30-day cost was divided by the number of visits. After deriving the unit cost for each patient, mean costs were generated for each category among the total number of patients.

Primary & secondary study end points

The primary end point was the difference in 30-day HF-related healthcare costs (USD) between patients with worsening HF who were discharged from the ED with Furoscix compared with matched controls treated in the hospital for ≤72 h. Secondary end points included the number of total HF-related hospital admissions, HF-related ED visits and HF-related clinic visits within 30 days postdischarge from the ED. Additionally, Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and percent change in BNP/NT-proBNP from baseline were evaluated for Furoscix patients. Safety assessments were also evaluated for patients in the Furoscix group; adverse events were recorded throughout the 30-day study period.

Sample size determination

Based on an average hospital cost of a patient hospitalized for ≤72 h with a primary diagnosis of HF (Diagnosis Related Group Code 291, 292 and 293) of $8,600 ± $3,045, 68 patients (34 in each group) were required to have an 80% chance of detecting a decrease in hospital costs to $6,500 at a significance level of 5%. An adaptive design was employed where the final sample size would be determined after prespecified interim analyses were conducted after first 10 and 34 patients completed the study with a sample size of no greater than 75 patients in the Furoscix group.

Results

Patient characteristics

27 patients signed informed consent. One patient withdrew consent prior to completion of screening and did not receive any study drug and there were 2 screen failures (1 patient had CrCl <30 ml/min and 1 patient had an oxygen saturation <90% on room air). After the first interim analysis was complete, enrollment was halted due to treatment benefit with 24 patients enrolled in the Furoscix group. These 24 patients were matched to 66 control group patients, with an average of 2.8 control patients per Furoscix patient, with 12 (50%) matching with 4 control patients. Key matching variables, patient characteristics and baseline HF medications were similar between groups (Table 2).

Healthcare costs (primary end point) & hospitalizations

A significant mean per patient reduction in 30-day HF-related costs of $16,995 was observed for the Furoscix group compared with the control group ($p < 0.001$) (Table 3). This difference was driven primarily by the avoidance of the initial HF hospitalization in the Furoscix group as all comparator patients were initially admitted to the

Table 2. Baseline key matching variables, patient characteristics and heart failure medications.

Outcome	Overall (n = 90)	Furoscix[†] (n = 24)	Comparator (n = 66)	p-value[‡]
Baseline characteristics (key matching variables)				
Age, median (IQR)	56.0 (18)	56.0 (20)	57.5 (13)	0.501
Males, n (%)	57 (63.3)	15 (62.5)	42 (63.6)	
HF, n (%)				>0.999
Systolic	39 (43.3)	11 (45.8)	28 (42.4)	
Diastolic	39 (43.3)	10 (41.7)	29 (43.9)	
Combined	12 (13.3)	3 (12.5)	9 (13.6)	
History of CKD, n (%)				>0.999
No history	62 (68.9)	17 (70.8)	45 (68.2)	
Stage 2	5 (5.6)	1 (4.2)	4 (6.1)	
Stage 3	23 (25.6)	6 (25.0)	17 (25.8)	
≥1 HF hospitalization within 6 months	43 (47.8)	15 (62.5)	28 (42.4)	0.425
COPD, n (%)	33 (36.7)	6 (25.0)	27 (40.9)	0.258
Diabetes, n (%)	62 (68.9)	12 (50.0)	50 (75.8)	0.119
Additional baseline characteristics				
BMI, kg/m^2; mean (SD) (n = 23)	–	44.4 (13.7)	–	–
Weight, pounds, mean (SD)	–	289.3 (89.2)	–	–
Serum creatinine, mg/dl, mean (SD)	–	1.35 (0.40)	–	–
eGFR (MDRD), mean (SD)		60.6 (24.3)		
BNP (pg/ml), mean (SD) (n = 12)	–	785.1 (1129.9)	–	–
NT-proBNP, mean (SD) (n = 11)	–	823.4 (1043.9)	–	–
Insurance, n (%)				
Medicare		8 (33.3)	18 (27.3)[§]	
Medicaid		4 (16.7)	0[¶]	
Commercial		10 (41.7)	48 (72.7)	
Missing		2 (8.3)	0	
Baseline comorbidities				
Prior MI, n (%)	15 (16.7)	2 (8.3)	13 (19.7)	–
Hypertension, n (%)	86 (95.6)	22 (91.7)	64 (97.0)	–
Hyperlipidemia, n (%)	70 (77.8)	15 (62.5)	55 (83.3)	–
Arrhythmia, n (%)	49 (54.4)	12 (50.0)	37 (56.1)	–
Valvular disease, n (%)	26 (28.9)	7 (29.2)	19 (28.8)	–
Unstable angina, n (%)	23 (25.6)	6 (25.0)	17 (25.8)	–
HF medication use 3 months prior to baseline				
Daily furosemide equivalents (mg), mean (SD) (n = 23)	NA	139.1 (98.1)	NA	–
Furosemide, n (%)	70 (77.8)	12 (50.0)	58 (87.9)	–
Bumetanide, n (%)	11 (12.2)	4 (16.7)	7 (10.6)	–
Torsemide, n (%)	19 (21.1)	7 (29.2)	12 (18.2)	–
None, n (%)	1 (1.1)	1 (4.2)	0	–
Metolazone, n (%)	11 (12.2)	5 (20.8)	6 (9.1)	–
Beta-blockers, n (%)	48 (53.3)	15 (62.5)	33 (50.0)	–
ARNI/ACEi/ARB, n (%)	63 (70.0)	11 (45.8)	52 (78.8)	–
Nitrate, n (%)	16 (17.8)	4 (16.7)	12 (18.2)	–
Spironolactone, n (%)	22 (24.4)	10 (41.7)	12 (18.2)	–
Hydralazine, n (%)	11 (12.2)	6 (25.0)	5 (7.6)	–

[†]Two Furoscix patients, who did not satisfy study inclusion criteria, were permitted to be included in the evaluable population.
[‡]p-values were weighted based on count of control patients within each Furoscix match set and were obtained from the t-test statistic.
[§]These patients also had Medicare Supplemental coverage.
[¶]Data did not include patients with Medicaid coverage.
ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor/neprilysin inhibitor; BMI: Body mass index; BNP: B-type natriuretic peptide; CKD: Chronic kidney disease; HF: Heart failure; IQR: Interquartile range; MDRD: Modification of diet in renal disease; MI: Myocardial infarction; NT-proBNP: N-terminal pro b-type natriuretic peptide; SD: Standard deviation.

Table 3. 30-day heart failure-related healthcare costs.

Outcome	Furoscix (n = 24)	Control (n = 66)	Difference (95% CI)	p-value
Primary end point				
HF-related healthcare costs[†, ‡]				
Mean (SD)	$2,920.30 (7,073.20)	19,915.60 (10,666.60)	-$16,995.30 (-22,187.90; -11,802.70)	<0.001[§]
Median (Q1, Q3)	$1,374.90 (1,374.90; 1,555.00)	$15,182.00 (12,658.10; 17,691.70)	-$13,807.10 (-16,846.50; -13,476.30)	<0.001[¶]
Minimum, maximum	$1,374.90; $36,122.60	$12,478.00; $102,614.90	NA	NA
Secondary end points				
Patients with HF-related hospital admission, n (%)	1 (4.2)	7 (10.6)	-6.4%	0.6765[#]
HF-related hospital admission, mean (SD)[††]	1.0 (-)	1.1 (0.2)	-0.1	0.5986[§]
Total length of stay, mean (SD)[††]	3.0 (-)	5.4 (1.1)	-2.4	0.1273[§]
Number of HF-related hospital admissions, n (%)				
0	23 (95.8)	59 (89.4)	6.4%	0.7574[#]
1	1 (4.2)	6 (9.1)	-4.9%	
2	0	1 (1.5)	-1.5%	
Patients with HF-related emergency department visit, n (%)	1.0 (4.2)	4.0 (6.1)	-1.9%	1.000[#]
HF-related emergency department visit, mean (SD)[††]	1.0 (-)	1.0 (0)	0	NA[‡‡]
Patients with HF-related clinic visit, n (%)	24.0 (100.0)	23 (34.9)	65.1%	<0.0001[§§]
HF-related clinic visit, mean (SD)[††]	1.8 (1.2)	1.2 (0.3)	0.6	0.0333[§]

[†]Weighted statistics were based on count of control patients within each Furoscix match set (i.e., 1/k, where k = 1, 2, 3 or 4). Weighting does not apply to Furoscix patients.
[‡]The costs include the index visit costs for both groups. Furoscix – HF-related emergency department; control – HF-related emergency department visit and hospitalization ≤3 days. Cost of Furoscix was not included in the analysis.
[§]p-value was obtained from the *t*-test statistic (weighted by matching weight).
[¶]p-value was obtained from the quantile regression (weighted by matching weight).
[#]p-value was obtained from the Fisher's exact test statistic since cell count was less than 5 (observed data were compared, weights could not be applied as the test can only compare integer values. Application of weights generates data with decimal values).
[††]Mean and SD were estimated among those who had an event.
[‡‡]p-value could not be estimated.
[§§]p-value was obtained from the Chi-square test statistic. Application of weights generates data with decimal values.
Total length of stay is total days/number of patients with a hospitalization.
Mean length of stay is the total days/number of hospitalizations for patients with hospitalizations.
HF: Heart failure; Q1: First quartile; Q3: Third quartile; SD: Standard deviation.

hospital for 72 h or less for decongestion (index hospitalization). The mean (SD) index hospital length of stay in the comparator group was 2.02 (0.81) days. During the 30-day follow-up period, 1 patient of the 24 (4.2%) from the Furoscix cohort was admitted to the hospital for HF and 7/66 (10.6%) of comparator patients (p = 0.6765) had a HF readmission.

HF-related emergency department & clinic visits

The percentage of patients with a subsequent HF-related ED visit within the 30-day follow-up period was similar between the two groups: Furoscix: 4.2% and Comparator 6.1%; p = 1.00. HF-related clinic visits occurred in 24/24 (100%) of Furoscix patients per protocol compared with 23/66 (34.9%) in the comparator group ($p < 0.001$). The mean number of HF-related clinic visits was 1.8 ± 1.2 in Furoscix patients and 1.2 ± 0.3 in comparator patients (p = 0.033).

Health-related quality of life (Furoscix cohort)

The Kansas City Cardiomyopathy Questionnaire – Short Form (KCCQ-12) was utilized to measure patients self-reported overall health status and complete data were available in 21 patients. Furoscix patients had an average increase of 12.8 points: 29.9 at baseline to 42.8 at day 30 (p = 0.044). Symptom Frequency Score increased by a mean of 17.4 points, from 33.1 at baseline to 50.5 (p = 0.03) at day 30. Other self-reported health status scores (Physical Limitation Score, Quality of Life Score and Social Limitation Score) had non-significant increases from baseline to day 30.

Effects on BNP/NT-proBNP (Furoscix patients)

Furoscix patients had a median reduction in BNP/NT-proBNP of 42.3% and 28% from study entry to first visit, and to day 30, respectively ($p < 0.01$). This was reflected by a mean (SD) weight decrease of 6.4 (16.2) pounds from study entry to first visit and 8.5 (20.6) pounds from study entry to day 30 (See Supplementary Table).

Furoscix safety

The most frequently reported adverse events (AEs) consisted of infusion site bruising (29.2%), infusion site pain (29.2%) and dizziness (12.5%). No hypokalemia, hypomagnesemia, hypotension or worsening renal function related to study drug use were reported. All adverse events were classified as mild in severity and did not result in treatment discontinuation.

Nine serious adverse events (SAEs) occurred in 6/24 (25.0%) of Furoscix patients. None of these were determined to be related to the study drug. One patient experienced hypovolemia 21 days after the last dose of Furoscix and within 10 days of initiating a new oral diuretic regimen. Another patient experienced acute kidney injury complicated by diabetic ketoacidosis that occurred 9 days after the last dose of Furoscix. There were no deaths, and no patients withdrew from the study due to an adverse event.

Discussion

Our study is the first to evaluate the home administration of subcutaneous furosemide to avoid an initial hospitalization in chronic HF patients who presented to the ED with worsening congestion despite receiving oral diuretic therapy. All 24 patients enrolled in the study were considered for admission prior to study enrollment and were discharged home with Furoscix instead of hospitalization. We demonstrated a significant cost reduction with this strategy, predominately related to the avoidance of index hospital admission compared with patients who were hospitalized for iv. diuresis. The short-term efficacy of therapy was further demonstrated by the fact that only one patient from the Furoscix cohort had a HF-related hospitalization during the 30-day follow-up period.

It is well established that HF hospitalization is associated with significant morbidity and mortality as well as substantial healthcare costs [12,16]. Considering the 1 million annual US ED HF visits resulting in hospitalization, applying the $16,995 cost decrease with a potential 20% admission avoidance rate would result in an annual savings in excess of $3 billion. Additional, prospective studies are warranted to validate these results and to further evaluate the paradigm shift in the management of congestion.

The extended period between hemodynamic and symptomatic congestion in patients with chronic HF offers a potential window for intervention [17]. Several studies have evaluated the use of iv. or subcutaneous diuretics for the management of worsening congestion in the outpatient setting and have reported effective symptomatic reduction with low adverse event risk profile [18–20]. However, the use of this approach is uncommon and is limited to select institutions owing to the associated logistical challenges [21]. Furthermore, existing formulations of furosemide have a low drug concentration (necessitating large injection volumes) and a basic pH (pH 8.0–9.3) that causes severe discomfort upon subcutaneous administration [22,23].

Knowledge of patients' maintenance diuretic regimen is of critical importance since it can provide a snapshot of HF acuity and better translate study results to the clinical setting. At baseline, 46% of patients in the Furoscix arm were receiving either oral torsemide or bumetanide (29.2% and 16.7%, respectively), and developed congestion significant enough to seek ED care. These diuretics are known to have significantly better and reliable bioavailability than oral furosemide. Additionally, 5/24 (20.8%) of patients in the Furoscix cohort was taking metolazone for sequential nephron blockade, on a regular basis. These suggest that many of the study patients were already on maximal oral diuretic therapy currently approved for home use. The only option to manage their congestion would have been parenteral diuresis.

The results of the current study also suggest that Furoscix is a cost effective and safe alternative to hospital admission in relatively low risk chronic HF patients who present to the ED with congestion. Given the successful home diuresis, it reduced the economic burden significantly with a $16,995 HF-related healthcare cost saving over 30 days compared with a matched cohort that was admitted for less than 72 h. The cost difference was primarily related to the avoidance of initial hospitalization but also to the subsequent reduction in HF hospitalizations over 30 days follow-up. Although the cost of Furoscix was not included in the analysis, if estimating the Furoscix course of therapy is based on the average number of doses used in the study (and is approximately $5,000), the economic benefit to the payer remains because of the initial hospital avoidance and reduction in HF hospitalization over the subsequent 30 days.

It is acknowledged that patients in the Furoscix group had more protocol-mandated healthcare contacts, yet clinic visits were accounted for in the cost analysis. No SAEs related to Furoscix were reported and the treatment was overall well-tolerated.

The average increase of 12.8 points in the mean KCCQ-12 score at day 30 relative to baseline is also an important finding from the study. It indicates that patients achieved effective and clinically meaningful decongestion with Furoscix use. This is further supported by the significant reduction from baseline in natriuretic peptide levels both at the day 2–4 and day 30 visits.

Study limitations

The study is limited by its small sample size, lack of randomization and open-label design. The major limitation of this study was its non-randomized design but given the fact that patients were presenting to the ED after failing escalation of their home oral diuretic regimen, investigators felt it would be unethical to randomize patients to home treatment with Furoscix versus home treatment with an already failing oral diuretic augmentation strategy. Randomization to home Furoscix versus hospital admission was also considered but would have led to the same situation of all control patients having an index HF hospitalization which was avoided by patients in the Furoscix arm. The investigators acknowledge that clinic visits were mandated in the intervention arm by the trial design, and this may have affected patient behavior, such as compliance with treatments and may have contributed to the reduced need for readmission in the Furoscix arm. That said, the ability to safely avoid the index admission in all but one of the Furoscix patients was thought to be a clinically significant finding and was responsible for the majority of the cost savings.

Given that a historical control group was used for matching based on coding data, many clinical parameters are not available, including vital signs at the time of admission and exact laboratory values, such as serum creatinine. The success and efficacy of decongestion was not available in this cohort. In addition, repeat visits were categorized as 'HF-related' or 'not-HF-related' based on billing codes, therefore the diagnostic accuracy is less certain although sensitivity analysis excluding patients with prolonged length of stay did not result in substantial changes to our findings. Finally, although the authors attempted to compare two populations with similar HF comorbidities, severity and hospitalization risk, there may be clinically relevant underlying differences not controlled for using the matched cohort design.

In evaluating limitations, it is important to remember the pilot nature of this study and its implications. Currently, over 90% of HF patients present to the ED with worsening signs and symptoms of congestion. Previous studies suggest that based on the volume of congestion at presentation, over 50% of these admissions may be avoidable if we have the appropriate tools for decongestion, as 66% of HF hospitalizations are considered uncomplicated. Screening and enrollment into FREEDOM-HF occurred after the ED physicians had made the decision to admit the patient to the hospital for iv. diuresis, thus our results are the first to show an effective treatment strategy to safely 'U-turn' HF patients prior to admission from the ED. Given the successfulness of our pilot intervention, larger trials randomizing selected HF patients to Furoscix versus hospital admission can be conducted to address any additional biases inherent in a non-randomized design.

Conclusion

Our study is the first to demonstrate that use of Furoscix at home resulted in significant cost savings to the healthcare system and was an effective and safe alternative to hospital admission in a subset of low to moderate-risk HF patients presenting to the ED with worsening congestion despite oral diuretics. Furoscix improved patient symptoms and quality of life by potentially terminating the 'revolving door' cycle of admissions for congestion. Further prospective studies are needed to confirm and extend these findings.

Summary points

- Symptoms related to congestion are the primary reason heart failure (HF) patients seek medical attention, which typically requires hospitalization for intravenous (IV) diuretic therapy.
- Furoscix is a new, pH-neutral subcutaneous formulation of furosemide that is bioequivalent to iv. furosemide injection which allows for outpatient administration.
- The objectives of this study were to evaluate differences in healthcare resource utilization costs for patients treated with Furoscix at home compared with patients who received in-hospital iv. furosemide for $\leq$72 h; and to evaluate safety, quality of life and patient satisfaction.
- Compared with a matched historical cohort of hospitalized patients who received iv. furosemide, use of Furoscix resulted in a 30-day HF-related healthcare cost saving of $16,995 per patient.
- Furoscix use led to significant improvements in overall Kansas City Cardiomyopathy Questionnaire – Short Form (KCCQ-12) summary score ($p = 0.0443$) and BNP/NT-proBNP ($p < 0.01$) from baseline.
- The most frequent adverse events in patients receiving Furoscix were mild and consisted of infusion site bruising (29.2%), infusion site pain (29.2%) and dizziness (12.5%).
- Furoscix at home resulted in significant cost savings to the healthcare system and was an effective and safe alternative to hospital admission in low to moderate-risk HF patients presenting to the ED with worsening congestion. Large, prospective, randomized studies are needed to confirm these findings.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fca-2023-0071

Author contributions

D Bensimhon, WS Weintraub and WF Peacock were responsible for study conception and design; D Bensimhon, WS Weintraub, WF Peacock, T Alexy, D McLean and D Haas were responsible for patient recruitment; JF Mohr and MM Goodwin were responsible for acquisition of data; KL Deering and SJ Millar were responsible for data analysis, and JF Mohr and M Goodwin were responsible for drafting and revision of the manuscript.

Financial & competing interests disclosures

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data. Data reported in this manuscript are available within the article or posted publicly at www.clinicaltrials.gov, according to the required timelines. Additional data from the study are available upon reasonable request.

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