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ORIGINAL RESEARCH

Continuous Versus Intermittent Loop Diuretics Step-by-Step Protocol in Acute Heart Failure (DIUR-AHF): A Propensity-Matched Analysis

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BACKGROUND: Loop diuretics are used to solve congestion in acute heart failure. However, a clear indication about the best infusion modality, dose, and duration of the treatment has not yet been established. In this analysis of the DIUR-AHF (Different Loop Diuretic Dosing and Administration in Acute Heart Failure) study, we aimed to investigate the effects of different diuretic administration modalities (ie, intermittent versus continuous furosemide infusion) and dose (high dose [HD] versus low dose) on congestion, renal function, and outcome.

METHODS: Patients received intermittent or continuous intravenous loop diuretics infusion combined as a 1:1 ratio for a period of 72 to 120 hours. HD was defined as a high loop diuretic dose >120 mg/d. Clinical outcome was evaluated in terms of death or heart failure rehospitalization over a 6-month follow-up period.

RESULTS: A total of 370 patients with AHF were included in this analysis, 189 treated with continuous intravenous loop diuretics infusion and 181 with intermittent intravenous loop diuretics infusion. At baseline, the continuous intravenous loop diuretic infusion group showed increased median values of blood urea (P=0.010) and creatinine (P=0.017). Dividing our sample according to loop diuretic dosage, the HD group revealed similar congestion and weight loss compared with the low-dose group; however, the HD group showed a reduced diuretic efficiency (−0.13 [−0.22 to −0.07] versus −0.32 [−0.59 to −0.20] kg/d; P<0.001) and an increased rate of adverse event occurrence (55% versus 20%; P<0.001). Multivariable analysis showed the association between HD treatment and poor postdischarge outcome (hazard ratio, 1.95 [95% CI, 1.23–3.10]; P=0.005).

CONCLUSIONS: An HD of loop diuretics infusion revealed an increased risk for adverse events together with reduced diuretic response. Our results extend previous findings revealing the association between HD diuretics and prognosis in patients with chronic HF. Additional studies may confer loop diuretic response in relation to the other decongestive treatments.

Key Words: acute heart failure ■ congestion ■ loop diuretics ■ management

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CLINICAL PERSPECTIVE

What Is New?

- Continuous intravenous loop diuretic infusion did not reduce the congestion burden at discharge, leading to a higher rate of worsening renal function and lower diuretic efficiency.
- A high dose of diuretics was related to poor prognosis at 180-day follow-up, and this condition is probably due to the diuretic resistance of these patients, depending on their worse baseline conditions.

What Are the Clinical Implications?

- The management of diuretic treatment in acute heart failure should include a better evaluation of baseline characteristics of the patients and also a step-by-step adjustment of the dose considering diuretic efficiency, urine output, and spot urine sodium to avoid a detrimental overtreatment.

Nonstandard Abbreviations and Acronyms

ALARM-HF	Acute Heart Failure Global Registry of Standard Treatment
CiV	continuous intravenous loop diuretics infusion
DE	diuretic efficiency
DIUR-AHF	Different Loop Diuretic Dosing and Administration in Acute Heart Failure
DOSE	Diuretic Optimization Strategies Evaluation in Acute Heart Failure
HD	high dose
IiV	intermittent intravenous loop diuretics infusion
LD	low dose
PUSH-AHF	Pragmatic Urinary Sodium–Based Treatment Algorithm in Acute Heart Failure
WRF	worsening renal function

Congestion represents the main cause of hospitalization in patients with acute heart failure (AHF), requiring urgent treatment mainly based on intravenous diuretic therapy.[1,2] Additionally, the residual congestion at discharge (about 50% of patients admitted with AHF diagnosis), mainly due to inappropriate decongestion treatment, is one of the most important prognostic factors in patients with AHF.[3–7] Despite loop diuretics remaining the first-choice drug for treatment of volume overload in AHF, their correct administration modality and dose are not universally accepted. Multiple studies have investigated different strategies or modalities with contrasting findings.[8,9] These gaps appear to be related to several factors, such as the heterogenicity of population enrolled, the timing of drug administration, the inclusion of ambiguous end points, and the quality of data.[8–11] Despite the lack of solid data, European Society of Cardiology recommendations confirmed the milestone role of loop diuretics to alleviate congestion in AHF setting, but there were no indications about the optimal modality administration and infusion time.[12] For instance, the DOSE (Diuretic Optimization Strategies Evaluation in Acute Heart Failure) trial, comparing high-dose (HD) versus low-dose (LD) and continuous (CiV) versus intermittent (IiV) loop diuretics infusion, did not show a significant difference among the 4 arms.[13] Moreover, a propensity-matched analysis of ALARM-HF (Acute Heart Failure Global Registry of Standard Treatment) study showed that an HD of intravenous loop diuretics did not affect the short-term mortality rate.[14] Finally, a recent retrospective analysis demonstrated that the wide variation in diuretic strategies was associated with a longer hospital stay, but there was no association with 30-day readmission.[15] Trying to fill the current gaps, the Heart Failure Association of the European Society of Cardiology published a theoretical algorithm suggesting initiating intravenous administration that doubled the oral dose and loop diuretic titration on the basis of diuretic response using urinary salt concentration and urine output.[16] However, the optimal diuretic strategies in AHF remain unclear; thus, a specific analysis evaluating different modality administration becomes a priority. Recently, the DIUR-AHF (Different Loop Diuretic Dosing and Administration in Acute Heart Failure) trial showed that CiV of furosemide for a period of 72 to 120 hours, even if associated with better decongestion (ie, higher NTproBNP [N-terminal pro B-type natriuretic peptide] decrease, weight loss, and daily mean urine output), led to a poorer outcome, suggesting that “more effective decongestion” does not necessarily indicate a better outcome. Similarly, HD was associated with an increased risk of both hospitalization and death.[17] To elucidate the effects of different diuretic regimen and administration modalities in patients with AHF, focusing on loop diuretic dosage and the consequent effect on the 180-day mortality rate and hospitalization, we performed a propensity matched analysis focused on high versus low dose.

METHODS

Data Availability

Data may be officially requested from Prof. Alberto Palazzuoli and will be available after his positive response.

Study Design

The DIUR-AHF study was a multicenter, prospective, open-label, observational case–control study originally designed to randomize patients with a diagnosis of AHF to CiV versus liV loop diuretic infusion.[18] However, due to the difficulties experienced during SARS-CoV-2 pandemic, we modified the nature of the study, changing it to an observational prospective study, opening to the physicians' decision the possibility to administer both CiV and liV loop diuretics, with an enrollment ratio of 1:1. The enrollment to follow-up period ranged from November 2018 to February 2023. Seven different centers participated in the study (Cardiovascular Diseases Unit, Siena, Italy; Clinical Cardiology, Siena, Italy; Cardiology Ward La Sapienza University, Rome, Italy; Cardiology Unit, Mondovì, Italy; Le Molinette Hospital, Turin, Italy; Cardiology Division San Paolo Hospital University of Milano, Italy; Internal Medicine Monaldi Hospital Federico II University, Naples, Italy). The details of patients' enrollment are shown in Figure S1. The study complies with the Declaration of Helsinki. The study was approved by the local ethics institutional board (Comitato Etico Regione Toscana – Area Vasta Sud Est approved on June 19, 2017) and registered at Clinicaltrial.gov (NCT02638142). All patients gave written informed consent. The statistical analyses were conducted in collaboration with the Department of Economics and Statistics of the University of Siena.

Inclusion Criteria

Patients were eligible if they were admitted with a main diagnosis of AHF or acute decompensated heart failure, regardless of left ventricular ejection fraction, with typical symptoms (dyspnea, orthopnea, peripheral edema, or major fatigue) and at least 2 clinical signs (rales, hepatomegaly, pulmonary congestion on chest radiography, jugular vein dilation, or a third heart sound) and NT-proBNP (N-terminal pro-B-type natriuretic peptide) level of >500 pg/mL. Additionally, patients were included if they presented radiographic or ultrasound indexes of pulmonary overload (pulmonary congestion, fluid redistribution, edema or pleural effusion, and B-line count >20 at lung ultrasound). Additional eligibility criteria were a history of chronic heart failure and use of an oral loop diuretic for at least 1 month before admission, at a dose ranging from 25 to 250 mg daily of furosemide.[17,18]

Exclusion Criteria

Patients were excluded if they received >40 mg of intravenous furosemide at emergency department presentation or if they had end-stage renal disease or needed renal replacement therapy. Other exclusion criteria were a recent diagnosis of myocardial infarction (within 30 days before the screening); systolic blood pressure <80 mm Hg; sepsis, liver diseases, inflammatory diseases, or neoplastic diseases or if they needed mechanical cardiac support.[17,18]

Administration Procedures

At enrollment, patients taking oral loop diuretics were stopped, and they received an intravenous loop diuretic at double the oral maintenance dose, administered as a single bolus immediately after inclusion in the study. Patients who had never taken diuretics were started on 40 mg of intravenous furosemide administered twice during the first 12 hours. Patients were then enrolled in a 1:1 ratio upon physicians' judgment to receive either twice-daily bolus injections liV or CiV combined as a 1:1 ratio in 5% saline solution for a period of 72 to 120 hours, receiving a starting dose of 80±20 mg/d. CiV was administered by syringe pump including furosemide, with velocity depending on the dose administered; in the intermittent arm, furosemide was administered every 12 hours in 2 distinct saline solutions in 1 hour. If a patient had a good response, the initial dose was continued; if a patient had a poor response, defined as diuretic efficiency (DE) <0.2 kg/d for 40 mg of furosemide and net urine output <1 L/day, the furosemide dosage was doubled (160±40 mg/d).[16–20] In case of continued diuretic resistance, defined as a poor response, the dosage was raised to 250±40 mg/d (Figure S2). Therefore, patients with poor DE underwent intensification treatment. Additionally, serum electrolytes, renal function, and urine output were monitored daily across the whole infusion period. It was strongly advised that the doses of neurohumoral blockers remained unchanged in accordance with the European Society of Cardiology guidelines; however, for patients with low blood pressure values or hypoperfusion signs needing inotropic infusion, the treatment was interrupted or reduced according to clinical status.[19] The use of additional agents (amine treatment, levosimendan, vasodilators, hypertonic saline infusions) was independently decided by the physicians on the basis of the laboratory values (creatinine, electrolyte balance, and natriuretic peptides) and the clinical and hemodynamic/congestion status, with daily dosages adjusted during the infusion periods. At admission, during the treatment period, and at discharge, patients underwent a clinical assessment of congestion, blood sample analysis (for NTproBNP, renal function variables, electrolytes), urine output measurement, and echocardiographic assessment (Figure S3).[17,18]

Definitions

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73

m^2 at baseline. Worsening renal function (WRF) was defined as an eGFR decrease ≥20% at any time from admission to discharge.[21] eGFR was calculated using the Cockcroft–Gault formula.[22] DE was calculated according to the following formula: (Weight change/days of infusion)/(Mean daily furosemide dosage/40 mg of furosemide).[23,24] HD was defined as a loop diuretic dose >120 mg/day; LD is defined as a loop diuretic dose ≤120 mg/day. A congestion score was calculated both at admission and at discharge. The following symptoms and signs were evaluated: pulmonary rales, peripheral edema, dyspnea, and pulmonary congestion at chest radiography (4 total points). Persistence of congestion was defined as a congestion score at discharge ≥2.[25]

Follow-Up

Clinical outcome was evaluated in terms of death or heart failure rehospitalization over a 6-month follow-up period. There was a scheduled outpatient visit or phone contact at 30, 60, 90, and 180 days after discharge. Heart failure rehospitalizations were defined as any hospital admission with a primary or secondary diagnosis of volume overload or low output due to pump failure, acute coronary syndrome complicated by heart failure, ventricular arrhythmia associated with left ventricular dysfunction, or heart failure related to WRF.

Primary and Secondary End Points

Primary end points were 180-day death and heart failure rehospitalization comparing IiV versus CiV and HD versus LD. Exploratory safety primary end points were the change in the serum creatinine level from baseline to the end of infusion period in the 2 arms and in the high versus low diuretic dose. Secondary end points were the evaluation of decongestion, NTproBNP decrease, and WRF occurrence in relation to high versus low diuretic dosage.

Sample Size Calculation

The study's sample size is based on our primary end points. Thus, we considered that the adverse events incidence (180-day cardiac death or rehospitalization) is likely to be 40% in patients undergoing continuous infusion and 25% in patients undergoing intermittent infusion. The sample size of 304 patients (152 in each arm) might be helpful in detecting the clinical outcome difference between the groups (CiV versus IiV) with a power of 80%. We assumed no patients would withdraw or be lost during the hospitalization period. We also considered that 20% of subjects could be lost during follow-up after hospital discharge.

Statistical Analysis

All data were analyzed with intention-to-treat principles. Continuous variables are expressed as median (interquartile range), while discrete variables are presented as counts with percentages. The Wilcoxon rank-sum test and χ^2 test were used to compare the 2 groups (CiV versus IiV and HD versus LD). With the aim of reducing selection bias and therefore approximating a randomized controlled trial in a setting of observational data, a propensity score adjustment was implemented. More precisely, a multivariate logistic regression model was used to estimate the probability of belonging to the IiV group. As predictors, we included the variables related to patient characteristics at admission that were associated with the treatment (P<0.2) (Table 1). The 7 regressors included in the propensity score were age, creatinine, blood urea nitrogen, eGFR, diabetes, dyslipidemia, and left ventricular ejection fraction. The adequacy of the propensity score adjustment was evaluated by examining the overlap between the propensity score distributions of the 2 treatments (Figure S4). A sufficient overlap indicates that there is a common support range, where both groups have comparable propensity scores. The multivariate model used to determine the propensity score representing the probability of receiving IiV is reported in Table S1. To assess the effectiveness of the propensity score adjustment, the overlap between the propensity score distributions of the 2 groups was evaluated. This was done by calculating the minimum value of the kernel density functions at each point along the score range and integrating the resulting curve. The overlap area was found to be 0.82, indicating substantial common support between the groups. Such a high degree of overlap suggests that the propensity score adjustment successfully balanced the baseline characteristics between the groups, thereby reducing potential confounding and enhancing comparability.[26]

A univariate Cox regression model was performed for each of the regressors listed in Figure 1 to assess their association with the outcomes of death and rehospitalization (within 180 days). Schoenfeld tests were performed for all univariate models, and residual congestion was the only variable showing evidence of proportional hazards violation (P<0.0001), indicating that its effect is not constant over time and that the corresponding hazard ratio (HR) should be interpreted with caution.

In addition, a multivariable Cox regression model was also performed, incorporating the propensity score adjustment and also including sex, hyponatremia, hypokalemia, sodium–glucose cotransporter 2 inhibitor use, and mineralocorticoid receptor antagonist use. This adjustment was applied to control for potential confounders and improve the accuracy of

Table 1. Differences in Baseline Characteristics Between CiV and IiV Groups

	All patients (n=370)	cIV (n=189)	IiV (n=181)	*P* value
Age, y	78 (71–84)	79 (73–85)	76 (69–84)	0.05*
Sex, n				
Male	206	104	99	1
Female	167	85	82	…
Laboratory data before the treatment				
Creatinine, mg/dL	1.4 (1.1–1.9)	1.5 (1.1–2.1)	1.4 (1.0–1.8)	0.017*
Blood urea nitrogen, mg/dL	65 (41–96)	67 (46–99)	57 (34–89)	0.01*
eGFR, mL/min per 1.73 m^2	41 (28–59)	38 (26–55)	44 (31–66)	0.02*
Serum sodium, mEq/L	138 (135–141)	138 (133–141)	138 (136–140)	0.225
Serum potassium, mEq/L	4.1 (3.8–7.5)	4.1 (3.8–4.4)	4.1 (3.8–4.5)	0.587
NTproBNP, pg/mL	7650 (4093–18352)	7200 (4210–19312)	7800 (3930–17725)	0.975
Risk factors, %				
Diabetes	38	34	41	0.163
Hypertension	72	75	70	0.34
Dyslipidemia	45	40	49	0.103
Atrial fibrillation, %	36	38	34	0.579
Coronary artery disease, %	54	57	51	0.314
Chronic kidney disease, %	55	58	51	0.267
Left ventricular ejection fraction, %	35 (25–40)	30 (25–40)	35 (25–40)	0.068
Home therapy with furosemide, dose, mg	100 (75–150)	100 (75–175)	100 (75–150)	0.349
Other heart failure home therapy				
Sodium–glucose cotransporter-2 inhibitors %	7	6	7	0.75
Mineralocorticoid receptor antagonists, %	20	21	19	0.755

cIV indicates continuous intravenous infusion; eGFR, estimated glomerular filtration rate; IiV, intermittent intravenous infusion; and NTproBNP, N-terminal pro-B-type natriuretic peptide.
*XXX.

the estimated associations between the variables and the outcomes of death and rehospitalization (within 180 days). In the multivariable Cox model, the proportional hazards assumption was again violated for residual congestion (Schoenfeld test, $P<0.005$), and the global test also indicated deviation from proportionality ($P<0.002$). Consequently, residual congestion was modeled using an extended Cox approach

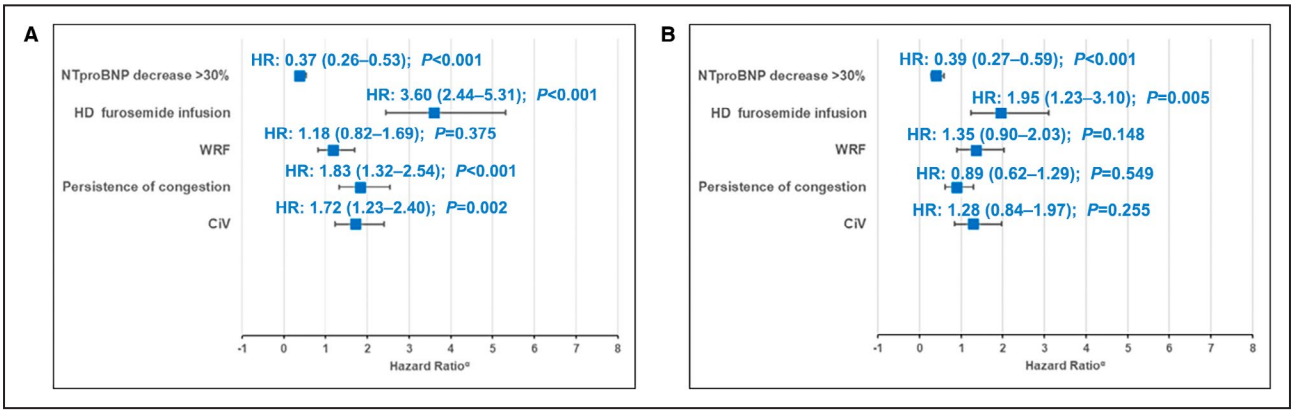

Figure 1. Univariate HR (A) and multivariable HR* (B) for 180-day death or rehospitalization.
*Adjusted for age, sex, creatinine, blood urea nitrogen, estimated glomerular filtration rate, diabetes, dyslipidemia, left ventricular ejection fraction, hyponatremia, hypokalemia, sodium–glucose cotransporter-2 inhibitor use, and mineralocorticoid receptor antagonist use. CiV indicates continuous intravenous infusion; HD, high dose; HR, hazard ratio; LD, low dose; NTproBNP, N-terminal pro B-type natriuretic peptide; and WRF, worsening renal function.

Table 2. Differences in After-Treatment Variables Between CiV and IiV Groups

	All patients (n=370)	cIV (n=189)	IiV (n=181)	*P* value
Laboratory data after treatment				
Creatinine, mg/dL	1.47 (1.10 to 1.90)	1.60 (1.20 to 2.20)	1.32 (1.00 to 1.63)	<0.001*
eGFR, mL/min per 1.73 m^2	38 (15 to 54)	34 (24 to 47)	43 (29 to 58)	<0.001*
Serum sodium, mEq/L	138 (136 to 141)	139 (136 to 141)	138 (136 to 140)	0.312
Serum potassium, mEq/L	4.1 (3.8 to 4.4)	4.1 (3.8 to 4.4)	4.1 (3.8 to 4.4)	0.244
NTproBNP, pg/mL	4405 (2501 to 11 750)	4110 (2075 to 11 145)	4955 (3110 to 12 400)	0.052
Additional hypertonic saline solution, %	13	17	9	0.031*
Inotrope agent administration, %	21	26	16	0.027*
Predischarge sodium levels, mEq/L	138 (136 to 141)	139 (135 to 141)	138 (136 to 140)	0.312
Predischarge potassium levels, mEq/L	4.1 (3.8 to 4.4)	4.1 (3.8 to 4.4)	4.1 (3.8 to 4.5)	0.244
Electrolyte imbalance, %				
Hyponatremia	26	25	24	0.997
Hypokalemia	10	13	6	0.032*
Weight loss, kg	3.0 (2.0 to 5.8)	4.0 (2.0 to 6.0)	3.0 (2.0 to 5.0)	<0.001*
Mean urine output, mL	2100 (1600 to 2500)	2100 (1600 to 2650)	2000 (1650 to 2400)	0.102
NTproBNP decrease >30%, %	51	61	40	<0.001*
Intravenous diuretic daily dosage, mg/d	125 (80 to 225)	200 (125 to 250)	100 (60 to 150)	<0.001*
DE, (kg/d for 40 mg furosemide	−0.20 (−0.33 to −0.10)	−0.16 (−0.27 to −0.10)	−0.24 (−0.40 to −0.10)	0.015*
Urinary spot sodium, (mEq/L)	71 (55 to 82)	71 (50 to 82)	72 (59 to 82)	0.229
WRF, %	26	34	18	<0.001*
Persistence of congestion after treatment, %	30	25	35	0.048*
Length of hospital stay, d	12 (9 to 14)	13 (9 to 15)	11 (8 to 14)	0.004*
180-d adverse event occurrence, %	39	47	31	0.002*

cIV indicates continuous intravenous infusion; DE, diuretic efficiency; eGFR, estimated glomerular filtration rate; IiV, intermittent intravenous infusion; NTproBNP, N-terminal pro-B-type natriuretic peptide; and WRF, worsening renal function.

*XXX.

with a time-varying effect through an interaction with log (time), confirming that its HR varies over time and cannot be interpreted within a standard proportional hazards framework.

The univariate analysis was used to examine the individual effects of each regressor, while the multivariable model adjusted for potential confounders to provide a more comprehensive understanding of the relationships between the variables and the outcomes. Influence diagnostics (dfβ) were performed for both univariate and multivariable models and did not identify any observations exerting abnormal influence on the coefficient estimates. Deviance residuals did not exceed diagnostic thresholds and did not correspond to elevated dfβ values, indicating the absence of influential outliers and supporting adequate overall model fit. The Kaplan–Meier method was used to generate survival curves, using the log-rank test, for the composite outcome. All statistical tests were 2-tailed, with a *P* value <0.05 considered significant. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We initially included in the protocol 402 patients with AHF. To reduce treatment selection bias and to homogenize between IiV and CiV arms, 370 subjects were subsequently selected through propensity score analysis; finally, 189 patients received CiV treatment and 181 were treated with IiV. No significant differences in sex; common risk factors; serum sodium; serum potassium; NTproBNP; presence of coronary artery disease, atrial fibrillation, or chronic kidney disease; and left ventricular ejection fraction were revealed. Significantly different median values of creatinine (*P*=0.017), blood urea nitrogen (*P*=0.010), and eGFR (*P*=0.02) in CiV group with respect to IiV were observed. All the baseline characteristics are shown in Table 1.

The analysis of variables after treatment showed significantly different levels of creatinine and eGFR values in the CiV group with respect to the IiV group (1.60 [1.20–2.20] versus 1.32 [1.00–1.63] mg/dL, *P*<0.001; 34 [24–47] versus 43 [29–58] mL/min per 1.73 m^2; *P*<0.001, respectively) associated with significantly increased

Table 3. Differences in After-Treatment Variables Between HD and LD Groups

	HD (n=204)	LD (n=166)	*P* value
Home therapy with furosemide, mg	150 (100 to 181)	75 (50 to 100)	<0.001*
NTproBNP, pg/mL	7650 (4344 to 19681)	7478 (3845 to 17259)	0.416
Additional hypertonic saline solution, %	19	6	<0.001*
Inotrope agent administration, %	32	8	<0.001*
Electrolytes unbalance, %			
Hyponatremia	27	21	0.196
Hypokalemia	12	7	0.198
Weight loss, kg	3.0 (2.0 to 6.0)	3.0 (2.0 to 5.0)	0.744
Mean urine output, mL	2100 (1600 to 2700)	2000 (1612 to 2388)	0.024*
DE, kg/d for 40 mg furosemide	−0.13 (−0.22 to −0.07)	−0.32 (−0.59 to −0.20)	<0.001*
Urinary spot sodium, mEq/L	65 (48 to 78)	78 (66 to 86)	<0.001*
WRF, %	32	19	0.009*
Persistence of congestion after treatment, %	32	27	0.378
Length of hospital stay, d	12.0 (9.8 to 15.0)	11.0 (8.0 to 14.0)	0.001*
CiV infusion, %	73	25	<0.001*
180-d adverse events occurrence, %	55	20	<0.001*

CiV indicates continuous intravenous infusion; DE, diuretic efficiency; HD, high dose; LD, low dose; NTproBNP, N-terminal pro B-type natriuretic peptide; and WRF, worsening renal function.

*XXX.

WRF prevalence in the CiV group (34% versus 18%; *P*<0.001). Therefore, in the CiV group, there was a significantly different rate of additional hypertonic saline solution administration (17% versus 9%; *P*=0.015), inotrope agent administration (26% versus 16%; *P*=0.02), and evidence of hypokalemia (13% versus 6%; *P*=0.03) compared with the liV group. Additional results showed significant weight loss (4.0 [2.0–6.0] kg versus 3.0 [2.0–5.0] kg; *P*<0.001), residual congestion reduction (35% versus 25%; *P*=0.048), NTproBNP decrease (61% versus 40%, *P*<0.001), and DE (−0.24 [−0.40 to −0.10] versus −0.16 [−0.27 to −0.10] kg/d for 40 mg of furosemide; *P*=0.015) in the CiV group with respect to liV group. Despite these results, no significant differences were found in urinary sodium level. Whereas CiV showed significantly different median values with respect to liV for the length of hospital stay (13 [9–15] days versus 11 [8–14] days; *P*=0.004) and adverse event rate (47% versus 31%; *P*=0.002; Table 2).

Dividing patients according to furosemide dose, we found that patients in the HD arm (204) were significantly treated with different proportions of inotropes and saline solution (32% versus 8% and 19% versus 6%, respectively; *P*<0.001) compared with those in the LD arm (166). Interestingly, significantly different median values for diuresis and DE for the HD and LD arms were observed (2100 [1600–2700] versus 2000 [1612–2388] mL, *P*=0.024; and−0.13 [−0.22 to −0.07] versus −0.32 [−0.59 to −0.20]; *P*<0.001, respectively); urinary sodium medians were found to be significantly different, with values higher in the LD arm compared with the HD arm (78 [66–86] versus 65 [48–78] mEq/L; *P*<0.001). Significant differences were also detected in the length of hospital stay (12.0 [9.8–15.0] versus 11.0 [8.0–14.0] days; *P*=0.001), CiV treatment (73% versus 25%; *P*<0.001), and combined end point of death and hospitalization (55% versus 20%; *P*<0.001; Table 3).

Univariate Cox analyses showed that NT-proBNP decrease (HR: 0.37 [0.26–0.53], *P*<0.001), HD (HR: 3.60 [2.44–5.31], *P*<0.001), residual congestion (HR: 1.83 [1.32–2.54], *P*<0.001), and CiV (HR: 1.72 [1.23–2.40], *P*<0.002) were all significantly associated with adverse outcomes (Figure 1A). However, at multivariable analysis, only HD (HR, 1.95 [95% CI, 1.23–3.10]; *P*=0.005) and NTproBNP decrease (HR, 0.39 [95% CI, 0.27–0.59]; *P*<0.001) can be considered as statistically significant (Figure 1B).

The Kaplan–Meier survival analysis, stratified by propensity score quintiles, showed a borderline nonsignificant difference in the composite outcome between the CiV and liV groups (log-rank test, *P*=0.051), suggesting a potential trend toward worse prognosis in the liV group, although the result did not reach conventional statistical significance (Figure S4). Furthermore, Kaplan–Meier survival curves confirmed the association between HD furosemide infusion and outcome (*P*<0.001; Figure 2).

DISCUSSION

Loop diuretics are the most common drugs used in the management of AHF. The primary goal of loop

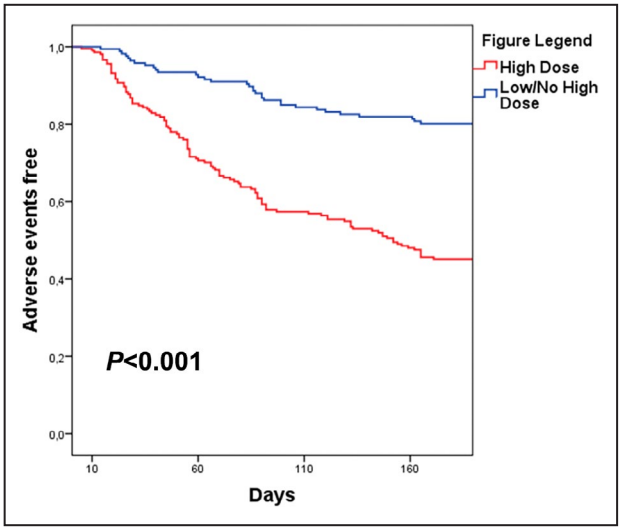

Figure 2. Kaplan–Meier survival plots according to furosemide dose: HD vs LD.
HD indicates high dose; and LD, low dose.

diuretic therapy is to reduce fluid overload promoting diuresis, reduce congestion, and provide symptom relief.[9–13] However, despite its routine use, robust data on the optimal infusion period, the modality of administration, and the long-term effects of this treatment, particularly during the acute phase, are lacking. Notably, most of the interventional trials evaluating diuretic treatment were focused on targeting euvolemia and symptom relief without significant effects on the disease's natural course. Moreover, HD and chronic use of loop diuretics may cause renal dysfunction, electrolyte imbalance, and progressive diuretic resistance. Thus, the choice between CiV and IiV loop diuretic treatment could significantly affect therapeutic outcomes.[8,14,15] Our propensity score analysis of DIUR-AHF data revealed that CiV administration leads to significative renal function deterioration, despite an increased daily diuresis, DE, weight loss, and significant NTproBNP decrease. Conversely, CiV was associated with prolonged hospital stays and an increased rate of adverse events. However, this ominous trend was not confirmed in the propensity-adjusted analysis matched for baseline characteristics; a possible explanation is that patients in the CiV arm had a more impaired congestion status and worse baseline renal function. This current assumption seems to be confirmed by the evidence that patients receiving CiV treatment showed longer timing of infusion duration and were discharged with a major dose of loop diuretics. Interestingly, the global congestion burden was improved, and it was associated with a more substantial weight loss and a decrease in NT-proBNP levels together with a higher rate of daily diuresis. However, an increased rate of WRF was observed. The complex relationship existing between congestion and renal function during decongestive treatment has been largely investigated in the literature without definitive results. Currently, the most accepted opinion is that if a slight WRF occurs together with effective decongestion, it is not harmful. However, this hypothesis needs to be confirmed according to the presence of baseline renal dysfunction, the treatment used, and the specific dose administered before the infusion period. To date, CiV is probably the best strategy to maintain a stable plasma concentration of the medication, which can lead to more stable therapeutic effects, minimizing the fluctuation related to the IiV infusion. Moreover, CiV may be preferred for preventing diuretic resistance, while bolus doses can be effective for rapid relief of symptoms, leading to a more rapid response without achieving an optimal drug plasma level.[4,27] Nevertheless, our data contradict earlier research indicating that CiV was linked to improved diuresis and decreased renal impairment.[28,29]

Several authors have suggested a changing paradigm from a diuretic-centered strategy to correction of pathophysiological mechanisms sustaining congestion and disease progression.[27] According to the recent studies, the best way to prevent diuretic resistance and to obtain optimal decongestion and diuresis is most likely to be reached by continuous administration.[28,30] However, a distinction should be made between the decongestion relief and long-term outcome related to the drug infusion strategy. Moreover, in the most robust trials from the literature, patients are often discharged with residual congestion signs. Finally, congestion assessment is generally judged by a simple clinical evaluation without an accurate diagnostic analysis based on ultrasound and hemodynamic evaluation.

The effects of various loop diuretic administration and strategies were recently studied. Unfortunately, most of the studies differed in terms of methodology, patients' characteristics, heart failure phenotype, and primary/secondary end points. Furthermore, most of the results derived from the retrospective and the interventional research and new biomarkers to predict DE and dose were proposed (ie, measurement of urine salts, together with urinary and blood creatinine values and the assessment of hydration status).[8,18,27,28,31] Different studies tried to investigate this topic with contrasting or neutral results. The larger trials on this topic did not demonstrate differences between CiV and IiV loop diuretic administration.[13,32–34] Several studies, including our previous data, revealed that CiV administration allowed a better decongestion through an efficacy diuresis and natriuresis.[29,35,36] However, for both modalities of infusion, there were no significant differences in terms of outcome.

The comparison between the HD and LD arms revealed that subjects in the HD arm were receiving a more increased oral loop diuretic dose before the infusion and were more often treated with the continuous modality. Despite a similar congestion profile after treatment, HD showed higher rate of daily diuresis but lower urinary Na^+ levels and DE. Conversely, the LD arm showed a shorter intravenous infusion period and a lower WRF prevalence without a significant hypokalaemia rate between the 2 groups, although saline solution was administered during the infusion period to avoid electrolyte imbalance. This is in line with the recent evidence that demonstrated that a treatment-induced increase in serum potassium levels was related to a significant adverse and arrhythmic events reduction.[37] Additionally, in the LD group, there was a lower rate of postdischarge adverse events, which was confirmed by the propensity score adjustment. The combination between reduced DE and lower urinary Na^+ observed in the HD arm implies that this strategy is adopted when the standard dose was ineffective, probably due to the diuretic resistance occurrence as a consequence of more interstitial fluid accumulation.[26,38,39] The differences found between CiV and IiV as well as between HD and LD should be contextualized in a more complex scenario involving the degree of diuretic response (based on urine output or DE measured by weight loss), the presence of chronic kidney disease, tubular sodium avidity, appropriate diuretic administration, and a universal definition of diuretic resistance.[16,28] Other relevant caveats appear related to the inability to account kidney perfusion and congestion status, abdominal hypertension, dietary sodium intake, loop diuretic delivery and filtration, and organic anion status. All these issues preclude the application of a preventive strategy to avoid diuretic resistance in clinical practice.[27,30]

Data from the literature about the high versus low loop diuretics dose have been not extensively investigated and with no standard procedures. In the PUSH-AHF (Pragmatic Urinary Sodium–Based Treatment Algorithm in Acute Heart Failure) trial, the increase of diuretic dose was decided on the basis of the urinary sodium levels using a dynamic protocol.[33] Additionally, a large cohort analysis from United States records on patients with AHF confirmed that an intravenous loop diuretic escalation dose was associated with an increased risk of death and hospitalization. However, the study did not report the exact loop diuretic dose related to poor outcome.[40] Recently, a study protocol was proposed with a dynamic approach to diuretic strategies considering urinary sodium levels as the index of diuretic response.[41] Accordingly, our data extend previous research on the detrimental relationship between HD oral diuretics and outcome in chronic heart failure, and they could offer a new perspective on various loop diuretic infusion modalities across a stepwise protocol taking into the account the DE.[42,43]

Our data demonstrated that despite similar congestion results at discharge, HD portends a prolonged hospital stay, greater prevalence of renal dysfunction, and increased risk in the postdischarge period.

This is related to a more advanced heart failure severity with higher rate of tubular diuretic resistance; in patients needing HD, both preadmission and postdischarge HD was found. This condition probably was due to the need for an early nephron blockade strategy to avoid diuretic resistance and unresponsiveness.[26,44] Overall, our data deserve 2 main observations: (1) the relevance usually attributed to the congestion and natriuretic peptides changes observed during hospitalization should be contextualized inside the diuretic therapy infusion modality and dose; and (2) the decongestion achieved by CiV and HD administrations is not associated with prognostic positive effects; therefore, it should be evaluated in the context of a dynamic protocol taking into account diuretic response and loop diuretic dose adjustment. This issue has been highlighted recently in an expert consensus document advising the urinary sodium and urine volume evaluation soon after initial loop diuretic administration to reach the target dose.[45]

STUDY LIMITATIONS

There are some limitations that must be discussed. First, the open-label nature of the protocol design with the lack of randomization, mostly related to the dynamic structure of the stepwise diuretic infusion protocol, lead to the possibility that physicians' decision may affect the interpretation of final results; however, the starting dose was fixed for all groups (ie, 80 mg/d), and the stepwise protocol was based on DE and daily urine output. However, the propensity-matched analysis allows, at least in part, the overcoming of this limitation. Second, it is necessary to acknowledge that some potential confounders not included in the propensity analysis, such as the use of other drugs, the underestimation of extracardiac comorbidity, and the absence of detailed kidney disease pathogenesis, may have influenced the results. Specifically, the concomitant use of mineral receptor antagonists or sodium–glucose transporter-2 inhibitors during the infusion period may have influenced the results on potassium level and decongestion, respectively. However, the number of patients taking a mineralocorticoid receptor antagonist was similar across the groups, and the number of subjects taking sodium–glucose cotransporter-2 inhibitors was low,

since the study started before their use in clinical practice. Indeed, these findings should be confirmed with the more recent guideline directed medical treatment including both mineralocorticoid receptor antagonists and sodium–glucose cotransporter-2 inhibitors. Third, the congestion assessment modality was restricted to clinical evaluation primarily identifying extravascular and systemic congestion. A better ultrasound and multimodality congestion assessment may be much more accurate for congestion status detection.[46] Fourth, the study lacks in the analysis of transient versus permanent WRF, which could explain the differences in terms of renal status following loop diuretic infusion. Finally, current findings may differ depending on the HF onset because our study included both patients with de novo AHF and patients with acute decompensated heart failure, which showed different background therapy.

CONCLUSIONS

In patients admitted for AHF and signs of congestion, IiV loop diuretic infusion was associated with a lower rate of WRF, a lower need for additional treatment, and a lower diuretic dose at discharge. Despite apparently better decongestion, HD was linked to a prolonged hospital stay, less diuretic response, and an increased risk of death and rehospitalization during 180-day follow-up. Additional research may be warranted to optimize the best intravenous diuretic modality administration according to congestion status, diuretic response, urinary sodium, and baseline renal function.

ARTICLE INFORMATION

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None.

Supplemental Material

Figures S1–S4
STROBE Checklist
Table S1

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