

# Rationale and study design of intravenous loop diuretic administration in acute heart failure: DIUR-AHF

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## Abstract

**Aims** Although loop diuretics are the most commonly used drugs in acute heart failure (AHF) treatment, their short-term and long-term effects are relatively unknown. The significance of worsening renal function occurrence during intravenous treatment is not clear enough. This trial aims to clarify all these features and contemplate whether continuous infusion is better than an intermittent strategy in terms of decongestion efficacy, diuretic efficiency, renal function, and long-term prognosis.

**Methods and results** This is a prospective, multicentre, randomized study that compares continuous infusion to intermittent infusion and a low vs. high diuretic dose of furosemide in patients with a diagnosis of acute heart failure, BNP  $\geq$  100 pg/mL, and specific chest X-ray signs. Randomization criteria have been established at a 1:1 ratio using a computer-generated scheme of either twice-daily bolus injection or continuous infusion for a time period ranging from 72 to 120 h. The initial dose will be 80 mg/day of intravenous furosemide and, in the case of poor response, will be doubled using an escalation algorithm. A high diuretic dose is defined as a furosemide daily amount  $>$ 120 mg/day respectively.

**Conclusions** Continuous and high dose groups could reveal a more intensive diuresis and a greater decongestion with respect to intermittent and low dose groups; high dose and poor loop diuretic efficiency should be related to increased diuretic resistance, renal dysfunction occurrence, and greater congestion status. Poor diuretic response will be associated with less decongestion and an adverse prognosis.

**Keywords** Acute heart failure; Treatment; Loop diuretics; Diuretic efficiency; Renal function; Outcome

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## Introduction

Acute heart failure (AHF) is characterized by a rapid progression of signs and symptoms resulting in the necessity of urgent therapy. Despite its high prevalence, the pathophysiological mechanisms and treatment options remain poorly defined and vastly understudied. Loop diuretics are the drugs most commonly used in the treatment of AHF, but their short-term and long-term effects are relatively unknown. The administration of intravenous loop diuretics in patients with heart failure and congestion typically results in a prompt diuretic effect and

decongestion. Nevertheless, high-quality data supporting the best modality of administration, the appropriate dosage, and infusion timing are lacking: It is not clear if continuous infusion is better than intermittent boluses in terms of worsening renal function (WRF), urine output, B-type natriuretic peptide (BNP) reduction, diuretic efficiency (DE), and prognosis. For all of these reasons, we aim to investigate the effect of the two different modalities of administration through a step-by-step algorithm based on the response to diuretic therapy.

Diuretics may be associated with neuro-hormonal activation, worsening renal insufficiency, electrolyte abnormalities,

and arrhythmias. Moreover, patients receiving high diuretic doses had significantly impaired survival rates during follow-up.<sup>1</sup> Recently, the Diuretic strategies in patients with acute decompensated heart failure (DOSE-AHF) trial has not found superiority in terms of loop diuretics dosage or administration modality.<sup>2</sup> However, it was found that continuous infusions at higher doses resulted in a greater incidence of impaired renal function.

A Cochrane analysis comparing continuous vs. intermittent infusion showed a better profile of continuous administration modality in terms of urine output, hospital adverse events, and length of hospitalization. However, it recommended larger studies to adequately settle this issue in particular in patients with preserved left ventricular ejection fraction.<sup>3</sup> It is still unclear what the impact of different types of diuretic infusion and DE is after discharge in predicting late adverse events occurrence. Indeed, previous studies in this field are post hoc analyses and mostly biased by new therapies tested in AHF.<sup>4,5</sup> Finally, the most similar protocol (DOSE) evaluated a shorter in-hospital and post-discharge outcome (60 days) with respect to our observational period (180 days).<sup>2</sup> For all of these reasons, we aim to clarify several aspects regarding renal function, drugs safety, and the best modality of infusion comparing the two groups (continuous vs. intermittent infusion). (Table 1) More precisely, we will investigate the following in-hospital endpoints: creatinine and estimated glomerular filtration rate (eGFR), mean urine output and body weight, BNP, and blood urea nitrogen before treatment and at the end of infusion period as both continuous vs. intermittent infusion and in low vs. high diuretic dose arms. The additional in-hospital outcomes assessment includes rate of WRF, use of hypertonic saline solution and inotropic agents, evaluation of DE, congestion signs (persistence of one or more of the following signs: pulmonary rales, peripheral oedema, jugular venous distension, hepatomegaly, third heart sound, and dyspnoea score), and length of hospital stay.

Late outcome endpoints during a 6 month follow-up period include (i) cardiac death and re-hospitalization for heart failure; (ii) evaluation of renal function and its potential relation to adverse events; and (iii) evaluation of post-discharge outcome with respect to congestion signs at discharge.

## Study design

DIUR-AHF is a prospective, multicentre, randomized study that compares continuous with intermittent infusion and low vs. high diuretic dose of furosemide in patients admitted with a diagnosis of AHF. A previous pilot study design was planned to anticipate a larger multicentre trial able to definitively evaluate the optimal loop diuretic use strategy in patients with AHF. In the pilot study, patients were

enrolled consecutively from the Department of Internal Medicine, Cardiology Section Center (Siena, Italy), from April 2010 to November 2012.<sup>6</sup> In this multicentre study, patients will be enrolled starting December 2015.

## Ethics

The study was approved by the local ethics institutional board (C.E.A.V.S.E. approved on 19 June 2017) and registered in Clinicaltrial.gov (identifier number: NCT02638142).

## Inclusion criteria

Patients will be enrolled in the study if they are older than 18 years and they meet the diagnostic criteria for AHF, independently of the systolic function, by exhibiting at least one symptom at rest among dyspnoea, orthopnoea, peripheral oedema, and major fatigue; and at least two clinical signs including rales, pulmonary congestion on chest X-ray (pulmonary oedema, pulmonary congestion, or pleural effusion), jugular vein dilatation, and a third heart sound.<sup>7</sup> An elevation in blood BNP  $\geq 100$  pg/mL is considered supportive for a diagnosis of AHF (Table 2).

## Exclusion criteria

Patients will be excluded from this trial if they received more than two intravenous doses of furosemide or any continuous infusion of furosemide up to 1 month before randomization; if they had end-stage renal disease (eGFR  $\leq 15$  mL/min/m<sup>2</sup>) or need renal replacement therapy (dialysis or ultrafiltration); or if they had recent myocardial infarction within 30 days of screening. Patients with a systolic blood pressure  $<80$  mmHg will also be excluded, as well as patients who have received recent intravenous iodinated contrast.

## Randomization procedure

Patients will be randomized in a 1:1 ratio using a computer-generated scheme divided into either twice-daily bolus injections or continuous infusion (mixed as a 1:1 ratio in 5% dextrose in water), for a time period ranging from 72 to 120 h. The cumulative daily dose of intravenous furosemide to be given in the initial 12 h will be decided by the attending physician. Boluses of furosemide will be administered in 100 mL of water solution over 1 h. The mean daily diuretic dosage will be similar in both groups. The specific doses of furosemide and the use of additional agents to manage AHF (dopamine, intravenous vasodilators, hypertonic saline infusions for hyponatraemia) will be decided based on the laboratory (creatinine, electrolytes balance,

**Table 1** Randomized trials of bolus vs. continuous infusion of diuretics in heart failure

Study	Number of patients	Design	Treatment	Time	Endpoint(s)	Follow-up period (months)	Conclusions
Lahav <i>et al.</i> (1992)	9	Randomized, cross-over, unblinded	Continuous infusion vs. Q8 bolus	48 h	Urine output	Not reported	Continuous better (trend)
Dormans <i>et al.</i> (1996)	20	Randomized, cross-over, unblinded	Continuous infusion vs. single i.v. bolus	24 h	Urine output	Not reported	Continuous better
Kramer <i>et al.</i> (1996)	8	Randomized, cross-over, unblinded	Continuous infusion vs. single i.v. bolus	24 h	Urine output	Not reported	No difference
Aaser <i>et al.</i> (1997)	8	Randomized, cross-over, unblinded	Continuous infusion vs. b.i.d. i.v. bolus	24 h	Urine output	Not reported	Bolus better
Schuller <i>et al.</i> (1997)	33	Randomized unblinded	Continuous infusion vs. bolus	72 h	Mortality	Not reported	No difference
Pivac <i>et al.</i> (1998)	20	Randomized, single blind, cross-over	Q12 4 h 'infusion' vs. Q12 bolus	24 h	Urine output	Not reported	Continuous better
Licata <i>et al.</i> (2003)	107	Randomized, single blind	Continuous infusion + hypertonic saline vs. Q12 bolus	6–12 days	Urine output at 24 h and length-of-stay mortality	31 ± 14	Continuous better on all endpoints
Thomson <i>et al.</i> (2010)	56	Randomized, single blind	Continuous infusion vs. bolus	36 h	Net urine output in 24 h	Not reported	Continuous better
Allen <i>et al.</i> (2010)	20	Randomized	Continuous infusion vs. bolus	>48 h	Change creatinine at discharge, change electrolytes, length of hospital stay	3	No difference
Felker <i>et al.</i> (2011)	308	Randomized, double blind, controlled	Continuous infusion vs. bolus	>72 h	Global assessment of symptoms, change in serum creatinine	2	No difference
Palazzuoli <i>et al.</i> (2014)	82	Randomized, double blind	Continuous infusion vs. bolus	>72 h	Change in renal function, BNP, body weight	6	Continuous infusion better for BNP and BW, worse for renal function and late outcome
Palazzuoli <i>et al.</i> (2016)	96	Randomized, double blind	Continuous infusion vs. bolus	>72 h	Weight loss, decongestion, BNP decrease, and renal function in low vs. high diuretic dose (HD) and on the basis of diuretic efficiency (DE).	6	HD and poor DE are two conditions associated with adverse outcome. They appear strictly related to WRF occurrence.

**Table 2** Inclusion and exclusion criteria of study protocol

Inclusion criteria	Exclusion criteria
Patients >18 years	Patients who receive more than two i.v. doses of furosemide or any continuous infusion of furosemide 1 month before randomization
Patients with diagnosis of ADHF Dyspnoea, orthopnoea, peripheral oedema, or major fatigue and at least two clinical signs including rales, pulmonary congestion on chest radiography, jugular vein dilatation, or a third heart sound Blood BNP > 100 pg/mL	End-stage renal disease or renal replacement therapy Recent myocardial infarction (within 30 days of screening) Systolic blood pressure < 80 mmHg Creatinine levels >4 mg/dL Patients who receive recent i.v. iodinated contrast

ADHF, acute decompensated heart failure.

and BNP) and clinical (congestion symptoms and signs) parameters, with daily dosages adjusted during the infusion periods (Figure 1). At admission, patients with AHF in both the intermittent and continuous infusion arms will be administered with 80 mg/day of intravenous furosemide. If a patient has a good response, the initial dose will be continued; if a patient has a poor response, defined as DE < 0.2 kg/day for 40 mg of furosemide (as mentioned in our recent paper) and a urine output <1 L/day, the furosemide dosage will be doubled (160 mg/day).<sup>8</sup> In case of continued diuretic resistance, defined as a poor response, the dosage will be raised to 250 mg/day. Therefore, patients with poor DE will undergo intensification treatment. A low diuretic dose is defined as a furosemide daily amount

<120 mg/day; conversely, a high dose is defined as a high loop diuretic dose >120 mg/day (Figure 2).

The diuretic response is defined as the mean daily weight change from hospital admission to the end of the intravenous loop diuretics treatment (time period ranging from 72 to 120 h) per 40 mg of daily furosemide dosage. To calculate DE, we performed the following formula: (Weight change/days of infusion)/(Mean daily furosemide dosage/40 mg of furosemide).<sup>4,5,8,9</sup>

In all patients, before randomization, the renal function parameters and BNP will be measured. Renal function is evaluated through serum blood urea nitrogen and serum creatinine measurement. Moreover, in all patients, eGFR is calculated by MDRD formula.<sup>10</sup> Worsening renal function is

**Figure 1** Study design describing timing assessment before and after treatment and follow-up evaluation.

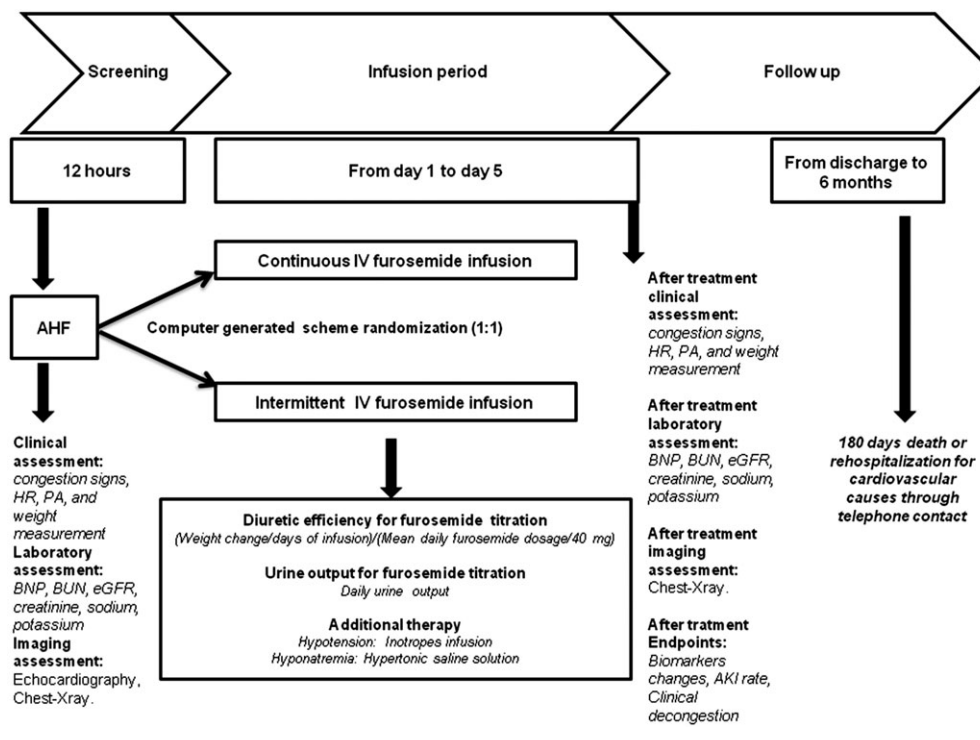
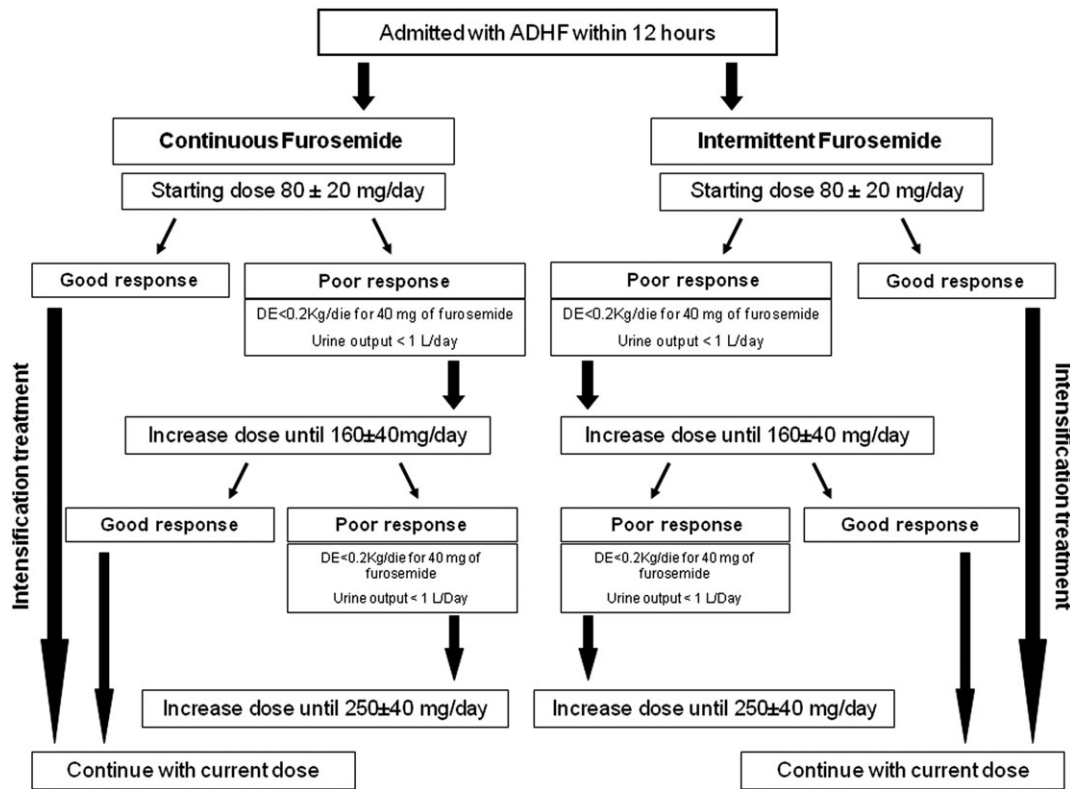


Figure 2 Scheme of diuretics dose administration by escalation algorithm based on diuretic response.



defined as creatinine increase  $\geq 0.3$  mg/dL during hospitalization or eGFR reduction  $\geq 20\%$  during the same period. Chronic kidney disease is defined as admission renal dysfunction with eGFR  $< 60$  mL/min/m<sup>2</sup>.<sup>11</sup> Therefore, all patients will be submitted to an echocardiography and a chest X-ray to assess pulmonary congestion. The chest X-ray will also be repeated prior to treatment suspension to verify the pulmonary congestion improvement. The subsequent titration of the furosemide dosage will be guided by a dose-escalation algorithm based on the patient’s response to the treatment (DE  $< 0.2$  kg/day for 40 mg of furosemide from the starting enrolment to the third day or urine output  $< 1000$  mL/day) and signs of decongestion (decreased pulmonary rales, venous jugular decongestion, lack of additive heart sounds, and improvement in pulmonary congestion in chest X-ray) and/or through important changes in renal function such as a sudden increase of creatinine  $> 0.8$  mg/dL compared with the baseline value or hypokalaemia  $< 3.2$  mEq/L.

### Additional therapy

Any additional treatment is left to the physician’s discretion. No thiazide diuretics, nesiritide, or arginine vasopressin antagonists will be administered during the hospitalization period. Hypertonic saline solution will be administered to

patients who develop hyponatraemia (serum Na<sup>+</sup> values  $< 130$  mEq/L) during treatment with the goal of restoring plasma sodium values up to 134 mEq/L. For this reason, the Na<sup>+</sup> concentration will be monitored each day during the infusion period. The hypertonic saline solution consists of NaCl in 500 mL saline solutions (0.9% of NaCl). Infusion will be administered at 80 mL/h once a day, depending on the Na<sup>+</sup> levels. The dopamine infusion will be administered to patients with systolic blood pressure  $< 90$  mmHg with the goal of restoring systolic values up to 100 mmHg, maintaining diuretic infusion. Inotropic therapy will be stopped when blood pressure values are sustained at  $\sim 105$  mmHg during the subsequent 12 h for four consecutive measurements.

### Collection of data

Clinical parameters will be recorded. For the data quality measurement to be optimized, the following instruction will be performed: The systolic and diastolic blood pressure will be calculated using the mean of three consecutive measurements; the heart rate will be monitored and registered by the investigators involved in the trial. Serial measurement of the above-cited laboratory parameters will also be collected. Finally, the clinical status of congestion will be registered at admission and after treatment. All the collected

data will be inserted and scheduled in an Excel file, which will be kept by the principal investigator of the study.

### Primary endpoints

Primary endpoints were (i) 180 days cardiac death and re-hospitalization and (ii) evaluation of adverse events in relation to the rate of WRF and to congestion signs after the infusion period during a 6 month follow-up period.

### Secondary endpoints

DIUR-AHF has been designed with some in-hospital endpoints: (i) mean paired changes of renal function, of urine output comparing continuous vs. intermittent administration; (ii) the evaluation of decongestion, BNP decrease, and WRF occurrence in relation to DE; (iii) post hoc analysis of WRF, congestion signs, inotropic infusion, and length of hospital stay (days) should be performed with respect to the specific dose groups (high vs. low).

### Sample size calculation

The study's sample size is based on our primary endpoints. Thus, we considered that the adverse events incidence (180 days cardiac death or re-hospitalization) is likely to be 40% in patients undergoing continuous infusion and 25% in patients undergoing intermittent infusion. The sample size of 240 patients (120 in each arm) might be helpful in detecting the clinical outcome difference between the groups (continuous vs. intermittent) with a power of 80%. We assumed no patients would withdraw or be lost during the hospitalization period. We also consider that 20% of subjects could be lost during follow-up after hospital discharge.

### Statistical plan

All data will be analysed with intention-to-treat principles. Continuous variables will be expressed as mean  $\pm$  standard deviation and will be compared with Student's *t*-test (unpaired and paired as appropriate) for independent groups if normally distributed; normality will be assessed by the Kolmogorov–Smirnov test. Analysis of variance will be done by Levene's test, and if it is breached, Welch's correction will be used. Qualitative variables will be expressed as a percentage and will be compared with  $\chi^2$  test. Data about weight loss and diuretic response (defined by weight change per 40 mg of furosemide or equivalent) will be described in quartiles and will be presented as median (interquartile range). Differences among diuretic response quartiles will be compared

through analysis of variance when normally distributed or Kruskal–Wallis test when skewed; Pearson  $\chi^2$  tests will be used to compare categorical data. Correlations between DE and eGFR will be expressed as Pearson's correlation coefficient. Cox regression analysis will be used to assess the independent relationship between the two methods of furosemide infusion for the outcome of re-hospitalization or death with adjustment for age, gender, creatinine, eGFR, and BNP at baseline; the use of hyperosmolar solution; dopamine infusion; and the development of WRF. Kaplan–Meier methods will be employed to generate survival plots that will be compared using a log-rank test for time to first hospitalization, death, or the composite. All statistical tests will be two tailed, with *P* value < 0.05 considered significant. All the analyses will be performed by using the SPSS 20.0 for Windows (SPSS Inc., Chicago, IL).

## Discussion

Loop diuretics remain the cornerstone of the decongestion therapy during AHF; however, which is the best modality administration and daily dosage to improve outcome is not yet understood: Post hoc analyses have previously shown that high dosage is associated with a poor prognosis, although specific analyses on diuretic response and studies comparing the dose administration during hospitalization and after discharge have not been done.<sup>12,13</sup> Recent guidelines recommend the use of these drugs to reduce left ventricular filling pressure and pulmonary congestion and avoid idro-saline retention.<sup>14</sup> Therapeutic recommendations focus primarily on symptoms relief since there are no specific studies evaluating the dose regimen nor modality of administration during acute management. Thus, despite the ubiquity of loop diuretic employments, there is a lack of data supporting their efficacy and the relative prognostic impact. In the Acute Decompensated Heart Failure National Registry (ADHERE) registry, the use of high loop diuretics dosage was associated with a higher rate of mortality, a prolonged hospital stay, and an increased renal dysfunction.<sup>15</sup> The current trend is also confirmed by other studies.<sup>16,17</sup> All together, these reports suggest an evaluation of potential strategies for avoiding exposure to high doses for a prolonged period. Thus, the administration of the lowest possible dosage to patients with AHF is recommended in order to relieve their symptoms.<sup>17</sup> However, as patients taking the more elevated regimen are probably the more compromised, the data interpretation needs to be evaluated with caution. Moreover, several items still remain challenging due to the frequent exclusion of patients with a more impaired haemodynamic status and advanced renal dysfunction from major AHF clinical trials.<sup>18–20</sup> Therefore, it is not clear whether continuous infusion is better than intermittent boluses and whether a

lower dose is better than a higher dose in terms of decongestion efficiency, maintenance of renal filtration function, and prognosis.<sup>21,22</sup> Finally, several concerns regarding short-term and long-term effects, the consequences of previous doses taken before hospitalization, and the effective response during the acute phase remain unknown. A post hoc analysis showed that the metric responsiveness (calculated by fluid output produced per 40 mg of furosemide) instead of the diuretic amount has a more prognostic impact.<sup>9</sup> These findings seem to be confirmed in two recent trials employing two new drugs serelaxin and rolofylline, providing indefinite results.<sup>5,23</sup>

In this context, the renal function deterioration seems to have a different significance in relation to different clinical situations: If it is transient, it could be simply a marker of effective decongestion; conversely, if it is permanent, it could be due to an increased systemic and renal atherosclerotic burden, a greater neuro-endocrine stimulation, and a reduced renal blood flow. Loop diuretics, *per se*, particularly higher doses, are associated with higher rates of WRF. This phenomenon is consistent with an increase of the renin–angiotensin and sympathetic nervous systems activation. This current overdrive is mediated by two distinct mechanisms: the inhibition of sodium chloride intake into the macula densa cells and the stimulation of prostacyclin that further increases the secretion of rennin. The indirect effects of loop diuretics include a reduction in renal blood flow and an enhanced proximal tubules recovery of sodium in both loop diuretic doses. Finally, aldosterone works at the collecting duct to recover the remaining sodium in the urine, while increased arginine vasopressin can recover as much as 25% of the free water in urine despite the use of loop diuretics. All of these factors combine to make the patient prone to adverse diuretics effects and to increase risk for renal function deterioration.<sup>24</sup> Higher doses of diuretics could be necessary in severe cases with more impaired renal function, and as consequence, adverse effects may result from the severity of the disease.<sup>23,25</sup> Therefore, our trial aims to answer questions regarding the better cumulative daily dose choice

and then to randomize patients in different modalities of administration.

## Expected results

(i) In all arms (continuous vs. intermittent and high vs. low infusion), some percentage of WRF will occur. (ii) Worsening renal function occurrence in chronic kidney disease patients has worse outcome. (iii) Continuous and high dose groups could reveal a more intensive diuresis and congestion signs relief with respect to intermittent and low dose groups. (iv) High dose and poor loop diuretics efficiency should be related to increased diuretic resistance, renal dysfunction occurrence, and a greater congestion status. (v) BNP decrease will be more consistent in patients with greater decongestion. (vi) Poor diuretic response will be associated with less decongestion and an adverse prognosis. (vii) Outcome will depend on congestion reduction and renal function deterioration.

## Conflict of interest

None declared.

## Author contributions

A.P. has given valuable intellectual contribution to study protocol writing; he has given substantial contributions to conception and design and has given final approval of the version to be published. G.R. has given substantial contributions to trial design, statistical analysis, and writing. G.V. has given contributions to endpoints definition and trial design. R.V. has given contributions to endpoints definition and trial design. S.D.S. has given contributions to endpoints definition and trial design. R.N. has been involved in drafting the manuscript or revising it critically for important intellectual content.

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