Protocol Investigator Initiated Study

PUSH AHF

Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure

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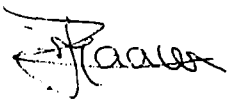
Coordinating investigator/project leader	**J.M. ter Maaten, MD, PhD** **University Medical Center Groningen** **Department of Cardiology** **P.O. Box 30 001, 9700 RB Groningen** **R. +31 (0) 50 361 2355** **Email: j.m.ter.maaten@umcg.nl**
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	**J.M. ter Maaten, MD, PhD** **University Medical Center Groningen** **Department of Cardiology** **P.O. Box 30 001, 9700 RB Groningen** **R. +31 (0) 50 361 2355** **Email: j.m.ter.maaten@umcg.nl** **K. Damman, MD, PhD** **University Medical Center Groningen** **Department of Cardiology** **P.O. Box 30 001, 9700 RB Groningen** **R. +31 (0) 50 361 2355** **Email: k.damman@umcg.nl**
Sponsor (in Dutch: verrichter/opdrachtgever)	**Investigator initiated study**

Subsidising party	**Hartstichting**
Independent expert (s)	**Dr. P.P. van Geel**
Laboratory sites	**NA**
Pharmacy	**NA**

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: **Head of Department of Cardiology:** **Prof. dr. D.J. van Veldhuisen**		18-10-21
Coordinating Investigator: **Dr. J.M. ter Maaten**		17-10-21

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AHF	**Acute Heart Failure**
ECG	**Electrocardiogram**
eGFR	**Estimated Glomerular Filtration Rate**
EHR	**Electronic Health Record**
ESC	**European Society of Cardiology**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HCT	**Hydrochlorothiazide**
HF	**Heart Failure**
IC	**Informed Consent**
JVP	**Jugular Venous Pressure**
LD	**Loop Diuretic**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NT-proBNP	**N-terminal pro blood natriuretic peptide**
NYHA	**New York Heart Association**
(S)AE	**(Serious) Adverse Event**
SGLT2i	**Sodium Glucose Transporter 2 inhibitor**
SOC	**Standard Of Care**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UMCG	**University Medical Centre Groningen**
VAS	**Visual Analog Scale**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Administration of loop diuretics to achieve decongestion is the current cornerstone of therapy for acute heart failure. Unfortunately, there is a lack of evidence of how to guide diuretic treatment. Recently, urinary sodium, as a response measure of diuretic response, has been proposed as a target for therapy.
The hypothesis of this study is that natriuresis guided therapy in patients with acute heart failure will improve diuretic response, decongestion, and reduce length of hospital stay, as well as heart failure rehospitalisations.
Objective: To assess the effect of natriuresis guided therapy in acute heart failure to improve diuretic response, decongestion, and clinical outcomes
Study design: Randomised, controlled, open label study
Study population: 310 patients admitted with the primary diagnosis of acute heart failure requiring intravenous loop diuretics.
Intervention (if applicable): natriuresis guided treatment versus standard of care
Main study parameters/endpoints:
Co-primary outcome: total natriuresis after 24 hours and first occurrence of all-cause mortality or heart failure rehospitalisation at 6 months
Secondary outcomes: 48- and 72-hours natriuresis, length of hospital stay, percentage change in NT-proBNP at 48 and 72 hours.
Safety endpoints: doubling of serum creatinine at 24 or 48 hours, occurrence of worsening heart failure
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Since this is a pragmatic trial, the study will be embedded within the normal care of patients with acute heart failure, which already includes timed urinary collections and laboratory assessment at set time points. The patients in the natriuresis guided therapy will undergo additional urinary assessments, and undergo more stringent monitoring of response, and therefore might receive more intravenous diuretics. For study parameters, blood and urine will be collected at set time points. Survival and rehospitalisation will be assessed after 6 months by telephone call.

1. INTRODUCTION AND RATIONALE

Heart failure is one of the leading causes of hospitalization in the world, is associated with significant morbidity and mortality, and as such responsible for a large proportion of health care expenses.(1) It is estimated that the total number of heart failure patients will continue to increase. An increase of 88% in 2040 is predicted, resulting in a further increase of health care expenditures attributable to heart failure.(1) While treatment for chronic heart failure has improved greatly over the last decades, this is not true for acute heart failure (AHF) where therapies with a proven positive effect on outcome are non-existent. Additionally, a large number of AHF patients show impaired response to the only available therapy, i.e. loop diuretics.(2) Over the last years several studies consistently showed that impaired diuretic response is associated with residual congestion and an increased risk of mortality and heart failure rehospitalisations.(3-7) Given the working mechanisms of loop diuretics, natriuresis might be a more sensitive, objective, quantifiable, and reliable marker to assess response. We recently showed that insufficient natriuretic response in AHF patients was indeed associated with an increased risk of poor outcome.(8) Additionally, even early assessment of natriuresis (one to two hours after initiation of loop diuretics) in AHF patients has been shown to be an accurate marker of insufficient diuretic response during hospitalization.(9) Therefore, natriuresis might have a role in actively assessing response to loop diuretics and to subsequently guide diuretic treatment in AHF patients. Natriuresis possesses all the characteristics required for a marker that can be used to actively guide decongestive treatment and move towards a personalized treatment approach in AHF. Interventions aimed at improving diuretic response, using natriuresis guided therapy have the potential to significantly improve effectiveness of decongestion, speed up inhospital treatment, prevent readmissions for heart failure, and decrease health care expenses (figure 1). We therefore hypothesize that *natriuresis guided therapy* in patients with AHF will *improve diuretic response, decongestion*, and *reduce length of hospital stay*, as well as *heart failure rehospitalisations.*

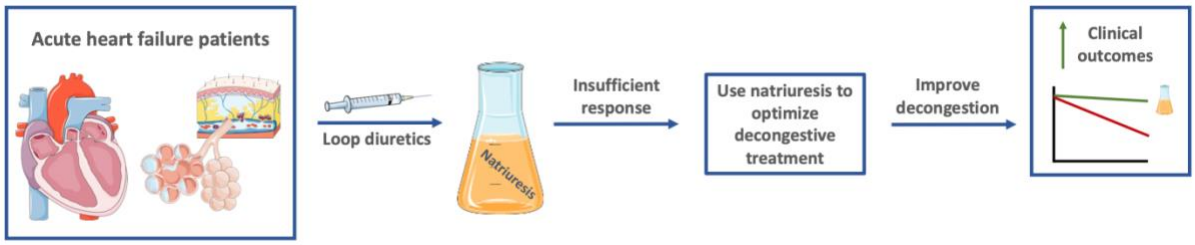


Figure 1.

Legend: in patients with AHF, loop diuretics are the first and only recommended choice of treatment aimed at relieving congestion by increasing diuresis and natriuresis. Actively assessing natriuresis and using this to optimize diuretic treatment could improve decongestion and clinical outcomes.

2. OBJECTIVES

Primary Objective:

To assess the effect of natriuresis guided therapy versus standard of care (SOC) on 24-hour urinary sodium excretion after the start of intravenous loop diuretic and the effect on first occurrence of all-cause mortality or heart failure rehospitalisation at 6 months in patients with acute heart failure

Secondary Objective(s):

To assess the effect of natriuresis guided therapy on:

- 48- and 72 hours urinary sodium excretion
- Length of hospital stay
- Percentage change in NT-proBNP at 48 and 72 hours

Safety endpoints:

- Doubling of serum creatinine at 24 or 48 hours
- Occurrence of worsening heart failure

3. STUDY DESIGN

This is a pragmatic, randomized, controlled, open label study in patients presenting with acute heart failure requiring intravenous loop diuretics. In total 310 patients will be randomized at the start of intravenous treatment (inhospital) to standard of care or natriuresis guided treatment. Due to the severe illness of acute heart failure patients, and the necessity to perform the first study assessment early (i.e. within the first hours of hospitalization) patients will be enrolled at the emergency department using deferred consent. Written informed will be obtained during the first four days of hospitalization. Patients will be followed for the duration of the hospitalization. Adverse clinical events, including all-cause mortality and heart failure rehospitalisation will be assessed by a telephone call after 6 months.

3.1 Study visits

Table 1 lists all of the assessments and indicates with an “X” when the required assessments and/or procedures are performed at a scheduled visit day. All laboratory assessments, including blood and urine assessment for the treatment algorithm and for the primary outcome will be integrated in clinical practice. The results of the urinary assessments will be blinded in the standard of care group during the study duration.

Study candidates will be identified upon arrival at the emergency department. When a patient is diagnosed with AHF and intravenous diuretic therapy is started, randomization will occur using Epic (Epic Systems Corporation). The study procedures will then start according to this protocol. Patients will receive a urinary catheter if this is deemed necessary by the treating physician.

Table 3.1 Assessment schedule

	Screening	**Participation**										**Follow-up**
Time points	Hour -6	Hour 0 (day 1)	Hour 2 (day 1) [d]	Hour 6 (day 1)	Hour 12 (day 1) [d]	Hour 18 (day 1) [d]	Hour 24 (day 1)	Hour 36 (day 2) [d]	Hour 48 (day 2)	Hour 72 (day 3)	Discharge	Day 180 (+/- 10 days) [a]
Visits	0	1	2	3.0	3.1	3.2	4.0	4.1	5	6	7	8
Written informed consent							X		X	X		
Inclusion/exclusion criteria	X											
Demography	X											
Medical history	X											
Heart failure history	X											
Concomitant medication	X	X					X		X	X	X	X
Physical examination	X	X		X			X		X	X	X	
Height	X											
Weight	X	X					X		X	X	X	X

	Screening	**Participation**										**Follow-up**
Time points	Hour -6	Hour 0 (day 1)	Hour 2 (day 1) [d]	Hour 6 (day 1)	Hour 12 (day 1) [d]	Hour 18 (day 1) [d]	Hour 24 (day 1)	Hour 36 (day 2) [d]	Hour 48 (day 2)	Hour 72 (day 3)	Discharge	Day 180 (+/- 10 days) [a]
Visits	0	1	2	3.0	3.1	3.2	4.0	4.1	5	6	7	8
Blood pressure and heart rate measurements	X	X	X	X	X	X	X	X	X	X	X	
NYHA class	X	X					X		X	X	X	X
Physician assessment of HF signs and symptoms	X	X		X			X		X	X	X	
Echocardiogram [b]												
X-ray [c]	X											
ECG	X											
Loop diuretics	X	X	X	X	X	X	X	X	X	X	X	X
Standard local laboratory analysis	X			X			X		X	X	X	
Timed urine collection (24h)							X		X	X		

	Screening	**Participation**										**Follow-up**
Time points	Hour -6	Hour 0 (day 1)	Hour 2 (day 1) [d]	Hour 6 (day 1)	Hour 12 (day 1) [d]	Hour 18 (day 1) [d]	Hour 24 (day 1)	Hour 36 (day 2) [d]	Hour 48 (day 2)	Hour 72 (day 3)	Discharge	Day 180 (+/- 10 days) [a]
Visits	0	1	2	3.0	3.1	3.2	4.0	4.1	5	6	7	8
Spot natriuresis		X	X	X	X	X	X	X	X	X	X	
Urine sample		X	X	X			X		X	X	X	
Plasma sample		X		X			X		X	X	X	
Fluid intake assessment							X		X	X		
Diuresis assessment			X	X	X	X	X	X	X	X		
Vital status and outcome assessments		X					X		X	X	X	X
Events and serious adverse events		X					X		X	X	X	X

[a] the day 180 visit will be a telephone visit

[b] if performed as part of standard of care at any time during hospitalization

[c] if performed as part of standard of care at admission

[d] in the natriuresis guided group

3.2 Screening

At screening the following assessments will be executed (all part of standard of care):

- Deferred informed consent
- Demographic data, including cardiovascular risk factors
- Medical history by chart review
- Vital signs
- Physical examination, including weight, height (only at screening), oedema, rales, jugular venous pressure (JVP), orthopnoea assessment, New York Heart Association (NYHA) class
- 12-lead electrocardiogram (ECG)
- NYHA class assessment
- Laboratory assessments, including haematology, renal function, NT-proBNP
- Concomitant medication
- In- and exclusion criteria

3.3 Assessment 1 (Baseline)

After having confirmed eligibility by confirming all inclusion criteria and by ruling out either one of the exclusion criteria, the following assessments will be executed:

- Randomization
- Vital signs
- Physical examination, including weight, oedema, rales, JVP, orthopnoea assessment, NYHA class
- Concomitant medication
- Initial loop diuretic dose in both groups will be determined based on several patients characteristics described in more detail in section 3.14.1 and figure 3
- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Start fluid balance by noting ingested and excreted fluid volumes

3.4 Assessment 2 (2 hours)

At two hours, in patients randomized to the natriuresis guided group, the following assessments will be executed:

- Vital signs
- Evaluate Diuretic Response:
    - Spot urine sodium

        - If applicable adjust loop diuretic therapy based on this result (please see also section 3.14.2, and figure 4)
- Loop diuretic dose
- Collection of spot urine sample for biomarker analysis (in both groups)
- Diuresis assessment

3.5 Assessment 3.0 (6 hours)

At six hours the following assessments will be executed:

- Vital signs
- Physical examination, including oedema, rales, JVP, orthopnoea assessment, NYHA class
- Spot urinary sodium (result will be blinded in the SOC group)
- 6 hours urine collection
- In the Natriuresis Guided Group:
    - Evaluate Diuretic Response based on spot urinary sodium and diuresis and adjust loop diuretic therapy based on these results (please see also section 3.14.2, and figure 4)
- Loop diuretic dose
- Laboratory assessments, including haematology, and kidney function
- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Diuresis assessment

3.6 Assessment 3.1 (12 hours)

In the natriuresis guided group the following assessments will be executed:

- Vital signs
- Evaluate Diuretic Response based on spot urinary sodium and diuresis and adjust loop diuretic therapy based on these results (please see also section 3.14.2, and figure 4)
- Loop diuretic dose

3.7 Assessment 3.2 (18 hours)

In the natriuresis guided group the following assessments will be executed:

- Vital signs

- Evaluate Diuretic Response based on spot urinary sodium and diuresis and adjust loop diuretic therapy based on these results (please see also section 3.14.2, and figure 4)
- Loop diuretic dose

3.8 Assessment 4.0 (24 hours)

At twenty-four hours the following assessments will be executed:

- Written informed consent (if not yet provided)
- Concomitant medication
- Vital signs
- Physical examination, including weight, oedema, rales, JVP, orthopnoea assessment, NYHA class
- Spot urinary sodium (result will be blinded in the SOC group)
- 24 hours urine collection
- In the Natriuresis Guided Group:
    - Evaluate Diuretic Response based on spot urinary sodium and diuresis and adjust loop diuretic therapy based on these results (please see also section 3.14.2, and figure 5)
- Loop diuretic dose
- Laboratory assessments, including haematology, and kidney function
- End of first timed twenty-four hour urine collection
- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Diuresis and first 24 hour fluid intake assessment
- (Serious) adverse events

3.9 Assessment 4.1 (36 hours)

In the natriuresis guided group the following assessments will be executed:

- Vital signs
- Evaluate Diuretic Response based on spot urinary sodium and diuresis and adjust loop diuretic therapy based on these results (please see also section 3.14.2, and figure 5)
- Loop diuretic dose

3.10 Assessment 5 (48 hours)

At forty-eight hours the following assessments will be executed:

- Written informed consent (if not yet provided)
- Concomitant medication
- Vital signs
- Physical examination, including weight, oedema, rales, JVP, orthopnoea assessment, NYHA class
- Loop diuretic dose
- Laboratory assessments, including haematology, NT-proBNP, and kidney function
- End of second timed 24 hour urine collection
- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Diuresis and second 24 hour fluid intake assessment
- (Serious) adverse events

3.11 Assessment 6 (72 hours)

At seventy-two hours the following assessments will be executed:

- Written informed consent (if not yet provided) – last opportunity
- Concomitant medication
- Vital signs
- Physical examination, including weight, oedema, rales, JVP, orthopnoea assessment, NYHA class
- Loop diuretic dose
- Laboratory assessments, including haematology, NT-proBNP, and kidney function
- End of third and final timed 24 hour urine collection
- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Diuresis and third 24 hour fluid intake assessment
- (Serious) adverse events

3.12 Assessment 7 (discharge)

At discharge the following assessments will be executed:

- Concomitant medication
- Vital signs
- Physical examination, including weight, oedema, rales, JVP, orthopnoea assessment, NYHA class
- Loop diuretic dose
- Laboratory assessments, including haematology, NT-proBNP, and kidney function

- Collection of EDTA blood sample for biomarker analysis and collection of spot urine sample for biomarker analysis
- Diuresis and first 24 hour fluid intake assessment
- (Serious) adverse events

3.13 Assessment 8 (180 days +/- 10 days)

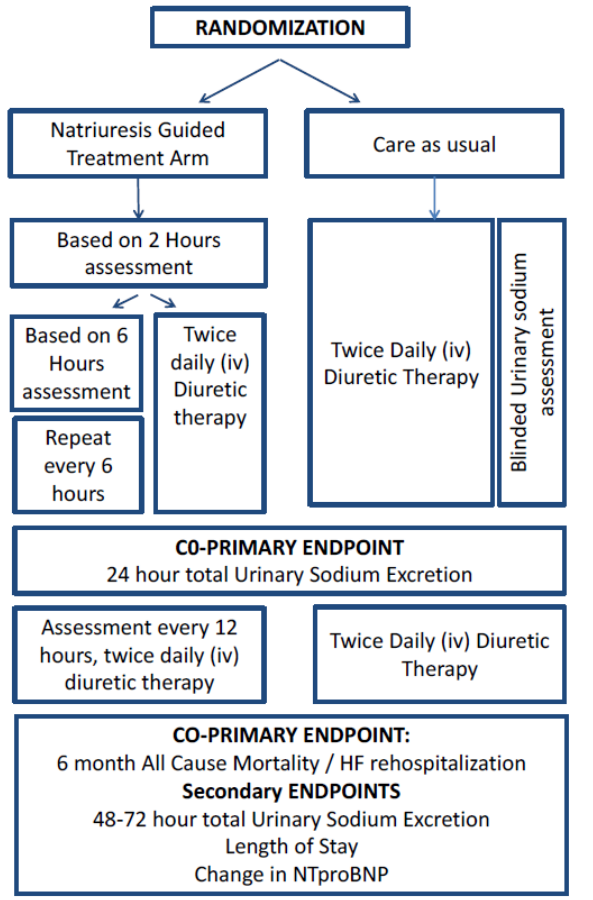
On day 180 the following assessments will be executed by phone call.

- Concomitant medication
- Weight (patient reported) and NYHA class
- Loop diuretic dose
- Heart failure admissions and/or mortality
- (Serious) adverse events

3.14 Treatment algorithm

Patients presenting with acute heart failure will be randomized to natriuresis guided therapy or standard of care (figure 2). When patients are randomized to the natriuresis guided treatment arm, decongestive treatment will be adjusted based on the spot urine sodium values assessed at set time points. The first natiuresis assessment takes place two hours after randomization. Patients will be required to empty the bladder at randomization (if deemed feasible), and a baseline urine sample will be obtained. In patients with a catheter the first sample (after placement of the urinary catheter) will be discarded. At two hours, a spot urinary sample will be obtained in patients with a urinary catheter after voiding the collected urine output in a container and obtaining the first produced urine after this. Patients without a catheter will be encouraged to urinate at this time point. This method will be repeated at the consecutive time points.

Figure 2: Overview of the treatment algorithm



Abbreviations: HF: heart failure, iv: intravenously, LD: loop diuretic, NTproBNP: N-terminal pro blood natriuretic peptide

3.14.1 Loop diuretic dose at baseline

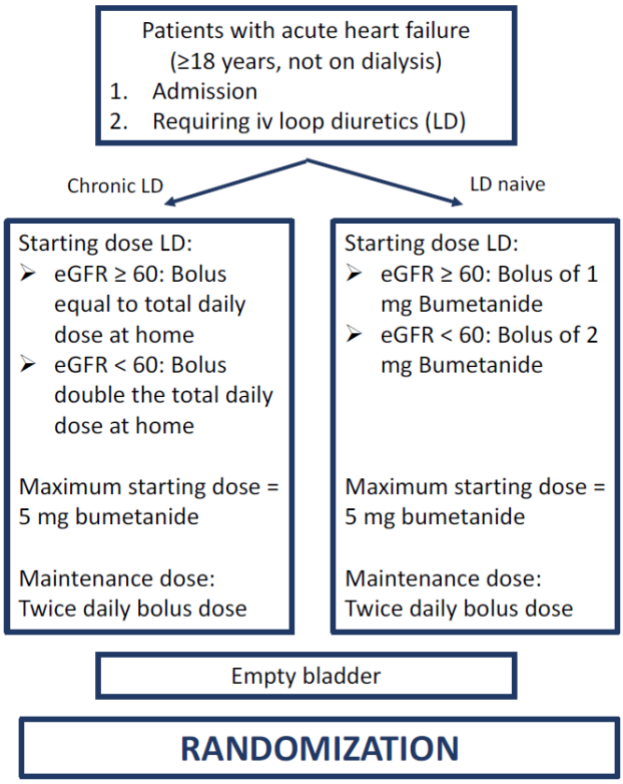
Baseline loop diuretic dose will be determined based on the renal function of the patient and his/her outpatient loop diuretic dose (figure 3). If available, bumetanide will be used, as this has better bioavailability than furosemide. Conversion from furosemide to bumetanide doses will be done by dividing the furosemide dose by 40. If bumetanide is not in stock at the UMCG, furosemide will be used.

If patients use loop diuretics in the outpatients setting and have a preserved renal function (estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m^2), starting intravenous loop diuretic dose will be the total daily outpatient dose as a bolus and consequently continued in twice daily dosing.
If patients use loop diuretics in the outpatient setting and have an impaired renal function (eGFR < 60 ml/min/1.73m^2), starting intravenous loop diuretic dose will be twice the total daily outpatient dose as a bolus and this consequently continued in twice daily dosing.

If patients do not use loop diuretics in the outpatient setting (naïve), the loop diuretic dose will only be determined based on the renal function. In case of a preserved renal function a starting dose of 1 mg bumetanide will be administered which will be continued in twice daily dosing. When renal function is impaired a starting loop diuretic dose of 2 mg bumetanide will be used, which will consequently be continued in twice daily dosing.
In all groups, the maximum bolus dose will be 5 mg of bumetanide (200 mg of furosemide) as an additional effect above this initial bolus dose is not expected.

The determination of the loop diuretic dose at baseline is further illustrated in the following figure:

Figure 3: Determination of the starting loop diuretic dose in all patients



Abbreviations: eGFR: estimated glomerular filtration rate, iv: intravenously, LD: loop diuretic

Patients will be randomized using Epic in a 1:1 ratio to natriuresis guided therapy or standard of care.

3.14.2 Standard of care group

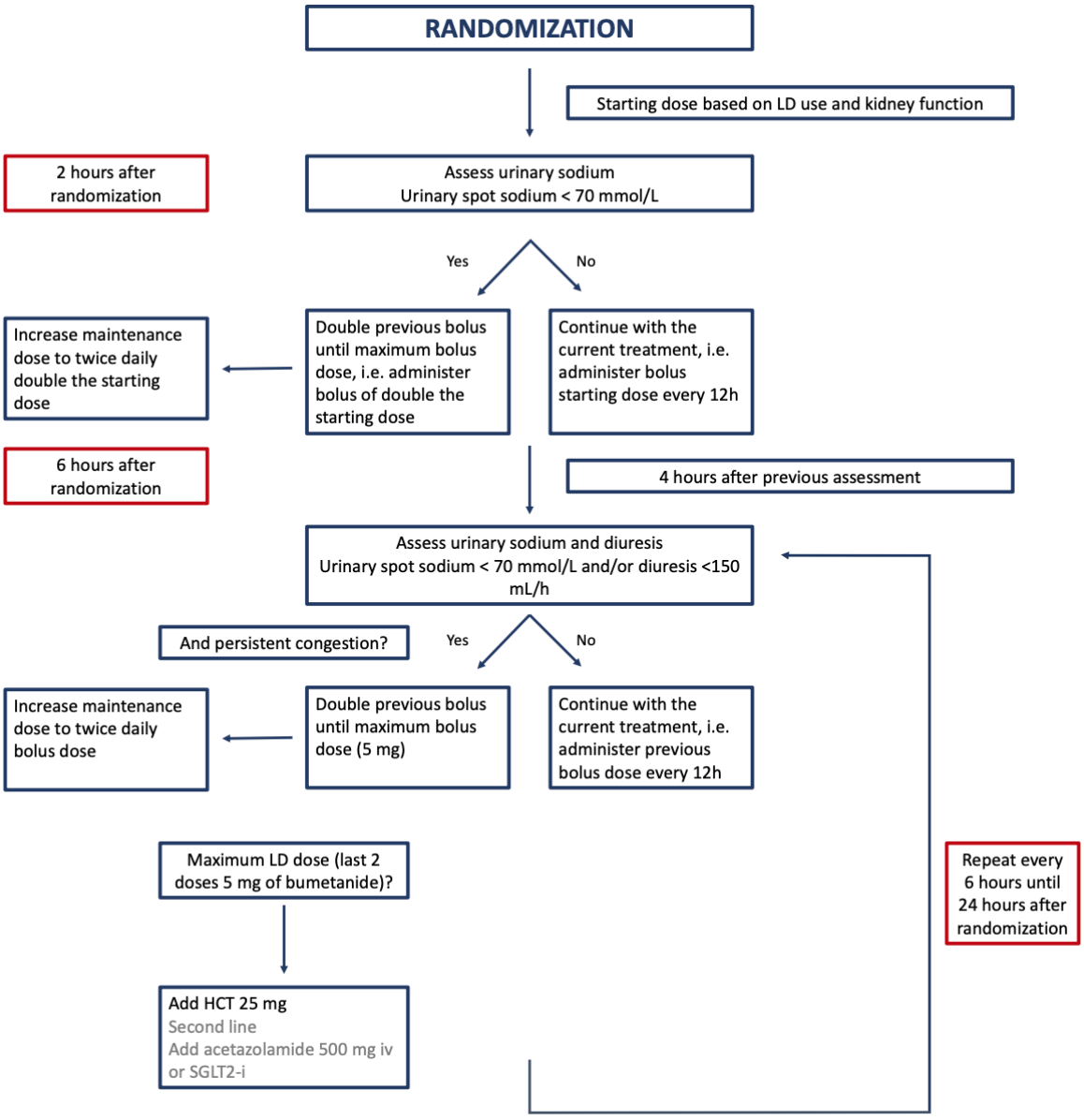
In the standard of care group decongestive treatment will be performed as it is currently done in clinical practice at the UMCG. After randomization patients will receive twice daily loop

diuretic doses intravenously, as previously described (figure 2 and 3). The maximum starting dose will be 5 mg of bumetanide (200 mg of furosemide) twice daily.

3.14.3 Natriuresis determined treatment algorithm

Based on the urinary sodium value obtained from 2 hours onwards in the natriuresis guided group, decongestive therapy will be adjusted using the following treatment algorithm.

Figure 4: Treatment algorithm for the natriuresis guided group during the first 24 hours after randomization



Abbreviations: HCT: hydrochlorothiazide, LD: loop diuretic, SGLT2-I (sodium glucose transporter 2 inhibitor)

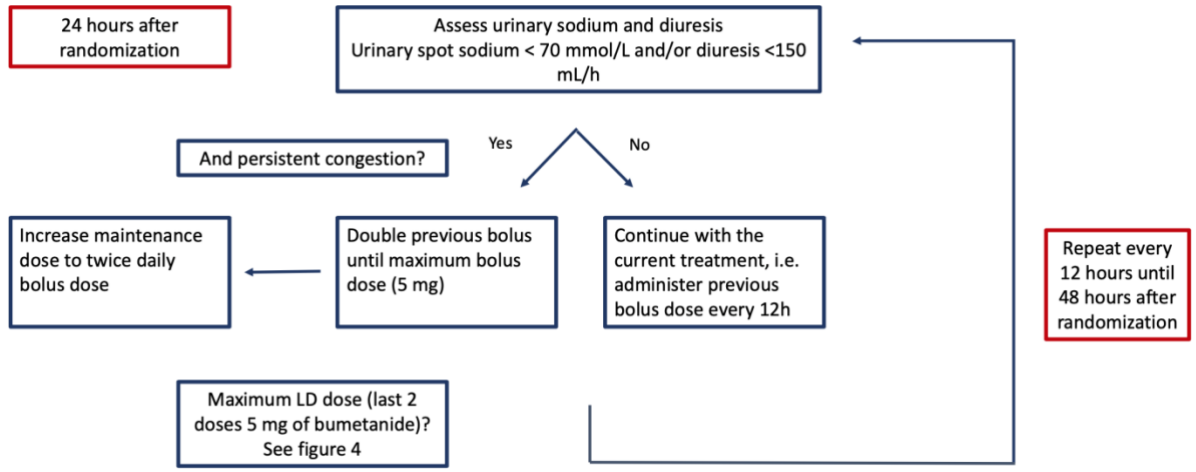
In patients randomized to natriuresis guided therapy, the first urinary sodium will be determined at 2 hours. All urinary sodium assessments will be spot urinary samples. These will be obtained from the urinary catheter (if applicable) at set time points. If spot urinary sodium at 2 hours is < 70 mmol/L, patients will receive an additional bolus of loop diuretic, which will be double the previous bolus with a maximum bolus dose of 5 mg of bumetanide or equivalent (figure 4). If the bolus dose is doubled, the maintenance dose of loop diuretics will be adjusted to twice daily the doubled bolus dose (figure 4). If a patient already received 5 mg of bumetanide as a first dose, this dose will be repeated when there is insufficient natriuresis at this time point.

The next urinary sodium assessment is at 6 hours. At this time point physicians are required to assess both urinary sodium, and urine output. If urinary sodium is < 70 mmol/L, and/or diuresis is < 150 mL/hour, patients will be eligible (if still deemed congested) for an additional dose of loop diuretic of double the previous dose (figure 4) with a maximum bolus dose of 5 mg of bumetanide or equivalent. The maintenance dose will consequently be adjusted to twice daily the doubled bolus dose. Again, if a patient already received 5 mg of bumetanide as a first dose, this dose will be repeated when there is insufficient natriuresis or diuresis at this time point. Furthermore, if a patient has had two doses of 5 mg of bumetanide and has insufficient natriuresis or diuresis at two consecutive time points, the initiation of combination diuretic therapy with the addition of hydrochlorothiazide 25 mg once daily is indicated. If patients at admission already use a thiazide diuretic, yet no loop diuretic, the thiazide diuretic will be stopped upon admission. These patients are still eligible for combination diuretic therapy with hydrochlorothiazide and a loop diuretic. If patients intentionally use combination diuretic therapy at admission this will be continued. These patients will qualify for second step combination therapy with either acetazolamide or a sodium-glucose-cotransporter 2 inhibitor (SGLT2i).

The above protocol will be repeated at 12, 18, and 24 hours. When a patients has insufficient natriuresis or diuresis at two consecutive time points after the addition of hydrochlorothiazide, acetazolamide 500 mg iv once daily will be added. If this is contra-indicated or acetazolamide has been added as a first step for combination diuretic therapy, the addition of a sodium-glucose transporter 2 inhibitor should be considered.

The treatment algorithm will be continued until 48 hours, however after 24 hours natriuresis and diuresis assessment will only take place every 12 hours (figure 5). At every time point it is essential for physicians to only administer additional doses of diuretics if a patients is still congested. Combination diuretic therapy will be stopped when the patient is euvolemic or when this is indicated based on significant electrolyte disturbances or renal function decline in the absence of decongestion.

Figure 5: Treatment algorithm during the second 24 hours after randomization



Abbreviations: LD: loop diuretic

3.15 Renal ultrasound substudy

3.15.1 Introduction and rationale ultrasound substudy

It is well known that assessment of congestion status remains difficult, as clinical symptoms and signs of HF are in part difficult to assess, have high inter-observer variability, and are mostly non-specific. Non-invasive technologies such as ultrasound imaging to assess congestion and fluid status could aid in the (early) clinical identification of these HF signs and symptoms, and detect change in congested state as response to diuretic treatment.

Ultrasound measurements are easily accessible, interpretable, non-invasive, inexpensive, safe, and can be performed at the bedside rapidly providing additional information and therefore might improve diagnosis and treatment in HF patients. Moreover, it may help detect patients in need of treatment (de)intensification to prevent (re-)admission for HF.

Therefore, patients enrolled during daytime hours on Monday till Wednesday will be eligible for participation in a substudy aimed at better assessment of congestion using ultrasound.

3.15.2 Objectives ultrasound substudy

Primary objective:

To assess congestion status through bedside renal, cardiac, and lung ultrasound assessments in patients with acute heart failure at baseline, day 1, day 2, day 3 and discharge, and change over time.

Secondary Objective(s):

To assess the effect of diuretic therapy, the effect of natriuresis guided therapy specifically, and the relationship between biomarkers of congestion and (change in) congestion status measured by serial ultrasound assessments (cardiac, renal, lung).

3.15.3 Study design ultrasound substudy

This will be a prospective, observational, exploratory study, in which we will evaluate renal, lung, and cardiac ultrasound measurements at baseline (day 1), day 2, day 3 and at day of discharge. Patients will be enrolled from the primary study, with corresponding inclusion and exclusion criteria. All patients will provide additional informed consent for enrollment in the substudy. Patients will be included on week days during day time hours on Monday, Tuesday or Wednesday. We aim to enroll a total of 50 patients and will strive for equal distribution between the natriuresis and the standard of care group of the primary study. Treating physicians will be blinded to the results of the ultrasound assessments. Ultrasounds will be performed by trained clinicians.

Study population

In a proof-of-concept study we performed in patients with acute heart failure, we observed that 54% of patients had a normalization of renal venous flow after 3 days of decongestive therapy. We expect this to increase to approximately 80% of patients in the natriuresis guided group. With an alpha of 0.05 and a power of 80%, we require 48 patients for this study, which we will increase to 50 patients to prevent being underpowered for instance due to insufficient image quality.

Study visits

Table 3.15. Assessment schedule ultrasound substudy

Assessments	Baseline (day 1)	Day 2	Day 3	Discharge
Renal ultrasound - Renal venous flow pattern - Venous impedance index - Venous discontinuity index - Intrarenal arterial resistance index	X	X	X	X
Transthoracic echocardiogram - Inferior vena cave diameter - Right ventricular peak pressure	X	X	X	X

- Pulmonary vein flow				
Lung ultrasound - B-lines	X	X	X	X

Statistical analysis

Baseline data will be presented using mean +- standard deviation for normally distributed variables, mean (interquartile ranges) for skewed variables, and as frequencies (percentages) for categorical variables. Participants will be divided into groups according to occurrence of change in renal, cardiac or lung ultrasound measurements. Baseline characteristics will be analyzed using t-test, linear regression models or Cuzick's nonparametric test for continuous variables, and chi-square test for categorical variables. Predictors at baseline for change in ultrasound measurements will be determined using regression models.

3.16 Pharmacodynamic substudy

In a subset of patients we will perform a pharmacodynamic study aimed at gaining a better understanding of the effect of a bolus of intravenous diuretics on sodium excretion trajectory in contemporary acute heart failure patients. At the moment the only data regarding this stems from the eighties and was obtained in patients with chronic heart failure. This pharmacodynamic substudy can be performed after an intravenous dose of loop diuretics during daytime hours before day 3. Only patients with a urinary catheter will be eligible for this substudy. In addition to the urine samples already obtained per protocol at baseline, after 2 hours and after 6 hours, additional urinary spot samples will be obtained every 30 minutes during the first 6 hours (12 urine samples). One additional plasma samples will be obtained. All patients will provide additional informed consent for enrollment in the pharmacodynamic substudy.

Study population

With an estimate of Urinary sodium content of 90 +/- 27 mmol/L after 2 hours, with 95% CI, and making sure that what we measure is within 12 mmol/L of the true population (margin of error), the formula will be as follows $N = (1.96(27)/12)^2$. This results in approximately 20 patients to ensure that the 95% CI of 2 hour Urinary sodium concentration is within 12 mmol/L of the true mean. Therefore, we aim to enroll 20 patients in this substudy.

4. STUDY POPULATION

4.1 Population (base)

The study population consist of male and female patients (≥18 years old) admitted to the hospital for acute heart failure and requiring intravenous diuretic therapy at the University Medical Centre Groningen.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Male or female ≥ 18 years of age
2. Primary diagnosis of acute /decompensated heart failure as assessed by treating physician
    a. Acute Heart failure can be de novo or exacerbation of known heart failure and diagnosis is based on criteria in the ESC HF guidelines
3. Requirement of intravenous diuretic use

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Dyspnoea primarily due to non-cardiac causes
2. Patients with severe renal impairment receiving dialysis or requiring ultrafiltration
3. Inability to follow instructions
4. Previous participation in this study
5. Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study

4.4 Sample size calculation

Based on our previous study in acute heart failure patients, the mean 24 hours sodium excretion was 398 ± 246 mmol.(8; METC 2019/437) In this population, not 2 hours but 6 hours measurements were available, and in these patients, 36% of patients had an insufficient response, defined as urinary sodium <90 mmol or urine output <900 mL at 6 hours. Assuming a 40% improvement in these 36% of patients, and a conservative 15% improvement in the remaining patients in their 24-hours urinary sodium excretion because of

closer monitoring, this will assume an overall 24% improvement in 24-hours urinary sodium excretion (0.36*1.40 + 0.64*1.15). Therefore, to obtain a power of at least 80% at a two-sided significance level of 0.025 (Bonferroni correction), we calculated a sample size of 125 patients in each group would be sufficient for the primary endpoint of 24-hour natriuresis. To prevent being underpowered due to drop-out or missing data, which is expected to be higher than average in this patient population and given the delicate nature of urinary collections, we will increase enrolment by 10% therefore requiring 140 patients per group, and enrolling a total of 280 patients.

Based on this sample size, we will have 81% power with a two-sided significance level of 0.025 to detect a HR of 0.49 for the other co-primary endpoint of all-cause mortality and heart failure rehospitalisation at 6 months (a reduction in events from 38% to 21%). However also accounting for 10% missing follow-up data, we will increase the total number of patients to 310 (155 patients per group).

5. TREATMENT OF SUBJECTS

The aim of this study is to establish the value of *natriuresis guided therapy* in acute heart failure, to *improve diuretic response, decongestion, and clinical outcomes*.

Patients will be randomized to either standard of care *or* natriuresis guided therapy. In the natriuresis guided group treatment will be adjusted based on urinary sodium values determined at set time points. The optimization of decongestive treatment will be done using a prespecified treatment algorithm (figures 4 and 5). In the standard of care group physicians are encouraged to treat patients according to current best practice consensus (figure 2).

5.1 Investigational product/treatment

The treatment algorithm used in this study is described in detail in section 3.14.2 and figures 4 and 5.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

To establish the effect of natriuresis guided therapy in patients with acute heart failure on 24-hours natriuresis and first occurrence of all-cause mortality or heart failure rehospitalisation at 6 months.

6.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes:

- 48- and 72-hours natriuresis
- Length of hospital stay
- Percentage change in NT-proBNP at 48 and 72 hours

6.1.3 Other study parameters (if applicable)

Safety endpoints:

- Doubling of serum creatinine at 24 or 48 hours
- Occurrence of worsening heart failure (for definition see section 7.2.1.)
- Adverse and serious adverse events

6.2 Randomization, blinding and treatment allocation

Subjects will be randomized 1:1 to natriuresis guided therapy or standard of care. Randomization will be executed using Epic. Treatment assignment will take place by Epic. Patients will maintain this randomization number throughout the study.
Randomization will be achieved within the EPIC electronic health record (EHR) system using an internal random number rule. Randomization starts the first time the patients chart is opened by a provider from the department of cardiology. The randomization group is maintained as fixed variable in the EPIC EHR. Then, when treatment with loop diuretic therapy (intravenous) is started, based on this randomization number, the EPIC EHR automatically chooses the correct treatment orders and diagnostic tests based on the randomization arm. After enrollment of 150 patients we will perform an interim analysis to check whether the distribution of patients to groups is indeed 1:1. If necessary the internal random number rule will be adjusted after this interim analysis.

6.3 Study procedures

Study patients will not be required to come to the hospital for additional visits. Blood will be drawn at 6 different time points during hospitalization. These are assessments that are already part of standard of care and therefore will not lead to additional blood draws. At these time points an additional sample of 5 mL will be obtained for additional assessments after completion of the trial.

A timed collection of urine will take place for the first 72 hours, from which urine samples will be obtained at a maximum of 7 different time points (and one additional urine sample at discharge) in the interventional arm. At these time points an additional sample of 5 mL will be obtained for additional assessments after completion of the trial.

In these urine and plasma samples, we will determine biomarkers to further elucidate response to treatment by assessing congestion markers, and markers specific for certain segments of the kidney. This will not only provide more insight in possible mechanisms of diuretic response, but may also lead to identification of (new) targets for therapy.

Finally, a telephone call 180 days after baseline will be performed to assess signs and symptoms, weight as well as current medications. Vital status will first be verified by contacting the general practitioner.

See also table 3.1 for a schedule of assessments.

Study assessments as part of clinical care:

- Physical examination
    - Height, weight
    - Blood pressure, heart rate (vital signs)
    - Jugular venous pressure, heart sounds and murmurs, pulmonary rales, edema and ascites
- NYHA functional class heart failure
    - Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities
    - Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
    - Class III: Patients with marked limitation of activity; they are comfortable only at rest
    - Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest
- HF signs and symptoms
    - Anamnesis: dyspnea d'effort, orthopnea, paroxysmal nocturnal dyspnea, edema, exercise tolerance

    - Physical examination (see above)
- Echocardiogram
    - Only if performed as standard of care during hospitalization
- X-ray
    - Only if performed as standard of care during hospitalization
- ECG
    - Only if performed as standard of care during hospitalization
- Standard laboratory analysis (standard of care)
    - At admission: hematology, renal function, electrolytes, NT-proBNP
    - After 6 hours: renal function, electrolytes, NT-proBNP
    - Daily: hematology, renal function
- Fluid intake assessment

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

6.5 Replacement of individual subjects after withdrawal

Withdrawn subjects will not be replaced.

6.6 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from treatment will be asked whether the investigator will be allowed to contact the patient for the 180-days visit in order to collect information regarding vital status and eventual (serious) adverse events. Investigators will be urged to have subjects consent to them gathering follow-up information of each withdrawn subject.

6.7 Premature termination of the study

The study may be prematurely terminated if the following criterion applies:

- Apparent inability to include sufficient subjects

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intensified treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All (serious) adverse events will be recorded from baseline to the final follow-up visit (phone call) at 180 days.

Pre-specified adverse events are defined as follows:

- Worsening heart failure defined as:
    - Addition or starting of inotropes or vasopressors
    - Mechanical ventilation
    - Palliative care due to progressive heart failure
    - Any intervention/treatment for heart failure that leads to prolonged hospitalization
- True worsening renal function
    - Doubling of creatinine from baseline to 48 or 72 hours without evidence of decongestion, or urine production < 10 cc / hour despite adequate dosing of loop diuretics

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;

- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events..

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

7.3 Annual safety report

Not applicable.

7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study.

7.5 Endpoint adjudication committee

This committee of experts will adjudicate all rehospitalizations to judge whether a hospitalization is due to heart failure. The committee will be blinded to the treatment allocation, and will independently review each case in order of appearance. Their independent opinions are reconciled at the endpoint adjudication committee meeting. If an endpoint is not unanimous, the case is reviewed further and discussed with the aim of developing a consensus. If the committee is unable to reach a consensus, the endpoint will be established by the committee chair.

A hospitalization for heart failure will be defined as follows:
Hospitalization for more than one day (change in calendar day) with an exacerbation of heart failure requiring treatment meeting the following criteria:

- Signs and symptoms of heart failure
    - One or more of the following symptoms consistent with heart failure:
        - Dyspnea
        - Orthopnea
        - Paroxysmal nocturnal dyspnea
        - Increasing fatigue/decreasing exercise tolerance
        - Edema/anasarca
        - Other symptoms of worsened end-organ perfusion such as dizziness, mental confusion
    - AND two or more of the following sign consistent with heart failure:
        - Weight gain
        - Pulmonary edema or rales
        - Elevated jugular venous pressure
        - Radiologic signs of heart failure
        - Peripheral edema
        - Abdominal distension or ascites
        - S3 gallop rhythm
        - Positive hepatojugular reflux
        - Elevated NT-proBNP
        - Congestive hepatomegaly
        - Invasive/non-invasive tests showing elevated cardiac filling pressures or low cardiac output
- AND treatment
    - The patient receives initiation or intensification of treatment specifically for heart failure,

STATISTICAL ANALYSIS

7.6 Primary study parameter(s)

The primary endpoint will be assessed in the intention to treat (ITT) population. The co-primary endpoint will be total 24-hour natriuresis and first occurrence of all-cause mortality or heart failure rehospitalisation at 6 months. Following the Bonferroni correction used for the sample size calculation, the study will be deemed positive if one or both of the components of the co-primary endpoint are positive (*P-value*<0.025).

24-hour natriuresis will be calculated and presented as mean +/- SD if normally distributed, or median (25^{th} and 75^{th} percentile) in the case of non-normal distribution. The between group difference will be tested using t-test if normally distributed, or Wilcoxon rank sum test if non-normally distributed. The effect of natriuresis guided treatment on long-term outcomes will be assessed using Cox regression for the between treatment difference.

For the presentation of baseline characteristics in both treatment arms, continuous variables will be presented as mean +/- SD, non-normally distributed variables as median (25^{th} – 75^{th} percentile), and categorical values as count (percentages).

7.7 Secondary study parameter(s)

Secondary response variables include 48- and 72-hour natriuresis, length of hospital stay and percentage change in NT-proBNP at 48- and 72-hours. Changes in biomarkers, natriuresis at subsequent time points, and length of hospital stay will be assessed using t-test for normal distributed variables, and Wilcoxon rank sum test if non-normally distributed.

7.8 Other study parameters

Adverse event rates, including doubling of serum creatinine at 24 or 48 hours, serious adverse events, as well as worsening heart failure will be analyzed using Fisher's exact tests, and presented as counts (percentages). To study differences in repeated assessments between treatment groups, such as natriuresis during hospitalization, repeated measures linear mixed effect modeling will be used.

7.9 Interim analysis (if applicable)

Not applicable

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This clinical study was designed and shall be implemented and reported in accordance with the guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles held down in the Declaration of Helsinki (date 19-10-2013). This study will be conducted in accordance with the medical Research involving Human Subjects Act (WMO). The guidelines mentioned in WMO will be the principle guidelines.
An institutional review board that complies with the requirements of applicable Law shall review and approve this protocol, including the informed consent form, in accordance with Applicable Law.

8.2 Recruitment and consent

Recruitment of patients will take place at the Emergency Department, Coronary Care Unit or Ward of the department of Cardiology of the University Medical Center Groningen. Once a potentially eligible patient is diagnosed with acute heart failure, the Principal Investigator or a sub-investigator (physician) will verify eligibility based on the in- and exclusion criteria. Once eligibility has been established, the patient will be enrolled. Because of the acute situation and the nature of the study treatment, there is limited time (at that moment) for the patient to consider participation, therefore deferred consent will be used. At this time treatment will start, as well as collection of urine. The patient will receive the patient information letter about the study during the first four days of hospitalization and will have a maximum of 24 hours to consider his/her participation. During this time written informed consent will be obtained by the researcher.

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10.3 Objection by minors

8.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

8.4 Benefits and risks assessment, group relatedness

Loop diuretics are the cornerstone of treatment in patients with acute heart failure. Loop diuretics are relatively safe and well tolerated by patients in acute heart failure. There is a wealth of data describing its use in this patient group, as well as in patients with a decreased kidney function. Combination of loop diuretics with other diuretic agents, such as acetazolamide has been shown to be able to improved decongestion. Risks of combination diuretic therapy are electrolyte disorders and decrease in kidney function. We will therefore

only initiate combination diuretic therapy in patients with insufficient decongestion already on maximal loop diuretic doses. We will additionally closely monitor renal function and electrolytes throughout the study. Furthermore, assessment of natriuresis is at low risk and minimal hassle to the patient as it does not involve additional invasive procedures. Based on the previous, the relative risk is estimated to be relatively low, while potential benefit may be expected.

8.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.6 Incentives

Patients will not receive any incentives, compensations or treatment through participation in the study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

A subject identification code list will be made to link the data to the subject in order to be able to trace data to an individual subject. This code will not be based on the patients initials and birth date. The key to the code will be safeguarded by the investigator since the data will be kept for a period of 15 years. The handling of personal data will comply with privacy laws, legislation, codes and/or guidelines that apply in the applicable jurisdictions the study is conducted.

9.2 Monitoring and Quality Assurance

Independent monitors will monitor the study according to a pre-specified monitoring plan. The monitors are trained in GCP and will be trained on study specific tasks and processes. As part of the UMCG Quality Management Strategy monitor oversight will be implemented through regular documentation reviews and co-monitoring activities.

9.3 Amendments

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the

accredited METC and the Competent Authority.

9.6 Public disclosure and publication policy

The trial will be registered in a public trial registry. The results will be disclosed unreservedly.

10. STRUCTURED RISK ANALYSIS

10.1 Potential issues of concern

Not applicable as the drugs in this study are used for their registered indication.

10.2 Synthesis

Loop diuretics are the cornerstone of treatment of acute heart failure by attempting to establish a negative sodium and consequently fluid balance. Loop diuretics inhibit the sodium-chloride-potassium co-transporter in the thick ascending loop of Henle and as such lead to decreased sodium and chloride reabsorption from the urine. There is ample data on loop diuretic use in acute heart failure patients as these are administered to >90% of patients hospitalization for acute heart failure. Loop diuretics currently have a class 1C indication in the heart failure guidelines to improve symptoms. All of the drugs used in the study have been used extensively in clinical trials of patients with (acute) heart failure and have been granted approval for their use in heart failure patients.

In this study adverse events of special interest are collected. These include worsening heart failure and true worsening renal function. These side effects are rare but will be monitored closely by regular monitoring of clinical status and renal function. The potential benefits of natriuresis guided therapy to improve the treatment of acute heart failure clearly outweigh the risk of developing these adverse events.

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