TAILOR-AHF: randomized controlled trial investigating a tailored diuretic algorithm in acute heart failure patients

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Primary Objective: Investigate if a tailored diuretic algorithm based on Ur-Na has a positive effect on a composite endpoint of mortality, HF events (HFE) and a change in quality of life (QoL) (assessed with the Kansas city cardiomyopathy…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON53791

Source
ToetsingOnline

Brief title
TAILOR-AHF trial

Condition

- Heart failures

Synonym
Heart failure, pump failure

Research involving
Human

Sponsors and support

Primary sponsor: Zuyderland Medisch Centrum
Source(s) of monetary or material Support: Er is geen sprake van financiering

Intervention

Keyword: Acute dyspnea, Acute heart failure, Diuretic, Urine sodium

Outcome measures

Primary outcome

The primary endpoint is a hierarchical composite calculated using a win-ratio approach of:

i) Mortality (all-cause) at 90 days after hospitalization;

ii) HF events at 90 days after hospitalization including hospitalization (see definition at 8.1.2 in the study protocol) wherein a single event or hospitalization will be sufficient to reach the combined endpoint;

iii) Delta in QoL measured using the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) from baseline to 90 days after hospitalization

Herein, all patients from the intervention group will be compared to all patients in the usual care group (see statistical methods). The win-ratio will prioritize according to the order above, and for any two patients a patient will win when advantage is shown defined by the conditions in table 2 in the study protocol. Thus, prioritizing mortality over HF events and events over QoL. When there is no win in any of the endpoints, there is a tie.

Secondary outcome

• Delta NT-proBNP from admission to discharge: assessed by ELISA-based blood evaluation (Roche Diagnostics), measured clinically and thus non-blinded on day of admission and at day of discharge (or day -1 to max -2); and 90-days. • Successful decongestion at day 3 (window 2 - 4) and discharge (% of patients); defined as a clinical congestion score of 2 or less (as detailed in figure 4);

and NYHA I-II (if NYHA >2 but clinical congestion is limited, use additional diagnostics to define the nature of dyspnea and confirm adequate decongestion); • Delta clinical congestion score from admission to discharge (continuous); • Quality of Life: assessed by several domains of the KCCQ questionnaire at 90 days after hospitalization (delta from baseline, continuous and number (%) of patients with an increase of >=10 points). • Adverse events (safety): all-cause readmissions at 90-days, all-cause and CV mortality at 90-days, (symptomatic) hypotension, hypokalemia, urinary tract infection, phlebitis, atrial fibrillation, fall/trauma and decompensated HF; • All-cause mortality and HF readmissions at 14 days after initial admission; • Worsening renal failure; analyzed as a continuous variable delta creatinine/baseline creatinine (in groups of 10%) at discharge and at 90-days follow-up; and dichotomous defined as delta creatinine >50%; • Occurrence of the need for chronic dialysis at 90-days FU; • Days alive outside the hospital (at 90-days FU); • Time to first HF hospitalization and number of HF hospitalizations • Number of outpatient visits in the first 90-days FU; • Number of worsening HF events at 90-days FU; i.e. a summation of i) a >2 times increase in oral loop diuretic dose, ii) the need for iv administration of loop diuretics, iii) hospitalization for HF; • Delta weight (in kilograms) from admission to discharge.

Study description

Background summary

ACUTE HEART FAILURE: SCOPE OF THE PROBLEM
Hospitalizations for acutely decompensated heart failure (AHF) are not only

prevalent - 30*985 in the Netherlands in 2018 - but also put a high burden on resource use because of their duration (mean length of stay 6.3 days in 2006 in a US Medicare registry; 9.7 days in Maastricht UMC in 2019). The total costs for heart failure (HF) in the Netherlands were estimated at 817 million euros in 2017; mainly driven by hospitalizations which are responsible for almost two thirds of the total HF costs [1]. On top of this, AHF hospitalizations impose a high risk of short-term mortality (in-hospital 4-9%, 30-day 11-21%, 1-year 17-27%) and re-admissions (30-day 16-21%; 1-year 31-44%). The already high and further increasing prevalence of HF (currently ~240*000 in the Netherlands; expected increase of 72% between 2018-2040 purely based on the ageing population) will only put more pressure on already tight resources.

AHF: NEED FOR A TAILORED DIURETIC ALGORITHM

Treatment of AHF relies mainly on diuretics to relieve congestion, by increasing renal water and sodium excretion. Early installation of diuretics and an adequate or *complete* decongestion are favourable factors with regard to re-admissions and mortality. However, in clinical practice this is often not achieved because it is very difficult to predict the individual response to diuretic therapy and thus to choose the right dose and type of diuretics for sufficient decongestion. One randomized trial previously investigated a high- versus low-dose of loop diuretics and a bolus versus continuous administration (2:2 factorial design). Both interventions did not improve patient-related nor clinical endpoints. The trial was limited by cross-over because clinicians were allowed to increase dosage of diuretics and indeed did so more often in the low-dose arm. Being too aggressive may be dangerous in terms of causing worsening renal failure. A more individualized, tailored approach taking into account a patient*s diuretic response is warranted.

TAILORED DIURETICS: NEED FOR A RANDOMIZED TRIAL

A tailored diuretic approach using repeated measures of urinary sodium (Ur-Na) was recently suggested by a working group paper [2] and mentioned by the European clinical practice guidelines. However, the guideline states that *this algorithm is entirely based on expert opinion.* Observational studies showed that Ur-Na can predict diuretic response and speed-up decongestion. Still, no study thus far investigated solid clinical endpoints and such an Ur-Na tailored approach has never been compared to a control group.

The need for a decent evaluation of this algorithm is underlined by several ongoing initiatives: i) an ongoing multicentre study investigating the feasibility of this approach (ENACT-HF), however this study is non-randomized and the primary endpoint is a non-clinical endpoint of natriuresis after 1 day; ii) an ongoing single-centre randomized study in UMC Groningen (PUSH-AHF; NCT04606927), using a more intense algorithm in a single-centre nature, prohibiting extrapolation to non-academic centres and prohibiting evaluation of implementation issues; iii) a randomized trial has been announced in the USA (NCT04481919), however results may be not extrapolated due to a very different organization of care in the Netherlands. Thus, we are still lacking an adequately powered, clinical endpoint driven evaluation of this diuretic

approach including a cost-effectiveness analysis. This is needed to obtain a sufficient level of evidence (B) to support implementation of this approach because it requires more effort from medical staff. That is, treatment by the diuretic algorithm becomes individualized and intensified, as medical staff (nurses, doctors) are required to evaluate and adjust diuretic dosing at 6 hourly intervals, whereas usual care currently entails only 1 evaluation and therapy adjustment each day. Moreover, evaluation of the intervention in different types of hospitals (academic vs non-academic, small vs large) is important to empower implementation in the entire NL. Finally, such a trial is needed to address safety concerns, specifically with regard to worsening renal failure.
In summary, diuretics are given on a daily basis in every Dutch hospital to our 32*500 annually admitted AHF patients. The individual response to diuretics varies greatly yet there is no sufficient evidence to support any specific dosing algorithm. It is hypothesized that a Ur-Na based, tailored and intensified algorithm can help tailor diuretics in an individual way, but sufficient evidence to support its implementation is lacking. This urgently calls for an adequately powered trial to address this issue: TAILOR-AHF.

Study objective

Primary Objective: Investigate if a tailored diuretic algorithm based on Ur-Na has a positive effect on a composite endpoint of mortality, HF events (HFE) and a change in quality of life (QoL) (assessed with the Kansas city cardiomyopathy questionnaire total symptom score (KCCQ-TSS) of >=5 points) versus standard clinical care in patients hospitalized with AHF. Secondary Objective(s): i) Show the effect of this algorithm on the single endpoints included in the combined primary endpoints (i.e., mortality and CV mortality, HF events, HF rehospitalizations, and QoL following KCCQ), effectiveness of decongestion based on a congestion score, days alive outside the hospital and change in N-terminal Pro-Brain Natriuretic Peptide from baseline (day of admission) to discharge (day of discharge +/- 2 days) ii) Show the safety of this protocol in terms of worsening renal failure. iii) Care consumption: number of outpatient and inpatient visits during 90 days follow-up iv) Provide an implementation plan for clinical practice. v) Correlate urinary spot sodium measurement at ~2hours after loop diuretic bolus with 8 hourly urine collection and with urinary chloride. vi) Correlate urinary potassium levels with treatment response (interaction analysis with MRA). vii) Exploratory subgroup analyses, being GFR>=30 versus <30 ml/min, age >=75 vs <75, gender and previous HF versus *de novo* HF.

Study design

Study design: Single-centre, Randomized, Single-blinded, Blinded-Endpoint Trial. Individual randomization is performed because cluster randomisation will introduce too much bias because only a limited number of clusters can be

created on our ward.

Blinding: This design prohibits blinding of the treating physicians/nurses since the treating physician is using the Ur-Na measures to guide and intensify therapy. The patient will be blinded.
Endpoints however will be blinded and evaluated by an independent endpoint committee. Also, the researchers/data-analysts performing data analysis will be blinded. Endpoints are chosen in a way to minimize bias by non-blinding (see endpoints).

Study arms: Arm I: Tailored, urinary-sodium based, intensified diuretic strategy;
Arm II: Usual care

Duration: the intervention will take place only during the hospitalization, follow-up 90 days. A study flow chart is provided in figure 1 in the study protocol.

Setting: Cardiology ward and First Heart AID / emergency department at a large non-academic top-clinical hospital (STZ) being Zuyderland Medical Centre (ZMC) location Heerlen.

Intervention

The proposed intervention (treatment arm I) is shown in Figure 3. It is adapted from a recent working-group paper based on findings from several observational studies and has been designed in consensus of an expert panel of HF specialists. After initial assessment and diagnostics (preferable <1 hour) the patient will be treated with a bolus of loop diuretics that can vary from a minimal dose of 40 mg to a maximum of 250 mg furosemide depending on whether the patient already uses diuretics or not and based on the eGFR, following the dosage conversion table in Figure 4. Acetazolamide (500 mg intravenously) once daily in the morning (7:00 am) is advised during the first 3 days of hospitalization (as long as the patient is still congested) according to the ADVOR-trial as part of routine clinical care and thus this is advised in both study arms. Two hours after the loop diuretic bolus, Ur-Na will be evaluated. Insertion of a urinary bladder catheter (UBC) is strongly recommended. In patients where this doesn*t prove possible (patient refuses UBC or has a medical contra-indication) the patient will be instructed to empty his/her bladder (which will be verified by means of bladder-scan) before sample collection. In case of urinary incontinence or insufficient bladder emptying, a UBC is mandatory. If Ur-Na is below target of 100 mmol/L, the next bolus will be doubled - up to 250 mg furosemide. Bolus administration of loop diuretics and Ur-Na evaluation thereafter are repeated 3x a day (approx. 7 am , 3 pm and 11 pm) in the first 48 hours, and diuretics will be further increased if the response remains sub therapeutic, including addition of other types of diuretics (See 5.2 use of co-interventions). Once the patient has reached an

adequate diuretic response, the effective loop diuretic dose (+/- other diuretic types) will be continued until the patient is decongested, or at discretion of the physician. Thus, the algorithm is designed to install an effective diuretic response as soon as possible in an individualized way. As long as patients are still showing signs of congestion (clinical congestion score >= 3, see section 8.1.2) a rise of serum creatinine up to 50% of baseline is accepted and is not a reason per-se to not further increase diuretic dosage. If creatinine increases above 50% of baseline (in combination with clinical signs such as hypotension etc), further diagnostics are recommended for example a (repeated) transthoracic echocardiography to confirm filling status of the patient, a renal ultrasound, a consultation of the nephrologist, etc. This will occur similarly as is currently done in clinical standard care. Standard care (treatment arm II) (reflecting usual care in NL) is a loop diuretic iv (either shots or continuous administration, to the discretion of the treating physician) and adjustment of therapy based on other parameters such as body weight changes or volume-balance. In both study arms, physicians are recommended to discharge the patient only when fully decongested (clinical congestion score <= 2 (see section 8.1.2) and NT-proBNP reduction of >=30%), evaluated by clinical evaluation and if needed by echocardiography or chest-X-ray. In both study arms, physicians are recommended to install optimal HF therapy and treat underlying triggers of HF according to standard care and guidelines. In both study arms, standard regimens on the ward are a sodium restricted diet (3 grams/24u) and a fluid restriction of 1.8L including meals per 24 hours.

Study burden and risks

As stated in the background section, intravenous loop-diuretics have been the cornerstone of treatment of AHF for decades. However, there is very little evidence about individual dosing in daily practise. Therefore it is often up to the treating physician with which dose to start and how fast to increase this dose. This trial will use an intensified Ur-Na based treatment algorithm which will provide physicians with the tools to be able to reach an adequate dose faster. Since there is no new medication involved in this trial, there are no medication related side-effects to be expected in the intervention group that weren*t already present during usual care. Possibly, a more aggressive approach at increasing diuretic dose could result in more prevalent regression of renal function due to dehydration. However, this is closely monitored by frequent laboratory analysis (in line with usual care but also in terms of a safety endpoint) so that diuretic dosing can be adjusted accordingly.
Furthermore, swift increase of diuretic dose will lead to a therapeutic dosage earlier during hospitalisation. Expectations are that therefore it will lead to earlier decongestion and shorter hospital admissions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age > 18 years; • HF (HFrEF, HFmrEF or HFpEF) diagnosed according to the 2021 HF Guidelines of the European Society of Cardiology; • Presentation with AHF meaning at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) of AHF; • An elevated NT-proBNP >300pg/ml; • Requiring the need for iv diuretics;

Exclusion criteria

• Terminal renal insufficiency defined as: dialysis patients or eGFR (estimated glomerular filtration rate) < 10 mL/min/1.73 m2; • Patients included in other

investigational studies regarding heart failure. • Presentation with cardiogenic shock or respiratory insufficiency or another reason requiring admission to the intensive care unit upon admission (IC transfer later in the hospitalization is not an exclusion).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-02-2023
Enrollment:	466
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2022
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	31-07-2023
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-04-2024

Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	24-06-2024
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL81341.096.22