Rationale and Design of the DECONGEST (Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment) Study

Peer-reviewed author version

Vanhentenrijk, S; VERBEECK, Johan; Kalpakos, T; Vandoren, Vincent; Braeckeveldt, L; L'Hoyes, W; Choustoulakis, E; Roosens, B; Tang, WHW; VERWERFT, Jan & VERBRUGGE, Frederik (2025) Rationale and Design of the DECONGEST (Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment) Study. In: Journal of Cardiac Failure, 31 (4) , p. 651 -660.

DOI: 10.1016/j.cardfail.2024.08.044
Handle: http://hdl.handle.net/1942/49366

Rationale and Design of the DECONGEST (Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment) Study

Simon Vanhentenriyk M.D. Pharm.D.[1,2]^, Johan Verbeeck M.Sc. Ph.D., Theodoros Kalpakos M.D.[1], Vincent Vandoren M.D.', Laura Braeckeveldt M.D.[1], Wouter L'Hoyes M.D.', Eleftherios Choustoulakis M.D.M.Sc.[1], Bram Roosens M.D. Ph.D.[1'], W. H. Wilson Tang M.D.^, Jan Verwerft M.D. , Frederik H. Verbrugge M.D. Ph.D. M.Se.'*

1. Centre for Cardiovascular Diseases, University Hospital Brussels, Jette, Belgium.
2. Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium.
3. Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, United States.
4. Data Science Institute, Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-Biostat), University of Hasselt, Hasselt, Belgium.
5. Department of Cardiology, Jessa Hospital, Hasselt, Belgium.

Word count: 3,809 (excluding references, tables, and figures)

Address for Correspondence

Frederik Hendrik Verbrugge, M.D. Ph.D. M.Sc.

Centre for Cardiovascular Diseases, University Hospital Brussels

Laarbeeklaan 101, 1090 Jette, BELGIUM

Tel.: +32 2 474 9657| Fax: +32 2 477 4159 | E-mail: frederik.verbrugge@uzbrussel.be

X handle: @FH_Verbrugge

Acknowledgements

The DECONGEST steering committee wants to express its gratitude to Ingrid Lemoine and Julie Bollen, who, as site coordinators, helped to prepare and submit the files for ethical approval at University Hospital Brussels and Jessa Hospitals, respectively.

Funding

Roche diagnostics has provided an undisclosed research grant to cover the costs of biomarker analyses in the DECONGEST study including all assessments of N-terminal pro-hormone of B-type natriuretic peptide (NT-proBNP), Cystatin C (CysC), and Cancer antigen 125 (CA-125). The Fund for Cardiac Surgery provided support to cover 10,000€ of running costs for the DECONGEST study (Ref. 489722).

Conflict of interest

S.V. has received travel grants from Daiichi Sankyo. V.V. has received travel grants from Bayer, Biotronik & Medtronic. E.C. has received travel grants from Daiichi Sankyo. W. H. W. T. has served as consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, WhiteSwell, Boston Scientific, CardiaTec Biosciences, InteIlia Therapeutics, Bristol Myers Squibb, Alleviant Medical, Alexion Pharmaceuticals, Salubris Biotherapeutics, and has received honorarium from Springer, Belvoir Media Group, and American Board of Internal Medicine. J.V.W has received travel grants from AstraZeneca, Daiichi Sankyo Belgium, Novartis Pharma, Pfizer, and St. Jude Medical Belgium. J.V.W has received travel grants from AstraZeneca, Bayer, and Novartis Pharma. F.H.V. has received speaker's and advisory fees from Abbott Laboratories, Abiomed, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb Belgium, Edwards Lifesciences, Johnson & Johnson, Menarini Benelux, MSD, Novartis Pharma, Novo Nordisk Pharma, Pfizer & Qompium. In addition, F.H.V. has received travel grants from Abbott Laboratories, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk Pharma & Pfizer.

Abstract

Aims: To evaluate whether early combination diuretic therapy guided by serial post-diuretic urine sodium concentration (UNa*) assessments in acute heart failure (AHF) facilitates safe and effective decongestion.

Methods: The Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) study is a pragmatic, 2-centre, randomized, parallel-arm, open-label study, aiming to enrol 104 patients with AHF and clinically evident fluid overload, requiring treatment with intravenous loop diuretics. Patients are randomized to receive standard of care or a bundled approach comprising: (1) systematic post-diuretic UNa' assessments until successful decongestion, defined as no remaining clinical signs of fluid overload with a post-diuretic UNa' 80 mmol/L; (2) thrice-daily intravenous loop diuretic bolus therapy, with dosing according to estimated glomerular filtration rate; (3) upfront use of intravenous acetazolamide (500 mg OD); and (4) full nephron blockade with high-dose oral chlorthalidone (100 mg OD) and intravenous canreonate (200 mg OD) for diuretic resistance, defined as persisting signs of fluid overload with a post-diuretic UNa* ñ80 mmol/L. The primary endpoint of the DECONGEST study is a hierarchical composite of (1) survival at 30 days; (2) days alive and out of hospital or care facility up to 30 days; and (3) greater relative decrease in natriuretic peptide levels from baseline to day 30.

Conclusion: The DECONGEST study aims to determine whether an intensive diuretic regimen focused on early combination therapy, guided by serial post-diuretic UNa+ assessments, safely enhances decongestion, warranting further evaluation in a larger trial powered for clinical events.

Keywords

cardio-renal syndrome; diuretics; heart failure; natriuresis; natriuretic peptides; sodium.

Highlights

- The DECONGEST study evaluates a diuretic strategy that includes early combination treatment, loop diuretic dosing based on estimated glomerular filtration rate, and diuretic titration based on serial urine sodium assessment.
- The primary endpoint of the DECONGEST study is a hierarchical composite of 30-day survival, days alive and out of hospital or care facility, and greater relative decrease in natriuretic peptides from baseline to 30-day follow-up.
- The DECONGEST intervention defines euvolemia as no clinical signs of fluid overload with a low (ñ80 mmol/L) urine sodium concentration, thereby effectively studying a desalinisation approach.

day Summary

This manuscript describes the design and methods of the DECONGEST study. This study evaluates a novel treatment algorithm for fluid overload in patients with decompensated heart failure, comparing it to current standard of care. Rather than focusing on one class of diuretics and considering other classes only in case of insufficient response, the DECONGEST intervention focuses on early combination of different diuretic classes and titrates them based on urine sodium (salt) content. The DECONGEST study evaluates whether this treatment algorithm improves the number of days alive and out of hospital or care facility with better relief of fluid excess.

Introduction

The prevalence of hospital admissions for heart failure is primarily attributed to signs and symptoms of fluid overload.[1] During acute heart failure (AHF) episodes, diuretics are the mainstay treatment. Effective diuretic action leading to complete decongestion consistently correlates with improved outcomes.[2] However, achieving these targets poses challenges in clinical practice due to frequent occurrences of diuretic resistance and the difficulty in confirming optimal volume status. This explains why clinical outcomes after an episode of AHF remain dismal, with recent European registry data demonstrating a 1-year readmission rate of 44.4% (25.9% for readmissions due to heart failure only) and an all-cause mortality of 26.7%.[3] Residual (subclinical) congestion is likely an important mediator of this risk.[4]

Post-diuretic spot urine sodium concentration (UNa“) is a reliable indicator of diuretic response. [6] Its use in AHF has been recommended by current guidelines of the European Society of Cardiology, to detect diuretic resistance early to allow appropriate treatment t4 intensification.[7] The Pragmatic Urinary Sodium-based Algorithm in Acute Heart Failure (PUSH-15 AHF) trial and Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure Study (ENACT-HF) study have demonstrated that systematic assessment of post-diuretic UNa* in AHF indeed leads to the use of more intensive diuretic regimens, which increases natriuresis and may facilitate decongestion. Moreover, observational data suggest that a *high* UNa' may indicate persistent sodium overload, even when clinical signs of fluid overload are not obvious.[6 10 11] Hence, the hypothesis arises that intensive diuretic therapy in AHF, until complete resolution of clinical signs of fluid overload *and* simultaneously reaching a low post-diuretic UNa* value 180 mmol/L before switching to oral maintenance therapy, could enhance the quality of decongestion.

While loop diuretics remain fundamental in AHF treatment, trials like Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) and Combining Loop with Thiazide Diuretics for Decompensated Heart Failure (CLOROTIC) advocate the upfront use of other diuretic classes, like acetazolamide and thiazide-like diuretics, to improve decongestion

and avert diuretic resistance.[12-14] Yet the challenge remains in integrating these trial results and making informed decisions regarding the most appropriate diuretic regimen for individual AHF patients.

The Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) study evaluates the effect of a care bundle on safe and effective decongestion. This bundle includes: (1) systematic UNa' assessments until complete decongestion, defined as no remaining clinical signs of fluid overload with a post-diuretic UNa+ '<80 mmol/L; (2) intravenous loop diuretic bolus therapy three times daily with bolus dose according to estimated glomerular filtration rate (eGFR); (3) systematic upfront use of intravenous acetazolamide; and (4) employment of high-dose oral chlorthalidone upfront in patients with an eGFR <30 mL/min/1.73m^2 as well as in any case of diuretic resistance, defined as persisting signs of fluid overload with a post-diuretic UNa" 80 mmol/L. Chlorthalidone is combined with intravenous canreonate to achieve full nephron blockade in instances of diuretic resistance since rebound renin-angiotensin-aldosterone system activation has also been proposed as a mechanism for diuretic resistance. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) did not confirm this hypothesis, but this might have been partly due to a delayed conversion to canreonate (>48 h).[1 16]

Study Design

The DECONGEST study is a pragmatic, 2-centre, randomized, parallel-arm, open-label study to assess whether an intensive diuretic regimen focused on early combination therapy, based on serial post-diuretic UNa* assessments, facilitates safe and effective decongestion in AHF (Figure 1). Ethical approval for the study was obtained from the ethics committees of both participating sites: University Hospital Brussels, Jette, Belgium, and Jessa Hospital, Hasselt, Belgium. The study is conducted in adherence to the principles outlined in the Declaration of Helsinki and the International Conference of Harmonization Guidelines for Good Clinical Practice. Written informed consent has been obtained from all enrolled participants. The trial is registered at ClinicalTrials.gov under the identifier NCT05411991. Enrolment commenced in June 2022 and was concluded in June 2024.

Study objectives

Primary objective

The primary objective of the DECONGEST study is to determine whether an intensive diuretic regimen focused on early combination therapy, based on serial post-diuretic UNa+ assessments, leads to faster and more effective decongestion reflected by a shorter admission length and greater plasma N-terminal pro-hormone of B-type natriuretic peptide (NT-proBNP) reduction, without harmful effect on death or readmissions within 30 days. A positive result would represent a strong incentive to test the intervention strategy in a larger trial powered for clinical endpoints such as mortality and worsening heart failure. The DECONGEST study would provide invaluable insights to design such a trial.

Secondary objectives

All study subjects undergo diverse and repetitive assessments of different aspects of their congestion status (Figure 2) to gain new insights into the cross-sectional and temporal relationship between clinical signs of fluid overload, hemodynamic congestion (i.e., cardiac

filling pressures on transthoracic echocardiography), lung ultrasound, venous Doppler echography (VExUS), UNa* profiles, bi-atrial function, and biomarkers such as plasma NT-proBNP and carboxyhydrate antigen-125 (CA-125). Finally, the DECONGEST study will provide unique prospective longitudinal data on the incidence and determinants of diuretic resistance in patients with AHF receiving combination diuretic treatment.

Study participants

The DECONGEST study enrols adult patients admitted for AHF, demonstrating clear clinical signs of fluid overload and a plasma NT-proBNP >1,000 ng/L, with an anticipated hospitalization duration exceeding 24 h. Comprehensive eligibility criteria are detailed in Table 1. The diagnosis of AHF is according to the treating physician and may include either de novo heart failure or an exacerbation of chronic heart failure. Given the significance of UNa+ measurements in the study intervention, a 6-hour diuretic washout period is adhered to, after which patients must meet all eligibility criteria to be considered for enrolment and randomization. Key exclusion criteria encompass severe kidney dysfunction, (eGFR <15 mL/min/1.73m*), severe hypotension or shock, any acute coronary syndrome within 30 days prior to enrolment, and a history of mechanical circulatory support, heart, or kidney transplant. The intentionally broad eligibility criteria aim to encompass a real-world, contemporary AHF cohort, enhancing the generalizability of study findings.

Randomization and allocation concealment

Patients are randomly assigned in a 1:1 ratio to standard of care or the care bundle that comprises the DECONGEST study intervention. After eligibility is confirmed, randomisation is performed through an online, protected website, using the Castor Electronic Data Capture system (Castor, Amsterdam, the Netherlands). Block randomization is applied, stratified by study centre and left ventricular ejection fraction (<50% versus a50%), with variable blocks of 2 or 4 subjects for allocation concealment.

Study intervention

Standard of care

All patients in the study are ~~op timally~~ treated according to ~~the standard of care in agreement with~~ current guideline recommendations.[7] The study protocol explicitly recommends administering an intravenous loop diuretic dose at least twice a day (or via continuous infusion). The initial dose should be equivalent to twice the oral maintenance dose, with the objective of achieving a urine output of 3-5 litres per day, until the patient is deemed adequately decongested. In loop diuretic naive patients, furosemide 20-40 mg BID is used as a starting dose. Urine electrolyte assessment in the standard of care arm is not allowed as it is a key component of the DECONGEST intervention. However, patients in the standard of care arm otherwise receive similar assessments of congestion status as in the intervention arm with a clinical exam, lung ultrasound, venous Doppler ultrasound, and comprehensive transthoracic echocardiography performed at baseline, after the switch from intravenous to oral diuretic treatment, at discharqe and durinq the 30-day follow-up evaluation (Fiqure 2.). Echo results are not used to make the decision to switch from intravenous to oral diuretic treatment. In fact, it is this decision (based on clinical assessment) that triggers the echo exams accordinq to the protocol.

DECONGEST intervention

A flowchart of the DECONGEST intervention is depicted in Figure 3. Immediately fFollowing randomization, patients allocated to the intervention arm receive an intravenous bolus of bumetanide, with the dose depending on the eGFR: 2 mg for >45 mL/min/1.73m^2; 3 mg for 45-30 mL/min/1.73m“; or 4 mg for <30 mL/min/1.73m^2. Additionally, an intravenous bolus of 500 mg acetazolamide is always administered unless hypernatremia (serum sodium concentration >145 mmol/L) or metabolic acidosis (serum bicarbonate <22 mmol/L) is present. Oral chlorthalidone 50 mg is only added from start in case of either hypernatremia (serum sodium concentration >145 mmol/L) ~~or~~, an eGFR <30 mL/min/1.73m^2, or both. This means for instance that patients with normal sodium levels and an eGFR <30 mL/min/1.73m* receive

both acetazolamide and chlorthalidone from the start. The patient is instructed to void empty or, in case of a bladder catheter, any urine present at the time of initial diuretic administration is discarded. A background maintenance infusion with 500 mL dextrose 5% and 3 g MgSO4is started at an infusion rate of 20 mL/h and continued until the switch to oral diuretic treatment S (see below). If serum potassium levels are <4 mmol/L at any time during the administration of intravenous diuretics, 40 mmol KCI is added to this maintenance infusion. In case of significant hyponatremia <130 mmol/L, the maintenance infusion is substituted by a daily bolus of 3 g MgSO4. The main qoal of this infusion is to prevent hypomaqnesemia and hvookalaemia. The additional free water load is not deemed to be problematic as acetazolamide significantly increases free water excretion. A similar approach was executed in the ADVOR trial.[12]

Following each morning and afternoon bolus administration of bumetanide, a spot urine sample is collected within 30-120 min for UNa+ assessment, which guides subsequent treatment. After the initial diuretic administration upon randomization (Day 0), an intravenous bolus of bumetanide is provided 3 times daily on the next consecutive days, at a dose based I § on the most recent eGFR value available (as described above). A minimal 6-hour interval is respected between consecutive bumetanide bolus administrations. Intravenous acetazolamide 500 mg OD is administered concurrently with the first bumetanide dose each day unless hypernatremia or metabolic acidosis is present. Oral chlorthalidone is continued at a dose of 50 mg OD in case it was indicated upon randomization (see above).

When UNa+ levels are >80 mmol/L, the protocol proceeds with the next scheduled bumetanide bolus, administered by the regimen described above (alongside acetazolamide and/or chlorthalidone if warranted). With UNa* 80 mmol/L, there are 2 possibilities: (1) the treating physician finds no clinical ~~arguments~~ signs of ~~for~~ residual fluid overload and there is no more than trace oedema, in which case the patient is switched from intravenous diuretics to oral therapy, started on the following morning, and the study intervention ends; or (2) there is residual fluid overload and/or more than trace oedema, indicating diuretic resistance for

which full nephron blockade is started in the morning of the next day. If UNa+ assessment is

unavailable due to collection errors, the protocol continues until the next scheduled UNa+ assessment, which informs subsequent intervention decisions as outlined above. Imaging by echocardioqraphy and/or venous ultrasound does not play a role in the assessment of residual volume overload to make a decision for switching from intravenous to oral diuretic therapy, as it is performed only after this decision had been made.

For patients with diuretic resistance, defined as a post-diuretic UNa' 80 mmol/L alongside persistent clinical signs of fluid overload, full nephron blockade is applied on the next morning as an intravenous bolus of acetazolamide 500 mg (unless hypernatremia or metabolic acidosis), an intravenous bolus of bumetanide 4 mg, oral chlorthalidone at a dose of 100 mg, and an intravenous bolus of potassium canrenoate 200 mg (unless hyperkalaemia >5 mmol/L). If the patient is already treated with an oral mineralocorticoid receptor antagonist (MRA) as part of their maintenance therapy, this medication is paused until the switch to oral treatment. If after full nephron blockade, post-diuretic UNa* rises >80 mmol/L, the bumetanide dose is repeated 3 times daily. This schedule is then continued until successful decongestion, as defined above. In case of refractory fluid overload with a post-diuretic UNa' ñ80 mmol/L despite full nephron blockade, all diuretics are withdrawn and ultrafiltration with or without renal replacement therapy is started and continued at the discretion of the treating physician, thereby concluding the randomized intervention.

Upon successful decongestion, acetazolamide and potassium canrenoate (if indicated according to the study protocol) are discontinued. Chlorthalidone is continued at a dose of 50 mg once daily only when it was previously added as part of the full nephron blockade because of diuretic resistance. If chlorthalidone was started because of hypernatremia and/or low eGFR at randomization, it is also withdrawn. Spironolactone 25 mg once daily or an equivalent MRA is started (or continued) unless serum potassium levels are >5 mmol/L. Intravenous bumetanide is replaced by oral administration, with dose according to eGFR (1 mg for a40 mL/min/1.73m^2; 2 mg for 30-39 mL/min/1.73m*; and 2.5 mg for <30 mL/min/1.73m*) and once daily administration, unless anticipated poor adherence to a low-sodium diet in which

case oral bumetanide was continued twice daily. The maintenance dextrose 5% infusion is halted, indicating the end of the randomized DECONGEST intervention.

Background guideline-directed medical treatment for head failure

In both the standard of care and DECONGEST intervention group, it is explicitly recommended to keep guideline-directed medical treatments with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin-neprilysin inhibitors, MRAs, and sodium-glucose co-transporter-2 inhibitors unchanged during the period of intravenous diuretic administration. However, withdrawal or dose reduction is permitted in case of emerging (relative) contraindications. Dose up-titration or initiation of these treatments is only allowed *after* transition from intravenous to oral diuretic therapy and is strongly recommended in patients with reduced ejection fraction.

Study endpoints

Primary study endpoint

The primary endpoint of the DECONGEST study is hierarchically composed of (1) survival at 30 days; (2) days alive and out of hospital or care facility up to 30 days; and (3) greater relative decrease in NT-proBNP levels from baseline to day 30, to declare a winner.

Secondary study endpoints

Secondary endpoints of the DECONGEST study will be assessed in a hierarchical order to limit alfa spending (Table 2). If the primary or any of the secondary study endpoints are negative, all following endpoints are considered explorative.

Safety **precautions**

Anticipated adverse events potentially related to the DECONGEST intervention include arterial hypotension, acute kidney injury (AKI) and electrolyte disorders. Arterial blood pressure is evaluated throughout the study protocol with frequent non-invasive assessments by cuff

manometry. Serum creatinine, eGFR, and serum electrolyte levels are followed daily during the administration of intravenous diuretics according to the study protocol and afterwards at the discretion of the treating physician.

Arterial hypotension

In case of significant arterial hypotension, defined as a systolic blood pressure <90 mmHg and/or mean arterial pressure <65 mmHg at any time during the period of intravenous diuretic therapy, all non-diuretic hypotensive medications are withdrawn and the next diuretic administration is postponed until blood pressure recovery. If vasopressors or inotropes are clinically indicated as rescue therapy according to the treating physician, the study intervention ends, and further treatment is at the discretion of the treating physician.

Acute kidney injury

If the serum creatinine doubles (compared to its baseline value) at any time during the period of intravenous diuretic therapy and has an absolute value »2 mg/dL, the study intervention ends, and further treatment is at the discretion of the treating physician.

Electrolyte disorders

In case of clinically significant hyperkalaemia >5.5 mmol/L, any treatment with renin-angiotensin system blockers and/or MRAs is temporarily interrupted. If serum potassium levels rise further >6.5 mmol/L despite these precautions, the study intervention ends, and further treatment is at the discretion of the treating physician. In case of hypokalaemia <3.5 mmol/L (despite daily administration of 40 mmol KCl as specified above), oral supplementation is provided to target serum potassium levels >4 mmol/L.

In case of hypotonic hyponatremia <135 mmol/L, chlorthalidone or potassium canrenoate that is specified according to the study protocol is withheld and treatment with MRA is temporarily interrupted until restauration of a serum sodium level a135 mmol/L. In patients

with serum sodium levels <130 mmol/L, the hypotonic maintenance infusion is not administered, but replaced by a bolus of 3 g MgSO4 until serum sodium levels ?130 mmol/L. In case of severe hyponatremia <125 mmol/L, a bolus of 150 mL hypertonic saline 3% is administered and repeated as necessary, until sodium levels are z135 mmol/L. In case of hypernatremia >145 mmol/L, additional free water is administered as dextrose 5% to keep serum sodium levels 145 mmol/L and the patient is encouraged to have more liberal fluid intake if possible. In case of severe metabolic acidosis with serum bicarbonate levels <20 mmol/L, 100 mL of intravenous NaHCO3 8.4% is administered.

Data collection

All study data are collected through a customised case report form in the open-source platform REDCap (Vanderbilt University, Nashville TN, United States). Subjects discharged before the end of the 30-day follow-up period are scheduled for a follow-up appointment with one of the study investigators between days 30 and 35. This ensures complete data capture and allows for the collection of a final blood sample for biomarker analysis. Patients who miss the follow-up appointment, or are unable to attend, are contacted by phone to minimise missing data.

Sample size and power calculation

According to a simulation study of the primary endpoint by our independent statistician (Jo.Ve.), with assumptions based on current literature (cfr. infra) including the raw dataset from the ADVOR trial, 96 patients need to be enrolled and analysed in the DECONGEST study, given a significance level (a) of 0.05, to yield a statistical power (1-§) equal to 90%. Based on the results of the ADVOR trial, which recruited a similar population in a comparable setting, the anticipated 30-day mortality for DECONGEST was estimated at 5%.[12] No impact of the DECONGEST study intervention on this first component of the hierarchical composite primary endpoint was expected. Both the ADVOR and PUSH-AHF trial showed a 1-day decrease on hospitalization length with respectively upfront acetazolamide and UNa+ assessment.[12] It is

hard to predict whether both independent interventions from the ADVOR and PUSH-AHF trials, when combined in the DECONGEST study, would yield synergistic, additive, or subadditive effects. No reliable data are available to simulate the impact of low-threshold use of chlorthalidone and canreonate for diuretic resistance or for the eGFR-based dosing of loop diuretics on total admission length. For the DECONGEST study, an additive effect was anticipated of the upfront acetazolamide and UNa+, yielding a total effect size of 2 days [IQR: 4 days] hospital length decrease for the DECONGEST care bundle. Based on the ADVOR trial a difference of 25% (with standard deviation of 22%) is anticipated in the relative decrease in NT-proBNP. To account for a potential drop-out and the impact of correlation between outcomes, the targeted study sample size was set at 104 subjects. Drop-out rates are carefully monitored during the execution of the study with the possibility to increase the sample size if necessary. Importantly, the DECONGEST study was powered for the generalized pairwise comparison method to assess its primary endpoint, but not necessarily for the individual composites of this endpoint.

Statistical analysis

The detailed Statistical Analysis Plan is provided as Appendix B together with this manuscript. The primary analysis of the study assesses a hierarchically composed primary end-point using the generalized pairwise comparison method.[17] If the primary study endpoint is positive, secondary endpoints will be assessed in a hierarchical sequence without further adjustment for multiple testing. If the primary endpoint or any of the secondary study endpoints is non-significant, all following endpoints are considered explorative. All analyses are performed according to a modified intention-to-treat principle, including all subjects who have been randomized and received at least one dose of diuretics according to the study protocol.

Discussion

Intravenous loop diuretics are recommended with a class I-C for all patients with AHF admitted with signs and/or symptoms of fluid overload to improve symptoms.[7] Furthermore, it is also recommended that such patients are carefully evaluated to exclude persistent signs of congestion before discharge (class I-C as well).[7] Congestion is typically assessed by evident clinical signs of fluid overload or demonstration of elevated cardiac filling pressures, either by invasive or non-invasive measurement. Interestingly, there is generally a poor correlation between cardiac filling pressures and fluid status per se.[18] [1] Metrics such as weight or weight loss, urine output or net fluid balance, or their values indexed for loop diuretic dose are indeed heavily influenced by hydration status.[20]

Increasing free water excretion with tolvaptan in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) did not show any meaningful benefits regarding clinical outcome.[21] Insights from the Renal Optimization Strategies Evaluation Acute Heart Failure (ROSE-AHF) and ADVOR trials suggest that net natriuresis might be a more impactful surrogate endpoint, paving the way towards an approach of *desalinization* in AHF.[22] [23] The DECONGEST study now postulates that with a strategy that directly aims to deplete sodium stores with aggressive combination diuretics (while allowing more liberal fluid intake), safe, rapid and effective decongestion can be achieved. An important secondary objective of the study is to investigate the relationship and mechanistic underpinning of different tools and metrics of decongestion. Finally, few if any studies have truly tested the safety of upfront segmental nephron blockade during acute decongestion and the transition of care with guideline-directed medical therapies at discharge. The DECONGEST will provide insightful data on how an intensive diuretic schedule impacts this important outcome. A comparison of the baseline characteristics from patients enrolled in the DECONGEST study versus recent diuretic trials in acute heart failure is presented in Table 3.

The DECONGEST study uses a different cut-off for UNa' (80 mmol/L), when compared to current guideline recommendations (50-70 mmol/L). However, recent data from the

ADVOR trial, which included the systematic use of acetazolamide as well, identified 80 mmol/L as a target that was discriminative for successful decongestion and associated with prognosis.[23] Patients with a good diuretic response easily achieve a post-diuretic UNa' >100 mmol/L.[6] Moreover, UNa+ was used in the DECONGEST study not only as a criterion to intensify diuretic treatment in diuretic resistance, but also as a stopping criteria for euvolemia when no clinical evidence of volume overload was present. Choosing a level that was too low would risk over-diuresis by the studied intervention and choosing 2 different cut-offs for diuretic resistance and euvolemia would have complicated the study protocol.

Conclusions

It remains insufficiently elucidated what constitutes the optimal diuretic regimen to achieve safe and fast decongestion in AHF. Upfront use of acetazolamide, serial assessment of UNa*, and low-threshold use of thiazide-like diuretics have all been shown to improve metrics of decongestion.[8 12 13] The DECONGEST study integrates those strategies into a comprehensive treatment algorithm, testing it against standard of care in patients presenting with AHF and clinically evident fluid overload. If the DECONGEST study shows promising results, its intervention can be easily implemented in clinical practice worldwide as diuretics and UNa* assessments are cheap and readily available. Results of the DECONGEST study are expected to be of great interest for designing a more definitive outcome trial with diuretics in AHF.

References

1. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149(2):209-16.
2. Verbrugge FH. Editor's Choice-Diuretic resistance in acute heart failure. Eur Heart J Acute Cardiovasc Care 2018;7(4):379-89.
3. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP, Investigators ESCHFL-TR. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19(10):1242-54.
4. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol 2013;61(4):391-403.
5. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. J Card Fail 2014;20(6):392-9.
6. Verbrugge FH. Utility of Urine Biomarkers and Electrolytes for the Management of Heart Failure. Curr Heart Fail Rep 2019;16(6):240-9.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel 0, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESCSD. 2021 ESC

Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599-3726.

8. Ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Postmus D, Coster JE, Nieuwland W, van Veldhuisen DJ, Voors AA, Damman K. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. Nat Med 2023;29(10):2625-32.

9. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, Borbely A, Erdal F, Benkouar R, Cobo-Marcos M, Barge-Caballero G, George V, Zara C, Ross NT, Barker D, Lekhakul A, Frea S, Ghazi AM, Knappe D, Doghmi N, Klincheva M, Fialho I, Bovolo V, Findeisen H, Alhaddad IA, Galluzzo A, de la Espriella R, Tabbalat R, Miro O, Singh JS, Nijst P, Dupont M, Martens P, Mullens W. Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study. Circ Heart Fail 2024;17(1):e011105.

10. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. Circ Heart Fail 2014;7(5):766-72.

11. Boonen L, Verbrugge FH, Nijst P, Noyens P, De Vusser P, Verhaert D, Van Lierde J, Vrolix M, Dupont M, Mullens W. Subclinical volume overload in stable outpatients with chronic heart failure. Acta Cardiol 2016;71(3):299-307.

12. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, Tartaglia K, Chenot F, Moubayed S, Dierckx R, Blouard P, Troisfontaines P, Derthoo D, Smolders W, Bruckers L, Droogne W, Ter Maaten JM, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M, Group AS. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med 2022;387(13):1185-95.

13. Trullas JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sanchez-Marteles M, Conde-Martel A, Davila-Ramos MF, Llacer P, Salamanca-Bautista P, Perez-Silvestre J, Plasin MA, Cerqueiro JM, Gil P, Formiga F, Manzano L, investigators Ct. Combining

loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J 2023;44(5):411-421.

14. Martens P, Verbrugge FH, Dauw J, Nijst P, Meekers E, Augusto SN, Ter Maaten JM, Heylen L, Damman K, Mebazaa A, Filippatos G, Ruschitzka F, Tang WHW, Dupont M, Mullens W. Pre-treatment bicarbonate levels and decongestion by acetazolamide: the ADVOR trial. Eur Heart J 2023;44(22):1995-2005.

15. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WHW, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E, National Heart L, Blood Institute Heart Failure Clinical Research N. Efficacy and Safety of Spironolactone in Acute Heart Failure: The ATHENA-HF Randomized Clinical Trial. JAMA Cardiol 2017;2(9):950-8.

16. de Denus S, Leclair G, Dube MP, St-Jean I, Zada YF, Oussaid E, Jutras M, Givertz MM, Mentz RJ, Tang WHW, Ferreira JP, Rouleau J, Butler J, Kalogeropoulos AP. Spironolactone metabolite concentrations in decompensated heart failure: insights from the ATHENA-HF trial. Eur J Heart Fail 2020;22(8):1451-61.

17. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med 1999;18(11):1341-54.

18. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008;134(1):172-8.

19. Aronson D, Abassi Z, Allon E, Burger AJ. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. Eur J Heart Fail 2013;15(6):637-43.

20. Marton A, Saffari SE, Rauh M, Sun RN, Nagel AM, Linz P, Lim TT, Takase-Minegishi K, Pajarillaga A, Saw S, Morisawa N, Yarn WK, Minegishi S, Totman JJ, Teo S, Teo LLY, Ng CT, Kitada K, Wild J, Kovalik JP, Luft FC, Greasley PJ, Chin CWL, Sim DKL, Titze J. Water Conservation Overrides Osmotic Diuresis During SGLT2 Inhibition in Patients With Heart Failure. J Am Coll Cardiol 2024;83(15):1386-98.

21. Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297(12):1319-31.

22. Hodson DZ, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J, Wilson FP, Tang WHW, Rao VS, Collins SP, Mullens W, Testani JM. Natriuretic Response Is Highly Variable and Associated With 6-Month Survival: Insights From the ROSE-AHF Trial. JACC Heart Fail 2019;7(5):383-391.

23. Verbrugge FH, Martens P, Dauw J, Nijst P, Meekers E, Augusto SN, Jr., Ter Maaten JM, Damman K, Filippatos G, Lassus J, Mebazaa A, Ruschitzka F, Dupont M, Mullens W. Natriuretic Response to Acetazolamide in Patients With Acute Heart Failure and Volume Overload. J Am Coll Cardiol 2023;81(20):2013-24.

Figure Legends

Figure 1. DECONGEST study design.

AHF, acute heart failure; BID, twice daily; eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology collaboration formula; NTproBNP, N-terminal of pro-hormone of B-type natriuretic peptide; TID, three times daily; UNa+, spot urine sodium concentration.

Figure 2. Timing and type of congestion assessments in the DECONGEST study.

CA-125, carbohydrate antigen 125; NTproBNP, N-terminal of pro-hormone of B-type natriuretic peptide.

Figure 3. DECONGEST intervention flowchart.

IV, intravenous; K', potassium; Na*, sodium; KCl, potassium chloride; PO, oral intake.

1 Tables

Table 1. Eligibility criteria of the DECONGEST study.
Inclusion criteria
Adult (ñ18 years) who is able to provide informed consent
Hospital admission with a diagnosis of acute heart failure according to the treating physician and an anticipated hospital stay >24 h
At least one of the following clinical signs of fluid overload: 1. Bilateral oedema 2+, indicating clear pitting 2. Ascites that is amenable for drainage, which is confirmed by echography 3. Uni- or bilateral pleural effusions that are amenable for drainage, which is confirmed by chest X-ray or lung ultrasound
Plasma NT-proBNP »1,000 ng/L
Exclusion criteria
No possibility to collect reliable urine spot samples after diuretic administration
Administration of any diuretic medication within 6 h before randomization, except for a mineralocorticoid receptor antagonist or sodium glucose co-transporter-2 inhibitor as part of the patient's maintenance treatment for heart failure.
Severe kidney dysfunction, defined as an estimated glomerular filtration rate <15 mL/min/1.73m* calculated by the Chronic Kidney Disease Epidemiology Collaboration formula and/or previous, current, or planned future renal replacement therapy
Severe hypotension or shock: • Systolic blood pressure <90 mmHg • Mean arterial pressure <65 mmHg • Use or need for inotropes/vasopressor therapy
Any acute coronary syndrome within 30 days prior to enrolment, defined as typical chest pain with a troponin rise above the 99th percentile of normal and/or electrocardiographic changes suggestive of cardiac ischaemia
History of heart or kidney transplantation
History of mechanical circulatory support
Known obstructive hypertrophic cardiomyopathy, congenital heart disease, acute mechanical cause of acute heart failure (e.g., papillary muscular rupture), acute myocarditis, or constrictive pericarditis according to the treating physician
Pregnant or breastfeeding woman
Concurrent participation in another interventional study

Table 2. Secondary endpoints of the DECONGEST study
Relative NT-proBNP decrease from baseline to 30 days after randomization [%]
Relative CA-125 decrease from baseline to 30 days after randomization [%]
Length of intravenous diuretic therapy [days]
Length of the index hospital admission [days]
Successful decongestion defined as no more than trace oedema, absence of jugular venous distension and no rales upon the moment of transition from intravenous diuretics to oral maintenance therapy
5-point Likert scale for overall well-being assessed upon the transition from intravenous diuretics to oral maintenance therapy compared to the moment of randomization (much improved/slightly improved/neutral/slightly worse/much worse)
Doubling of the serum creatinine or plasma cystatin C compared to baseline with an absolute value >2 mg/dL or >2 mg/L, respectively, or the need for ultrafiltration and/or renal replacement therapy during the index hospital admission (renal safety endpoint)
Systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg or need for vasopressors and/or inotropes during the index hospital admission (hemodynamic safety endpoint)
Death, non-elective rehospitalization or non-elective medical contact
Death or non-elective hospital readmission rate

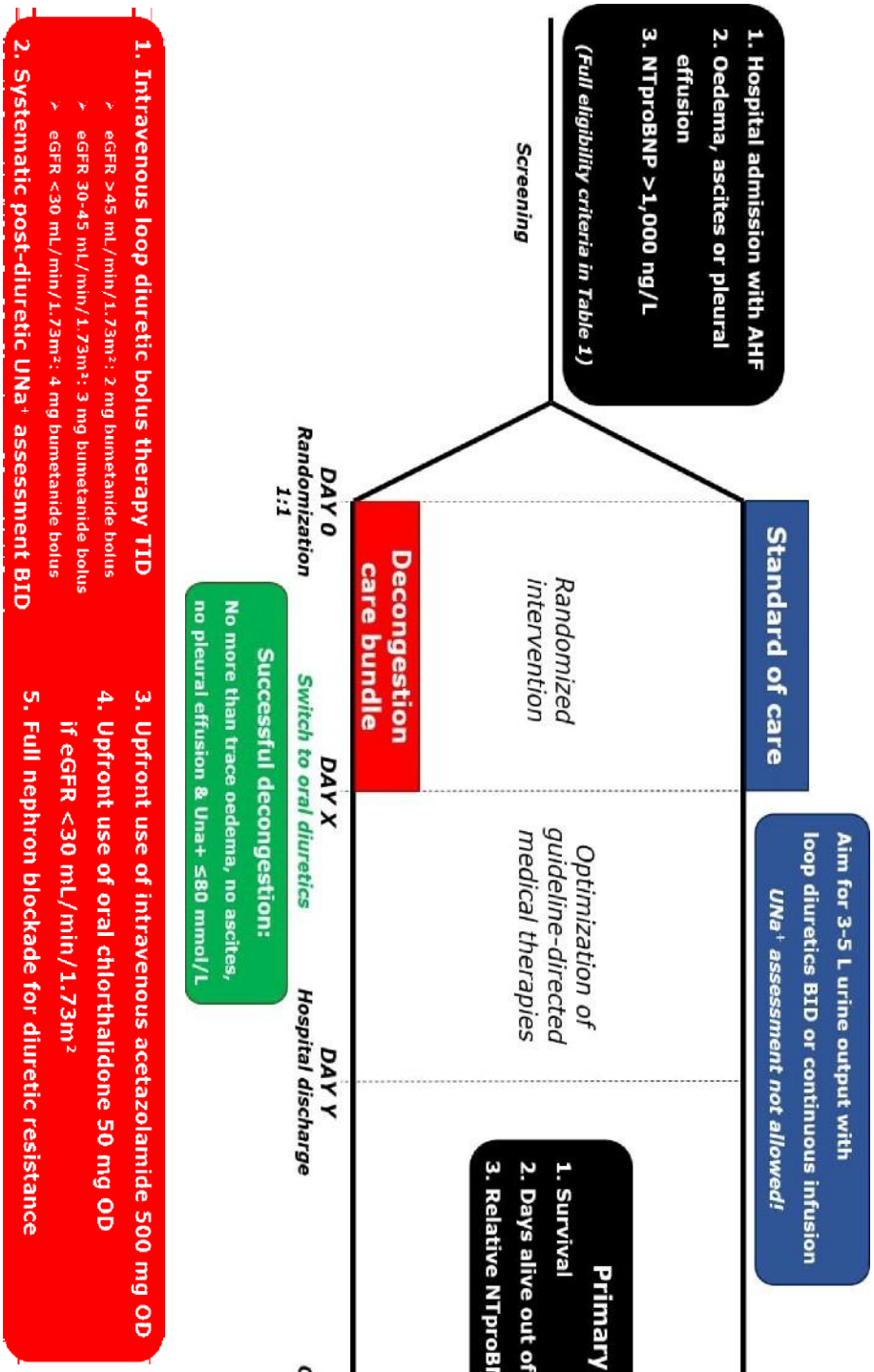
1 CA-125, cancer antigen-125; NT-proBNP, N-terminal of pro-hormone B-type natriuretic peptide.

Table 3. Baseline characteristics in the DECONGEST study versus contemporary diuretic trials.					
	DECONGEST	**PUSH-AHF**	**ADVOR**	**CLOROTIC**	**DOSE-AHF**
Age (years)	81 (73 — 87)	74 (65 — 82)	78 + 9	83 (76 — 87)	66 + 14
Men	56%	55%	63%	48%	27%
Ejection fraction (%)	41 + 14	37 (27 — 51)	43 + 15	55 (40 — 63)	35 + 18
Ischaemic heart failure	28%	36%	45%	33%	57%
History of atrial **fibrillation**	69%	56%	72%	69%	53%
Systolic blood pressure (mmHg)	134 + 21	128 (112 — 149)	127 + 21	126 (114 — 141)	120 + 20
Serum creatinine (mg/dL)	1.2 (1.0 — 1.7)	1.2 (0.9 — 1.7)	1.5 (1.2 — 1.9)	1.4 (1.1 — 1.8)	1.5 + 0.5
Serum sodium (mmol/L)	140 + 4	137 (134 — 140)	139 + 4	140 (137 — 142)	138 + 4
NTproBNP (ng/L)	4,727 (2,499 — 8,714)	4,710 (2,553 — 8,750)	6,173 (3,068 — 10,896)	4,672 (2,325 — 9.011s	Mean: 7,439
Loop diuretics	49%	57%	100%	100%	100%
Dose (mg furosemide eq)	40 (40 — 80)	80 (40 — 160)	60 (40 — 100)	80 (80 — 110)	Median: 80
ACEi/ARB/ARNi	54%	55%	52%	55%	64%
Betablocker	73%	69%	81%	60%	83%
MRA	32%	35%	42%	35%	28%
SGLT2i	22%	6%	0%	N/A	0%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal of pro-hormone B-type natriuretic peptide; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

1 Figures

2 Figure 1 (Visual take home graßhic).



3

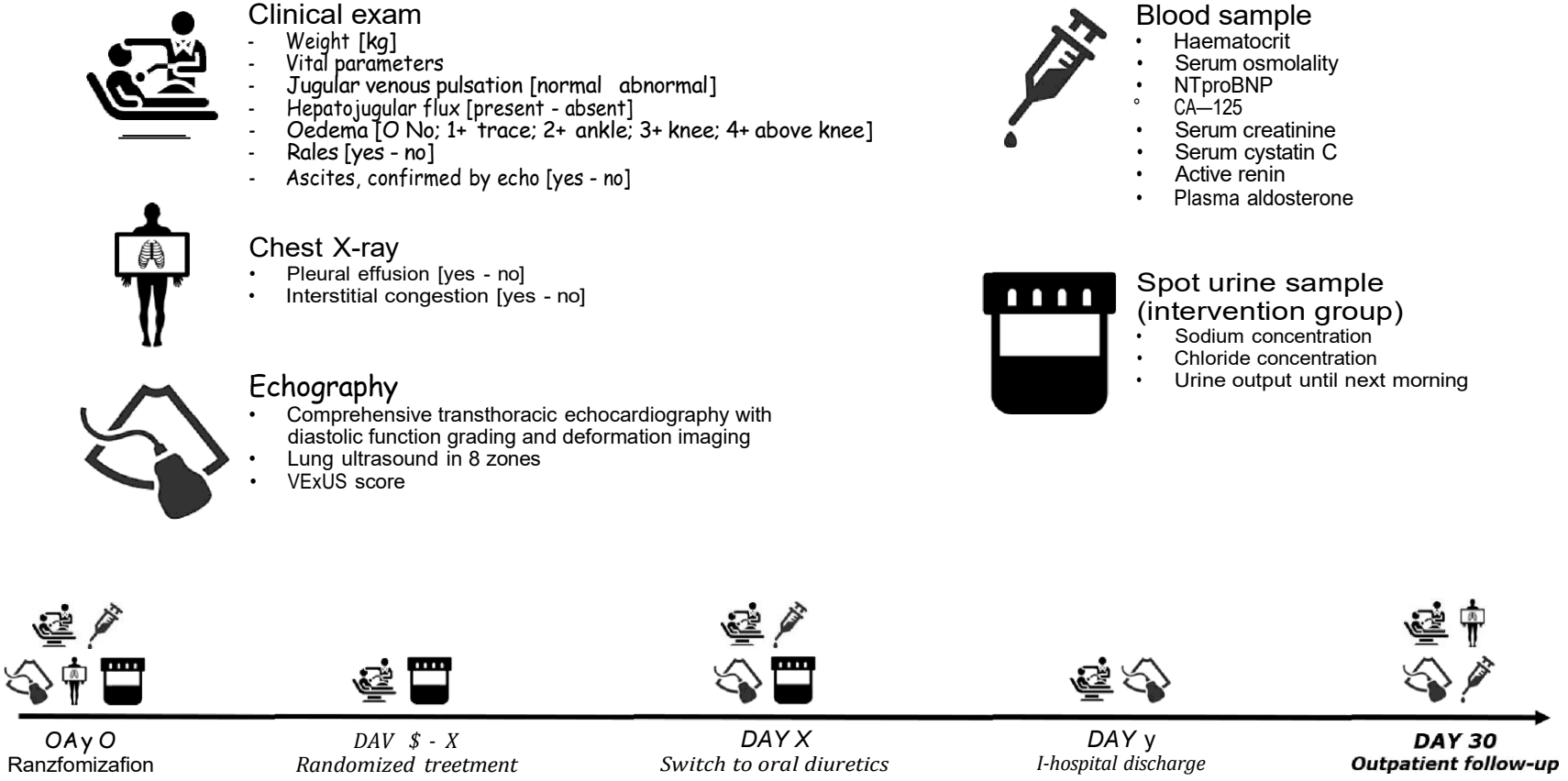
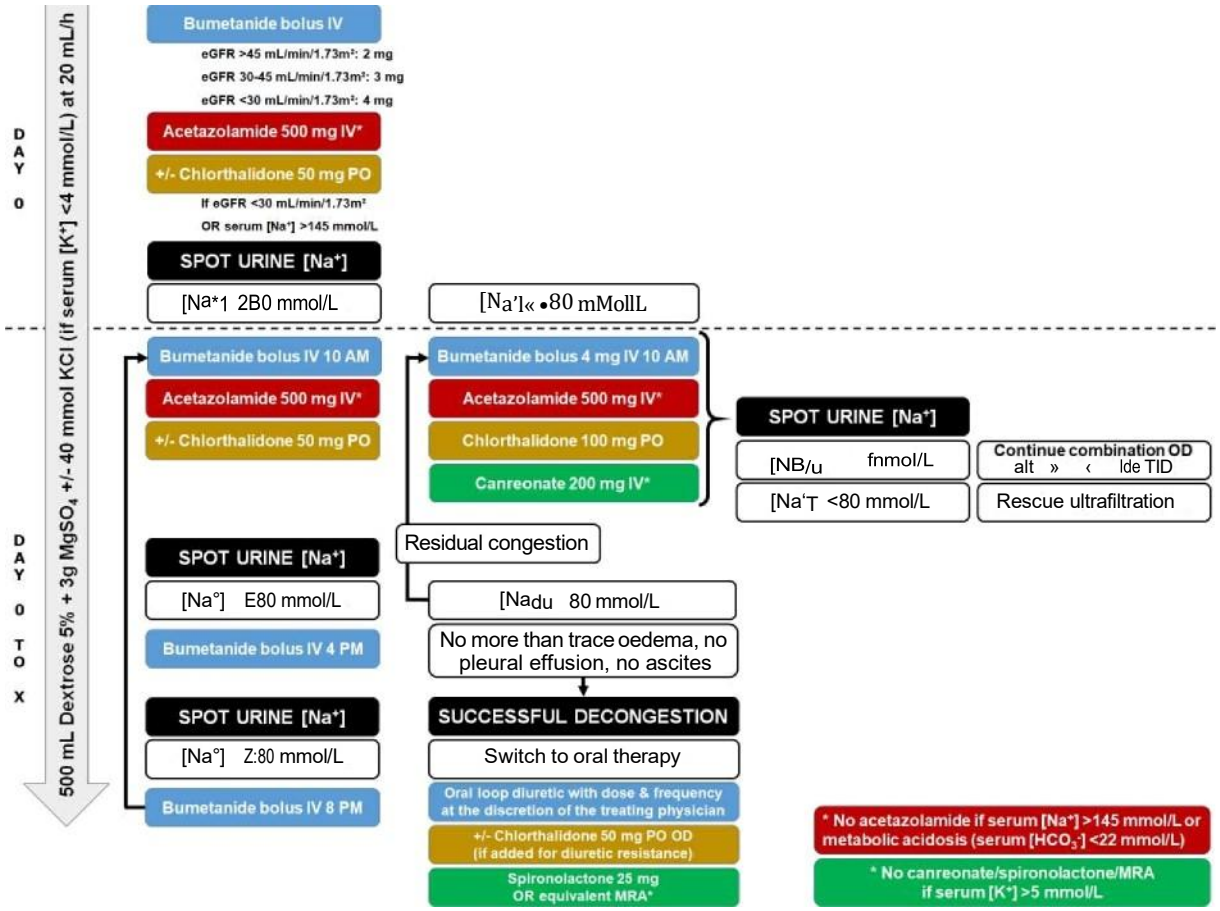

Clinical exam
- Weight [kg]
- Vital parameters
- Jugular venous pulsation [normal abnormal]
- Hepatojugular flux [present - absent]
- Oedema [O No; 1+ trace; 2+ ankle; 3+ knee; 4+ above knee]
- Rales [yes - no]
- Ascites, confirmed by echo [yes - no]
Chest X-ray
• Pleural effusion [yes - no]
• Interstitial congestion [yes - no]
Echography
• Comprehensive transthoracic echocardiography with diastolic function grading and deformation imaging
• Lung ultrasound in 8 zones
• VExUS score
Blood sample
• Haematocrit
• Serum osmolality
• NTproBNP
° CA—125
• Serum creatinine
• Serum cystatin C
• Active renin
• Plasma aldosterone
Spot urine sample (intervention group)
• Sodium concentration
• Chloride concentration
• Urine output until next morning
OAy O
Ranzfomizafion
DAV $ - X
Randomized treetment
DAY X
Switch to oral diuretics
DAY y
I-hospital discharge
DAY 30
Outpatient follow-up

Figure 2.

1 Figure 3.


DAY 0
Bumetanide bolus IV
eGFR >45 mL/min/1.73m²: 2 mg
eGFR 30-45 mL/min/1.73m²: 3 mg
eGFR <30 mL/min/1.73m²: 4 mg
Acetazolamide 500 mg IV*
+/- Chlorthalidone 50 mg PO
If eGFR <30 mL/min/1.73m²
OR serum [Na⁺] >145 mmol/L
SPOT URINE [Na⁺]
[Na*1 2B0 mmol/L
[Na'l« •80 mMollL
DAY 0 TO X
500 mL Dextrose 5% + 3g MgSO4 +/-40 mmol KCl (if serum [K⁺] <4 mmol/L) at 20 mL/h
Bumetanide bolus IV 10 AM
Acetazolamide 500 mg IV*
+/- Chlorthalidone 50 mg PO
Bumetanide bolus 4 mg IV 10 AM
Acetazolamide 500 mg IV*
Chlorthalidone 100 mg PO
Canreonate 200 mg IV*
SPOT URINE [Na⁺]
[NB/u fnmol/L
[Na'T <80 mmol/L
Continue combination OD
alt » ‹ Ide TID
Rescue ultrafiltration
Residual congestion
SPOT URINE [Na⁺]
[Na°] E80 mmol/L
Bumetanide bolus IV 4 PM
[Nadu 80 mmol/L
No more than trace oedema, no pleural effusion, no ascites
SUCCESSFUL DECONGESTION
Switch to oral therapy
Oral loop diuretic with dose & frequency at the discretion of the treating physician
+/- Chlorthalidone 50 mg PO OD (if added for diuretic resistance)
Spironolactone 25 mg OR equivalent MRA*
SPOT URINE [Na⁺]
[Na°] Z:80 mmol/L
Bumetanide bolus IV 8 PM
* No acetazolamide if serum [Na⁺] >145 mmol/L or metabolic acidosis (serum [HCO3⁻] <22 mmol/L)
* No canreonate/spironolactone/MRA if serum [K⁺] >5 mmol/L

2