The ICARUS project : study protocol for a randomised controlled trial Investigating aCute heArt failuRe decongestion guided by lung UltraSonography

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The ICARUS project: study protocol for a randomised controlled trial

Investigating aCute heArt failuRe decongestion guided by lung UltraSonography

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Abstract

Background: Acute congestive heart failure (AHF) is a leading cause of hospital admission, with decongestion serving as the cornerstone of its treatment. In the absence of congestion-specific quantitative measures, however, undertreatment often occurs and it is associated with an increased risk of readmission. Lung ultrasonography (LUS) has high accuracy for detecting extravascular lung water. Its use for guiding decongestion in ambulatory patients has shown a reduction in hospital admission and urgent outpatient visits, whereas data are lacking for AHF inpatients. Our aim is to investigate the effect of a LUS-guided decongestive therapy on early clinical outcomes, as compared to physical-examination, in hospitalised AHF adults.

Methods: The ICARUS project is a multicentric, multi-blinded, randomised, controlled, superiority study, aiming to recruit 222 adult, hospitalised AHF patients with raised value of natriuretic peptide. Participants will be randomised to a decongestive strategy guided by either daily LUS findings (8-point protocol) or daily physical examination. The randomisation will be stratified by study centre and inclusion delay (i,e, within 24h or more). The primary outcome is the number of days spent alive and out of hospital in a 40-day timeframe from study inclusion (DAOH-40). Secondary outcomes include successful decongestion, length of hospital stay (index hospitalisation), early readmission and mortality, dyspnea and quality of life (EQ-5D-5L).

Discussion: Incomplete decongestion at discharge is frequent in patients hospitalised for AHF and it is strongly associated with rehospitalisation and mortality. There is a need to clarify the role of LUS as guide of decongestive therapies. the ICARUS project will provide strong evidence on the usefulness of LUS as guide for decongestive therapy in hospitalised AHF patients.

Study registration: The present protocol is registered in ClinicalTrials.gov (NCT 06465498, registered 20 Juin 2024, https://clinicaltrials.gov/study/NCT06465498) and in the Swiss human research platform HumRes of the Federal Office of Public Health (CCER 2024-00268).

Keywords (max 6): Lung ultrasonography, ultrasound, heart failure, congestion, decongestion, diuretic

Introduction and rationale

Decompensated acute heart failure (AHF) is the leading cause of hospital admission over the age of 65 years and one of the most frequent reasons for readmission in northern hemispheric countries.(1-3) The risk of readmission is highest on day 3 after discharge and up to 30% of patients are readmitted or die within 30 days after hospital discharge.(3, 4) Since AHF patients are hospitalised essentially because of congestion-related symptoms, residual congestion at discharge seems to play a key role in re-hospitalisations. Indeed, significant residual congestion is noted in a third of patients at discharge and is associated with an increased risk of re-admission and mortality in the following months.(5) When compared to physical examination, lung ultrasonography (LUS) has better accuracy for extravascular lung water (ELW) detection and provides a semi-quantitative evaluation of residual congestion, even at subclinical stage.(6, 7) A decrease in B-lines which is the sonographic hallmark of ELW correlates with clinical improvement and can be used to guide decongestion,(8-11) whereas their persistence after treatment is strongly associated to an increased risk of hospital re-admission.(12-15) Recent randomised controlled trials suggest that a LUS-driven decongestion strategy may reduce hospital readmissions or urgent ambulatory visits in patients with chronic heart failure.(9-11) In contrast, no difference in days alive and out of hospital (DAOH) 30 days after discharge was observed when the LUS-guided decongestion was applied to AHF patients only during the first 6 hours after arrival at the emergency room.(16) Only a few exploratory studies addressed AHF inpatients and reported encouraging results on a decreased hospital length of stay, early readmission and mortality rates.(17-19) However, these pioneer studies have methodological flaws (e.g. absence of randomisation, lack of blinding, lack of power) and confirmatory data are required (Table 1). The Investigating aCute heArt failuRe decongestion guided by lung UltraSonography (ICARUS) trial is a multicentric, randomised, blinded study testing the hypothesis that LUS outperforms physical

examination in decongestion guidance, thus providing benefits on early clinical outcomes. This article presents the rationale and methodology of the study.

Methods

Setting

The study is conducted in four academic hospitals: Geneva University Hospitals, Geneva, Switzerland (two recruiting centres); University Hospital of Bern, Bern Switzerland; Fribourg University Hospital, Fribourg, Switzerland; and University Hospital of Lugano, Lugano, Switzerland

Study design

The ICARUS trial is a multicentric, multi-blinded, randomised, controlled, superiority trial. The randomisation list is centrally and computer-generated, using different sized block permutations, and stratified for the recruiting centre and inclusion delay (i.e. within 24h versus ≥24 h of hospital arrival). Patients hospitalised with AHF who meet all the inclusion and none of the exclusion criteria are eligible for enrolment. When eligible, the patient and/or a representative is approached by a member of the study personnel who will give a full explanation of the study. After obtaining written informed consent participants are allocated in the two parallel study groups (LUS and physical examination) with a 1:1 ratio. Patients are allocated using Research Electronic Data Capture (REDCap) tool, a secured web-based application designed to support data capture and randomisation for research studies. The allocation sequence will be implemented via a module integrated into the REDCap system. Site investigators will enrol eligible participants and obtain their allocation through REDCap only after baseline data have been entered, ensuring concealment. Figure 1 shows the study flow-chart and participant timeline is available in supplementary file 1.

Study objectives and hypothesis

The main objective of the ICARUS trial is to investigate the effect of a bedside LUS-guided decongestive therapy, as compared to a structured physical-examination-guided strategy. With better

performance in detection of ELW, we hypothesised that more rapid and complete decongestion will be achieved through LUS-guidance, translating into a positive impact on relevant clinical outcome.

Eligibility

Eligible participants are screened during working days within 48 hours of their first hospital arrival. Patients presenting with signs and symptoms of acute congestive heart failure, a raised value of N terminal-pro-brain natriuretic peptide (≥1000 ng/l) and none of the exclusion criteria (Table 2) are approached by a member of the study personnel who will give a full explanation of the study and obtain written informed consent, including additional consent for the future re-use of participant data where applicable.

. Patients admitted on non-working days can be recruited on the following working day, provided that the first study visit can be performed no later than 48h after the patient's hospital arrival.

Study procedures

From the day of randomisation, all participants will undergo both daily LUS and a structured physical examination, on each working day until day 8 (i.e. between 4 to 6 working days), or until the day of discharge if earlier. Study intervention can be interrupted before in the absence of congestion for 2 consecutive days, according to the generic congestion score (see later in text). LUS and physical examination are performed independently by two reciprocally blinded physicians, masked to patient clinical data and to the study arm. Physicians performing LUS and physical examination are not in charge of the patient's care.

Lung ultrasonography congestion score

The anterolateral thorax is examined using an 8-point protocol (20, 21) previously validated in our pilot study(22), which is a simplified version of the widely used 8-zone protocol.(23) Each region is coded positive in presence of ≥3 B-lines simultaneously on a frozen image or in presence of significant pleural effusion (i.e. extending over the costophrenic angle) (Figure 2). Subsequently a 4-level congestion score is defined: absence of congestion (0-1 positive points), mild congestion (2-3

positive points), moderate congestion (4-5 positive points) and severe congestion (6-8 positive points). Study sonographers are required to have obtained a Swiss LUS certificate (24) or equivalent, or to attend specific training including 20 supervised LUS scans. Images are acquired using high-end point-of-care ultrasonography devices with a phased-array or curvilinear probe and a lung pre-set. Sonographers may adjust machine settings (knobology) at their discretion. Patient are placed in a standardised semi-recumbent position (30-45°), resting for at least five minutes prior to LUS acquisition.

Physical examination congestion score

Congestion is clinically assessed by calculating the Everest score (Table 3).(25) This is a standardised score, previously used in clinical trials, composed of 3 congestion symptoms (i.e. dyspnea, orthopnoea and fatigue) and 3 congestion signs (i.e. jugular vein distension, lung rales, oedema), each graded from 0 to 3. From the total score, a sub-score, ranging from absence of congestion to severe congestion, is derived. To maintain blinding, the procedure used to obtain the sub-score will only be disclosed only in the publication following the completion of the study.

Common Congestion score for the physician in charge

Every working day, LUS (intervention arm) and physical examination (control arm) results are documented in the electronic case report form and converted into a common score ranging from absence of congestion to severe congestion. According to the allocated arm, the generic congestion score derived from LUS or physical examination is communicated to the treating physician by the research personnel along with a proposal of stepping-up, maintaining or stepping-down the decongestive therapy. When available, the physician's attitude toward the management of decongestive therapy will be recorded before communicating the study finding and proposal. Treatment propositions, adapted from those used in the CARRESS-HF study(26), are in line with the position statement of the Heart Failure Association of the European Society of Cardiology (ESC) (27), and are detailed in Figure 3. The procedure used to obtain this generic congestion score remains blinded (i.e. physical examination or LUS) and concealment of allocation is maintained over the entire

study period. In both arms, the treating physicians are strongly encouraged to follow the treatment recommendations, but they may pursue other treatment options at their discretion, particularly for considerations of clinical safety. On non-working days, decongestive therapy is adapted at their discretion by the clinicians in charge of the patient. Study procedures will be resumed on the next working day. The discharge decision is made by the treating physician.

Blinding

To reduce the risk of bias the following levels of blinding are introduced:

1. Patients are blinded to their study arm allocation.

2. All the members of the clinical staff in charge of the patient are blinded to the patient's study arm (both physical examination and LUS arms will benefit from recommendations for decongestive therapy based on a generic congestion score).

3. Both sonographers and clinical investigators are reciprocally blinded; they are masked to the patient's study arm and clinical data.

4. Primary outcomes adjudicators are blinded to the patient's study arm

5. Biostatisticians are blinded to the patients' study arm

Follow-up

As recommended by the ESC guidelines, an outpatient visit will be planned between 7- and 14-days following discharge, where possible. During this visit, patients undergo structured physical examination and LUS, results are converted in the common congestion score, again according to the randomisation arm and communicated in a blinded manner to the physician in charge of the patient. Oral decongestive therapies are increased in presence of significant congestion (i.e. mild to severe) and guidelines-directed medical therapies are collected, verified and adapted according to international guidelines. A follow-up phone call is made at 90 days post hospital discharge (+ 14 days) by a blinded investigator to assess time to unplanned emergency visits, rehospitalisation, and mortality. Schedule of enrolment, interventions, and assessments are reported in Table 4.

As the validity of the clinical trial could be compromised by the destruction of personal health-related data, their encoded use will be permitted in the event of patient withdrawal. In presence of protocol deviations, the patient will stay in the randomized arm for the intention-to-treat analysis and will be excluded for the per protocol analysis. If the patient is lost to follow-up, the data will be censored after the last visit.

Study outcomes

Primary outcome

Number of days spent alive and out of hospital in a 40-day timeframe from study inclusion (DAOH-40). This outcome integrates length of stay, early readmission, unplanned emergency or outpatient visits and mortality.

Main secondary outcome

Proportion of participants achieving successful decongestion in the 3 working days after randomisation, i.e absence of signs of volume overload as defined by the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) congestion score within.(28)

Secondary outcomes

Other secondary outcomes are 30- 60- and 90-day post-discharge readmission and all-cause mortality either as single or combined outcomes; 30- 60- and 90-HF-related hospitalisation (i.e. worsening signs and symptoms of HF and intensification of diuretic therapy), mean length of hospital stay, mean daily dose of diuretic therapy during hospital stay (in furosemide iv equivalent), mean number of changes in diuretic posology, patient quality of life (EQ-5D-5L questionnaire), dyspnea assessed with a 100-mm Visual Analog Scale (VAS), general well-being (using a 100-mm scale with ends marked “the best health you can imagine” / “the worst health you can imagine.”, six minute walk test, patient anxiety and depression assessed with the Hospital Anxiety and Depression Scale (HADS).

Safety considerations

In both arms, the treating physicians are encouraged to follow the treatment recommendations, but they may pursue other treatment options at their discretion for considerations of clinical safety (e.g. presence of hypoperfusion signs, severe electrolyte imbalance). Additionally the following safety outcomes are recorded : worsening of renal function developed during intervention period, defined by a ≥50% rise of serum creatinine from baseline value (i.e. the lowest value available in the year preceding hospital admission, or, if unavailable, the lowest value obtained during hospital stay) or the need for renal replacement therapy, severe hyponatremia (<120 mmol/l), severe hypokaliemia (<2.5 mmol/l), severe hypocalcemia (<1.9 mmol/l), number of falls during hospital stay, need for vasopressor/inotropic agents due to sustained hypotension, secondary admission to a monitored unit and in-hospital mortality rate.

Sample size

Based on our pilot study we expect a mean DAOH-40 of about 26 (SD +/- 10) days in control group.(22) Ninety-nine patients are needed in each arm to demonstrate an increase the primary outcome of at least 15%, with a power of 80%, an alpha risk of 0.05. This is generally considered clinically relevant with similar increases in DAOH having been used in previous AHF studies.(29) A total sample of 222 subjects will allow us to compensate for a 10% loss to follow-up. Recruitment started in October 2024 and will continue until completion. Five recruiting centres and a period of two years is anticipated to complete both the inclusions and the follow-up of the last included patient.

Statistical analysis

The primary analysis will be conducted following the intention-to-treat principle. A per-protocol sensitivity analysis will be conducted including only patients for which ≥66% of decongestive therapy step-up, maintain, or step-down study recommendations were followed by the treating physician. The mean difference in DAOH-40 between study groups will be adjusted for the centres and inclusion delay (<24hours versus ≥24 hours), both factors involved in the stratified randomisation, by using a linear regression model. Because the distribution of the residuals will likely strongly deviate from the Gaussian, the 95% confidence interval of the mean difference will be calculated with a bootstrap

procedure. An adjusted permutation test will be used to test the absence of intervention's effect: a linear regression model will be fitted with only the centres and inclusion delay as independent variables to predict the primary outcome. The residuals from this model are expected to be equal on average under the null hypothesis and the mean difference of residuals will be the test statistic of the permutation test.(30) A two-sided p value of 0.05 will be used to infer statistical significance. Survival analysis with Kaplan-Meier estimator will be used to assess time to mortality and readmission for each group in a 90-days post-discharge timeframe. Survival functions will be compared with a log rank test stratified on centres and the hazard ratio will be assessed by using Cox regression model adjusted for centres and inclusion delay (<24hours versus ≥24 hours). Continuous variables will be compared using the same statistical method applied for primary outcome. For binary outcomes odds ratios with 95%CI will be obtained with a logistic regression adjusted on centre and inclusion delay. Concordance between physical examination and LUS congestion rating will be assessed by kappa statistics. No interim analyses are planned. Multiple imputation will be performed if more than 10% of data are missing.

Baseline factors, such as ventricular systolic function, baseline eGFR may influence the primary outcome. Primary outcome will therefore be analysed in these predefined subgroups of interest.

Prespecified subgroup analyses

Primary analysis will be conducted in the following pre-specified subgroups: sex at birth, left ventricular ejection fraction (≤40% versus >40%), natriuresis (UNa spot ≥70 mmol/l versus <70 mmol/l) 24h to 72h after diuretic therapy initiation, inclusion delay (<24h versus ≥24 hours), chronic kidney disease (eGFR <30 ml/min versus eGFR ≥30 ml/min).

Discussion

Fluid congestion management lies at the core of AHF management. Indeed, congestion and particularly ELW, is the most common clinical presentation and reason for hospital admission in patients with HF.(31) Achievement of euvolemia, by means of sodium and water removal, is a primary therapeutic goal. Decongestive strategies in patients with AHF can be summarised in two main

approaches: enhancement of fluid excretion through improved diuresis and identification of a reliable marker of euvolemia.

Strategies targeting improved diuresis

The DOSE-AHF (Diuretic Optimization Strategies Evaluation in Acute Heart Failure), comparing high- to low-dose IV loop diuretics demonstrated that high-dose diuretics allow a greater weight loss, urine output and dyspnoea relief.(32) More recently combined-diuretic strategies, such as adding acetazolamide or thiazides to loop diuretics, have shown incremental benefits in terms on urine output, weight loss and short-term decongestion.(28, 33) Similarly, natriuresis-based decongestion has shown to effectively enhance diuresis.(34, 35) In contrast, no advantage has been demonstrated from renal ultrafiltration over a combination of high-dose loop diuretics and metolazone.(26) Although all these approaches lead to a significant increase in diuresis, none have demonstrated benefits on early post-discharge clinical outcomes (rehospitalisation and mortality). This is likely linked to inadequate addressing of residual congestion at discharge. In fact, in these studies euvolemia was primarily judged through physical examination.

The search for the optimal target

Brain natriuretic peptides (BNP and NT-pro-BNP) are non-invasive markers of elevated filling pressure. In the PRIMA II trial, NT-pro-BNP-guided decongestion did not result in improved patient outcomes.(36) In this study, however, patients were included only in the post-acute phase (≥72h post-admission). Since treatment delay seems to play a key role in diuretic resistance, the ICARUS trial has a maximum delay of 48h for including patients. Implanted haemodynamic monitoring devices may reduce HF-related hospitalisations in chronic heart failure. However, no data are currently available regarding their use in AHF. Moreover, they are limited to a selected subset of HF patients, due to invasiveness and cost.(37, 38) In contrast, LUS is a sensitive, dynamic and widely available non-invasive marker of volume status. LUS-guided decongestion seems to reduce hospital admissions and urgent ambulatory visits in patients with chronic HF.(9-11) However, evidence remains limited in the context of AHF.

In moving forward, the ICARUS trial combines both approaches: a high-dose combination diuretic strategy and the use of a sensitive marker of euvolemia.

It is worth noting that fluid removal during a decompensated phase should not be dissociated to guidelines-directed medical therapies. Early contrast of neuro-humoral imbalance with chronic heart failure therapies is needed to achieve long term decongestion.(39, 40) For this reason, in the ICARUS trial an early clinical follow-up is organised for all study participants.

Conclusions

ICARUS is a multicentric, multi-blinded, randomised, controlled trial with an ambitious objective of better defining the role of LUS in the management of AHF. By tackling residual congestion at discharge this trial aims to improve early clinical outcomes in hospitalised patients suffering from AHF.

Trial status

This article summarizes the ICARUS study protocol (version 3.0, April 4, 2025). Recruitment commenced on October 22, 2024, and the last-patient, last-follow-up is scheduled for September 2026.

Coordinating centre

Geneva University Hospitals, Geneva, Switzerland. Principal investigator: Antonio Leidi; study coordinator: Pauline Gosselin.

Data management and data monitoring

Data management and monitoring will be conducted by the Clinical Research Centre (CRC) of the Geneva University Hospitals and Faculty of Medicine, using a validated REDCap™ database, developed and administered in accordance with GCP and applicable Swiss regulations. The CRC is responsible for configuring and maintaining the eCRF, managing user access, and ensuring data integrity, while the sponsor oversees data cleaning and validation with CRC support as needed. Built-in validation rules, audit trails, and a query system ensure high-quality data capture. Before final analyses, CRC will perform the required database lock, and after study completion the database will

be archived on secure institutional servers in accordance with legal retention requirements. The Geneva Ethics Committee will be notified via an annual safety report, in accordance with local regulatory requirements. Four on-site monitoring visits are planned at the coordinating centre. In addition, central data monitoring will be conducted after every 55 patients enrolled.

List of abbreviations

AHF: acute heart failure; DAOH: days alive and out of hospital; DAOH-40: days alive and out of hospital 40-days from study inclusion; ELW: extravascular lung water; ESC: European Society of Cardiology; HADS: Hospital Anxiety and Depression Scale; HF: heart failure; LUS: lung ultrasonography; SD: standard deviation.

Declarations

Ethics approval and consent to participate: The investigation conforms with the principles outlined in the *Declaration of Helsinki* and is approved by the ethical review board of Geneva (CCER 2024-00268). Written, informed consent to participate will be obtained from all participants (Supplementary files 2 and 3). Any protocol amendments are submitted for review and approval prior to implementation.

Consent for publication: Not applicable

Availability of data and materials: The full study protocol will be made publicly available as a supplementary file upon publication of the main results. Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. All study data will be pseudonymised, with participants identified only through coded IDs. Access to the REDCap™ database is strictly role-based and managed by the Unité d'Investigation Clinique (UIC), whose staff are bound by professional confidentiality obligations regarding all study-related information, including the protocol, CRF, and collected data. Data are stored on secure institutional servers in compliance with Swiss data protection laws. All data entries and modifications are automatically recorded in a full audit trail, ensuring complete traceability and compliance with GCP requirements. De-identified participant-level datasets and the statistical

code used for analyses will be available from the corresponding author on reasonable request, in accordance with applicable data protection regulations and institutional policies.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

AL is the Sponsor-Investigator, he originally conceived the study, led the proposal and protocol development. TM, JLR, JS and OG contributed to study design and to development of the proposal. CC is the biostatistician. All authors have read, critically revised, and approved the final version of this manuscript.

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Dissemination

The results of the study will be disseminated through presentations at national and international conferences, as well as through peer-reviewed manuscripts published in open-access journals. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) criteria.

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Tables

Table 1. Summary of published trial on LUS-guided decongestion in AHF

Study name, First author (year)	**Study Design**	**Population**	**Intervention**	**Main findings**
Mozzini (2018)(18)	Open-label, randomised, single-centre, Italy	Hospitalised AHF (n=40)	Daily 28-point LUS vs standard care	Shorter LOS (-1.8 days)
BLUSHED-AHF, Pang (2021)(16)	Open-label, randomised, multi-centre, USA	ED AHF (n=130)	8-zone LUS at ED (6h) vs standard care	No difference in B-lines at 6h or 30d DAOH
CAVAL US-AHF, Burgos (2024)(17)	Single-blind, randomised, single-centre, Argentina	Hospitalised AHF (n=60)	Daily IVC + 8-zone LUS vs standard care	Less subclinical congestion at discharge (13.3% vs 66.6%); fewer 90d HF events (13.3% vs 36.7%)
LUDT-ADHF, Kashoob (2025)(19)	Open-label, non-randomised, single-centre, Oman	Hospitalised AHF (n=77)	Daily 8-zone LUS vs standard care	fewer 90d AHF readmissions (10.5% vs 35.9%)

AHF: acute heart failure; LUS; lung ultrasonography; vs: versus; LOS: Length of stay; ED: emergency department; DAOH: days alive and out of hospital; IVC: inferior vena cava; HF: heart failure.

Table 2. Eligibility criteria

Inclusion criteria (all the following)
Patient ≥ 18 years old admitted with a diagnosis of congestive AHF
Presence of ≥1 symptom or sign according to ESC
Raised value of N terminal-pro-brain natriuretic peptide (≥1000 ng/l)
Signed informed consent
Exclusion criteria (any of the following)
Isolated right heart failure
Severe stenotic valvular disease
Hypertrophic obstructive cardiomyopathy
Constrictive pericarditis
Systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg

The following conditions generating B-lines on LUS: interstitial lung disease, lung cancer or metastasis, acute respiratory distress syndrome, pulmonary contusion, virologically confirmed SARS-CoV-2 pneumonia
Known pregnancy or breastfeeding
Probable end-of-life within 30 days
Oligo-anuric end-stage kidney disease
Previous adverse reaction to furosemide or metolazone

Table 3. The Everest Congestion score

Grading scale for investigator-assessed signs and symptoms of congestion				
Signs/symptoms	**0**	**1**	**2**	**3**
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVD (cm H2O)	≤6	6-9	10-15	≥15
Lung Rales	None	Bases	To <50% lung field	To >50% lung field
Peripheral Oedema	Absent/trace	Slight	Moderate	Marked

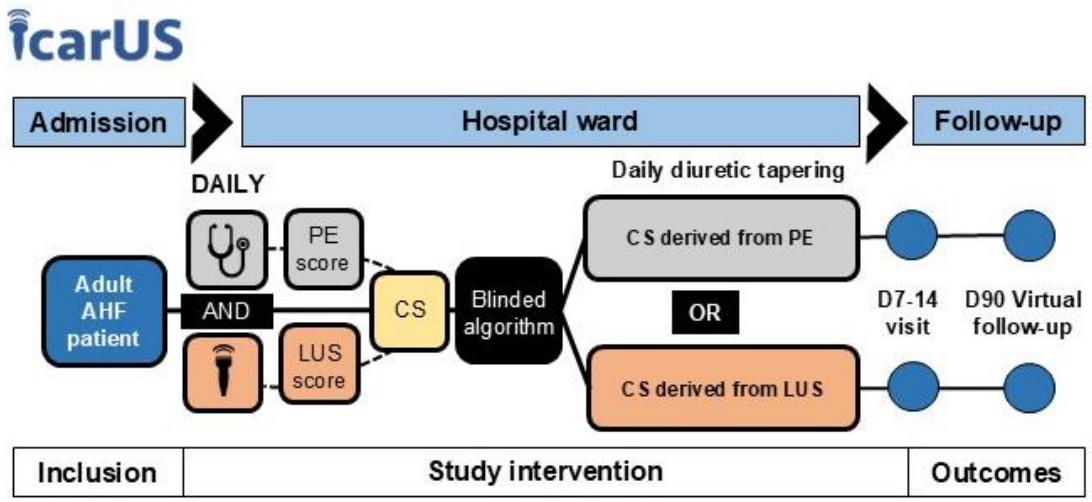
JVD: jugular vein distention

Table 4. Participant timeline: Schedule of enrolment, interventions, and assessments

	TRIAL PERIOD					
	Enrollment	**Post-randomisation**				**Close-out**
Timepoint	**Day -2 to 0**	**Day 0**	**Day 0 to +8**		**7 to 14 post-discharge**	**Day ≥90 post-discharge**
Visit	Screening	Inclusion	1st to 6th visit	3d visit	In-person visit	Virtual follow-up
ENROLLMENT						
Oral and written patient information	+					
Written consent		+				
Inclusion-/ exclusion criteria	+					
Medical history		+				
Demographics		+				
Vital Signs	+	+	+		+	
QoL questionnaire		+			+	+
Randomisation		+				
INTERVENTION/ COMPARATOR						
Procedures (LUS and PE)			+		+	
Intervention			+		+	
ASSESSMENTS						
Weight, fluid balance			+		+	
Six-minute walking test				+	+	
Primary outcome						+
Secondary outcomes			+	+	+	+
Safety outcomes	+		+		+	

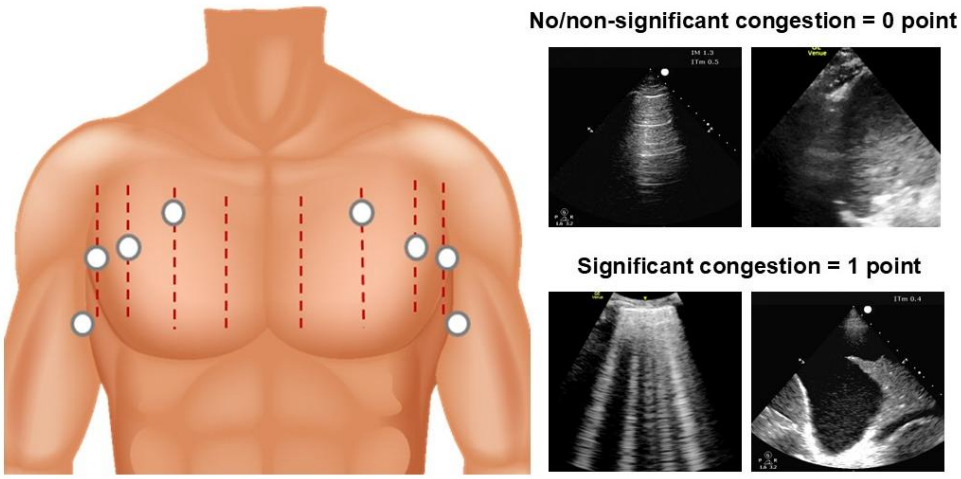
Figures

Figure 1. Study Flow Chart



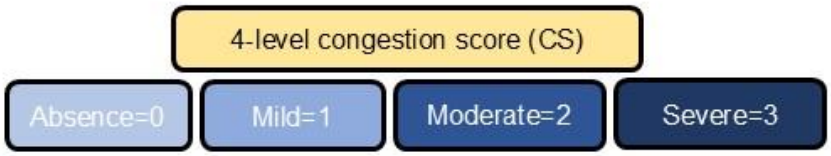
To maintain blinding, LUS and PE findings are converted into a common congestion score ranging from absence of congestion to severe congestion. Depending to the allocated arm, the generic congestion score is communicated to the treating physician along with a proposal of decongestive therapy tapering. AHF = acute heart failure; PE = physical examination; LUS = lung ultrasonography; CS = common congestion score

Figure 2. Eight-point ICARUS lung ultrasonography protocol



In eight-point ICARUS protocol, the thorax is explored bilaterally in second intercostal space (ICS) on mid-clavicular line, in fourth ICS on anterior axillary line, in fifth ICS on mid-axillary line and in the seventh ICS beyond the posterior axillary line. Each point is coded positive in presence of ≥3 B-lines simultaneously on a frozen image or in presence of significant pleural effusion (i.e. extending over the costophrenic angle).

Figure 3. Stepped decongestive therapy suggestions



Day 1

CS	Suggestion
0	Stop, switch to/maintain oral maintenance dose
1	Maintain current dose
2	Weight loss ≥2 kg/24h : maintain current dose Weight loss <2 kg/24h : Step-up (see table)
3	Step-up (see table)

From Day 2

CS	Suggestion
0	Stop, switch to/maintain oral maintenance dose
1 AND Δ* -2	Maintain or step-down (see table)
1 AND Δ* -1	Maintain current dose
1 AND Δ* ≥0 OR 2	Weight loss ≥2 kg/24h : maintain current dose Weight loss <2 kg/24h : Step-up (see table)
3	Step-up (see table)

*delta between current and previous day CS

Table. Stepped decongestion treatment

Current Dose	Suggested Dose		
Loop (mg/day)*	Furosemide (iv)	Metolazone (po)	Other options
≤ 80	40 mg TID	0	IV acetazolamide or oral SGLT2i
81-160	10mg/h or 80 mg TID	0	IV acetazolamide or oral SGLT2i
161-280	40 mg bolus + 20mg/h	5 mg QD	IV acetazolamide or oral SGLT2i
>280	80 mg bolus + 30 mg/h	5 mg BID	IV acetazolamide or oral SGLT2i

*IV furosemide equivalent. Bolus given only in case of step-up recommendation