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ORIGINAL PAPER

Lung ultrasound and diuretic therapy in chronic heart failure: a randomised trial

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Abstract

Background Lung congestion is frequent in heart failure (HF) and is associated with symptoms and poor prognosis. Lung ultrasound (LUS) identification of B-lines may help refining congestion assessment on top of usual care. Three small trials comparing LUS-guided therapy to usual care in HF suggested that LUS-guided therapy could reduce urgent HF visits. However, to our knowledge, the usefulness of LUS in influencing loop diuretic dose adjustment in ambulatory chronic HF has not been studied.

Aims To study whether to show or not LUS results to the HF assistant physician would change loop diuretic adjustments in "stable" chronic ambulatory HF patients.

Methods Prospective randomised single-blinded trial comparing two strategies: (1) open 8-zone LUS with B-line results available to clinicians, or (2) blind LUS. The primary outcome was change in loop diuretic dose (up- or down-titration).

Results A total of 139 patients entered the trial, 70 were randomised to blind LUS and 69 to open LUS. The median (percentile$_{25\text{-}75}$) age was 72 (63–82) years, 82 (62%) were men, and the median LVEF was 39 (31–51) %. Randomisation groups were well balanced. Furosemide dose changes (up- and down-titration) were more frequent among patients in whom LUS results were open to the assistant physician: 13 (18.6%) in blind LUS vs. 22 (31.9%) in open LUS, OR 2.55, 95%CI 1.07–6.06. Furosemide dose changes (up- and down-titration) were more frequent and correlated significantly with the number of B-lines when LUS results were open (Rho = 0.30, P = 0.014), but not when LUS results were blinded (Rho = 0.19, P = 0.13). Compared to blind LUS, when LUS results were open, clinicians were more likely to up-titrate furosemide dose if the result "presence of pulmonary congestion" was identified and more likely to decrease furosemide dose in the case of an "absence of pulmonary congestion" result. The risk of HF events or cardiovascular death did not differ by randomisation group: 8 (11.4%) in blind LUS vs. 8 (11.6%) in open LUS.

Conclusions Showing the results of LUS B-lines to assistant physicians allowed more frequent loop diuretic changes (both up- and down-titration), which suggests that LUS may be used to tailor diuretic therapy to each patient congestion status.

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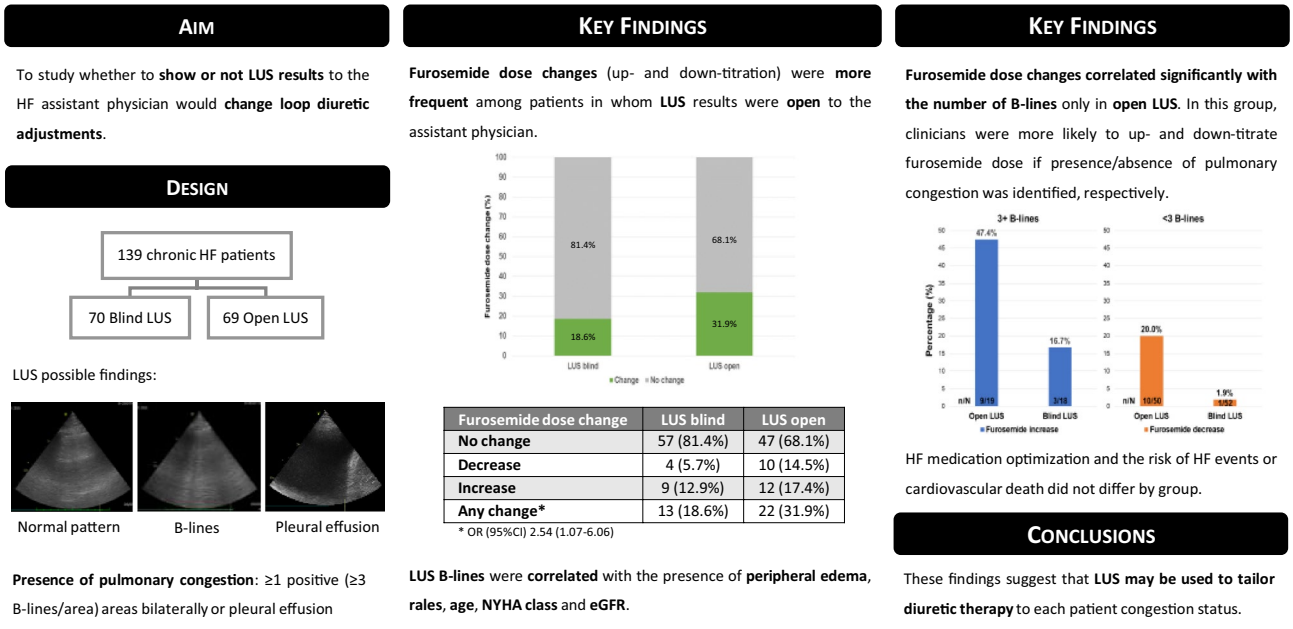
Graphical abstract



Keywords Cardiovascular diseases · Heart failure · Cardiac edema · Lung ultrasound · Congestion

Introduction

Lung congestion is frequently present in patients with heart failure (HF) and is associated with severe symptoms, poor quality of life and adverse outcomes [1–3]. In routine outpatient clinical practice the assessment of lung congestion is often performed using symptoms questionnaire and pulmonary auscultation. These methods lack sensitivity and specificity for correctly quantifying lung congestion and, consequently, under- and over-treatment may occur, particularly regarding diuretic adjustment [4, 5].

Lung ultrasound (LUS) has emerged as a sensitive, specific and quantitative tool for the assessment of pulmonary congestion in HF, by allowing the identification of B-lines (i.e., echogenic lung artefacts arising vertically from the pleural surface) in several zones of the chest [1, 6]. Pulmonary congestion identified by LUS is correlated with increased filling pressures in the heart and has shown strong prognostic value in acute and chronic HF [1, 3, 7, 8].

Three small trials comparing LUS-guided therapy to usual care in HF suggested that LUS-guided therapy could lead to a reduction in urgent HF visits [9–13]. Loop diuretic doses were generally higher in the LUS-guided group, without differences in other HF evidence-based medications [9, 10, 12]. Only one of these trials was performed in ambulatory chronic HF patients [12], and none of these trials specifically addressed if changes in diuretic therapy were tailored to patient's congestion status as provided by LUS results [9, 10, 12].

Diuretic therapy tailored to patient's congestion status is important to provide symptomatic relief while avoiding unnecessary side-effects even in ambulatory HF patients with mild or no symptoms. If congestion is not adequately managed these patients may become more symptomatic and their risk of being hospitalized and dying increases [14]. In this regard, we designed a prospective randomised single-blinded trial to specifically address whether to show or not LUS results to the assistant physician in the ambulatory HF clinic would change loop diuretic adjustments (up- and down-titration) in "stable" chronic HF patients.

Methods

Trial design

This was a prospective, randomised, single-centre, single-blinded trial performed at the HF clinics of the *Centro Hospitalar de São João*, Porto, Portugal. The HF clinics appointment was performed as part of routine medical evaluation.

From July 2020 until November 2021 patients who signed informed consent and who met inclusion criteria (see below) entered the study.

The protocol was approved by the ethics committee of the study institution and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Written informed consent was obtained from all patients prior to randomisation.

Randomisation was performed using a computer-generated number sequence i.e., patients attending clinics on a given day would have their LUS results open or blind to the assistant physician according to randomisation allocation.

No patient refused to participate in the study.

Study population

Patients could enter the study if they were older than 18 years, had signed informed consent and were compliant with HF therapy for at least 3 months.

Patients were excluded if they had a concomitant respiratory infection, severe chronic obstructive pulmonary disease, interstitial lung disease or were on chronic dialysis.

Study procedures

Routine clinical evaluation with detailed clinical history and physical examination was performed in all patients by the respective assistant physicians. LUS was performed by the first author (M. C.) in all randomised patients before the appointment with their assistant physician using an ultrasound device (GE®, Vivid T9 v203, cardiac probe), following international recommendations [15]. LUS (Supplementary Fig. 1a–c) was recorded in 8 thoracic sites (4 sites in each hemithorax) with the transducer in sagittal orientation and at 18-cm imaging depth with the patient in the semi-recumbent position [15]. The number of B-lines reported was the sum of the B-lines visualized in each thoracic site. The presence of pleural effusion was also recorded. Images were evaluated and B-line quantified in real time. A positive area was considered when ≥ 3 B-lines were present and pulmonary congestion was considered present if the patient had ≥ 1 positive areas bilaterally or pleural effusion [15].

According to randomisation allocation, patients were allocated to either: (1) open LUS results with written information presented as "presence of pulmonary congestion" or "absence of pulmonary congestion" provided by M. C. to the assistant physician before the appointment at the outpatient HF clinic (i.e., before the patient entered the room); or (2) blind LUS results without any information given to the assistant physician.

No guidance regarding treatment was provided and the treatment to be adopted was left at the discretion of the treating physician.

Additionally, all patients collected baseline data on left ventricular ejection fraction (LVEF), and laboratory data including B-type natriuretic peptide value (BNP), hemoglobin, creatinine, urea, and electrolytes (we used the last available information before performing LUS).

Study outcomes

The primary outcome was the change in loop diuretic (only furosemide was used) dose from before to after the outpatient HF clinic appointment i.e., up- or down-titration of furosemide.

Secondary outcomes included changes in other HF medications, including up-titration of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI), and beta-blockers to ≥ 50% of the target dose [16, 17], initiation of spironolactone (any dose), and sodium glucose co-transporter 2 inhibitors (SGLT2i, any dose).

A composite outcome of urgent emergency room (ER) visit for worsening HF, HF hospitalisation or cardiovascular mortality was also analysed.

Statistical procedures

Our primary hypothesis was that having open LUS results would lead to twice more changes in furosemide dose (either up- or down-titration) than having blind LUS results. The estimated sample size was 140 patients, with a power of 80% and 5% alfa, to detect a doubling in furosemide dose changes, from an estimated proportion of change of 20% based on clinical history and physical examination alone to more than 40% when adding LUS. Patient's characteristics were described by randomisation group (blind vs. open LUS) with categorical variables described using absolute numbers and proportions (%) and continuous variables using medians and 25–75th percentile. P-values were generated using Chi-square tests for categorical variables and Mann–Whitney tests for continuous variables. Despite this being a randomised trial, we opted to present P-values for comparison of randomised groups because the sample size was small which could have led to between-group imbalances. Furosemide changes were calculated by comparing the dose before the appointment to the dose after the appointment, and categorized as "decrease", "stable", or "increase". Furosemide dose changes (any) were compared using a logistic regression model with furosemide change (yes vs. no) as dependent/outcome variable, randomisation group (open LUS vs. blind LUS) as independent variable, and age, sex, peripheral edema and pulmonary rales on auscultations as adjustment variables. HF-medication up-titration changes (yes vs. no) were studied using a similar logistic regression model adjusting on the same variables. These variables were chosen for adjustment as they could have influenced treatment decisions based on congestion assessment by clinical history and physical examination. Variables used in the

models did not have missing values. Outcome associations were explored by means of an univariate Cox model. Spearman correlations were performed to explore the association between B-lines and clinical parameters. All analyses were performed using Stata® (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). A two-sided P value < 0.05 was considered statistically significant. No adjustment for multiple comparisons was performed and all outcomes other than the primary should be regarded as exploratory.

Results

Baseline patient's characteristics by randomisation group

A total of 139 patients entered the trial, 70 randomised to blind LUS and 69 to open LUS results. The median ($percentile_{25-75}$) age was 72 (63–82) years, 82 (62%) were men, 61 (44%) had diabetes, 117 (87%) were on NYHA class I or II, 35 (25%) had rales on pulmonary auscultation, 37 (27%) had peripheral edema, and 37 (28%) had 3 or more bilateral B-lines on LUS. The median LVEF was 39 (31–51) %, median BNP was 150 (56–352) pg/mL, and the median eGFR was 62 (40–85) ml/min/1.73m^2. Randomisation groups were well balanced overall, with exception of spironolactone use that was more frequent among patients randomised to open LUS results (28 [40%] vs. 41 [59%]) and thiazide diuretic use that was more frequent among patients randomised to blind LUS results (4 [6%] vs. 0) Table 1.

The detailed number of LUS B-lines within the 8 thoracic areas is described in Supplementary Table 1.

Furosemide changes by randomisation group

Furosemide dose changes (up- and down-titration) were more frequent among patients in whom LUS results were shown to their assistant physicians (i.e., open LUS results group): 13 (18.6%) in blind LUS vs. 22 (31.9%) in open LUS, OR 2.55, 95%CI 1.07 to 6.06. Table 2 and Fig. 1.

Furosemide dose changes (up- and down-titration) were more frequent and correlated significantly with the number of B-lines when LUS results were open (Rho = 0.30, P = 0.014), but not when the assistant physician was blind to LUS results (Rho = 0.19, P = 0.13). When LUS results were open, clinicians were more likely to up-titrate furosemide dose if the result "presence of pulmonary congestion" was identified and more likely to decrease furosemide dose in the case of "absence of pulmonary congestion" results. Specifically, 9/19 (47.4%) of the patients with ≥ 3 B-lines and open LUS results had furosemide dose increased vs. 3/18 (16.7%) with ≥ 3 B-lines and blind LUS results. Conversely, 9/50

Table 1 Patient's characteristics by randomisation group

Characteristic	LUS blind	LUS open	P value
N	70	69	
Age, years	73 (62, 81)	72 (63, 82)	0.96
Men	40 (57%)	46 (67%)	0.25
Weight, Kg	73 (65, 84)	72 (63, 84)	0.92
BMI, Kg/m^2	28.0 (25.0, 32.0)	27.5 (23.3, 30.0)	0.65
Hypertension	41 (59%)	41 (59%)	0.92
Diabetes	28 (40%)	33 (48%)	0.35
Dyslipidemia	27 (39%)	35 (51%)	0.15
COPD	12 (17%)	9 (13%)	0.50
Smoker	10 (14%)	12 (17%)	0.51
AFib/Flutter	32 (46%)	29 (42%)	0.66
Ischemic HF	23 (33%)	25 (36%)	0.68
Valvular disease	6 (9%)	8 (12%)	0.55
NYHA I/II	57 (85%)	60 (88%)	0.59
JVD	9 (14%)	7 (14%)	0.93
Rales	19 (27%)	16 (24%)	0.63
Peripheral edema	19 (27%)	18 (26%)	0.89
LVEF, %	39 (30, 51)	39 (32, 49)	0.81
BNP, pg/mL	147 (62, 338)	153 (53, 360)	0.91
Hemoglobin, g/dL	13.5 (12.0, 14.3)	13.3 (12.0, 14.8)	0.76
eGFR, ml/min/1.73m^2	63 (38, 85)	57 (40, 85)	0.74
Urea, mg/dL	56 (45, 76)	54 (40, 80)	0.38
Sodium, mmol/L	140 (139, 141)	140 (138, 141)	0.60
Potassium, mmol/L	4.5 (4.2, 4.8)	4.6 (4.3, 5.0)	0.091
ACEi/ARB			0.44[a]
No	29 (41%)	25 (36%)	
Yes	41 (59%)	44 (64%)	
< 50% target dose	12/41 (29%)	18/44 (41%)	
≥ 50% target dose	29/41 (71%)	26/44 (59%)	
ARNi			0.76[a]
No	56 (80%)	58 (84%)	
Yes	14 (20%)	11 (16%)	
< 50% target dose	4/14 (29%)	4/11 (36%)	
≥ 50% target dose	10/14 (71%)	7/11 (64%)	
Beta-blocker			0.45[a]
No	8 (11%)	10 (14%)	
Yes	62 (89%)	59 (86%)	
< 50% target dose	19/62 (31%)	24/59 (41%)	
≥ 50% target dose	43/62 (69%)	35/59 (59%)	
Spironolactone	28 (40%)	41 (59%)	0.022
SGLT2i	21 (30%)	18 (26%)	0.61
Furosemide			0.26
0	28 (40%)	26 (38%)	
≤ 40 mg/d	25 (36%)	18 (26%)	
> 40 mg/d	17 (24%)	25 (36%)	
Dose, mg/d	40 (0, 40)	40 (0, 80)	0.37
Thiazide	4 (6%)	0 (0%)	0.044
B-lines (bilateral)			0.89
< 3	52 (74%)	50 (72%)	
≥ 3	18 (26%)	19 (28%)	

Table 1 (continued)

Characteristic	LUS blind	LUS open	P value
ICD	5 (7%)	2 (3%)	0.25
CRT	1 (1%)	2 (3%)	0.55

Missing values, n (%): weight = 40 (29%); BMI = 60 (43%); NYHA = 4 (3%); JVD = 25 (18%); BNP = 21 (15%); Hemoglobin = 14 (10%); eGFR = 14 (10%); Urea = 14 (10%); Sodium = 20 (14%); Potassium = 19 (14%). All other variables did not present missing values

LUS lung ultrasound; *COPD* chronic obstructive pulmonary disease; *JVD* jugular venous distension; *AFib* atrial fibrillation; *ICD* implantable cardioverter-defibrillator; *CRT* cardiac resynchronization therapy; *BMI* body mass index; *LVEF* left ventricular ejection fraction; *BNP* brain natriuretic peptide; *eGFR* estimated glomerular filtration rate; *ACEi/ARB* angiotensin converting enzyme inhibitor/angiotensin receptor blocker; *ARNi* angiotensin-receptor neprilysin inhibitor; *SGLT2i* sodium glucose co-transporter 2 inhibitor

[a]P value corresponds to the comparison of no medication, < 50% or ≥ 50% target dose

Table 2 Change in furosemide dose by randomisation group

Furosemide dose change	LUS blind	LUS open	OR (95%CI)[a]
No change	57 (81.4%)	47 (68.1%)	–
Decrease	4 (5.7%)	10 (14.5%)	–
Increase	9 (12.9%)	12 (17.4%)	–
Any change	13 (18.6%)	22 (31.9%)	2.54 (1.07–6.06)

One patient with furosemide dose increase also was added metolazone

LUS lung ultrasound; *OR* odds ratio; *CI* confidence interval

[a]Adjusted for age, sex, rales, and peripheral edema. P-value = 0.034

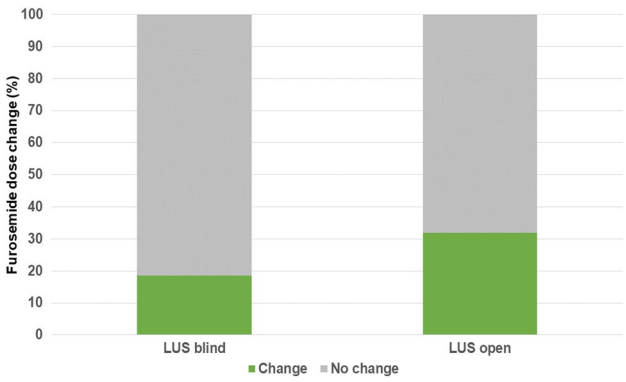


Fig. 1 Proportion of furosemide dose change (up- and down-titration) by randomisation group. LUS, lung ultrasound. Patients randomized to show the LUS B-line results to the assistant physicians were more likely to have their furosemide dose changed: 13 (18.6%) vs. 22 (31.9%); adjusted OR 2.54, 95%CI 1.07–6.06

(18.0%) with < 3 B-lines and open LUS results had furosemide dose decreased vs. 1/52 (1.9%) with < 3 B-lines and blind LUS results Supplementary Table 2 and Fig. 2.

HF medication changes and outcome events by randomisation group

HF medication optimization did not significantly differ by randomisation group. Still, spironolactone initiation was more frequent among patients with open LUS results: 0 vs. 4 (5.8%). Table 3.

Median furosemide dose did not significantly change after LUS results. The full description of HF medications after LUS results are shown in the Supplementary Table 3.

Over a median follow-up time of 161 (92–268) days, outcome events (composite of ER visit, HF hospitalisation or cardiovascular death) did not differ by randomisation group: 8 (11.4%) in blind LUS vs. 8 (11.6%) in open LUS results Table 3.

Correlation of B-lines with clinical characteristics and outcomes

LUS B-lines were correlated with the presence of peripheral edema (Rho = 0.42), rales (Rho = 0.39), age (Rho = 0.34 per 1 year older), NYHA class (Rho = 0.22 per 1 NYHA class higher), and eGFR (Rho = 0.20 per 1 ml/min/1.73m^2 lower eGFR) Supplementary Table 4.

The presence of 3 or more bilateral B-lines was associated with outcome events (composite of ER visit, HF hospitalisation or cardiovascular death): HR 3.03, 95%CI 1.04–8.81 Supplementary Table 5.

Discussion

The results of this trial show that LUS B-lines help in tailoring diuretic therapy among patients with stable chronic HF, with more frequent (≈ 2.5-fold) furosemide changes (up- and down-titration) observed in patients with open LUS vs. blind LUS results. Assistant physicians were more likely to up-titrate furosemide dose if patients with presence of pulmonary congestion and more likely to down-titrate furosemide dose if patients had absence of pulmonary congestion when the results were available to them, but not when LUS results were blinded. Specifically, among patients with presence of pulmonary congestion (N = 37), 47.4% (9/19) had furosemide dose increased when LUS results were open to HF clinicians vs. 16.7% (3/18) when LUS results were blinded. Conversely, among patients with absence of pulmonary congestion (N = 102), 18.0% (9/50) had furosemide dose decreased when LUS results were open to HF clinicians vs. 1.9% (1/52) when LUS results were blinded. These

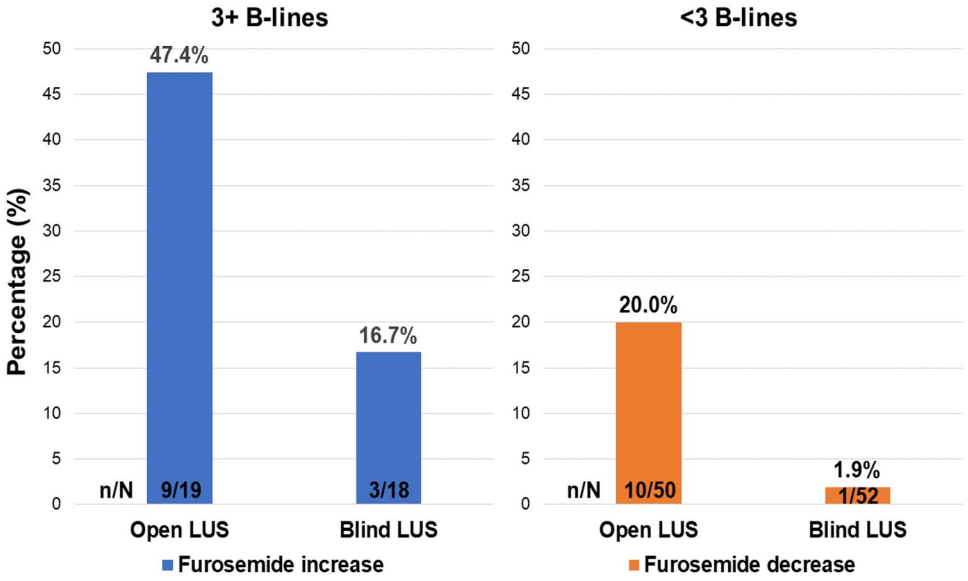


Fig. 2 Furosemide dose increase and decrease according to B-line number in open and blind LUS groups. *LUS* lung ultrasound

Table 3 Heart failure medications optimization and events by randomisation group

HF meds optimization	LUS blind	LUS open	OR (95%CI)[a]
ACEi/ARB/ARNI[b]	6 (8.6%)	6 (8.7%)	1.02 (0.30–3.46)
Beta-blocker[b]	2 (2.9%)	3 (4.4%)	1.58 (0.25–9.81)
Spironolactone[c]	0	4 (5.8%)	–
SGLT2i[c]	7 (10.0%)	5 (7.3%)	0.72 (0.22–2.40)
Thiazide[d]	3 (4.3%)	1 (1.5%)	0.33 (0.03–3.33)
Outcome events[e]	8 (11.4%)	8 (11.6%)	1.17 (0.36–3.78)

HF heart failure; *LUS* lung ultrasound; *OR* odds ratio; *CI* confidence interval; *ACEi/ARB/ARNi* angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin-receptor neprilysin inhibitor

[a]Adjusted for age, sex, rales, and peripheral edema. Outcome events variable was analyzed by means of a Cox model over a median follow-up time of 161 (92–268) days

[b]Changes to ≥ 50% of target dose

[c]Any new treatment initiation was considered as an optimization

[d]Any dose change or new initiation was considered

[e]A composite of time-to-first of emergency room visit or hospitalisation for worsening heart failure or death from cardiovascular causes presented as hazard ratio resulting from a Cox model (as described above)

findings were observed on top of clinical history and physical examination, whose measures (e.g., pulmonary rales, peripheral edema, NYHA class) were correlated with LUS B-lines. This supports LUS as a refinement tool for clinical decisions on top of usual care, particularly regarding the adaptation of diuretic therapy tailored to each patient's congestion status. Despite no major changes observed in other HF medications, spironolactone initiation was more frequent among patients with open LUS results. It is also worth noting that despite being only mildly symptomatic, nearly one-third of the patients had presence of pulmonary congestion on LUS, which has been associated with a poor prognosis [14, 18], including in our study. Having open LUS results did not have an impact on HF outcomes but this study was not powered for studying potential outcome effects. In fact, none of the trials performed to date were well powered to study the impact of LUS-guided therapy on HF outcomes [11]. Despite the limited power of our study for assessing "hard" outcomes, the observation that no excess events were the open LUS group (where a higher percentage of patients had furosemide down-titration) is reassuring and suggests that such diuretic down-titration was adapted to the congestion status of the patient.

Our study is original because it included only ambulatory "stable" HF patients with mild symptoms and without any specific guidance regarding diuretic doses or other HF therapies provided to the assistant physicians, who were simply informed of the LUS results in the open arm of the trial. Marini C. et al. [12] also included 244 ambulatory HF patients with stable HF therapy and a LVEF < 45% randomized to either LUS on top of physical examination or physical examination alone. The authors' aim was to assess the impact of LUS on HF hospitalisations at 90 days of follow-up (37 events in total) assuming an event reduction of 50% or greater with LUS, and not on how LUS would be used to guide diuretic therapy. In the study by Marini C. et al. and in our study, loop diuretic doses were not different according to randomisation allocation [12]. The CLUSTER-HF [9] (N = 126) and LUS-HF [10] (N = 123) studies enrolled patients at hospital

discharge to assess the impact of LUS on urgent HF visits and readmissions also assuming event reduction greater than 50% with LUS on a total of 89 primary events in both trials (50 events in CLUSTER-HF and 39 events in LUS-HF). In LUS-HF the mean loop diuretic dose increased in patients with more extensive B-lines but adjustments in furosemide doses (i.e., increases or decreases according to congestion status) were not different between LUS and usual care groups [10]. In CLUSTER-HF an increase in furosemide dose was observed only in the 6-week visit after randomisation [9].

Adding to prior reports, our study shows that LUS can be used to tailor diuretic therapy directed to patient's congestion status for which B-lines can help on top of clinical history and physical examination. The finding that diuretic changes occurred more often and correlated with the presence of pulmonary congestion only in open LUS group, strongly supports the role of LUS for guiding diuretic strategies. We believe this finding is novel and clinically relevant. Pocket ultrasound devices will become widely available, and LUS may be integrated in routine practice as an extension of physical examination [3].

Our results along with the other LUS trials are complementary to the findings from the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, showing an adaptation of diuretic therapy according to the volume status of each patient [19]. Notwithstanding, LUS is inexpensive and non-invasive potentially allowing a more widespread, low-cost, no risk implementation than the CardioMEMS device.

Still, future adequately powered trials should assess whether the use of LUS may reduce HF hospitalisations and mortality and if so, which would be the putative mechanisms mediating the clinical benefit (e.g., a diuretic strategy more tailored to each patient needs?).

Limitations

Some limitations should be acknowledged in this trial. This is a single centre study with only one person performing the LUS; hence, the generalisability of these results should be applied with caution. We did not collect follow-up data on natriuretic peptides, which could be informative as means to correlate natriuretic peptides changes with diuretic changes according to LUS results. Our study was only powered to assess diuretic changes and it was underpowered to study the impact of LUS on "hard" outcomes (e.g., HF hospitalizations or renal failure). Future larger randomized studies could study whether using LUS to tailored diuretic therapy would impact HF outcomes.

Conclusions

Showing LUS B-line results to the assistant physician allowed more frequent loop diuretic changes (both up- and down-titration), which suggest that LUS may be used as a refinement tool (on top of clinical history and physical examination) to tailor diuretic therapy adapted to each patient congestion status.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-023-02238-9.

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Data availability Data may be shared upon reasonable request to the corresponding author.

Declarations

Conflict of interest The authors have nothing to disclose regarding the content of this work.

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