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A randomized multicenter trial on a lung ultrasound–guided treatment strategy in patients on chronic hemodialysis with high cardiovascular risk

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Lung congestion is a risk factor for all-cause and cardiovascular mortality in patients on chronic hemodialysis, and its estimation by ultrasound may be useful to guide ultrafiltration and drug therapy in this population. In an international, multi-center randomized controlled trial (NCT02310061) we investigated whether a lung ultrasound-guided treatment strategy improved a composite end point (all-cause death, non-fatal myocardial infarction, decompensated heart failure) vs usual care in patients receiving chronic hemodialysis with high cardiovascular risk. Patient-Reported Outcomes (Depression and the Standard Form 36 Quality of Life Questionnaire, SF36) were assessed as secondary outcomes. A total of 367 patients were enrolled: 183 in the active arm and 180 in the control arm. In the active arm, the pre-dialysis lung scan was used to titrate ultrafiltration during dialysis and drug treatment. Three hundred and seven patients completed the study: 152 in the active arm and 155 in the control arm. During a mean follow-up of 1.49 years, lung congestion was significantly more frequently relieved in the active (78%) than in the control (56%) arm and the intervention was safe. The primary composite end point did not significantly differ between

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the two study arms (Hazard Ratio 0.88; 95% Confidence Interval: 0.63-1.24). The risk for all-cause and cardiovascular hospitalization and the changes of left ventricular mass and function did not differ among the two groups. A *post hoc* analysis for recurrent episodes of decompensated heart failure (0.37; 0.15-0.93) and cardiovascular events (0.63; 0.41-0.97) showed a risk reduction for these outcomes in the active arm. There were no differences in patient-reported outcomes between groups. Thus, in patients on chronic hemodialysis with high cardiovascular risk, a treatment strategy guided by lung ultrasound effectively relieved lung congestion but was not more effective than usual care in improving the primary or secondary end points of the trial.

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Volume overload is a leading risk factor for death and cardiovascular events in patients with chronic kidney failure who are maintained on chronic dialysis,[1] particularly in those with myocardial ischemia and heart failure (HF), which represent a substantial fraction (about 30%–40%)[2] of this population. Early identification of volume overload may prevent cardiovascular complications in these patients, but clinical signs of volume expansion are inadequate to reliably identify patients at risk and to monitor them over time.[3] However, reliable, standard techniques for measuring extracellular or circulating (blood) volume applied in clinical practice do not convey information on fundamental heart function parameters that determine the individual hemodynamic tolerance to volume excess and the response to ultrafiltration: that is, left ventricular (LV) filling pressure and LV function. Extravascular lung water is critically dependent on these parameters and represents a proxy of both circulating volume and LV filling pressure and function[4] and may therefore be a better criterion to identify patients at a higher risk of adverse clinical outcomes and to monitor the effect of therapy aimed at preventing these outcomes. A fast (<5 minute), easy to learn, simple, and inexpensive technique that measures extravascular lung water by using standard ultrasound (US) machines has been validated in patients on dialysis.[5] Lung US is applied to monitor treatment of decompensated HF.[6,7] Whether systematic measurement of lung water by this technique may translate into better clinical outcomes in patients with chronic kidney failure has never been tested.

The aim of this randomized clinical trial is that of testing a treatment policy guided by extravascular lung water measurements by US to prevent all-cause death, decompensated HF, and nonfatal myocardial infarction in high-risk patients on hemodialysis with myocardial ischemia or HF as compared to standard care based on clinical signs and symptoms.

METHODS

The Lung Water by Ultrasound-Guided Treatment in Hemodialysis Patients (LUST) trial is registered in ClinicalTrials.gov (identifier: NCT02310061). The study was approved by the institutional review board at each study site, and all participants provided written informed consent. An international independent Data Safety Monitoring Committee monitored patient safety

Trial participants

To set up the trial, an Web-based platform was created and an open call to all members of the European Cardiovascular and Renal Medicine (EURECAm) working group of the European Renal Association and the European Society of Dialysis and Transplantation (ERA-EDTA) was made. Investigators representing 24 European renal units expressed an interest for the trial and entered in the study platform the clinical data of patients potentially eligible for the study. Six renal units were dropped for organizational problems, leaving 18 participating renal units.

To be enrolled into the trial, patients had to be >18 years of age, on hemodialysis >3 months prior to study day 1, and have a high-risk cardiovascular profile: that is, a history of myocardial infarction with or without ST elevation or unstable angina, acute coronary syndrome documented by electrocardiogram recordings, and cardiac troponins or stable angina pectoris with documented coronary artery disease by prior coronary angiography or electrocardiography or HF with dyspnea class III-IV according to New York Heart Association functional classification. Exclusion criteria were cancer or other advanced noncardiac disease or comorbidity (e.g., end-stage liver failure) imposing a poor short-term prognosis, active infections or relevant intercurrent disease, and inadequate lung scanning and echocardiographic studies. An echocardiographic study was performed in all participants to document anatomical (LV hypertrophy) or functional (or both) alterations of the LV.

Lung US

Lung water assessment by chest US is a quick (∼5 minutes) and easy to learn technique that requires just a 2-hour training session. A detailed description of the technique and its validation in patients on hemodialysis is described elsewhere.[5] Nephrologists and cardiologists of participating units were trained by a remote Web-based program and, after training, all of them were certified by the lung US expert of the trial (LG) who acted also as study trainer.[8] All centers participating to the trial were provided a handheld US machine (VS scan, General Electric) to be used during the trial.

Intervention

Patients were randomized to a lung US–guided treatment policy or to standard clinical care. Given the nature of the intervention, treatment assignment was not blinded. In patients randomized to the active arm of the study, lung US was performed by nephrologists before and after hemodialysis session and the predialysis lung scan was used to titrate ultrafiltration (UF) during dialysis and drug treatment. In patients in this arm with moderate to severe lung congestion (>15 lung comets predialysis; see Supplementary Figure S1) lung US was repeated at least once a week until the treatment goal (<15 US-B lines) was achieved and once a month thereafter. Depending on the severity of lung congestion, specific weight reduction targets were suggested to nephrologists of

participating centers.[9] The same (monthly) monitoring frequency was adopted also in patients without or with mild pulmonary congestion at baseline (<15 US-B lines). Furthermore, the use of the technique was allowed whenever its application was deemed useful to assume clinical decisions by attending physicians. Patients in the active arm of the study without evidence of lung congestion at baseline who developed pulmonary congestion (i.e., clinical signs or >15 US-B lines or both) during the trial received the same treatment contemplated for those with lung congestion at baseline.[9] The treatment goal was pursued by UF intensification realized either by lengthening the duration of dialysis or by extradialysis sessions, according to individual tolerance and feasibility. If the treatment goal was not achieved within the first 3 to 4 weeks or intolerance to UF supervened, adjustment of drug treatment was considered including the introduction or dose adjustments of drugs of proven efficacy for cardiovascular prevention in patients on hemodialysis along the algorithm of a consensus document by Kidney Disease: Improving Global Outcomes[10] (see Supplementary Table S1). Other cardiovascular and noncardiovascular medications were maintained unchanged or appropriately adapted in relationship to the individual needs.

Patients in the control arm of the study were followed up and managed with standard criteria according to current recommendations (implying optimization of fluids volume control based on clinical criteria and the use of carvedilol, angiotensin-converting enzyme inhibitors or sartans whenever deemed necessary) and the use of lung US was not allowed in these patients.

In addition to peridialysis measurements in the active arm of the trial, lung US recordings were made in both arms during the baseline visit and in subsequent visits at 6, 12, and 24 months by a cardiologist blind to study intervention. During the same visits patients of both groups underwent echocardiography.

The occurrence of clinical events was accurately registered in the Web platform of the trial in both study arms, and the platform was actively surveilled by an investigator at the coordinating center (CT). In the case of doubt, clinical events were adjudicated by an external panel of physicians unaware of the allocation of patients into the trial.

Methods against bias

Randomization (permuted blocks of random length) stratified by center was made at the coordinating center and communicated to participating centers by e-mail or telephone.

Study outcomes

The main study endpoint was a composite of all-cause death, nonfatal myocardial infarction, or decompensated HF. The secondary clinical endpoints of the trial were all-cause and cardiovascular hospitalizations and changes in echocardiographic parameters including LV mass index, left atrial volume index, ejection fraction, and the Early diastolic trans mitral flow velocity (E) to early diastolic mitral annular tissue velocity (e′). In the trial we also collected information on patient-reported outcomes (Depression and the Standard Form 36 Quality of Life Questionnaire, SF36) and 2 questionnaires collected by doctors (Berlin Questionnaire and Karnofsky score).

Sample size, study power

A total sample size of 500 patients (250 per group) was expected to provide approximately 80% power to detect a difference in the

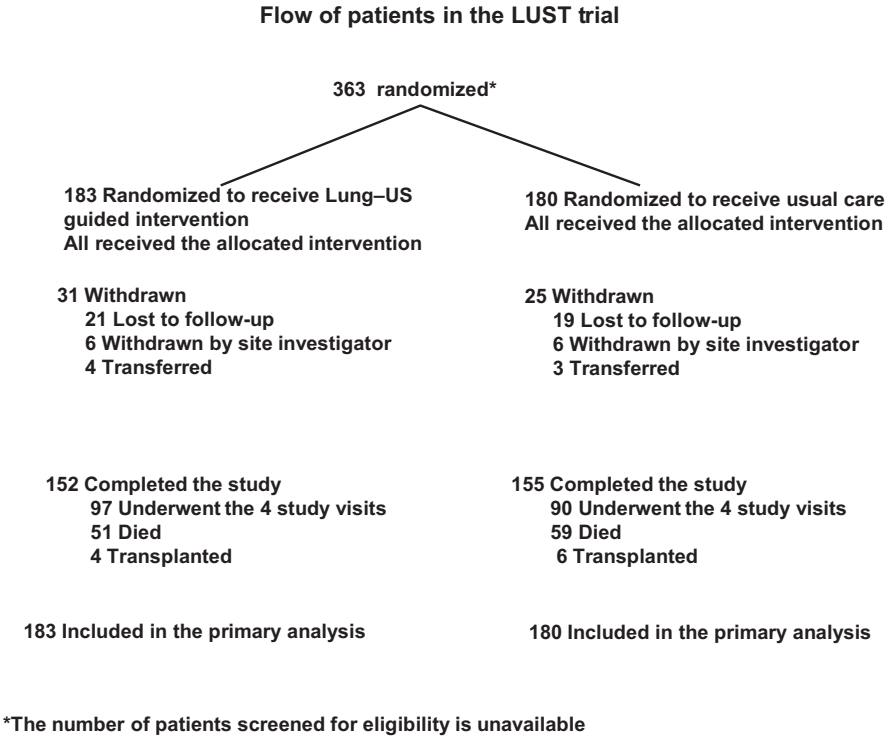

Figure 1 | CONSORT flow diagram for patients in the Lung Water by Ultrasound-Guided Treatment in Hemodialysis Patients (LUST) trial. US, ultrasound.

primary endpoint with an assumed type 1 error rate of 0.05, 2-sided. We estimated that the 2-year event rate for the composite endpoint would be 45% in the usual care group and 30% (a 33% risk reduction) in the arm with the lung US–guided intervention. According to protocol, all patients were to be followed for 24 months after randomization. For the analysis of the primary, composite endpoint and all-cause and cardiovascular hospitalizations (secondary endpoints), we analyzed the data by the Kaplan-Meier method and the univariate Cox's regression hazard ratio (HR) was considered as the main estimate of the effect of the intervention. Missing baseline categorical variables were replaced with the mean or median value, as appropriate. The effect of the allocation arm on the number of US-B lines and on echocardiographic parameters was investigated by linear mixed models. After the publication of the protocol at ClinicalTrials.gov, 2 studies reporting a benefit of lung US–guided treatment strategies in patients with HF were published.[11,12] For this reason, we also made separate secondary analyses (*post hoc*) of recurrent episodes of decompensated heart failure and repeated cardiovascular events as well as *post hoc* analyses of the individual components of the composite endpoint. Cardiovascular events were prespecified and listed in the study platform. These included a series of events demanding hospitalization including myocardial infarction, acute coronary syndrome, coronary artery graft or coronary angioplasty, decompensated HF, atrial fibrillation or flutter, other arrhythmias, cardiac arrest or sudden death, stroke, transient ischemic attack, *de novo* peripheral vascular disease, peripheral arteries angioplasty or stenting, amputation, and vascular surgery. Total (recurrent) episodes of decompensated HF and total cardiovascular events were expressed as events per 100 person-years. The impact of the study intervention on these secondary (*post hoc*) analyses was analyzed by the zero inflated binomial regression, which is a method for modeling count variables with excessive zeros and for overdispersed count-based variables.[13] No effect of the intervention on these metrics was registered. All analyses were based on the principle of intention to treat and were performed using SPSS version 24 (IBM Corp) and STATA 16 (StataCorp). The threshold for statistical significance was 2-sided with a type 1 error rate of 0.05.

RESULTS

At the time we started the trial, the interest of nephrologists for the technique was modest and most nephrologists felt that the same technique was complex and time-consuming, which slowed the recruitment rate. After a 4.5-year recruitment period, considering the slow recruitment rate, patient enrollment was stopped when 363 of the 500 planned patients (77%) had been enrolled in the trial. Final study visits for all patients still actively participating in the trial had to be completed prior to the database lock (July 10, 2020).

Study patients

Three hundred and sixty-three patients were randomized (lung US–guided therapy: 183; standard care: 180) at 18 renal units in Europe between March 1, 2013, and December 31, 2017 (The CONSORT flow diagram is presented in Figure 1). All patients but 1 were of White descent and for legal reasons race could not be specified for the 54 French patients of the trial. The groups were generally well balanced with respect to baseline characteristics (Table 1). As the study enrolled patients on hemodialysis who were at high cardiovascular risk, the study population was characterized a high prevalence of major cardiovascular comorbidities (Table 1). Most patients were receiving pharmacologic therapy for hypertension and cardiovascular comorbidities with no difference between the 2 groups (Supplementary Table S2).

Table 1 | Main demographic, somatometric, and clinical characteristics in patients as divided according to the study interventions

	Active arm (n = 183)	Control arm (n = 180)
Age, yr	70 ± 10	70 ± 11
BMI, kg/m^2	26 ± 5	26 ± 5
Male sex	127 (69)	128 (71)
Current smokers	23 (13)	27 (15)
Diabetics	74 (40)	73 (41)
On antihypertensive treatment	138 (75)	136 (76)
Dialysis vintage, mo	51 (22–141)	59 (27–166)
Acute CS or stable angina	135 (74)	124 (69)
Myocardial infarction	92 (50)	90 (50)
Atrial fibrillation	47 (26)	45 (25)
Heart failure	69 (38)	85 (47)
NYHA functional class III-IV	61 (33)	69 (38)
Stroke	25 (14)	16 (9)
Peripheral vascular disease	50 (27)	53 (29)
Systolic/diastolic BP, mm Hg	138 ± 25/71 ± 15	136 ± 24/70 ± 12
LVM indexed by height, g/m	51.0 (42.7–61.3)	50.2 (41.9–60.7)
Ejection fraction, %	60 (55–65)	57 (52–61)
E/e′	11.2 (8.3–14.4)	10.8 (7.8–15.0)
Biochemistry		
Cholesterol, mmol/l	4.1 ± 1.2	3.9 ± 1.1
Hemoglobin, g/l	111 ± 15	112 ± 15
Albumin, g/l	38 ± 6	39 ± 7
CRP, mg/l	4.3 (2.0–10.0)	5.0 (2.4–13.3)
Calcium, mmol/l	2.2 ± 0.2	2.2 ± 0.2
Phosphate, mmol/l	1.6 ± 0.5	1.5 ± 0.4

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CS, coronary syndrome; E/e′, early diastolic transmitral flow velocity (E) to early diastolic mitral annular tissue velocity (e′); LVM, left ventricular mass; NYHA, New York Heart Association.
Values are mean ± SD, median (interquartile range), or n (%), as appropriate.

Medical treatment by strategy and follow-up

Patients randomized to the lung US–guided strategy underwent 4103 predialysis and an equal number of postdialysis lung US recordings made by attending nephrologists (on average 24 ± 17 for each measurement per patient). In the lung US studies blindly made by cardiologists in coincidence of the four prefixed visits of the trial, patients in the active arm had a decline in the number of US-B lines (baseline: 15; 95% confidence interval [CI]: 12–19; study end: 9; 95% CI: 5–12) while those in the control arm (from 16 [95% CI: 13–20] to 30 [95% CI: 20–39]) had an increase in US-B lines (Figure 2a). Data analysis by linear mixed models showed that the allocation arm was a strong modifier of the evolution of US-B lines across the trial ($P = 0.002$) (Figure 2b). Accordingly, the number of patients who achieved the treatment target (<15 US-B lines) was higher ($P < 0.001$) in the active

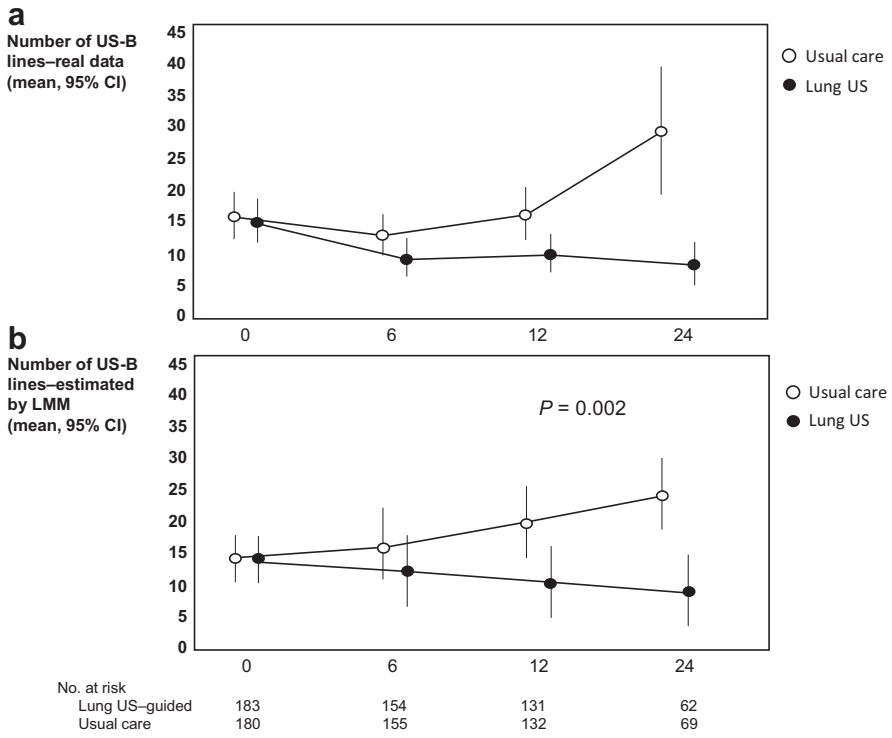

Figure 2 | Trend of ultrasound (US)-B lines in the active and control group. (**a**) Data are mean and 95% confidence interval (CI). (**b**) Data (mean and 95% CI) are fitted by the linear mixed model (LMM). The *I* value was derived from the LMM and indicates that the allocation arm modified the evolution of US-B lines across the trial.

(n = 117; 78%) than in the control (n = 85; 56%) arm. Adjustment of the antihypertensive therapy along the prespecified treatment algorithm was performed in 21 patients in the US-B lines group and in 10 patients in the usual care group ($P = 0.045$) and the corresponding total number of adjustments was 38 and 15, respectively. The incidence rate was 14.1 adjustments per 100 person-years in the first and 5.5 adjustments per 100 person-years in the second group ($P = 0.001$).

Predialysis systolic blood pressure (lung US group: baseline: 138 ± 25 mm Hg, last study visit: 139 ± 26 mm Hg; usual care group: baseline: 136 ± 24 mm Hg, last study visit: 137 ± 21 mm Hg), postdialysis systolic blood pressure (lung US group: baseline: 131 ± 25 mm Hg, last study visit: 129 ± 25 mm Hg; usual care group: baseline: 130 ± 25 mm Hg, last study visit: 132 ± 23 mm Hg), predialysis body weight (lung US group: baseline: 76 ± 16 kg, last study visit: 76 ± 16 kg; usual care group: baseline: 74 ± 16 kg, last study visit: 73 ± 17 kg), and postdialysis body weight (lung US group: baseline: 74 ± 16 kg, last study visit: 74 ± 16 kg; usual care group: baseline: 72 ± 15 kg, last study visit: 72 ± 17 kg) did not change across the trial.

Safety

The intervention was safe, and the risk of dialysis hypotension was less in the active arm of the trial (Table 2). Other possible adverse effects of the intervention including vascular access (AV fistula or graft) problems and intradialysis and extradialysis arrhythmia did not differ between the 2 groups.

Study outcomes

During a mean follow-up of 1.49 ± 0.72 years the main composite endpoint occurred in 62 patients (34%) in the lung US–guided therapy arm and in 71 patients (39%) in the control arm and the HR was statistically not significant (HR: 0.88; 95% CI: 0.63–1.24, $P = 0.47$) (Figure 3). No effect modification by age, sex, diabetes, ischemic heart disease, HF, systolic blood pressure, and ejection fraction (Supplementary Figure S2) nor by center (Supplementary Figure S3) was found. The analysis of secondary endpoints, including the echocardiographic parameters (left atrial volume, LV mass index, ejection fraction, and the E/e′) (Supplementary Table S3), and the risk for all-cause and cardiovascular hospitalizations were similar in the 2 arms (all-cause hospitalizations: HR: 1.03; 95% CI: 0.77–1.36; $P = 0.86$; cardiovascular hospitalizations: HR: 1.02; 95% CI: 0.71–1.46; $P = 0.92$). Death occurred in 51 patients (28%) in the lung US–guided group and in 59 (33%) in the usual care group (HR: 0.89; 95% CI: 0.61–1.29; $P = 0.53$). The time to the first episode of myocardial infarction and decompensated HF did not significantly differ between the 2 groups (Table 2). A *post hoc*, secondary analysis of the total number of repeated episodes of decompensated HF and repeated cardiovascular events in the 2 groups (Figure 4[14]) showed a significant reduction in the incidence rate for these outcomes in the

Table 2 | Adverse events

Rates of adverse events of interest	Lung US arm	Usual care arm	*P* value
Dialysis hypotension	858; 3.20 (3.00–3.42)	1292; 4.73 (4.48–5.00)	<0.001
Total episodes of arrhythmia on and off dialysis across the trial	31; 11.6 (7.8–16.4)	34; 12.5 (8.6–17.4)	0.76
Vascular access problems	25; 9.3 (6.0–13.7)	19; 7.0 (4.2–10.9)	0.34

Values are total number and incidence rate; events × 100 person-years (95% confidence interval).

lung US arm as compared to those in the usual care arm (Table 3).

Other secondary analyses

Secondary analyses on patient-reported outcomes (Depression and the Standard Form 36 Quality of Life Questionnaire, SF36) as well as the results of 2 additional questionnaires collected by doctors (Berlin Questionnaire and Karnofsky score) are reported in Supplementary Tables S4 and S5. No effect of the intervention on these metrics was registered.

DISCUSSION

The primary finding of this study is that in patients at on hemodialysis who are at high risk for cardiovascular events, a strategy of guiding therapy based on lung US successfully and safely reduced lung congestion in the active arm of the trial but this strategy was not more effective than a usual care strategy in reducing the composite endpoint of time to death or myocardial infarction or decompensated HF.

In a trial in 123 patients hospitalized for HF randomized to either standard follow-up or to a lung US–guided diuretic therapy,[11] patients in the active arm had a 48% risk reduction for a combined endpoint, including mortality, time to an urgent visit, and hospitalization for worsening HF, but mortality did not differ between the 2 groups. In

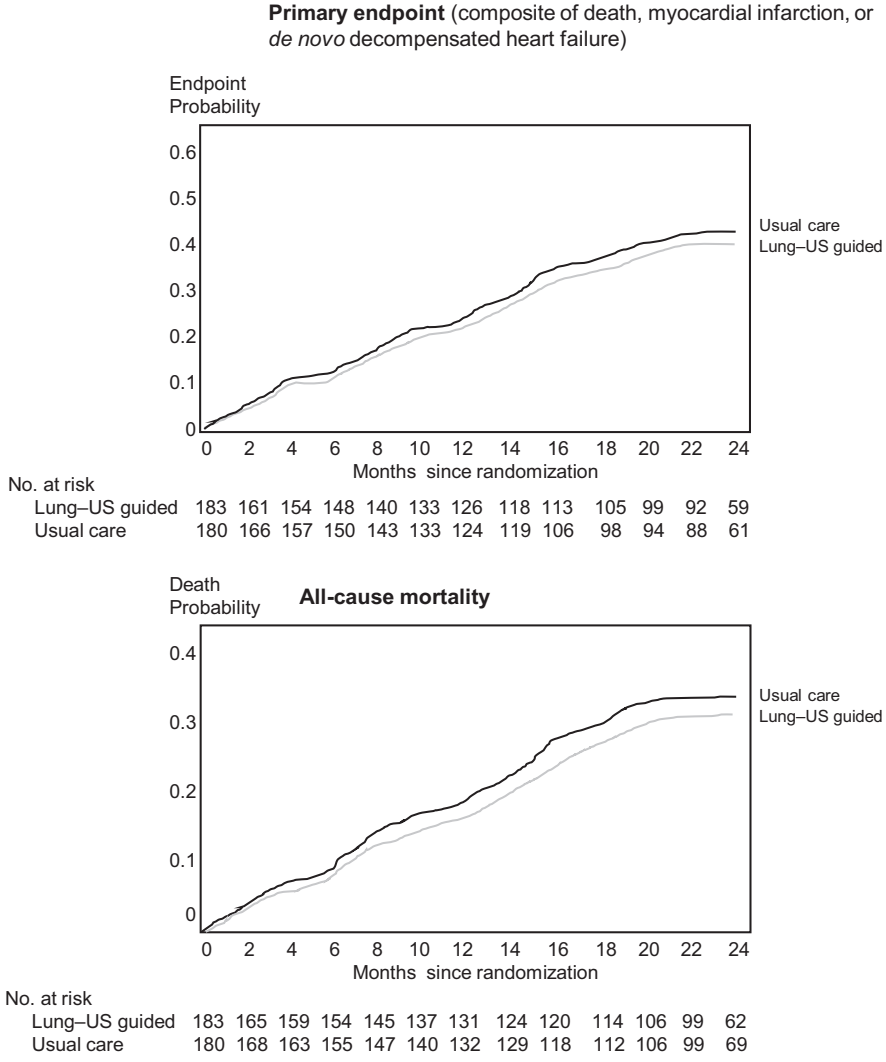

Figure 3 | Kaplan-Meier cumulative curves for the primary endpoint. US, ultrasound.

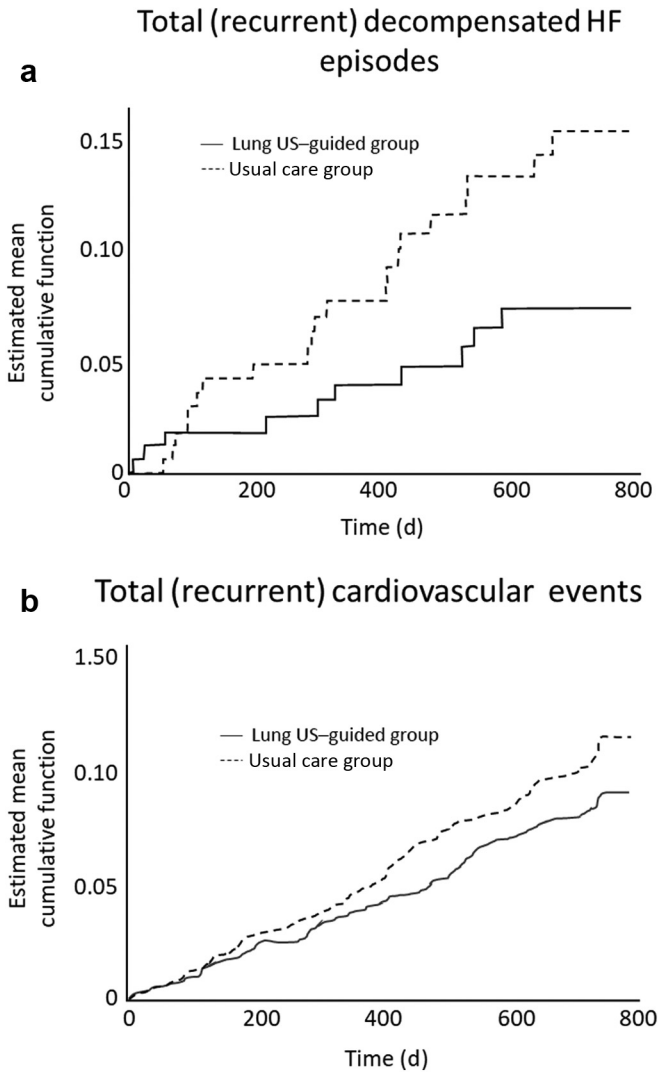

Figure 4 | Cumulative (repeated) episodes of decompensated heart failure (HF) (a) and cardiovascular events (b). Data plotting was done according to Nelson's hazard plotting method.[14]

another trial in 244 patients with chronic HF randomized to lung US–guided in addition to physical examination–guided therapy or to physical examination–guided therapy alone,[12] a marked reduction (56%) for the risk of hospitalization for acute decompensated HF was registered but again no difference in mortality was registered between the 2 study arms.

In the LUST study, the intervention reduced markedly the degree of lung congestion, which is *per se* a condition predisposing to pulmonary edema, and the proportion of patients achieving the target level of lung water (<15 US-B lines) was substantially higher in the active arm of the trial (78%) than in the control arm (56%). Similarly, intensification of concomitant antihypertensive therapies occurred more frequently in the active arm. B-lines reduction was achieved with a smooth lung decongestion, as witnessed by the reduction of number of hypotensive episodes during dialysis in the lung US group. In spite of these changes, body weight did not change in either group. A similar phenomenon was noted in the frequent hemodialysis trial,[15] where both predialysis and postdialysis body weight remained constant in both arms of the study while total body water decreased in the active arm of the trial (6 hemodialysis treatments per week) but increased in the control arm (3 hemodialysis treatments per week). Notwithstanding the efficacy and the safety of the lung US–guided treatment strategy in relieving lung congestion, the risk reduction (−12%) observed in the active arm of the trial for the composite endpoint was largely nonsignificant as were the changes in echocardiographic parameters. Only in a *post hoc* analysis stimulated by 2 trials in patients with HF[11,12] did we observed a risk reduction for repeated episodes of decompensated HF and cardiovascular events (Figure 4). The difference observed in this *post hoc* analysis is difficult to interpret and may be a pure chance effect. However, it is possible that because the decongestion process was slow and maximized at the end of the trial, it may take a long time for this process to have an impact on clinical outcomes. In the frequent hemodialysis trial no effect of hemodialysis intensification on mortality was observed during the trial,[16] while a marked reduction (−46%; range: 10%–90%) in the death risk was registered in a secondary analysis made 3.6 years (range: 1.5–5.3 years) after randomization.[17] In a LUST substudy including also patients on hemodialysis who were non-high-risk hypertensive, the lung US–guided strategy safely reduced 48-hour ambulatory blood pressure.[18] In any case, the analysis of the total number of events (decompensated HF and

Table 3 | Secondary and *post hoc* analyses

Secondary analyses	Lung US arm n (%); (95% CI)	Usual care arm n (%); (95% CI)	HR (95% CI)	*P* value
Deaths	51 (28); (22–35)	59 (33); (26–40)	0.89 (0.61–1.29)	0.53
First myocardial infarction	16 (9); (5–14)	10 (6); (3–10)	1.61 (0.73–3.55)	0.24
First episode of decompensated HF	12 (7); (3–11)	19 (11); (6–16)	0.64 (0.31–1.32)	0.23
	n; Incidence rate per 100 person-years (95% CI)	**n; Incidence rate per 100 person-years (95% CI)**	**IRR (95% CI)**	***P* value**
Total (recurrent) episodes of decompensated HF	15; 5.6 (3.1–9.2)	24; 8.8 (5.6–13.1)	0.37 (0.15–0.93)	0.035[a]
Total (recurrent) cardiovascular events	127; 47.3 (39.4–56.3)	157; 57.5 (48.9–67.2)	0.63 (0.41–0.97)	0.038[a]

CI, confidence interval; HF, heart failure; HR, hazard ratio; IRR, incidence rate ratio; US, ultrasound.
[a]Zero-inflated binomial regression.

cardiovascular events in general) is a secondary analysis and as such has just a hypothesis-generating value.

This study has important limitations making the results inconclusive as for the primary endpoint. First, at the time of the study design there was no previous trial testing lung US, neither in chronic kidney failure nor in other conditions. Available information in observational studies suggested a substantial benefit of fluid overload correction. Indeed in a previous multicenter cohort study by us[19] the risk of death (adjusted for New York Heart Association functional class and other risk factors) of patients with severe lung congestion was 4.2-fold (HR:4.20; 95% CI: 2.45–7.23) higher than that in patients with milder forms of lung congestion or no congestion and the corresponding risk for cardiac events was 3.2× higher (HR: 3.20; 95% CI: 1.75–5.88). *Ex post*, the 33% risk reduction we hypothesized was unrealistic. Observational studies are a suboptimal source of information to make quantitative inferences on the expected effect of experimental interventions. Extending the observation of patients to the posttrial period and, more importantly, a second trial adopting a protocol similar to LUST and a metanalysis of this trial with ours are needed to obtain conclusive results about the usefulness of lung US for guiding therapy in high-risk patients on hemodialysis. Second, we did not achieve the enrollment targets planned for the trial. However, the data analysis of enrolled patients (n = 383; 77% of the planned study population) showed a largely nonsignificant difference between the 2 arms of the trial. Third, because of the type of the intervention, the study was unblinded, which could have generated bias. Fourth, a possible favorable effect of the intervention was observed only in exploratory secondary analyses considering recurring episodes of decompensated HF and recurring cardiovascular events. Even though biologically plausible, these effects are merely hypothesis-generating. Additional trials need to be done to prove the usefulness of lung US in this population.

In conclusion, in patients on hemodialysis who are at high cardiovascular risk, a strategy of lung US-guided therapy safely reduced congestion but was not more effective than a usual care strategy in improving the primary (composite) endpoint of the LUST trial.

DISCLOSURE

CZ and FM received lecture fees from Amgen in 2019. LG received fees from General Electric Healthcare, Philips Healthcare, and Caption Health outside the submitted work. AW received fees from GlaxoSmithKline, personal fees from Astellas, and fees from AstraZeneca outside the submitted work. PR received fees from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, G3P (stocks), Grunenthal, Idorsia, KBP, Novartis, NovoNordisk, Relypsa, Sanofi, Sequana Medical, Servier, Stealth Peptides, Vifor, and Vifor Fresenius Medical Care Renal Pharma outside the submitted work; and is a cofounder of CardioRenal. ZAM received grants and other support from Amgen, Sanofi-Genzyme, and Baxter; grants from the French government, MSD, GSK, Lilly, FMC, and Outsuka; and other support from Daichi and Astellas outside the submitted work. KJJ received fees from Fresenius Medical Care outside the submitted work. All the other authors declared no competing interests.

DATA AVAILABILITY STATEMENT

Individual deidentified participant data whereupon the main results of the trial described in this manuscript are based will be shared with interested investigators. The data will become available 3 months after the publication of this study, and data access will end after 2 years. Interested investigators should contact the first author of the study for explaining the hypotheses they intend to test, the methods they will apply, and to obtain the study data.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Treatment algorithm according to the number of US-B lines.

Figure S2. Effect modification by age, sex, heart failure, ejection fraction, and study site of the effect of the lung US–guided policy on the composite endpoint (all-cause death, nonfatal myocardial infarction, and decompensated HF).

Figure S3. Effect modification by center.

Table S1. Cardiovascular drugs administration in patients where the treatment goal (<15 US-B lines/comets) is not achieved by UF alone.

Table S2. Pharmacological treatment at baseline in the 2 study groups.

Table S3. Echocardiographic parameters in the 2 study arms. (Left) Unadjusted data. (Right) Data fitted according to the linear mixed model.

Table S4. Secondary analyses on patient-reported outcomes (Depression and the Standard Form 36 Quality of Life Questionnaire, SF36) of 3 additional questionnaires collected by doctors (the Subjective Global Assessment score, the Berlin Questionnaire, and the Karnofsky score).

Table S5. Berlin Questionnaire proportion of patients classified at high risk for sleep apnea according to the Berlin Questionnaire score.

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