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Assessment and prevalence of pulmonary oedema in contemporary acute heart failure trials: a systematic review

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Abstract

Aims—Pulmonary oedema is a common and important finding in acute heart failure (AHF). We conducted a systematic review to describe the methods used to assess pulmonary oedema in recent randomized AHF trials and report its prevalence in these trials.

Methods and results—Of 23 AHF trials published between 2002 and 2013, six were excluded because they were very small or not randomized, or missing full-length publications. Of the remaining 17 (n = 200–7141) trials, six enrolled patients with HF and reduced ejection fraction (HF-REF) and 11, patients with both HF-REF and HF with preserved ejection fraction (HF-PEF). Pulmonary oedema was an essential inclusion criterion, in most trials, based upon findings on physical examination ('rales'), radiographic criteria ('signs of congestion'), or both. The prevalence of pulmonary oedema in HF-REF trials ranged from 75% to 83% and in combined HF-REF and HF-PEF trials from 51% to 100%. Five trials did not report the prevalence or extent of pulmonary oedema assessed by either clinical examination or chest x-ray. Improvement of pulmonary congestion with treatment was inconsistently reported and commonly grouped with other signs of congestion into a score. One trial suggested that patients with rales over >2/3 of the lung fields on admission were at higher risk of adverse outcomes than those without.

Conclusion—Although pulmonary oedema is a common finding in AHF, represents a therapeutic target, and may be of prognostic importance, recent trials used inconsistent criteria to define it, and did not consistently report its severity at baseline or its response to treatment. Consistent and ideally quantitative, methods for the assessment of pulmonary oedema in AHF trials are needed.

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Cochrane Collaboration's tool for assessing risk of bias.

Table S2 PRISMA 2009 checklist.

Conflict of interest: none declared.

Keywords

Acute heart failure; Clinical trials; Pulmonary oedema

Introduction

Acute heart failure (AHF) is a leading cause of hospitalization in patients over 65 years of age, in both the USA and Europe, with 20–30% of patients dying within 6 months after discharge.[1,2] Despite the improved survival seen over the past three decades with the advances in pharmacotherapy and device treatment of chronic heart failure with reduced ejection fraction (HF-REF), patients hospitalized with AHF remain at high risk of both inpatient and post-discharge morbidity and mortality. Therefore, identification of effective treatments for AHF represents an important unmet clinical need.[1] Hence, the timely and accurate identification and characterization of patients with AHF is crucial for the successful conduct of clinical trials.

Currently, the diagnosis of AHF is made on the basis of a constellation of signs and symptoms, supported by imaging and laboratory testing.[3] The presence of pulmonary oedema is a common sign in AHF and often used as an entry criterion in trials of therapies in patients with this condition.[4] Clinical evidence of pulmonary oedema includes rales on auscultation and findings of pulmonary congestion on chest radiography.[4] Newer, less subjective methods of assessing pulmonary oedema include impedance measurement (by external or implanted devices) and lung ultrasonography, although these are currently not routinely used in the diagnosis or monitoring of pulmonary oedema in AHF trials.[5–9] Given that more severe pulmonary oedema is associated with a greater risk of death and re-hospitalization, it is important to assess pulmonary oedema accurately in a reproducible manner.[10] Quantification of pulmonary oedema is important in describing the baseline characteristics of patients (and the balance between treatment arms), estimating patient risk, and is in itself a potential endpoint in clinical trials.

We conducted a systematic review of randomized trials involving patients with AHF to describe the methods used to assess pulmonary oedema, how the presence and degree of oedema is reported, and the prevalence of pulmonary oedema in these trials.

Methods

We collected data regarding pulmonary oedema from randomized controlled clinical trials (RCTs) which enrolled participants with AHF.

Literature search strategy and data extraction

The electronic databases Embase (269 articles), Medline (4439 articles), and the Cochrane Registry of Controlled Clinical Trials (113 articles) were searched with the terms ‘heart failure, acute, decompensated, heart decompensation, pulmonary oedema, pulmonary congestion, rales, crepitations’. We excluded trials in patients with acute myocardial infarction. The search was limited to RCTs in humans, and studies reported in English and published after January 2000 were included. We excluded two studies that had only reported

data in abstract form (RITZ I and CASINO), three studies that had a sample size of <200 people,[11–13] and one study in which patients with suspected but not confirmed AHF were randomized.[14] Trials meeting the inclusion criteria, study design papers, the main trial results paper, and supplemental files/appendices were reviewed. In addition, if secondary papers were published using the full data set, these were also reviewed for relevant data. We did not contact authors directly, but did use additional source documents from the Food and Drug Administration (FDA) website if available, in addition to the published information. Baseline characteristics and mortality rates are reported for the placebo groups if pooled baseline characteristics were not reported. Manuscripts were independently reviewed by two readers (P.S.J, and E.P.), with any discrepancies being resolved by a third reader (J.J.M.). The Cochrane Collaboration's tool was used for assessing risk of bias. We found that the included trials had low risk for bias (Supplementary material online, Table SI). In addition, the PRISMA 2009 checklist was used to examine the fidelity in reporting of results (Supplementary material online, Table S2).

Results

We identified 17 RCTs which enrolled patients with AHF and which met our inclusion criteria. These were published between the years 2002 and 2013. Eleven trials enrolled patients irrespective of EF and six trials included only patients with HF-REF The sample sizes ranged from 200 to 7141 (Table 1). Trials published after 2006 were more likely to include natriuretic peptides as part of their inclusion criteria and were less likely to exclude patients with heart failure with preserved ejection fraction (HF-PEF) (Table 1).

Pulmonary congestion as an inclusion criterion

Most trials required evidence of pulmonary oedema on either physical or radiographic examination for inclusion (Table 1). The presence of 'rales' on auscultation was the most commonly reported requirement on physical examination. Only one trial recruiting patients with HF-REF (REVIVE-2), and two enrolling patients with HF-REF and HF-PEF (PROTECT, RELAX-AHF), assessed rales in a semi-quantitative way, reporting the presence of rales in thirds from the lung bases.[15–17] The radiographic criteria for inclusion were less clearly defined and usually the requirement was described as 'signs of congestion' on the chest X-ray (CXR). One trial required findings on both physical and radiographic examination (3CPO) and two trials (Pre-RELAX-AHF and RELAX-AHF) required radiological pulmonary congestion in all patients. One study (UNLOAD) included evidence of pleural effusion as an indicator of pulmonary congestion.

Pulmonary congestion as the study endpoint

Pulmonary congestion alone was not used as a primary efficacy endpoint in any of the reviewed AHF trials, although relief of dyspnoea (presumably secondary to pulmonary oedema) and pulmonary oedema itself was used in conjunction with other markers of congestion as part of the primary endpoint in three trials and as a secondary endpoint in five trials (Table 2).

Although worsening HF has recently become an outcome of interest in AHF trials, only three of the studies reviewed reported on whether or not worsening of pulmonary oedema occurred (as a safety outcome). The REVIVE-2 trial (HF-REF) reported 6% of patients with worsening pulmonary oedema in their placebo group, and the HF-REF and HF-PEF trials RITZ-2 and VERITAS reported 3% and 6% with worsening pulmonary oedema.

Pulmonary congestion at baseline

The prevalence of pulmonary oedema at baseline in trials enrolling patients with HF-REF ranged from 75% to 83% and in trials enrolling both patients with HF-REF and HF-PEF from 51% to 100%, in part depending on the inclusion criteria (Table 3). Five trials did not report the prevalence or degree of pulmonary oedema assessed by either physical examination or CXR. The EVEREST investigators found in a post-hoc analysis that subjects with the highest congestion score at the time of discharge/day 7 were more likely than other patients to have baseline jugular venous distension, and lower extremity oedema, as well as have the highest natriuretic peptide levels and the highest rate of prior hospitalization for heart failure.[18] Yet these subjects had the lowest proportion of rales on auscultation at baseline.

Only seven trials reported the prevalence of lung disease which may cause signs similar to pulmonary oedema. The prevalence of COPD ranged from 9% to 30%.

Effect of therapy on pulmonary congestion

Improvement of pulmonary congestion with treatment was also inconsistently reported and commonly grouped with other signs of congestion, e.g. dyspnoea, heart rate, rales, and jugular venous pressure, into a composite ‘congestion score’ or ‘oedema score’, in which each sign or symptom was assigned a point value (Table 3).[19,20] The treatment effect on the degree of congestion/oedema was then assessed longitudinally as measured by the score. For instance, the Heart Failure Score in a HF-REF trial, OPTIME-CHF, in which a maximum number of two points could be assigned to the presence of rales, with a higher score indicating more congestion, improved from baseline (score: 6) to hospital discharge (score: 2) in the placebo group.[21] Similarly, the SURVIVE trial reported 81% of subjects with at least mild improvement in a global assessment score, the VMAC trial reported that global clinical status ‘improved’ between 3 and 24 h, and investigators from the PROTECT trial reported that 36% of patients had ‘treatment success’ (defined as patient-reported improvement in dyspnoea at both 24 and 48 h from treatment start in the absence of treatment failure, including worsening HF) in the placebo group.[16,22]

Improvement of pulmonary congestion was reported separately in only one HF-REF (EVEREST) and two combined HF-REF/HF-PEF trials. The EVEREST trial reported that 77% of patients had at least a 1 point improvement (scale 0–4) in rales on hospital day 4, the Pre-RELAX-AHF trial reported that 67% of subjects had no rales on day 5, and RELAX-AHF reported that ~40% had no rales on day 2.[17,23,24]

Baseline pulmonary congestion and clinical outcomes

All-cause mortality rates in the reviewed AHF trials were reported for time frames ranging from 28 days to 10 months and are hence difficult to compare with respect to the presence/degree of pulmonary oedema. Where reported, all-cause mortality ranged from 3% to 16% (30 days) and from 11% to 38% (180 days), respectively (Table 3). In a post-hoc analysis of the HF-REF trial, EVEREST, a higher congestion score at the time of discharge/day 7 was associated with increased risk of 30-day HF hospitalization and all-cause mortality [hazard ratio (HR) 1.13, 95% confidence interval (CI) 1.06–1.17]. However, patients with absent or minimal resting signs and symptoms at discharge still experienced a high 30-day mortality (19%) and readmission rate (26%). Pulmonary congestion was not analysed independently in this report. A multivariable analysis of the HF-REF and HF-PEF trial, PROTECT, demonstrated that rales >2/3 from the bases (compared with no rales) on admission were associated with higher risk for death or hospitalization for any reason at 30 days (HR 1.49, 95% CI 0.96–2.29), death or rehospitalization for cardiovascular or renal reasons at 30 days (HR 1.53, 95% CI 0.96–2.41), and all-cause mortality at 180 days (HR 1.65, 95% CI 1.07–2.54).[10] However, it was not included in their prediction model since interobserver variability was presumed to be high for rales on auscultation.

Discussion

In this systematic review of the assessment of pulmonary oedema in trials enrolling patients with AHF, we found a wide range of mainly qualitative methods of assessing and reporting of pulmonary oedema detected by physical or radiological examination. Although the majority of trials listed pulmonary oedema as one of their inclusion criteria, change of pulmonary oedema with treatment was rarely reported alone, and was often combined with other markers of congestion, such as jugular venous distension and lower limb oedema. At the same time, while improvement of pulmonary congestion was part of the primary or secondary endpoint in at least 8 of 17 of the reviewed trials, improvement of pulmonary oedema was not the sole endpoint in any. The lack of any quantitative assessment of pulmonary oedema is a concern, given that incomplete decongestion has been reported as a potential predictor of both HF rehospitalization and mortality[25,26] Moreover, worsening HF as currently reported is a quite subjective outcome, and objective identification and quantification of pulmonary oedema would increase the robustness of this endpoint.

In 2010, the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology (ESC) published a scientific statement on the assessment and grading of congestion in AHF. The authors of this document recognized that rales (crepitations or crackles) on auscultation are neither a sensitive nor a specific marker for pulmonary oedema but have the advantage of allowing rapid assessment of the patient.[4] In addition, it was noted that a CXR was likewise not sufficiently sensitive to exclude pulmonary congestion.[4] Similarly, the most recent ESC heart failure guidelines mention ‘pulmonary crepitations’ as a less specific sign in the diagnosis of HF. They also suggest that CXR may be of limited use in the diagnostic evaluation of patients with suspected HF but can be useful to identify alternative diagnoses and may show findings consistent with pulmonary oedema/congestion.[3]

In trials of patients with AHF with similar age, LVEF, baseline renal function, and systolic blood pressure, the prevalence of pulmonary oedema ranged from 54% in ROSE to 90% in PROTECT. While this wide variation could be due to other differences in the patients enrolled, it is perhaps more likely to be due to inconsistent definition of pulmonary oedema, either on physical or on radiological examination, or due to interobserver variability related to both methods. While independent imaging core laboratory review of echocardiographic studies is commonly performed in HF trials, similar evaluation of CXR findings is not undertaken. Standardized criteria for both auscultation and analysis of imaging studies may help reduce this variability and allow for better monitoring of pulmonary oedema with treatment, as well as assessment of residual pre-discharge congestion.

Although the composite reporting of signs of congestion as a ‘congestion score’ may be useful as a primary or secondary study endpoint, reporting of individual congestion components may be equally important to gain a better understanding of the treatment effect of new therapies on each of these components. It is conceivable that pulmonary oedema, when measured consistently and with sensitive and specific methods, may be present at baseline and change to variable degrees with treatment in different AHF phenotypes, depending on the chronicity and aetiology of AHF, as well as the associated pathophysiological and anatomical pulmonary changes. In a time-to-first event analysis in the RELAX-AHF trial, the effect size for the treatment comparisons in physician-assessed HF signs and symptoms through day 5 ranged from 19% (rales) to 33% (peripheral oedema) relative improvement in serelaxin compared with placebo patients, but did not significantly change estimated jugular venous pressure.[27]

Quantitative imaging markers of pulmonary oedema, such as lung ultrasonography, would make such standardization more feasible. The reported sensitivity of lung ultrasound is 94% (95% CI 81–98%) with a specificity of 92% (95% CI 84–96%) for the identification of a cardiogenic aetiology in patients presenting to emergency departments with undifferentiated dyspnoea.[28,29] When interpreted by clinicians at the point of care, lung ultrasound had a significantly higher accuracy (sensitivity 97%, 95% CI 95–98%; specificity 97%, 95% CI 96–99%) in differentiating AHF from non-cardiac causes of acute dyspnoea than the initial clinical work-up or CXR alone in a recent European multicentre study in >1000 dyspnoeic patients.[29] Interobserver agreement for lung ultrasound findings in pulmonary oedema is high,[28,30,31] and this technique is a potentially useful method of accurately identifying patients with HF and monitoring pulmonary congestion in trials of patients with AHF, although these findings need to be confirmed in larger studies.[9,32–34] In addition, external and implanted impedance measurement devices have been proposed as potential future tools in the assessment of pulmonary congestion.[4] These devices have been investigated as assessment and monitoring devices for pulmonary oedema, although with inconsistent findings with respect to their diagnostic and prognostic utility in HF populations.[35–37]

Data from one of the reviewed AHF trials in both HF-REF and HF-PEF patients suggest that rales on auscultation at the time of admission may provide additional prognostic information.[10] Composite congestion scores make the identification of individual signs and symptoms of congestion with respect to prognostic importance more difficult. Similar to other outcome measures, reporting of individual congestion components may allow for a

better understanding not only of the effects of therapy but also of their relationship to outcomes. Whether baseline or pre-discharge pulmonary congestion is as important as other signs of congestion (e.g. peripheral oedema) is equally unclear without consistent assessment and reporting in AHF trials.

Recommendation for assessment of pulmonary congestion in future acute heart failure trials

Based on the heterogeneity of definitions and criteria, we recommend a standardized approach for the assessment and reporting of pulmonary oedema in future AHF trials. We suggest the following definitions for pulmonary oedema (Table 4, Figures 1 and 2).

Clinical examination—Presence of crackles or rales on auscultation should be assessed in thirds from the lung bases:[10]

- No crackles/rales
- Crackles/rales ≤1/3 from bases
- Crackles/rales ≤2/3 from bases
- Crackles/rales >2/3 from bases

Lung ultrasound—B-mode lung ultrasound assessment of the anterior and lateral chest can be performed with a variety of ultrasound machines routinely used in clinical practice. A curvilinear or phased array transducer in 6– 8 intercostal spaces [3 (or 4) on each hemithorax] can be used to assess for the presence of B-lines (vertical lines arising from the pleural line) at an imaging depth of ~18 cm, although imaging of four intercostal spaces (zones) may be sufficient in AHF (Figure 2).[29,38–40] The presence of ≥3 B-lines per zone in at least two zones on each hemithorax should be considered diagnostic for pulmonary oedema in suspected AHF.[28,29,38] Both patient positioning (upright vs. supine) and duration of recorded clips should be kept constant if serial assessments are performed.[39,40] A decrease in B-line number can be observed with treatment of AHF.[9] Potential false-positive results can be seen in a variety of interstitial lung processes, such as pulmonary fibrosis, so it is important to interpret the findings in the clinical context and taking account of the results of other investigations, e.g. natriuretic peptides.[38] The presence of pleural effusions can be assessed at the diaphragmatic level laterally on each hemithorax (Figure 2).[41,42]

Chest radiography—Chest radiography may be useful in identifying alternative aetiologies of dyspnoea. In settings where ultrasound is not available, CXR can be used to identify pulmonary congestion, however, with lower sensitivity than lung ultrasound (Table 4).

Limitations

This systematic review should be considered in the context of its limitations. Given the heterogeneity in the assessment methods and reporting of pulmonary congestion in the reviewed AHF trials, we could not perform a meta-analysis of the reviewed data. Although all reviewed studies were randomized trials in AHF cohorts, differences with respect to

inclusion criteria and time to intervention make it difficult to compare the response to therapeutic interventions.

Conclusions

Although pulmonary oedema is a common sign in patients with AHF, and may be of prognostic importance, recent trials have used variable diagnostic criteria, and have not consistently reported either baseline severity or response to treatment. When reported, the prevalence of pulmonary oedema has varied greatly. Consistent, ideally quantitative, methods for the assessment of pulmonary oedema in AHF are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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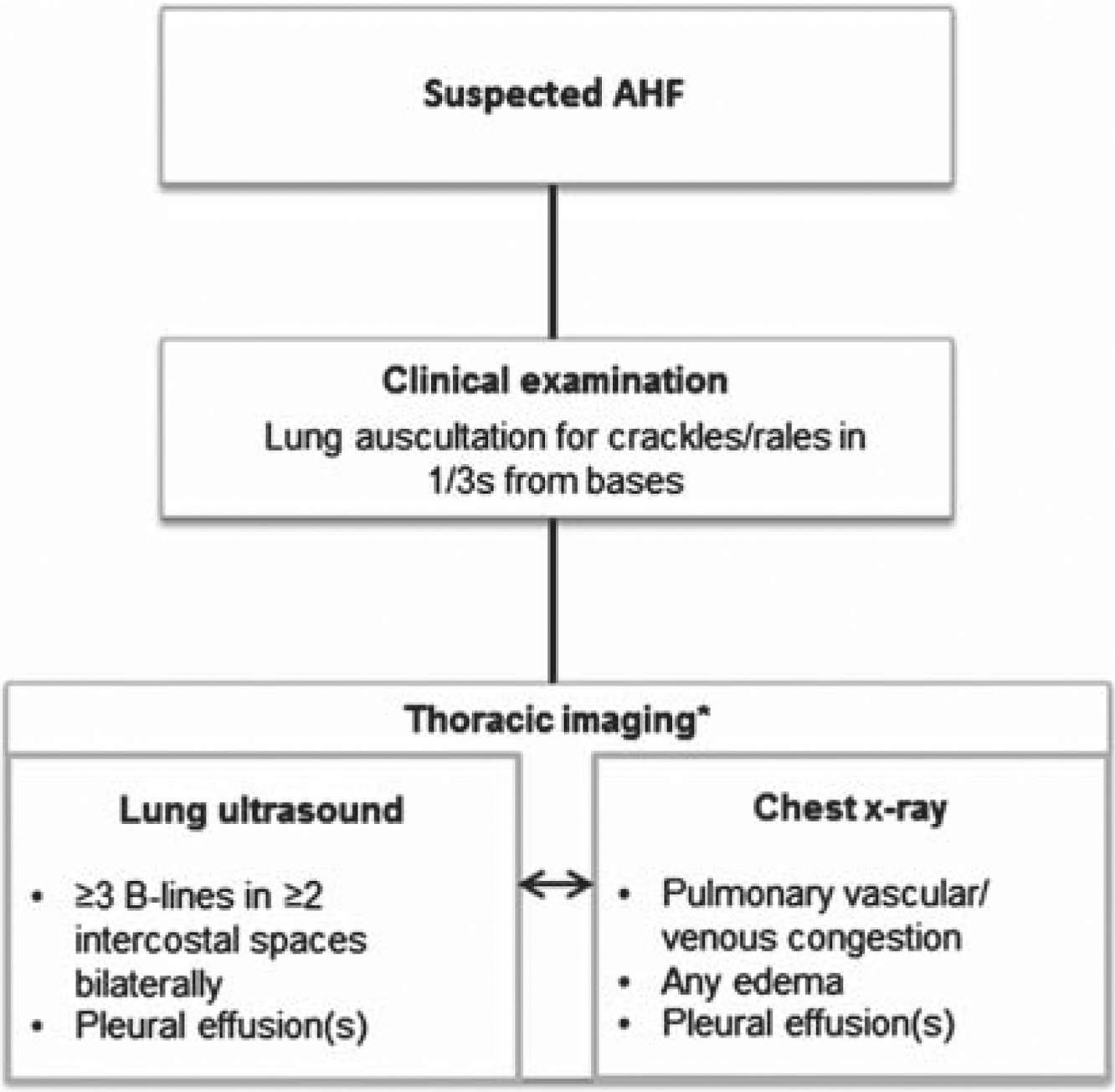

Figure 1.

Diagnostic flowchart for pulmonary congestion assessment in acute heart failure (AHF) trials. *Depending on the availability of imaging modalities and operator experience, lung ultrasound or chest radiography can be used in the assessment of pulmonary congestion. However, lung ultrasound will identify pulmonary oedema with higher sensitivity and specificity than chest radiography. Both imaging techniques may be useful in identifying alternative aetiologies of dyspnoea (e.g. pneumonia, pneumothorax, lung mass).

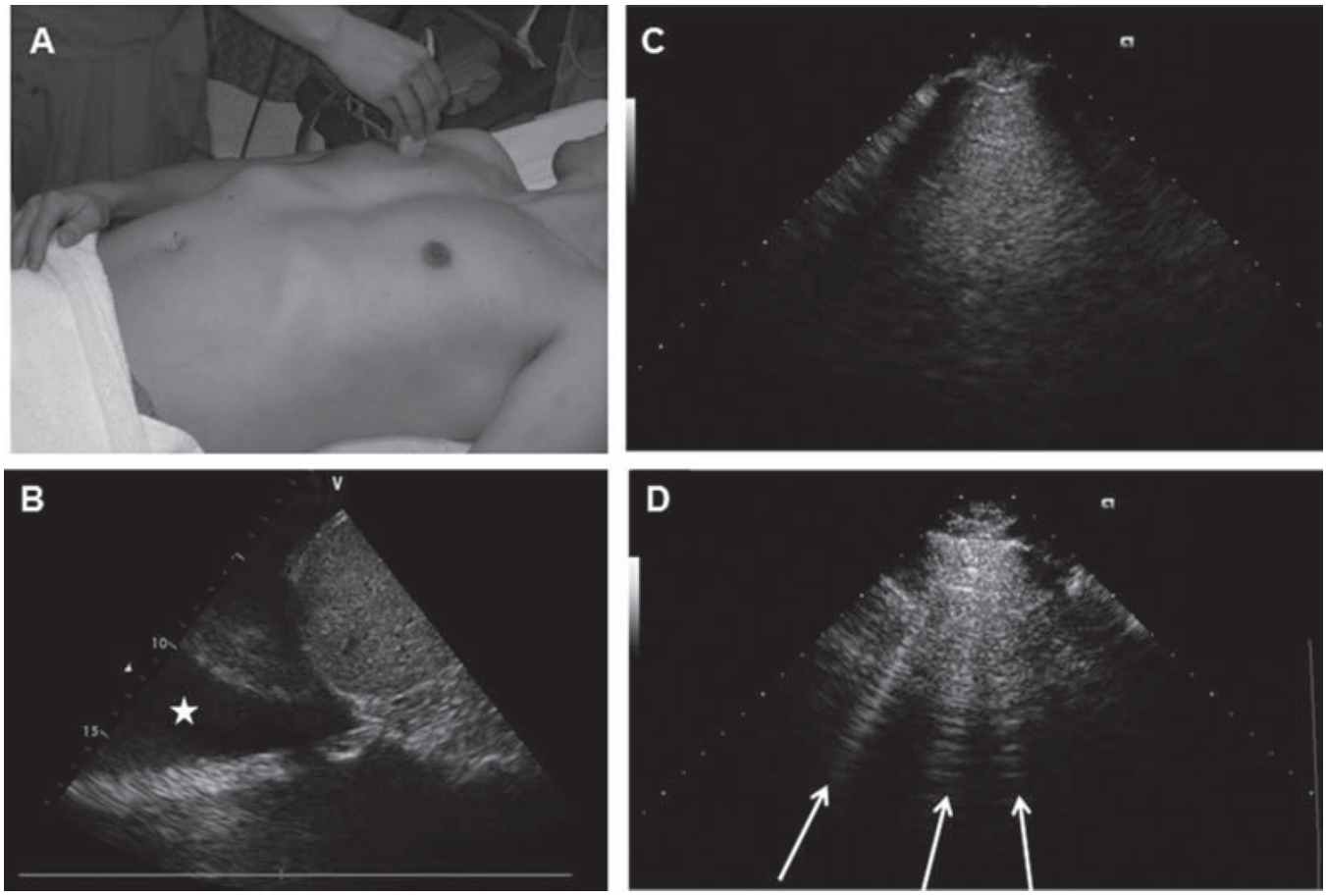

Figure 2.

Lung and pleural ultrasound. (*A*) Lung ultrasound: probe positioning for image acquisition. (*B*) Pleural ultrasound: the star indicates pleural effusion. (*C*) Lung ultrasound: normal appearance without B-lines. (*D*) Lung ultrasound: multiple B-lines; arrows indicate vertical B-lines.

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Table 1

Methods of pulmonary congestion assessment (inclusion criteria)

Trial (year)	*n*	Intervention	PC on physical exam part of inclusion criteria?	Physical exam criteria for PC	PC on CXR part of inclusion criteria?	CXR criteria for PC	(NT-pro)BNP inclusion criterion? (cut-off)	EF inclusion criterion?
HF-REF								
OPTIME-CHF (2002)[19,21]	951	Milrinone	Yes	Rales (bases only vs. >bases)	–	–	–	EF <40% within 12 months
LIDO (2002)[43]	203	Levosimendan	–	–	–	–	–	EF <35% within 1 month
ACTIV in CHF (2004)[44,45]	319	Tolvaptan	Yes	Rales	Yes	Signs of radiographic congestion	–	EF <40% within 12 months
EVEREST A and B (2007)[18,20,23,46]	4133	Tolvaptan	–	–	–	–	–	EF <40% within 12 months
SURVIVE (2007)[22]	1327	Levosimendan (vs. dobutamine)	–	–	–	–	–	EF ≤30% within 12 months
REVIVE-2 (2013)[15]	600	Levosimendan	?	Rales (basal only, >1/3, >2/3)	–	–	–	EF ≤35% within 12 months
HF-REF and HF-PEF								
VMAC (2002)[47]	489	Nesiritide (vs. nitrates vs. placebo)	–	–	Yes	Findings consistent with CHF	–	–
RITZ-2 (2003)[48]	292	Tezosentan	–	–	–	–	–	–
UNLOAD (2007)[49]	200	Ultrafiltration	Yes	Rales	Yes	Pulmonary oedema, pleural effusion	–	–
VERITAS 1 and 2 (2007)[50,51]	1435	Tezosentan	Yes	Rales/crackles >1/3 above bases	Yes	Evidence of PC	Elevated BNP or NT-proBNP (>3× upper limit of normal) or echo criteria	EF <40% or wall motion index ≤1.2 within 12 months
3CPO (2008)[52,53]	1069	CPAP/NIPPV	Yes	Bilateral crackles	Yes	Typical features of interstitial oedema	–	–
Pre-RELAX-AHF (2009)[24]	234	Relaxin	–	–	Yes (mandatory)	PC	BNP ≥350 pg/mL or NT-proBNP ≥1400 pg/mL	–
PROTECT (2010)[10,16,54]	2033	Rolofylline	Yes	Rales ≥1/3, not clearing with cough (in 1/3 s)	–	–	–	–

Trial (year)	*n*	Intervention	PC on physical exam part of inclusion criteria?	Physical exam criteria for PC	PC on CXR part of inclusion criteria?	CXR criteria for PC	(NT-pro)BNP inclusion criterion? (cut-off)	EF inclusion criterion?
DOSE (2011)[55]	308	Furosemide (bolus vs. cont. infusion)	Yes	Rales	Yes	Pulmonary vascular congestion	–	–
ASCEND-HF (2011)[56,57]	7141	Nesiritide	Yes	Rales ≥1/3	Yes	PC/oedema	BNP ≥400 pg/mL or NT-proBNP ≥1000 pg/mL (or echo or congestion criteria)	EF <40% within 12 months (or BNP or congestion criteria)
RELAX-AHF (2013)[17,27]	1161	Serelaxin	–	–	Yes (mandatory)	PC	BNP ≥350 pg/mL or NT-proBNP ≥1400 pg/mL	–
ROSE (2013)[58]	360	Nesiritide vs. dopamine	Yes	Rales	Yes	Pulmonary vascular congestion	–	–

CPAP, continuous positive airway pressure; CHF, chronic heart failure; CXR, chest X-ray; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; NIPPV, non-invasive positive pressure ventilation; PC, pulmonary congestion.

Table 2

Methods of pulmonary congestion assessment (endpoints)

Trial (year)	PC on physical exam part of endpoint criteria?	Physical exam criteria for PC	PC on CXR part of endpoint criteria?	CXR criteria or PC	Primary endpoint	PC part of safety endpoint?
HF-REF						
OPTIME-CHF (2002)	Yes (secondary endpoint: treatment failure)	Rales bases only vs. >bases	–	–	Days of hospitalization for CV events within 60 days	Yes (persistent PC)
LIDO (2002)	–	–	–	–	Proportion of patients achieving haemodynamic improvement at 24 h	–
ACTIV in CHF (2004)	Yes (secondary endpoint)	Rales	–	–	2 Co-primary: change in body weight at 24 h; worsening HF at 7 weeks (unscheduled hospitalization or visit for HF, death)	–
EVEREST A and B (2007)	Yes (secondary endpoint)	Rales (4-point scale)	–	–	2 Co-primary: time to all-cause mortality; time to CV mortality or HF hospitalization	-
SURVIVE (2007)	–	–	–	–	All-cause mortality (180 days)	-
REVIVE-2 (2013)	Yes (primary endpoint: ‘worsening clinical status’)	Increased pulmonary oedema	?	?	Composite: patient-reported clinical improvement, death or worsening clinical status (day 5)	?
HF-REF and HF-PEF						
VMAC (2002)	Yes (secondary endpoint: ‘global clinical status’)	?	?	?	Co-primary: change in PCWP; self-reported dyspnoea	–
RITZ-2 (2003)	–	–	–	–	Mean change in cardiac index from baseline to 6 h	?
UNLOAD (2007)	–	–	–	–	Weight loss and patient-reported dyspnoea	–
VERITAS 1 and 2 (2007)	Yes (primary endpoint: ‘worsening HF’)	Rales/crackles >1/3 above bases	Primary endpoint (‘worsening HF’)	Evidence of PC	2 Co-primary: death or worsening HF (7 days); dyspnoea	–
3CPO (2008)	–	–	–	–	7 day mortality (and intubation)	–
Pre-RELAX-AHF (2009)	? Yes (rales on day 5)	Rales	–	–	‘None’ (dose finding phase II trial)	–
PROTECT (2010)	Yes (primary endpoint: ‘worsening HF signs’)	Rales ≥1/3, not clearing with cough	–	–	Composite: dyspnoea, death/HF readmission day 7, worsening HF signs and symptoms	–
DOSE (2011)	–	–	–	–	2 Co-primary: patient-assessed symptom improvement (72 h); change in serum creatinine (72 h)	–
ASCEND-HF (2011)	–	–	–	–	2 Co-primary: change in self-reported dyspnoea (6	–

Trial (year)	PC on physical exam part of endpoint criteria?	Physical exam criteria for PC	PC on CXR part of endpoint criteria?	CXR criteria or PC	Primary endpoint	PC part of safety endpoint?
					and 24 h); composite: HF rehospitalization or death (30 days)	
RELAX-AHF (2013)	Yes (secondary endpoint: change from baseline HF symptoms; rehospitalization due to HF)	Rales, in 1/3 s	Secondary endpoint (rehospitalization due to HF)	Radiographic evidence consistent with HF	2 Co-primary: change in self-reported dyspnoea (day 5); dyspnoea improvement from baseline	–
ROSE (2013)	–	–	–	–	2 Co-primary: 72 h cumulative urine volume; change in cystatin C (72 h)	–

CV, cardiovascular; CXR, chest X-ray; HF, heart failure; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; PC, pulmonary congestion; PCWP, pulmonary capillary wedge pressure.

Table 3

Prevalence of baseline pulmonary congestion and outcomes[a]

Trial (year)	Baseline characteristics									Outcomes	
	Age (years)	EF (%)	SBP (mmHg)	BNP/NT-proBNP (pg/mL)	Creatinine (mg/dL)	COPD (%)	Physical exam: rales (%)	CXR: pulmonary oedema/vascular congestion (%)	CXR: pleural effusions (%)	Improvement of PC	All-cause mortality (%)
HF-REF											
OPTIME-CHF (2002)	66	(EF <40% within 12 months)	120	–	1.5	22	81	–	–	Heart failure score[b] improved from baseline (score 6) to day 3 (score 3) and discharge (score 2)	9 (60 days)
LIDO (2002)	60	(EF < 35% within 1 month)	117	–	–	–	–	–	–	–	17 (31 days) 38 (180 days)
ACTIV in CHF (2004)	60	25	116	–	1.8	10	78	–	–	-	9 (60 days)
EVEREST A and B (2007)	A: 66 B: 66	A: 27 B: 28	A: 119 B: 121	BNP: 734 NT-proBNP: 4857	1.3–1.5	A: 9[c] B: 11[c]	A: 81 B: 83	–	–	77% had at least 1 point (scale 0–4) improvement in rales on hospital day 4.	26 (10 months)
SURVIVE (2007)	66	24	116	BNP: 1667	–	–	–	–	–	81% at least mild improvement in global assessment score	21 (90 days) 28 (180 days)
REVIVE-2 (2013)	63	24	116	Only change in BNP reported	–	–	≤1/3: 47 1/3–2/3: 23 >2/3: 5	–	–	Safety: 6% worsening pulmonary oedema	12 (90 days)
Both: **HF-REF and HF-PEF**											
VMAC (2002)	62	27[d]	121	–	>2 mg/dL in 21%[d]	–	73[d]	–	–	Global clinical status ‘improved’ between 3 and 24 h	21 (6 months)
RITZ-2 (2003)	62	23	–	–	1.4	–	–	–	–	Safety: 3% pulmonary oedema	1 (28 days) 16 (168 days)
UNLOAD (2007)	63	(70% EF <40%)	129	BNP: 1309	1.5	30	51	–	–	–	12 (90 days)
VERITAS 1 and 2 (2007)	V1: 70 V2: 70	V1: 30 V2: 30	V1: 130 V2: 132	–	V1: 1.3 V2: 1.3	-	V1: 91 V2: 88	V1: 84 V2: 83	-	Safety: 6% pulmonary oedema (day 7), 8% on day 30	Pooled: 5 (30 days)
3CPO (2008)	79	–	161	–	–	19	100[e]	100[e]	–	–	10 (7 days), 16 (30 days)

Trial (year)	Baseline characteristics									Outcomes	
	Age (years)	EF (%)	SBP (mmHg)	BNP/NT-proBNP (pg/mL)	Creatinine (mg/dL)	COPD (%)	Physical exam: rales (%)	CXR: pulmonary oedema/vascular congestion (%)	CXR: pleural effusions (%)	Improvement of PC	All-cause mortality (%)
Pre-RELAX-AHF (2009)	68	(44% EF <40%)	148	BNP ≥350/NT-proBNP ≥1400[e]	1.4	–	67	100[e]	–	67% of subjects no rales on day 5	16 (180 days)
PROTECT (2010)	70	33	124	BNP 1198; NT-proBNP 3000[e]	1.4	19[f]	<1/3: 29 1/3–2/3: 51 >2/3: 10	–	–	36% ‘treatment success’	5 (30 days), 18 (180 days)
DOSE[f] (2011)	66	35	118	NT-proBNP 7308	1.5	–	–	–	–	–	8 (60 days)
ASCEND-HF (2011)	67	(80% EF <40%)	124	BNP 989; NT-proBNP 4461	1.2	–	–	–	–	–	4 (30 days)
RELAX-AHF (2013)	73	39	142	NT-proBNP 5003	eGFR 53 mL/min/ 1.73 m^2	15[g]	–	100[e]	–	~40% of subjects no rales on day 2	3 (30 days) 11 (180 days)
ROSE (2013)	70	30	116	NT-proBNP 5046	1.6	–	54	–	–	–	21 (180 days)

CXR, chest X-ray; eGFR, estimated glomerular filtration rate; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; PC, pulmonary congestion; SBP, systolic blood pressure.

[a] Data presented are for placebo group only unless noted otherwise.

[b] Maximum 2 points for rales.

[c] Severe COPD.

[d] Data for both placebo and treatment group.

[e] Inclusion criterion.

[f] Data for 12 h diuretic group.

[g] COPD or asthma.

Table 4

Recommendations for assessment of pulmonary congestion in acute heart failure trials

Diagnostic modality	Findings	Sensitivity (%)	Specificity (%)	Comments
Physical examination[59]	Crackles/rales	60	78	Crackles/rales >2/3 from lung bases associated with increased risk of CV events and mortality[10]
Lung ultrasound[28,29]	≥3 B-lines in ≥2 intercostal spaces bilaterally	94 (95% CI 81–98)	92 (95% CI 84–96)	False-positive examinations include acute and chronic conditions with interstitial involvement, such as pulmonary fibrosis[38]
Pleural ultrasound[41,42]	Pleural effusion(s) (any EF)	84	83	
	Pleural effusion(s) (if EF <45%)	79 (95% CI 63–89%)	98 (95% CI 92–99)	
Chest radiography[59]	Pulmonary vascular/venous congestion	54	96	
	Any oedema	70	77	
	Pleural effusion(s)	26	92	

CI, confidence interval; CV, cardiovascular.