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Vasoactive drugs for the treatment of pulmonary hypertension associated with interstitial lung diseases: a systematic review

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ABSTRACT

Objectives Vasoactive drugs have exhibited clinical efficacy in addressing pulmonary arterial hypertension, manifesting a significant reduction in morbidity and mortality. Pulmonary hypertension may complicate advanced interstitial lung disease (PH-ILD) and is associated with high rates of disability, hospitalisation due to cardiac and respiratory illnesses, and mortality. Prior management hinged on treating the underlying lung disease and comorbidities. However, the INCREASE trial of inhaled treprostinil in PH-ILD has demonstrated that PH-ILD can be effectively treated with vasoactive drugs.

Methods This comprehensive systematic review examines the evidence for vasoactive drugs in the management of PH-ILD.

Results A total of 1442 pubblications were screened, 11 RCTs were considered for quantitative synthesis. Unfortunately, the salient studies are limited by population heterogeneity, short-term follow-up and the selection of outcomes with uncertain clinical significance.

Conclusions This systematic review underscores the necessity of establishing a precision medicine-oriented strategy, directed at uncovering and addressing the intricate cellular and molecular mechanisms that underlie the pathophysiology of PH-ILD.

PROSPERO registration number CRD42023457482.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary hypertension-associated interstitial lung disease (PH-ILD) is poorly curable and associated with a great burden of morbidity and mortality.

⇒ Vasoactive drugs have shown contradicting evidence and potentially harmful effects depending on the analysed population.

WHAT THIS STUDY ADDS

⇒ The salient studies are limited by population heterogeneity, short-term follow-up and the selection of outcomes with uncertain clinical significance.

⇒ The indiscriminate use of vasoactive drugs has shown significant harm in some populations with ILD (eg, ambrisentan in idiopathic pulmonary fibrosis (IPF), riociguat in idiopathic interstitial pneumonia (IIP)-PH), while it could have beneficial effects on others (eg, bosentan in sarcoidosis-associated PH).

⇒ Some vasoactive drugs portend potential disease-modifying characteristics and could act directly on ILD course (eg, treprostinil in IIP and IPF).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ PH-ILD management cannot rely on a single universal strategy and must keep track of the underling ILD and severity of PH.

⇒ Disease endotypes must be unveiled to find rational and effective therapies.

INTRODUCTION

Pulmonary hypertension (PH) encompasses a group of conditions characterised by increased pressures in the pulmonary artery.[1] Gathering evidence allowed a better stratification of PH in terms of prognostic impact, thus prompting a reconsideration of the definition of PH in the recently published European Society of Cardiology (ESC) and European Respiratory Society (ERS) 2022 guidelines.[2] In particular, the mean pulmonary arterial pressure (mPAP) threshold for diagnosing PH was revised from 25 mm Hg to >20 mm Hg.[3] Moreover, the former definition of severe PH, based on mPAP >35 mm Hg or mPAP >25 and cardiac index <2.5 L/min/m^2, was abandoned in favour of pulmonary vascular resistance (PVR) thresholds.[3] Pre-capillary PH is now defined with PVR >2 Wood units (WU), leading to recognition of severe PH whenever PVR exceeds 5 WU.[2]

PH is divided into five WHO groups according to clinical presentation, pathophysiology and haemodynamic profile[2]: (1) pulmonary arterial hypertension (PAH), (2) PH associated with left-sided cardiac disease,

(3) PH secondary to lung disease, (4) chronic thromboembolic PH and (5) multifactorial conditions.[2]

Progressive interstitial lung diseases (ILDs) are frequently complicated by PH—for example, PH-ILD occurs in 30–50% of patients with idiopathic pulmonary fibrosis (IPF).[4] Furthermore, PH-ILD has been associated with impaired functional capacity, increased risk of hospitalisation and higher mortality.[5] Progressive lung damage, parenchymal fibrosis and architectural distortion are the main contributors to the pathogenesis of haemodynamic alterations leading to PH.[6 7] Therefore, prompt diagnosis and appropriate treatment of PH-ILD are paramount in progressive pulmonary fibrosis.

The treatment options for WHO groups 1, 2 and 4 have established guidelines. A wide variety of pharmacological strategies are effective for PAH and have improved morbidity and mortality, as well as improved pulmonary haemodynamics and exercise capacity in PAH.[8–10] Maintaining euvolemia and restoring adequate cardiac output are central in the management of group 2 PH.[2] Pulmonary thromboendarterectomy may be curative for patients with group 4 PH.[11–14] In non-surgical disease, riociguat, treprostinil and macitentan increase 6-minute walking distance (6MWD) and reduce PVR.[15–17]

The decision to use vasoactive drugs in PH-ILD is challenging because it remains unclear when PH becomes maladaptive rather than an adaptive pathophysiological response. Lung transplantation represents the only curative strategy available for selected patients with group 3 PH.[18] Based on preliminary data derived from PAH, a role for vasoactive drugs has been hypothesised for patients with PH-ILD. Results of recent trials have shown promising but conflicting data for vasoactive drugs in PH-ILD.[19 20]

Thus, in this systematic review, we aim to explore the clinical efficacy of vasoactive therapy in patients with PH secondary to ILD. For this purpose, prospective randomised controlled trials (RCTs) comparing vasoactive drugs versus placebo and secondary analysis of the above-mentioned trials have been evaluated.

MATERIALS AND METHODS

Objective and 'population, intervention, control and outcomes' question

The aim of this systematic review is to summarise existing evidence of clinical efficacy of vasoactive therapy in PH-ILD. RCTs comparing vasoactive drugs versus placebo and secondary analysis of the above-mentioned trials have been considered. The primary outcome of this systematic review was clinical efficacy, defined by any measurable effect in haemodynamics, clinical status, pulmonary function tests, performance in activities, progression in pulmonary or vascular disease.

Search methodology

Two investigators (AT and GB) independently performed a PubMed search and assessed the studies according to predefined criteria. This systematic revision was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21] Moreover, the reference list of every systematic review identified with the above-mentioned strategy was screened for additional RCTs. Finally, a search on ClinicalTrials.gov was performed. A preliminary search on PROSPERO for similar systematic reviews was conducted, but no records were detected. Thus, the review protocol was registered on the PROSPERO International Prospective Register for Systematic Reviews website (registration no: CRD42023457482) in August 2023.

Conditions used in the PubMed search were PH (fulfilling the diagnostic criteria adopted at the time of study enrolment) secondary to ILD and limited to adult subjects (equal to or greater than 18 years old). Interventions with 10 different vasoactive drugs were considered (riociguat, sildenafil, tadalafil, bosentan, macitentan, ambrisentan, treprostinil, iloprost, selexipag, isosorbide dinitrate). ClinicalTrials.gov was screened using the keywords "Pulmonary Hypertension" associated with the name of each vasoactive drug. Data from PubMed, ClinicalTrials.gov and the additional reference list gained through the screening of detected systematic reviews were cross-tabulated.

Study selection

Ten vasoactive drugs were chosen to perform this systematic review, based on past literature on the theme. For each drug, a research string was generated. The full search strategy is reported in the online supplemental material. PubMed database was later searched, by inserting one string at the time on the research bar. No limitations or filters were set during our PubMed search.

As no backward time limitation was set, we included studies published up to 10 September 2023.

Strings for each drug are listed below:

- *Riociguat*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("riociguat"[Supplementary Concept] OR "riociguat"[All Fields])
- *Sildenafil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All

Fields])) AND ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "sildenafil"[All Fields] OR "sildenafil s"[All Fields])

- *Tadalafil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("tadalafil"[MeSH Terms] OR "tadalafil"[All Fields])
- *Bosentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("bosentan"[MeSH Terms] OR "bosentan"[All Fields])
- *Macitentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("macitentan"[Supplementary Concept] OR "macitentan"[All Fields])
- *Ambrisentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("ambrisentan"[-Supplementary Concept)] OR "ambrisentan"[All Fields])
- *Treprostinil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("treprostinil"[Supplementary Concept] OR "treprostinil"[All Fields])
- *Iloprost*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("iloprost"[MeSH Terms] OR "iloprost"[All Fields])
- *Selexipag*: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("selexipag"[Supplementary Concept] OR "selexipag"[All Fields])
- *Isosorbide*: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("isosorbide"[All Fields] OR "isosorbide"[MeSH Terms] OR "isosorbide"[All Fields])

Review articles were identified during the PubMed string search. Those reviews were considered significant whenever the title/abstract described a therapeutic strategy on ILD or PH of a vasoactive drug (any of the above-mentioned). References of these reviews were screened for clinical trials.

ClinicalTrials.gov was also employed to search for clinical trials. The words [*vasoactive drug*] (in, for example, riociguat) and "*pulmonary hypertension*" were inserted in the research string panel for each vasoactive drug. The resulting clinical trials were then considered for screening if their status was addressed as 'completed with results'.

Data extraction

Titles and abstracts of any clinical trial detected with the above-mentioned search strategy from the PubMed database, the review references and ClinicalTrials.gov were reviewed by two independent investigators (AT and GB). Full texts were analysed when necessary. In case of disagreement between the two investigators, a final decision was taken by an independent investigator (FA). Records were considered eligible if: (1) the study explored clinical efficacy of a vasoactive drug against placebo in PH-ILD adult subjects; (2) the abstract reported the results of an interventional study.

Records were excluded if: (1) the full text did not report the results of an RCT (eg, case reports and case series, study designs, comments, letters to the editor); (2) they were on animal or laboratory models; (3) the full text was unavailable; (4) multiple copies of the same

Table 1 Evaluation of the selected publications according to the GRADE methodology

Vasoactive drug	Study	GRADE
Riociguat	Nathan *et al*[19]	Moderate
Sildenafil	Jackson *et al*[23]	Very low
	Behr *et al*[24]	Moderate
Tadalafil	No study identified	–
Bosentan	Corte *et al*[25]	Low
	Baughman *et al*[26]	Very low
Macitentan	No study identified	–
Ambrisentan	Raghu *et al*[27]	Very low
	Raghu *et al*[28]	Very low
	NCT00879229	Very Low
Treprostinil	Waxman *et al*[20]	Moderate
	Nathan *et al*[29]	Low
	Nathan *et al*[30]	Low
Iloprost	No study identified	–
Selexipag	No study identified	–
Isosorbide	No study identified	–

GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

study were obtained (duplicates); (5) they only assessed the pharmacokinetics or safety profile of drugs; (6) they assessed PH in a pulmonary disease other than ILD (eg, chronic obstructive pulmonary disease (COPD)).

Data analysis

Data of interest included the name of the first author, journal and year of publication, study design, number of patients, criteria defining PH-ILD, type of ILD, type of vasoactive drug that was investigated, population, exclusion criteria, primary outcome and side effects. Corresponding authors were contacted if the necessary data were not present or were unclear in the full text.

Critical assessment of evidence quality

Each publication was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria by one investigator (FA), independently checked and then agreed upon by all authors.[22] GRADE assessments were conducted to assign the quality of the evidence from each reference as high, moderate, low or very low according to factors that include the study methodology, consistency and precision of the results, and directness of the evidence (table 1).

Patient and public involvement

None.

RESULTS

Figure 1 shows the selection process of the included articles. For the 10 prespecified drugs, a total of 530 articles were found by PubMed search (last revision of literature was made by 10 September 2023). After reviewing titles and abstracts, 78 articles remained. 69 studies were removed due to presence of exclusion criteria. 463 clinical trials were identified through ClinicalTrials.gov. 27 fulfilled the inclusion criteria, of which 26 were excluded. 449 RCTs were identified in the references of published reviews. Of these, 33 were included. After removal of duplicates, 32 articles were excluded. A total of 11 RCTs were thus considered, respectively, 9 from PubMed search, 1 from ClinicalTrials.gov and 1 from bibliography of reviews identified. There were no identified studies of tadalafil, macitentan, iloprost, selexipag or isosorbide dinitrate in PH-ILD.

Table 2 summarises the characteristics of the 11 included studies that investigated riociguat, sildenafil, bosentan, ambrisentan and treprostinil. Whenever possible, intention-to-treat analysis was considered in distilling the results of clinical trials. A meta-analysis was not feasible due to the heterogeneity in the definition of PH and the reported outcomes.

Riociguat

RISE-IIP was a phase 2b RCT conducted in patients with idiopathic ILD affected by PH (defined by mPAP ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg measured by right heart catherisation (RHC)).[19] Patients were randomised to riociguat 2.5 mg three times a day or placebo. The trial was stopped early due to an excess of mortality in the intervention arm. Indeed, mortality and serious adverse events (SAEs) were more frequently reported in the riociguat group (SAE: 37% vs 23%; mortality: 11% vs 4%). There was no difference in 6MWD (p=0.21), pulmonary function or haemodynamic parameters between the two groups at 26 weeks.

Interestingly, patients with combined pulmonary fibrosis and emphysema (CPFE) were included in the study population. However, no data regarding this subpopulation are available in the original manuscript.

Sildenafil

Jackson *et al* designed an RCT in which PH secondary to IPF was defined by echocardiographic estimation of PAP alone. Thus, the diagnosis of PH is unconfirmed.[23] Patients were randomised to sildenafil 20 mg three times a day (14 patients) or placebo (15 patients). Inclusion criteria required an echocardiographic estimation of right ventricular systolic pressure or pulmonary artery systolic pressure between 25 and 50 mm Hg. In the sildenafil group, the primary outcome analysis showed no statistically significant differences in 6MWD at 0, 3 and 6 months. No statistically significant differences were also noted for secondary outcomes, including dyspnoea, pulmonary function and haemodynamic

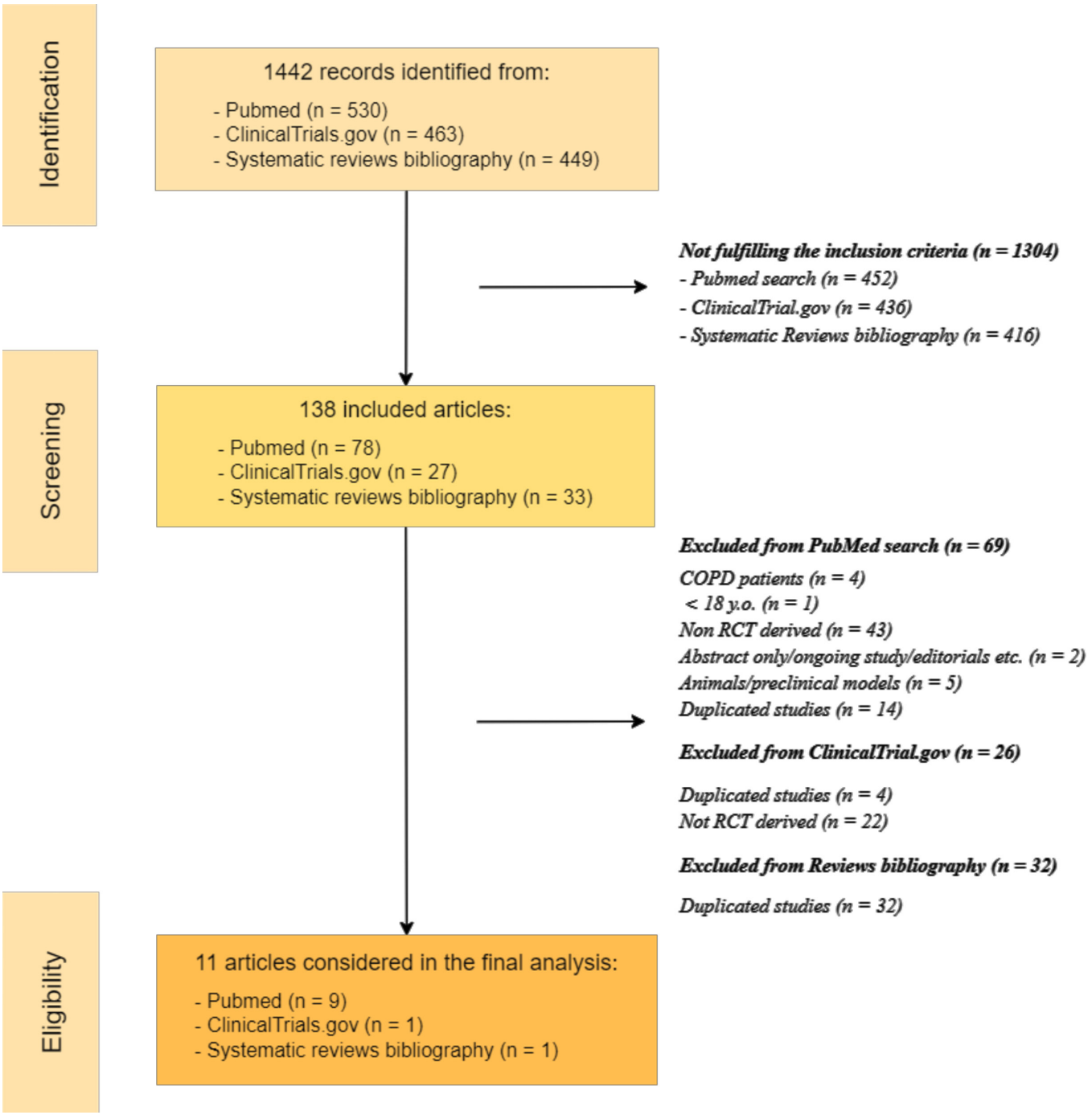

Figure 1 Identification of studies via databases. COPD, chronic obstructive pulmonary disease; RCT, randomised controlled trial.

parameters, while haemodynamic-related AEs (eg, syncope or flushing) were mostly reported with sildenafil.

In another phase 2b RCT, Behr *et al* enrolled 177 patients with PH associated with advanced IPF, defined either on RHC (mPAP ≥20 mm Hg and PCWP ≤15 mm Hg) or intermediate/high probability of PH on echocardiographic tricuspid regurgitation valvular jet measurement.[24] PH-ILD was considered likely by excluding other causes of PH. Participants were randomised to sildenafil 20 mg three times a day or placebo. Difference in disease progression at 52 weeks was the prespecified primary outcome, defined as occurrence of any among: (1) relevant 6MWD decline; (2) respiratory-related hospitalisation; (3) death by any cause. No statistically significant differences were outlined between the two groups (difference 3.06%; 95% CI −11.30% to 17.97%; p=0.65). Moreover, independent analysis of 6MWD decline, hospitalisation for respiratory cause and death by any cause showed no statistically significant differences. Rates of SAEs (61% vs 62%), as well as death events (17% vs 20%), were similar between groups.

Table 2 RCTs, selected subgroup and post-hoc analyses on vasoactive drugs in PH-ILD

Study (first author, journal, year)	Study type	Population	Exclusion criteria	Drug arm	Comparator arm	Primary outcome	Results (primary outcome)	Safety
Riociguat								
Nathan, *Lancet Respir Med*, 2019[19]	RCT Phase 2b 1:1	Idiopathic ILD-PH, RHC confirmed (mPAP ≥25 mm Hg, PCWP ≤15 mm Hg)	Active smoking Use of vasoactive or antifibrotic drugs in the previous 3 months CPFE with FEV_1/FVC <0.65 (with emphysema>fibrosis)	73 2.5 mg tid (oral)	74 placebo	Mean difference in 6MWD at week 26	No statistically significant differences: +21 m (95% CI –9 to 52; p=0.2074)	Overall AE: 89% vs 86% Deaths: 11% vs 4% Serious AE: 37% vs 23% AE leading to discontinuation: 15% vs 4%
Sildenafil								
Jackson, *Lung*, 2010[23]	RCT Phase 2 1:1	IPF population with mild PH by echocardiography (RVSP or sPAP 25–50 mm Hg)	Severe PH HF Recent use of steroids, pirfenidone, immunomodulant drugs FEV_1/FVC <0.7	14 20 mg tid (oral)	15 placebo	Mean difference in 6MWD at 6 months	No statistically significant differences: 324±41 m vs 355±82 m; p=0.256	Overall AE: 6 vs 1
Behr, *Lancet Respir Med*, 2021[24]	RCT Phase 2b 1:1	Advanced IPF (DLCO ≤40%) and PH (either mPAP ≥20 mm Hg with PWP of ≤15 mm Hg on RHC or intermediate/high probability of group 3 PH on echocardiography)	Type 3 PH other than ILD Emphysema greater than fibrosis FEV_1/FVC <0.7 predicted Severe oxygen requirement Recent tobacco smoking Illicit drugs/drugs predisposing to PH QT prolongation	88 20 mg tid (oral)	89 placebo	Proportion of patients developing disease progression* at 52 weeks	No statistically significant differences: +3.06% (95% CI –11.30 to 17.97); p=0.65	Overall AE: 99% vs 93% Deaths: 17% vs 20% Serious AE: 61% vs 62% AE leading to discontinuation: 25% vs 33%
Tadalafil								
No studies identified								
Bosentan								
Corte, *Am J Respir Crit Care Med*, 2014[25]	RCT Phase 2 2:1	IPF/NSIP-PH, RHC confirmed (mPAP ≥25 mm Hg, PCWP <15 mm Hg)	Unstable disease/acute exacerbation Significant comorbidities Low BP Clinically overt CAD Emphysema greater than interstitial changes	25 125 mg bid (oral)	14 placebo	PVR decrease >20% over 16 weeks	No statistically significant differences: 28% vs 28.6%; p=0.97	Deaths: 7.5% vs 15% Serious AE: 45% vs 50% AE leading to discontinuation: 5 vs 0 patients
Baughman, *Chest*, 2014[26]	RCT Phase 2 2:1	Sarcoidosis ILD-PH confirmed by RHC (mPAP >25 mm Hg PCWP <15 mm Hg)	Pulmonary vasodilator drugs in the prior 28 days FEV_1/FVC <0.35 WHO class IV LVEF <35% CI <2.0 and/or RAP >15 mm Hg Severe comorbidities	23 125 mg bid (oral)	12 placebo	Change in mPAP (baseline vs 16 weeks) in the bosentan and placebo group, respectively	Bosentan: 36±7.1 mm Hg vs 32±8.8 mm Hg; p=0.02 Placebo: 30±4.1 mm Hg vs 31±6.3 mm Hg; p not significant	No deaths reported
Macitentan								
No studies identified								
Ambrisentan								

Continued

Table 2 Continued

Study (first author, journal, year)	Study type	Population	Exclusion criteria	Drug arm	Comparator arm	Primary outcome	Results (primary outcome)	Safety
Raghu, *Ann Intern Med*, 2013[27]	Subgroup analysis of ARTEMIS-IPF RCT Phase 3 2:1	IPF-PH, RHC confirmed at baseline (mPAP >25 mm Hg, PCWP ≤15 mm Hg)	FVC <50% Honeycombing on HRCT ≤5% NYHA III or IV LVEF <40% Airflow defect or prominent emphysema Recent hospitalisation Chronic treatment for PH Immunosuppressive therapy SpO_2 <80% in room air during 6MWT	32 10 mg qd (oral)	16 placebo	Time to disease progression† in 48-month follow-up	No statistically significant differences: HR 2.42 (CI 0.79 to 7.38; p=0.121)	Not addressed for subgroups with ILD-PH
Raghu, *ER J*, 2015[28]	Subgroup analysis of ARTEMIS-IPF RCT Phase 3 2:1	IPF-PH, RHC confirmed at baseline and during follow-up (mPAP ≥25 mm Hg and PCWP ≤15 mm Hg)	FVC <50% Honeycombing on HRCT ≤5% NYHA III or IV LVEF <40% Airflow defect or prominent emphysema Recent hospitalisation Chronic treatment for PH Immunosuppressive therapy SpO_2 <80% in room air during 6MWT	12 10 mg qd (oral)	7 placebo	Change in mPAP, CO and PVR between baseline and 48 weeks in patients with multiple RHC measurements	mPAP: −5.3±4.27 mm Hg vs −1.1±9.39 mm Hg CO: 0.03±1.38 L/min vs 0.44±0.9 L/min PVR: −0.70±1.31 mm Hg/min/L vs −0.51±1.56 mm Hg/min/L	AE not reported Progression events‡: Moderate PH: 28% vs 17%, HR 1.74 (95% CI 0.68 to 3.57) Severe PH: (HR 1.18 (95% CI 0.21 to 6.49); p=0.85)
Treprostinil								
Waxman, *N Engl J Med*, 2021[20]	RCT Phase 3 1:1	ILD-PH, RHC confirmed (PVR >3 WU, PCWP ≤15 mm Hg, mPAP ≥25 mm Hg)	PH other than group 3 due to ILD Intolerance/lack of efficacy of a prostacyclin or prostacyclin analogue PAH-approved therapy within 60 days of randomisation PCWP >15 mm Hg or LVEF <40% Oxygen supplementation >10 L/min Tobacco/drug abuse Recent exacerbation or lung infection PR within 12 weeks	163 inhaled treprostinil	163 placebo	Difference in 6MWD at week 16 vs baseline	Statistically significant difference: +31.12 m (95% CI 16.85 to 45.39; p<0.001)	Overall AE: 890 vs 793 event Deaths: 2.5% vs 2.5% Serious AE: 23.3% vs 25.8% AE leading to discontinuation: 47 vs 38 patients
Nathan, *Lancet Respir Med*, 2021 [29]	Post-hoc analysis of INCREASE RCT Phase 3 1:1	ILD-PH, RHC confirmed (PVR >3 WU, PCWP ≤15 mm Hg, mPAP ≥25 mm Hg)	PH other than group 3 due to ILD Intolerance/lack of efficacy of a prostacyclin or prostacyclin analogue PAH-approved therapy within 60 days of randomisation PCWP >15 mm Hg or LVEF <40% Oxygen supplementation >10 L/min Tobacco/drug abuse Recent exacerbation or lung infection PR within 12 weeks	163 inhaled treprostinil	163 placebo	FVC variation at weeks 8 and 16 in overall, IIP and IPF subgroups	Overall population: no statistically significant difference IIP: significant difference at week 16 (108.2±46.9 mL; 95% CI 15.3 to 201.1; p=0.023) IPF: significant difference at week 16 (168.5±64.5 mL; 95% CI 40.1 to 297.0; p=0.011)	AE not reported

Continued

Table 2 Continued

Study (first author, journal, year)	Study type	Population	Exclusion criteria	Drug arm	Comparator arm	Primary outcome	Results (primary outcome)	Safety
Nathan, *Chest*, 2023[30]	Post-hoc analysis of INCREASE RCT Phase 3 1:1	ILD-PH, RHC confirmed (PVR >3 WU, PCWP ≤15 mm Hg, mPAP ≥25 mm Hg); 4 subgroups based on received BPS	PH other than group 3 due to ILD Intolerance/lack of efficacy of a prostacyclin or prostacyclin analogue PAH-approved therapy within 60 days of randomisation PCWP >15 mm Hg or LVEF <40% Oxygen supplementation >10 L/min Tobacco/drug abuse Recent exacerbation or lung infection PR within 12 weeks	70 patients with ≥9 BPS and 79 patients with <9 BPS at week 4	86 patients with ≥9 BPS and 67 patients with <9 BPS at week 4	Clinical worsening or clinical improvement§ at week 16	Clinical worsening: significant difference at week 16, favouring treprostinil ≥9 BPS (p=0.006) Clinical improvement: significant difference at week 16, favouring treprostinil ≥9 BPS (p=0.003)	(T>9; T<9; P>9; P<9) Hospitalisation for cardiopulmonary disease: 9.1% vs 12.8% vs 13.4% vs 19.2% Death: 1.8% vs 2.6% vs 0.8% vs 11.5% > 15% decrease in 6MWD: 5.5% vs 12.8% vs 18.1% vs 11.5% Lung transplant: 0 vs 2.6% vs 0 vs 0
Iloprost								
No studies identified								
Selexipag								
No studies identified								
ISDN								
No studies identified								

*Progression was defined as either (1) relevant 6MWT decline, (2) respiratory-related hospitalisation, (3) death from any cause.
†Progression was defined as whichever of the following occurred first: (1) death from any cause, (2) hospitalisation due to respiratory events, (3) significant decrease in lung function (either a 10% or greater decrease in FVC plus a 5% or greater decrease in the DLCO or a 15% or greater decrease in DLCO plus a 5% or greater decrease in FVC).
‡ Progression events were defined as either (1) a prespecified decline in FVC and DLCO; (2) an adjudicated respiratory hospitalisation event; (3) death from any cause.
§Clinical worsening was defined as (1) significant decrease in 6MWD, (2) cardiopulmonary hospitalisation, (3) lung transplantation or death. Clinical improvement was defined as a significant increase in the 6MWD with a concomitant 30% reduction in N-terminal prohormone of brain natriuretic peptide without any clinical worsening event.
AE, adverse event; bid, two times per day; BP, blood pressure; BPS, breaths per session; CAD, coronary artery disease; CI, cardiac index; CO, cardiac output; CPFE, combined pulmonary fibrosis and emphysema; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity; HF, heart failure; HRCT, high-resolution CT; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ISDN, isosorbide dinitrate; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; 6MWD, 6-minute walking distance; 6MWT, 6-minute walking test; NSIP, non-specific interstitial pneumonia; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PR, pulmonary rehabilitation; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; qd, once a day; RAP, right atrial pressure; RCTs, randomised controlled trials; RHC, right heart catheterisation; RVSP, right ventricular systolic pressure; sPAP, systolic pulmonary artery pressure; SpO_2, oxygen saturation; tid, three times a day; WU, Wood units.

Bosentan

A double-blind RCT by Corte *et al* selected 60 patients with fibrotic ILDs and PH, as confirmed by RHC (mPAP ≥25 mm Hg, PCWP <15 mm Hg). Patients were 2:1 randomised to bosentan 125 mg two times per day or placebo.[25] The prespecified primary outcome, the rate of patients with a 20% fall in PVR index, was not statistically different between groups at 16 weeks (28% for bosentan vs 28.6% for placebo, p=0.97). A trend towards stabilisation in 6MWD was observed in bosentan group, but it did not reach statistical significance (−25.9±56.7 m vs −53.1±66.9 m, p=0.42). No statistically significant results were found for haemodynamic parameters, disease progression (defined as 15% fall in diffusion lung capacity for carbon monoxide (DLCO), death or transplantation) nor forced vital capacity (FVC) decline between groups. Rates of patients experiencing SAEs were similar (45% vs 50%).

Patients with sarcoidosis-associated ILD were recruited in a phase 2 RCT conducted by Baughman *et al*.[26] Pulmonary haemodynamic parameters were assessed by RHC; patients matching the inclusion criteria had mPAP >25 mm Hg and PCWP <15 mm Hg. A total of 35 patients were 2:1 randomised to bosentan 125 mg two times per day or placebo. mPAP variation at 16 weeks was considered as the primary outcome. Bosentan was effective in reducing mPAP at 16 weeks (−4±6.6 mm Hg, p<0.02), compared with placebo. PVR values were consistent with the primary outcome, showing a statistically significant fall in the bosentan group (−1.7±2.75 WU, p=0.02), whereas a non-significant elevation (0.1±1.42 WU; p>0.05) was observed in the placebo arm. Patients treated with bosentan showed a trend towards increase in 6MWD, compared with a slight decrease in the placebo arm. However, differences between groups were not statistically significant.

Ambrisentan

ARTEMIS-IPF was a phase 3 RCT on patients with IPF in which subjects were 2:1 randomised to ambrisentan 10 mg daily versus placebo.[27] The primary outcome was the improvement in disease progression defined as one of the following: (1) a prespecified decline in FVC and DLCO; (2) a respiratory hospitalisation event; (3) death from any cause. However, the trial was stopped early due to the lack of efficacy in the interim analysis.

More SAEs were observed in the overall population (disease progression: 27.4% vs 17.2%; p=0.010; respiratory hospitalisation: 13.4% vs 5.5%; p=0.007) and populations without PH (disease progression: HR 1.64; CI 1.04 to 2.60; p=0.03; respiratory hospitalisation: HR 2.72; CI 1.21 to 6.10; p=0.015). PH, defined as mPAP >25 mm Hg and PCWP <15 mm Hg, was present in 10% of intervention and placebo groups, respectively, and was associated with a similar trend towards increase in disease progression (HR 2.42; CI 0.79 to 7.38; p=0.121) and respiratory hospitalisation rate at 48 weeks (HR 2.21; CI 0.45 to 10.69; p=0.334).

While only 10% of patients met the definition of PH as used in the study, both the placebo and intervention groups were reported as having a mean mPAP of 20 mm Hg on RHC; thus, about half of the population would have met the current definition of PH. A subgroup analysis of these patients is not available.

In 2015, Raghu *et al* published another analysis of ARTEMIS-IPF considering only those patients whose RHC measurements were available both at baseline and follow-up: 12 patients were receiving ambrisentan and 7 placebo.[28] Haemodynamic measurements showed reductions in both mPAP (−5.3±4.27 mm Hg with ambrisentan vs −1.1±9.39 mm Hg with placebo) and PVR (−0.70±1.31 mm Hg/min/L with ambrisentan vs −0.51±1.56 mm Hg/min/L with placebo) in the ambrisentan group, compared with placebo.

ARTEMIS-PH (NCT00879229; table 3) was designed as a phase 3 RCT in patients with IPF with PH, defined as mPAP ≥25 mm Hg, PVR >240 dyn/s/cm^5 and PCWP ≤15 mm Hg. The study was planned to enrol 220 patients, allocated to receive ambrisentan 10 mg once daily or placebo, but was early terminated due to the slow enrolment. Data were available for 21 patients in ambrisentan arm and 9 patients in placebo arm. Patients receiving ambrisentan had a trend toward greater deterioration of 6MWD from baseline to 16 weeks (−29 m; CI −54 to +17, p=0.696). Moreover, a trend toward a greater burden of SAEs was reported in the intervention group compared with placebo (48% vs 20%), neither reaching significance probably due to the small number recruited before the study was terminated.

Treprostinil

INCREASE was a phase 3 RCT enrolling 326 patients with PH-ILD based on RHC haemodynamic parameters (PVR >3 WU, PCWP ≤15 mm Hg, mPAP ≥25 mm Hg).[20] Patients were 1:1 randomised to receive inhaled treprostinil 72 µg four times daily or placebo. The primary outcome, the change in 6MWD from baseline to 16 weeks, was met in the treprostinil group (+31.12 m; 95% CI 16.85 to 45.39; p<0.001). Moreover, a significant reduction in N-terminal pro b-type natriuretic peptide (NT-proBNP) was reached at 16 weeks in the treatment arm group (treatment ratio, 0.58; 95% CI 0.47 to 0.72; p<0.001). Treprostinil also demonstrated protection against disease progression defined as: (1) hospitalisation for cardiopulmonary complications (11.0% vs 14.7%; p=0.41); (2) significant decrease in 6MWD; (3) death; (4) lung transplantation (HR 0.61; 95% CI 0.40 to 0.92; p=0.04); (5) exacerbation of lung disease (26.4% vs 38.7%; p=0.02). AEs and SAEs occurred at a comparable rate between the two groups. A subgroup analysis on the most represented populations with ILD was reported, including idiopathic interstitial pneumonia (IIP) (45% of the overall population), CPFE (25%) and connective tissue disease (CTD)-ILD (22%).

Table 3 Ongoing or interrupted RCTs on vasoactive drugs in PH-ILD (from ClinicalTrials.gov)

Study code	Study type	Population	Exclusion criteria	Drug arm	Comparator arm	Primary outcome	Results (primary outcome)	Safety
Ambrisentan								
NCT00879229* (ARTEMIS-PH)	RCT Phase 3 2:1	IPF with RHC-proven PH (mPAP ≥25 mm Hg; PVR >240 dyn/s/cm^5; PCWP ≤15 mm Hg)	Non-IPF ILD; PH due to disease other than IPF; lung biopsy patterns other than UIP; obstructive lung disease; recent acute lung disease; severe cardiac, hepatic or renal comorbidity; recent vasoactive therapy, steroids or imatinib	21 10 mg qd	9 placebo	6MWD change from baseline to week 16	−29 m (CI −54 to +17, p=0.696)	Overall AE: 72% vs 80% Severe AE: 48% vs 20% Long-term survival: KM% estimate at 48 weeks, 22% vs 23%

*ARTEMIS-PH data were analysed as reported in the dedicated ClinicalTrials.gov page. The study has been terminated due to slow enrolment. However, no manuscript was ever published. Last update is reported to have occurred in 2014.
AE, adverse event; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KM, Kaplan-Meier; mPAP, mean pulmonary artery pressure; 6MWD, 6-minute walking distance; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; qd, once a day; RCTs, randomised controlled trials; RHC, right heart catherisation; UIP, usual interstitial pneumonia.

A trend towards improvement, although non-statically significant, in the 6MWD, was described in all the aforementioned subsets at week 16 with treprostinil, particularly for IIP (mean difference 39.5, CI 18.3 to 60.7) and CTD-ILD (mean difference 43.5 m, CI 9.6 to 77.4 m). PVR was available at baseline in the majority of patients, with most of them having values >4 WU in both the placebo and intervention groups. Treprostinil showed efficacy in improving the 6MWD at week 16 in this subset of patients with more severe PH (mean difference 40.8 m, CI 24.1 to 57.6 m).

A post-hoc analysis of the INCREASE trial attempted to analyse the role of inhaled treprostinil on lung function.[29] In the overall population, inhaled treprostinil showed a statistically significant improvement in FVC %predicted at week 16; the change in absolute FVC did not reach significance. Interestingly, both the subgroup analyses regarding IIP (45% overall population (OP)) and of IPF (27% OP) showed a statistically significant increase in FVC compared with placebo at week 16 (IIP: FVC difference 108.2 mL±46.9, 95% CI: 15.3 to 201.1, p=0.023, FVC% difference 2.9%±1.1, 95% CI: 0.7 to 5.0. p=0.0096; IPF: FVC difference 168.5 mL±64.5, 95% CI: 40.1 to 297.0, p=0.011, FVC% difference 3.5%±1.4, 95% CI: 0.7 to 6.3, p=0.015).[29]

Another post-hoc analysis stratified patients according to the number of breaths per session (BPS).[30] Disease progression and clinical improvement were considered as the primary outcomes. Disease progression was defined by one of the following: (1) significant decrease in 6MWD; (2) cardiopulmonary hospitalisation; (3) lung transplantation; (4) death. Clinical improvement was defined by a significant increase in the 6MWD with a concomitant 30% reduction in NT-proBNP and without any clinical worsening event. Patients receiving at least 9 BPS of treprostinil experienced a statistically significant reduction in disease progression (17.1% in patients receiving treprostinil ≥9 BPS vs 22.8% in patients receiving treprostinil <9 BPS vs 33.7% in patients receiving placebo ≥9 BPS vs 34.3% in patients receiving placebo <9 BPS; p=0.006) and reached more often clinical improvement (15.7% in patients receiving treprostinil ≥9 BPS vs 12.7% in patients receiving treprostinil <9 BPS vs 7% in patients receiving placebo ≥9 BPS vs 1.5% in patients receiving placebo <9 BPS; p=0.003).

Although a benefit was demonstrated with higher doses of treprostinil (clinical improvement: +3% patients in the ≥9 BPS group, respectively, to the <9 BPS group), this requires confirmation in a dedicated study.

DISCUSSION

The treatment of PH-ILD aligns almost completely with the current guidelines for group 3 PH, encompassing strategies such as optimising underlying ILD therapy, addressing respiratory insufficiency, managing comorbidities and considering lung transplantation. Recent approval of inhaled treprostinil by the Food and Drug Association (FDA) has represented a step forward in the management of PH-ILD.

The incorporation of PVR into the haemodynamic classification of PH allows for a more refined stratification of outcomes in PH-ILD. From this perspective, the identification of severe PH poses a significant challenge in assessing the evidence for a therapeutic approach. Current guidelines endorse a personalised approach, advocating for a cautious trial of phosphodiesterase 5 inhibitor (PDE5i).[2] Our literature search did not identify trials specifically designed to include patients with severe PH, with only a few incorporating PVR in their inclusion criteria (eg, NCT00879229). The recent revision of haemodynamic definitions of PH, coupled with the high degree of heterogeneity in patient selection, contributes to the fragmented and limited evidence

currently available. While not fully aligned with the ESC/ERS 2022 guidelines, the INCREASE trial demonstrated the benefits of inhaled treprostinil in a population with a mean PVR of 6.2 WU. A PVR of over 4 WU was reported in 78% of patients enrolled. Finally, it may be worth making to point that to date, the only PAH medicine to show efficacy in ILD-PH is an inhaled therapy. Route of administration may be as important as mechanism of action in this condition. Vasoactive agents employed in the treatment of PAH target three signalling pathways: nitric oxide, prostacyclin and endothelin. Preclinical and clinical models have suggested an antifibrotic effect for prostacyclin analogues and endothelin receptor antagonists (ERAs).[31–34] The potential impact of these agents on both vascular and parenchymal components has fostered interest in their role for PH-ILD treatment. However, the accumulated evidence often falls short of expectations, and the aforementioned data indicate that desired outcomes were rarely achieved, while AEs and mortality were more pronounced in treatment groups.

Several considerations are necessary to better comprehend this discrepancy. By inhibiting the degradation of cyclic guanosine monophosphate (cGMP), PDE5i (specifically sildenafil and tadalafil) induce vasodilation, with a predominant effect on pulmonary circulation compared with systemic circulation.[35] Although tadalafil has not been subject to any RCT, sildenafil was investigated in two patient populations with PH secondary to IPF.[23 24] In both instances, the primary outcome was not achieved, with the first study focusing on the 6MWD, while the second assessing disease progression. Additionally, significant heterogeneity existed among the recruited populations in terms of IPF and PH severity. Notably, one of the two studies did not allow concurrent antifibrotic treatment, which now represents the standard of care in patients with IPF.[23 36] Furthermore, subgroup analyses considering the severity of both IPF and PH were not performed. Tadalafil has not been thoroughly investigated in well-designed studies within the population with PH-ILD, while sildenafil has only produced limited evidence supporting its effectiveness in improving outcomes for this group. As indicated by the authors in the ESC 2022 guidelines, the existing evidence does not provide sufficient grounds to make recommendations either for or against the use of this drug in PH-ILD. Thus, a patient-centred approach in PH expert centres is recommended.[2] Further investigations are necessary to elucidate the role of PDE5 inhibition in treating PH secondary to ILD. Moreover, different diagnoses (eg, IPF, sarcoidosis, etc), disease radiological patterns (eg, UIP, non-specific interstitial pneumonia (NSIP), etc), behaviours (eg, progressive fibrosing ILD) and endotypes should be taken into account for better stratification of patients.

Riociguat stimulates guanylate cyclase activity, leading to elevated intracellular levels of cGMP, with consequent pulmonary vasodilation.[35] In addition to its approval for the treatment of PAH, riociguat has demonstrated efficacy in managing inoperable or persistent group 4 PH following surgery.[15] Preclinical evidence has highlighted a potential antifibrotic effect of riociguat.[37] The drug was examined in a cohort of patients with PH secondary to idiopathic ILDs, mainly IPF and NSIP, who were not receiving antifibrotic treatment. However, the trial was prematurely halted due to excessive mortality and AEs, including worsening ILD and pulmonary events in the riociguat arm.[19] Based on these findings, current guidelines advise against the use of riociguat for the treatment of IIP-PH.[2] Thus, strategic population selection based on endotypes should be considered.[38] As an example, the pathogenesis of ILD associated with systemic sclerosis (SSc) is characterised by the convergence of inflammation, fibrosis and vasculopathy, and riociguat has been hypothesised to stabilise lung function in such patients, compared with placebo.[39 40]

Endothelin, a potent endogenous vasoconstrictor, is the focal point of ERAs, a group of drugs sanctioned for PAH therapy including bosentan, ambrisentan and macitentan.[35] The impact of bosentan was assessed in a limited-scale RCT involving patients with IPF and NSIP, where no notable haemodynamic changes emerged in the short term.[25] In contrast, a favourable outcome was observed in a small cohort of patients afflicted with sarcoidosis-associated PH, revealing a significant reduction in mPAP in the treatment group.[26] PH often complicates sarcoidosis, possibly stemming from overlapping conditions such as myocardial involvement or compression of pulmonary arteries by enlarged thoracic lymph nodes, making it intricate to determine whether sarcoidosis-associated PH is solely justified by the presence of ILD.[41] Given the favourable haemodynamic effects demonstrated with bosentan, further studies should be encouraged. ARTEMIS-IPF and ARTEMIS-PH (NCT00879229) Studies fail to demonstrate any significant positive effects of ambrisentan in patients with PH-IPF.[27] Moreover, it has been shown that ambrisentan carries an elevated burden of SAEs.

Prostanoids encompass prostacyclin analogues, such as iloprost and treprostinil, as well as receptor agonists like selexipag.[35] By increasing intracellular cyclic AMP levels, prostanoids prompt relaxation of arterial smooth muscle fibres leading to a reduction in vascular resistances. Within this drug class, the INCREASE Study exclusively investigated inhaled treprostinil among patients with PH-ILD, demonstrating a statistically significant improvement in the 6MWD at 16 weeks compared with placebo.[20] This effect was notably associated with the total administered dose, particularly with a threshold of 9 BPS, as corroborated by a post-hoc analysis.[30] Additionally, treprostinil administration led to significant improvements in lung function, specifically FVC at 16 weeks.[29]

This effect was specifically highlighted for subpopulations with IIP and IPF, leading to hypothesise a potential role as disease-modifier drug in selected and still unclear ILD endotypes.[29] Systemic effects of vasoactive drugs (ie, haemodynamic disturbances, flushing, headaches) frequently contribute to limited tolerance, particularly

with prostanoids.[42 43] Apart from enabling targeted and localised drug action within pulmonary circulation, the inhalation route of administration of treprostinil offers several advantages, including a reduced likelihood of systemic spillover with subsequently lower rates of AEs.[44] Furthermore, as suggested by FVC improvement in specific populations of patients with ILD, the inhaled route may enhance the pleiotropic actions of treprostinil on lung parenchyma. It remains to be determined whether the outcomes described in the INCREASE Study cohort represent a treprostinil-specific or class-wide effect of all prostanoid molecules.

The inclusion of patients with CTD in the INCREASE trial demonstrated efficacy in this population, yet it left some questions unanswered. Certain CTDs are associated with an increased risk of multifactorial PH, as seen in SSc.[45] It is recognised that the localised variant of SSc often leads to the development of PAH with little or no interstitial lung involvement, while diffuse SSc results in a mixed pattern of modest inflammatory and fibrotic ILD, potentially leading to secondary PH.[46] To prevent the inclusion of patients with PAH, the inclusion criteria for the INCREASE trial specifically stated that in patients with CTD, FVC needed to be less than 70%, thereby admitting patients with a higher probability of ILD-related PH. Vasoactive drugs have demonstrated improved outcomes in SSc-PAH.[47] However, limited information is available about their potential in CTD-ILD-associated PH. A subgroup analysis of patients with SSc has not been performed in any of the trials considered in our systematic review. Therefore, the beneficial role of vasoactive drugs in SSc ILD-PH cannot be assumed. Nevertheless, treprostinil showed a statistically significant benefit in the overall population with CTD in the INCREASE trial, and further trials are needed to understand the potential role of this vasoactive drug in specific subsets of CTD-related ILD-PH.

Since FDA approval, several formulations of treprostinil have been developed, including inhalation and capsule-based dry powder inhaler (DPI) devices.[48] DPI devices, similar to well-known devices for asthma and COPD, could enhance patients' comfort and thus improve compliance. It has been demonstrated that even with lower inhaled volumes and peak inspiratory flows, the administration of fine particles is acceptable.[48 49] Moreover, a new pro-drug formulation, treprostinil palmitate, has recently been tested, resulting in fewer AEs and a more sustained effect.[48 49]

Selexipag, an oral prostacyclin receptor agonist, has demonstrated clinical efficacy in treating PAH.[35 50] While clinical trials for selexipag are lacking in the PH-ILD domain, the drug should be investigated.

Our systematic review highlights several gaps in knowledge. Not all vasodilators have been studied in populations with PH-ILD. The GRADE analysis exposed an absence of high-quality trials, with only three studies reaching a moderate level of quality, and the remainder were low or very low-quality evidence.[21] Additionally, significant heterogeneity was noted among the selected studies. Consistent variations existed among the study populations, encompassing a range of different diseases and severity stages considered. Moreover, despite the adopted definition of PH often aligning with the previous criteria based on RHC (specifically, mPAP ≥25 mm Hg and PCWP <15 mm Hg), echocardiographic assessment was infrequently regarded as a sufficient criterion for inclusion. Additionally, in some studies, inclusion criteria were established based on definite PAP values.

No study incorporated the new PH threshold (mPAP ≥20 mm Hg) as outlined by the ESC and ERS. Heterogeneity was also evident in terms of permissible concurrent administration of immunosuppressive and antifibrotic medications, which significantly limits implementation in clinical practice. Furthermore, dissimilar and challenging-to-compare outcomes were reported across studies. These outcomes were primarily centred around changes in functional or haemodynamic parameters, with limited applicability to routine clinical practice. Moreover, study outcomes were predominantly evaluated over a short duration (eg, 16–26 weeks), with no trial investigating the prolonged effects of the drug. Notably, patient-centred outcomes such as mortality, dyspnoea, hospitalisation or respiratory failure were never designated as primary outcomes. Given these limitations, a meta-analysis was not conducted.

Our systematic review has also identified several unmet needs. First, there is a pressing requirement for high-quality RCTs concentrating on promising molecular targets. Enrolment of patients ought to be in line with the latest definition and stratification of PH. Facilitating the recruitment of patients affected by PH-ILD necessitates the implementation of international study groups. Second, studies should emphasise on clinically relevant and long-term outcomes. Existing RCTs have predominantly focused on haemodynamic and functional parameters (eg, RHC measurements, 6MWD), which inadequately capture clinically actionable disease characteristics such as mortality, rates of hospitalisation due to cardiac and respiratory causes, or the need for oxygen therapy. Outcomes should be evaluated over medium-term and long-term periods to explore clinically meaningful issues beyond statistical significance. Third, there is a compelling need to differentiate among ILD diagnosis and ILD phenotypes and endotypes.[38] This underscores the need of adopting a 'treatable trait' approach.[38 40] It is plausible to hypothesise the existence of distinct forms of PH-ILD, each characterised by different clinical and functional/haemodynamic features, varying risk of progression and response to therapies. A precision medicine approach is crucial for both comprehensively characterising PH-ILD and severity of PH from this perspective. Finally, the pleiotropic effects of selected vasoactive drugs warrant consideration. A mounting body of evidence indicates that the impact of these drugs extends beyond vascular tone regulation, encompassing diverse and less clearly defined immunological and fibrotic processes.

Identifying the distinct molecular targets of these molecules would ensure robust preclinical evidence to support their application in patients with different forms of PH-ILD.

CONCLUSION

Our systematic review explored the existing evidence concerning the role of vasoactive drugs in the management of PH-ILD. Data from the RCTs analysed indicate that desired outcomes were rarely achieved, while AEs were more pronounced in patients treated with vasoactive drugs. However, several limitations including population heterogeneity, short-term follow-up and the selection of outcomes with uncertain clinical significance were identified. The indiscriminate use of vasoactive drugs has shown significant harm in some populations with ILD (eg, ambrisentan in IPF, riociguat in IIP-PH), while it could have beneficial effects in others (eg, bosentan in sarcoidosis-associated PH). Some vasoactive drugs portend potential disease-modifying characteristics and could act directly on ILD course (eg, treprostinil in IIP and IPF).

This underscores the necessity of establishing a precision medicine-oriented strategy directed at uncovering and addressing the intricate cellular and molecular mechanisms that underlie the pathophysiology of PH-ILD. Future RCTs must consider these specific drug–disease interactions.

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SEARCH STRATEGY

The full content of each string is reported below. PubMed database was searched, by inserting one string at the time on the research bar. No limitations or filters were set during our PubMed search. No backward time limitation was set, we included studies published up to September 10th, 2023.

PubMed Strings:

- *Riociguat*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("riociguat"[Supplementary Concept] OR "riociguat"[All Fields]).
- *Sildenafil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "sildenafil"[All Fields] OR "sildenafil s"[All Fields])
- *Tadalafil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All

Fields] AND "hypertension"[All Fields])) AND ("tadalafil"[MeSH Terms] OR "tadalafil"[All Fields])

- *Bosentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("bosentan"[MeSH Terms] OR "bosentan"[All Fields])
- *Macitentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("macitentan"[Supplementary Concept] OR "macitentan"[All Fields])
- *Ambrisentan*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("ambrisentan"[Supplementary Concept] OR "ambrisentan"[All Fields])
- *Treprostinil*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields]))

AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("treprostinil"[Supplementary Concept] OR "treprostinil"[All Fields])

- *Iloprost*: ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "interstitial"[All Fields]) OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields] AND "lung"[All Fields] AND "diseases"[All Fields])) AND ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("iloprost"[MeSH Terms] OR "iloprost"[All Fields])
- *Selexipag*: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("selexipag"[Supplementary Concept] OR "selexipag"[All Fields])
- *Isosorbide*: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("isosorbide"[All Fields] OR "isosorbide"[MeSH Terms] OR "isosorbide"[All Fields])

ClinicalTrials.gov was also employed to search for clinical trials. The words of [*vasoactive drug*] *(*in eg., riociguat) and "*pulmonary hypertension*" were inserted in the research string panel for each vasoactive drug. The resulting clinical trials were then considered for screening if their status was addressed as "completed with results". No backward time limitation was set, we included studies published up to September 10th, 2023.

ClinicalTrial.gov string panel:

- *Riociguat* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Sildenafil* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Tadalafil* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Bosentan* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Macitentan* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Ambrisentan* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Treprostinil* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Iloprost* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Selexipag* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")
- *Isosorbide* ("intervention/treatment") AND *pulmonary hypertension* ("condition/disease")