Vascular involvement in idiopathic pulmonary fibrosis

Michele Mondoni [1], Rocco Rinaldo [2], Christopher J. Ryerson[3], Cristina Albrici [1], Andrea Baccelli[4], Claudio Tirelli[1], Francesca Marchetti[1], Jacopo Cefalo[1], Giulia Nalesso [1], Giulia Ferranti [1], Fausta Alfano[1], Giovanni Sotgiu [5], Marco Guazzi[6] and Stefano Centanni[1]

[1]Department of Health Sciences, Respiratory Unit, ASST Santi Paolo e Carlo, Università degli Studi di Milano, Milan, Italy. [2]Department of Medical Sciences, Respiratory Diseases Unit, AOU Città della Salute e della Scienza di Torino, Molinette Hospital, University of Turin, Turin, Italy. [3]Department of Medicine and Centre for Heart Lung Innovation, University of British Columbia, Vancouver, Canada. [4]Department of Respiratory Medicine, Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK. [5]Dept of Medical, Clinical Epidemiology and Medical Statistics Unit, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy. [6]Department of Cardiology, University of Milano School of Medicine, San Paolo Hospital, ASST Santi Paolo e Carlo, Milan, Italy.

Corresponding author: Michele Mondoni (michele.mondoni@asst-santipaolocarlo.it)

Shareable abstract (@ERSpublications)
Pulmonary vasculature plays a key role in the natural history of IPF https://bit.ly/4ffluUv

Cite this article as: Mondoni M, Rinaldo R, Ryerson CJ, *et al*. Vascular involvement in idiopathic pulmonary fibrosis. *ERJ Open Res* 2024; 10: 00550-2024 [DOI: 10.1183/23120541.00550-2024].

Received: 29 May 2024
Accepted: 17 July 2024

Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing and progressive interstitial lung disease of unknown aetiology with a pathogenesis still partly unknown. Several microvascular and macrovascular abnormalities have been demonstrated in the pathogenesis of IPF and related pulmonary hypertension (PH), a complication of the disease.

Methods We carried out a non-systematic, narrative literature review aimed at describing the role of the vasculature in the natural history of IPF.

Results The main molecular pathogenetic mechanisms involving vasculature (*i.e.* endothelial-to-mesenchymal transition, vascular remodelling, endothelial permeability, occult alveolar haemorrhage, vasoconstriction and hypoxia) and the genetic basis of vascular remodelling are described. The prevalence and clinical relevance of associated PH are highlighted with focus on the vasculature as a prognostic marker. The vascular effects of current antifibrotic therapies, the role of pulmonary vasodilators in the treatment of disease, and new pharmacological options with vascular-targeted activity are described.

Conclusions The vasculature plays a key role in the natural history of IPF from the early phases of disease until development of PH in a subgroup of patients, a complication related to a worse prognosis. Pulmonary vascular volume has emerged as a novel computed tomography finding and a predictor of mortality, independent of PH. New pharmacological options with concomitant vascular-directed activity might be promising in the treatment of IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial lung disease (ILD) of unknown aetiology [1, 2]. IPF primarily affects older people, and its incidence increases with age [1–4]. It is characterised by worsening respiratory symptoms and physiological impairment, but its progression is unpredictable and heterogeneous [2, 3]. Antifibrotic therapy may slow the progression of disease by reducing the rate of lung function decline and risk of exacerbations [1, 2].

The pathogenesis of IPF remains partly unknown. In recent years, several studies have demonstrated that, in patients with genetic susceptibility, repeated micro-injuries of the alveolar epithelium are a key driver of a maladaptive repair process [5]. An altered repair process is characterised by alveolar epithelial cells apoptosis and proliferation, epithelial-to-mesenchymal transition, fibroblast and myofibroblasts proliferation and accumulation of extracellular matrix (ECM) thus inducing distortion of the lung architecture [5].

IPF also affects pulmonary vasculature [6, 7]. Several microvascular and macrovascular disarrangements are key to IPF pathogenesis and pulmonary hypertension (PH) development, a complication of the disease and a strong marker of poor prognosis [6, 8].

Lessons for clinicians
The vasculature plays a key role in the natural history of idiopathic pulmonary fibrosis (IPF). The exact knowledge of vascular involvement in patients with IPF since the earliest phase of disease might be key to define a vascular phenotype, predict prognosis and the most appropriate pharmacological treatment for these patients.

The aim of this review is to summarise the role of the pulmonary vasculature in the natural history of IPF and its impact on disease outcomes. The main pathogenetic mechanisms involving pulmonary vessels, pathophysiological aspects and clinical outcomes related to pulmonary vasculopathy are discussed along with current and future treatment options.

Methods

We carried out a non-systematic, narrative literature review. The search engines PubMed and Embase were used to retrieve the most relevant articles in English without any time restrictions. The following keywords were selected: idiopathic pulmonary fibrosis; pulmonary hypertension; vasculature; genetics; endothelium; pathogenesis; PH-IPF; remodelling; therapy; and vasodilator (supplementary table 1).

Prevalence and clinical relevance of PH-IPF

In patients with IPF, PH represents the advanced involvement of pulmonary vasculature in the clinical course of the disease. The prevalence of PH in these patients is difficult to estimate due to differences in the definition (either through right heart catheterisation (RHC), using mean pulmonary artery pressure (mPAP) or echocardiogram with the estimation of systolic pulmonary artery pressure (sPAP)) and to the different grade of IPF severity reported in the literature [9]. Particularly, RHC data are described in highly selected populations of patients referred for lung transplantation [10]. Due to these limitations, PH has a wide reported prevalence, ranging from 3% to 86% in IPF patients, with most estimates being between 30% and 50% [11].

The cross-sectional design for most of these studies may limit the ability to prove the relationship between the severity of the disease and progression of the involvement of the pulmonary vascular bed. NATHAN *et al*. [12] showed, in a cohort of patients evaluated for lung transplantation, a large increase in prevalence of PH from 39% to 86% from the time of addition to the waiting list to the time of transplant (average interval of 8 months). Nevertheless, IPF patients with mild-to-moderate restriction did not show significant changes in the prevalence of PH during the 12-month clinical trial with ambrisentan [13]. The recent change in the haemodynamic cut-off for defining PH in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines (to a mPAP >20 mmHg) might also affect epidemiological estimates [14].

Echocardiography is a screening tool that can identify PH and its detrimental effects on right ventricular coupling and geometry. The peak tricuspid regurgitation velocity can help assess the echocardiographic probability of PH, beyond right ventricular abnormalities including dilation or enlargement and a low tricuspid annular plane systolic excursion (TAPSE). In a recent multidisciplinary Delphi consensus assessment [15] on the screening strategies for PH in patients with ILD, echocardiography, the heart overload dependent brain natriuretic peptide (BNP) or NT-pro-brain natriuretic peptide (NT-proBNP) were suggested as the preferred screening tools [15].

RHC is the gold standard for the diagnosis of PH, despite being more invasive. It provides reliable data on the pulmonary vascular involvement. Beyond an accurate measurement of the mPAP, RHC provides a measure of the pulmonary vascular resistance (PVR), which has a high prognostic value, reflecting the extent of pulmonary vascular remodelling. According to the most recent guidelines, PH associated with lung disease (group 3) is graded as severe based on a cut-off value of PVR >5 Wood Units [14]. RHC, along with echocardiographic signs of a left ventricular disease, is useful to assess any left-sided cause or contributory mechanism to PH in patients with IPF, defined by pulmonary artery wedge pressure (PAWP) $\geqslant$15 mmHg. Left-sided heart diseases are frequent comorbidities and should always be evaluated [11, 13, 16].

PH disproportionately affects the diffusing capacity of the lung for carbon monoxide (D_{LCO}) more than other lung function measurements. Compared with a proportional fall of both D_{LCO} and forced vital capacity (FVC) in IPF, the FVC%/D_{LCO}% ratio has been proposed as a predictor of PH in ILD [17]. In the Delphi consensus [15], a D_{LCO} (% predicted) <40%, a rapid decline in D_{LCO} (>15%) and an FVC/D_{LCO} ratio >1.6 reached consensus as pulmonary function test-related triggers to prompt PH screening.

An impaired exercise capacity is a typical feature of IPF. The 6-min walk test (6MWT) is unable to distinguish the main underlying pathophysiological mechanism, such as heart failure or pulmonary vasculopathy or parenchymal fibrotic disease/restrictive physiology [18]. Nonetheless, cardiopulmonary exercise testing (CPET) allows a deeper evaluation of the causes for exercise intolerance. The hallmark of a reduced exercise capacity is the evidence of a low peak oxygen uptake (peak V_{O_2}) during incremental CPET. Gas exchange abnormalities (increased alveolar-arterial gradient at peak) and an altered breathing pattern (shallow breathing) due to fibrotic lung restriction typically lead to an elevated minute ventilation to carbon dioxide output (V'_E/V'_{CO_2}) ratio slope [19]. An increased V'_E/V'_{CO_2} slope is seen in pulmonary arterial hypertension (PAH) as well, mainly due to the ventilation–perfusion mismatch and as a result of the increased peripheral and central chemosensitivity and increased ergoreceptor drive related to increased autonomic activation [20]. Nevertheless, limited data in the literature suggest that IPF patients who develop PH may present more marked signs of ventilatory inefficiency (a higher V'_E/V'_{CO_2} slope and lower values of end-tidal pressures for CO_2) at CPET, compared with IPF without PH, suggesting that CPET might be useful in the detection of pulmonary vasculopathy in the setting of IPF, although this needs further assessment [21–23]. Figure 1 summarises the diagnostic work-up for PH in patients with IPF.

In a recent study, NATHAN *et al.* [24] derived and validated a clinical prediction model to identify patients with IPF who were at high risk of PH, and thus possible candidates for invasive testing. Four noninvasive variables were included in the model (FORD index): FVC%/D_{LCO}% ratio, race, oxygen saturation nadir and distance walked during the 6MWT. Despite lacking echocardiographic parameters, it might prove a valuable initial screening tool due to its simplicity.

Role of vasculature in the pathogenesis of IPF

Several molecular disarrangements involving the lung vasculature occur in the early phases of the pathogenesis of IPF (figure 2). In addition, overt pulmonary vascular involvement becomes evident in the form of PH in a subgroup of patients, especially in the later phase of the disease.

Endothelial-to-mesenchymal transition

Endothelial-to-mesenchymal transition (EndMT) is a complex biological process characterised by endothelial cells (ECs) losing endothelial features and acquiring a mesenchymal cell-like phenotype. A key involvement of EndMT in the vascular remodelling process and its association with IPF has been described

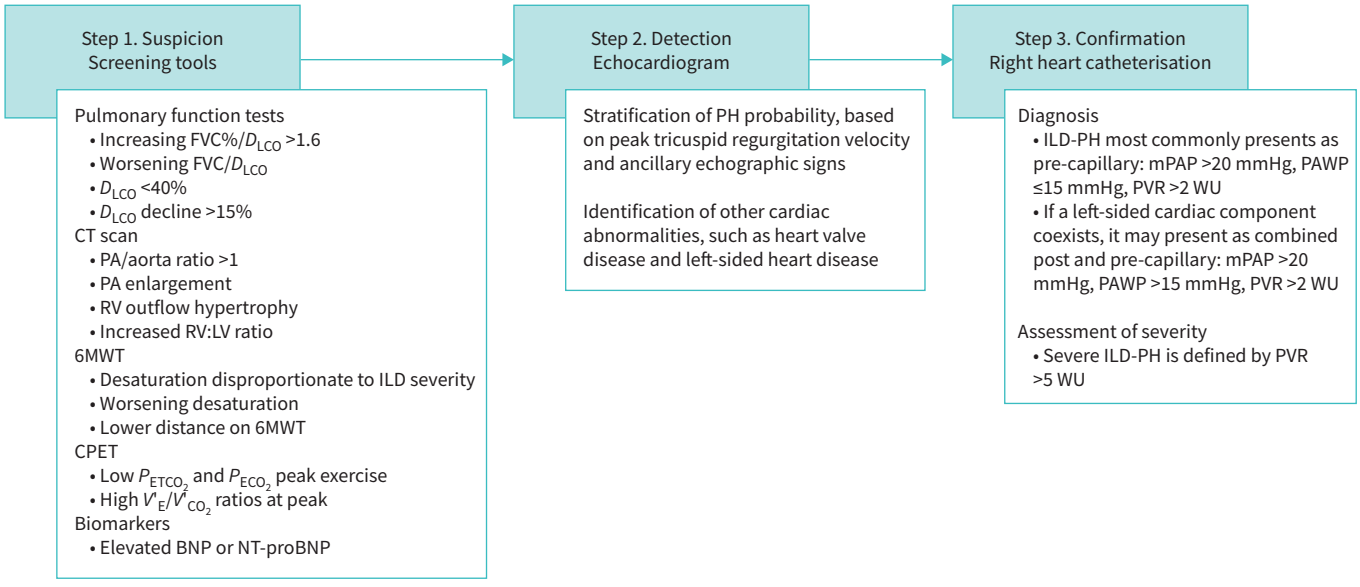

FIGURE 1 Diagnostic work-up for pulmonary hypertension (PH) in patients with interstitial lung disease (ILD)/idiopathic pulmonary fibrosis (IPF). FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; CT: computed tomography; PA: pulmonary artery; RV: right ventricle; LV: left ventricle; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; P_{ETCO_2}: end-tidal pressure of carbon dioxide; P_{ECO_2}: mixed-expired carbon dioxide pressure; V'_E/V'_{CO_2}: minute ventilation to carbon dioxide output ratio; BNP: brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; WU: wood unit.

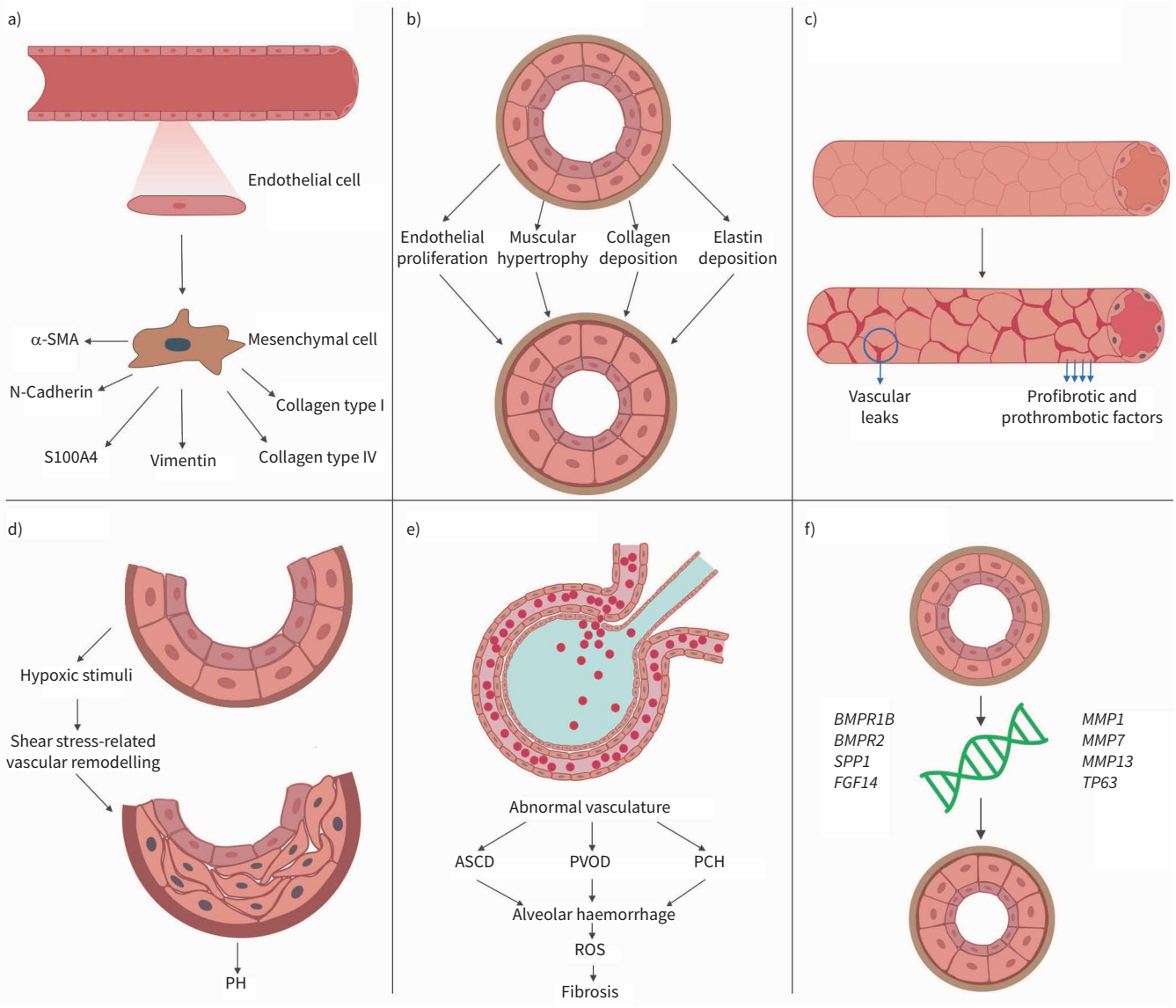

FIGURE 2 Main molecular mechanisms involving vasculature in the pathogenesis of idiopathic pulmonary fibrosis (IPF). a) Endothelial-to-mesenchymal transition. b) Vascular remodelling. c) Endothelial permeability and occult alveolar haemorrhage. d) Hypoxia. e) Alveolar haemorrhage. f) Genetic basis. PH: pulmonary hypertension; ASCD: alveolar septal capillary density; PVOD: pulmonary venous occlusive disease; PCH: pulmonary capillary haemangiomatosis; ROS: reactive oxygen species.

in two recent studies [25, 26]. They showed an increased expression of mesenchymal biomarkers N-cadherin, S100A4 and vimentin in the entire arterial layers, an increase in myofibroblast marker α-SMA and ECM proteins collagen type I and IV in intimal layers associated with a downregulation of junctional endothelial VE-cadherins in the intimal layers of IPF patients compared with controls. These mesenchymal markers showed a negative impact on D_{LCO}. These findings suggest EndMT as an active process in pulmonary vessels of IPF patients, strongly related to arterial remodelling and driving physiological changes triggering PH [25, 26]. Transforming growth factor-β (TGF-β), interleukin (IL)-11 and MMP19 are the main cytokines driving the EndMT process [27–30].

Vascular remodelling

A possible role of vascular remodelling in the pathogenesis of IPF was first postulated in the 1960s, when the presence of microvascular anastomoses between the pulmonary and systemic circulation and areas of neoangiogenesis within lungs affected by fibrosis were found [31].

Subsequent studies [6, 32–34] described the concomitant presence of areas of increased capillary density and vascular depletion in nonfibrotic and fibrotic areas, respectively. Neovascularisation leads to increased capillary density in nonfibrotic lung tissues [35], while new vessels in fibrotic areas lack an elastin layer [33]. The presence of elevated angiogenic chemokines (*e.g.* CXCL5 and CXCL8) was observed in IPF lungs [36].

The abnormal new vasculature, in combination with a reduced expression of angiogenic factors, such as vascular endothelial growth factor (VEGF), induces an imbalance between angiogenesis and angiostasis that can ultimately lead to an increased PVR [37]. Together with oxidative stress, it leads to endothelial cell apoptosis and dysfunction of endothelial progenitor cells involved in endothelial damage [34].

Recent studies that compared histological samples of lung tissues from IPF patients and healthy controls confirmed that, in IPF patients, large and medium size arteries show structural changes of endothelial proliferation, muscular hypertrophy of the intima and medial layer, proliferative intima, excessive collagen and elastin deposition in the adventitia. This leads to an increased vascular wall thickening and to the development of plexiform lesions, the histological hallmark of PAH [12, 25, 34, 38, 39]. The early vascular remodelling may induce a reduction in pulmonary capillary blood volume and thus of D_{LCO}. On this basis, some authors postulated a possible role of vascular remodelling in the development of IPF and subsequent PH [25].

Endothelial permeability

Endothelial permeability is a key finding and may predict mortality in IPF. Injured epithelial and ECs, in combination with activated immune cells, release mediators to recruit and activate fibroblasts. The increased permeability may increase extravasation of profibrotic and prothrombotic factors from blood into the alveolar space thus sustaining fibrogenesis [7, 40, 41].

Within fibrotic areas, endothelial permeability may promote several profibrotic responses, including intra-alveolar coagulation, fibrin deposition and provisional matrix establishment. RhoA/Rho kinase, S1P–S1PR1 axis, VEGF, angiopoietin 1/2 ND IL-1 and tumour necrosis factor are the main signalling pathways regulating endothelial permeability. Altered levels of these molecules were described in stable and exacerbated IPF. In addition, lungs affected by IPF show a defective re-endothelialisation due to the decreased number of endothelial progenitor cells, which results in endothelial dysfunction. These changes lead to the development of PH [42].

Occult alveolar haemorrhage

Histological studies have reported vascular abnormalities such as increased alveolar septal capillary density (ASCD), aspects of pulmonary venous occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) [32, 38, 43, 44]. They may also induce occult alveolar haemorrhage and iron accumulation, a marker of the risk of an oxidative stress reaction. This process, along with iron-dependent increased production of reactive oxygen species by activated alveolar macrophages, may represent a recurring epithelial injury, leading to fibrogenesis [45]. Moreover, Puxeddu *et al.* [46] confirmed an increased alveolar iron burden and haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of IPF patients. These alterations correlate with echocardiographic estimation of pulmonary haemodynamics, disease progression and prognosis.

Vasoconstriction and hypoxia

Pulmonary arterial vasoconstriction is involved in IPF pulmonary vasculopathy in different disease stages. Milara *et al.* [47, 48] demonstrated that the expression of Janus kinase 2, a non-receptor tyrosine kinase and STAT3, a transcription activator, were upregulated in the pulmonary arteries of patients with IPF. This upregulation induces epithelial-to-mesenchymal and fibroblast-to-myofibroblast transitions and leads to the vasoconstriction of small pulmonary arterial vessels through the modulation of large conductance calcium-activated potassium channels. This may reflect a primary role of pulmonary vasculature *per se* in the vasoconstriction of pulmonary arterial vessels in patients with IPF [47–49]. Nevertheless, hypoxic pulmonary vasoconstriction is considered a critical mechanism inducing secondary PH in lung diseases in the long term.

When fibrosis and gas exchange impairment occur, hypoxic pulmonary vasoconstriction acts as a coping mechanism, attempting to restore ventilation–perfusion matching to maintain an adequate oxygen tension with limited haemodynamic effects [49]. A larger part of the vasculature is affected in patients with severe alveolar wall destruction and interstitial fibrosis with sustained hypoxia [50]. Thus, prolonged vasoconstriction induces shear stress-related vascular remodelling [51], characterised by medial and adventitial thickening

due to hypertrophy and proliferation of vascular smooth muscle cells, fibroblasts and myofibroblasts and increased ECM production. This collectively results in an increase in pulmonary arterial pressure [52]. Sustained hypoxia activates rho kinase, which reinforces vasoconstriction and hypoxia-inducible factor 1α, thus, resulting in increased pulmonary resistance and the development of PH [53–55].

Genes involvement in vascular remodelling associated with IPF and PH-IPF

IPF is characterised by fibrogenesis, epithelial-to-mesenchymal transition and vascular remodelling. Possible contributing gene expression profiles have been proposed [5, 56, 57] (figure 1). Several genes are upregulated in IPF, including phosphoprotein 1 (*SPP1*), bone morphogenic protein receptor-1b (*BMPR1B*), fibroblast growth factor-14 (*FGF14*), matrix metallopeptidases 1, 7 and 13 (*MMP1*, *MMP7* and *MMP13*) and tumour protein P63 (*TP63*), which are involved in fibroblast migration, ECM remodelling and pulmonary artery smooth muscle cell proliferation and migration [56].

SPP1 encodes for osteopontin, which induces overexpression of MMP1 and MMP13 and drives vascular remodelling through the disruption of vessels basal membrane, ECM deposition and adventitial thickening around pulmonary vessels [58, 59], thus further aggravating IPF.

Gene encoding for bone morphogenetic protein receptor type 2 (*BMPR2*) [60] can suppress TGF-β signalling, contributing to the inhibition of vascular smooth muscle cell proliferation. Mutations inducing loss of function of *BMPR2* are relevant mechanisms in the development of lung fibrosis and vascular remodelling and are the main cause of hereditary PAH [61–64]. Indeed, a perturbed balance of *BMPR2* and TGF-β signalling might contribute to enhanced phosphorylation of SMAD 2/3 (small mother against decapentaplegic proteins 2/3), which are activated by TGF-β [65] and SMAD1/5/8 reduction of activity. These processes are linked to the pathogenesis of both lung fibrosis and vascular remodelling [66, 67].

IL-6 levels can be influenced by mutations in *BMPR2*. This cytokine plays a role both in the development of IPF and PH-IPF [34, 68]. Elevated levels of IL-6 are present in patients with PH-IPF [69]. The authors suggested a potential pathogenic role for IL-6 in the genesis of vascular injury, as elevated levels of IL-6 were associated with increased mean pulmonary artery pressure.

Vascular involvement as a prognostic marker of IPF outcomes

High pulmonary artery pressure is associated with mortality in IPF, with a reported median survival time from IPF diagnosis among patients with PH of 2–4 years [11]. The COMPERA registry on 449 newly diagnosed patients with PH-ILD (40% with a reported diagnosis of usual interstitial pneumonia computed tomography (CT) pattern) identified a cut-off of 8 WU in PVR as the best discriminative parameter for mortality at 5 years [70]. Nathan *et al.* [71] demonstrated that an increase in PVR in IPF patients, even without the presence of an elevation in pulmonary artery pressures, is related to a worse survival compared with normal PVR. However, echocardiographic indirect evidence of a right ventricular maladaptation to the increasing pressure workload represented by dysfunctional pulmonary circulation (right ventricular–pulmonary circulation uncoupling) [72] is related to a detrimental effect on survival [73, 74]. Conclusive data are needed on whether these features are part of the continuum of the natural history of IPF or if they represent different phenotypical profiles of the disease [71, 74].

In recent years, new tools have been developed to classify and quantify parenchymal features on CT datasets (*e.g.* CALIPER). Beyond typical ILD features (*e.g.* honeycombing and reticulations), novel CT patterns such as pulmonary vessel volume (PVV) can be recognised by quantitative tools but cannot be reliably quantified visually. PVV quantifies the volumes of pulmonary arteries and veins, excluding vessels at the lung hilum, as a percentage of lung volume [75, 76]. Increase in PVV is an independent predictor of mortality and is correlated with lung function variables (*i.e.* total lung capacity and D_{LCO}) and composite physiological index, thus standing as a prognostic marker in IPF patients, independent of PH [75–77].

The reasons for this PVV signal are unclear. The main hypothesis involves the blood-flow diversion from more fibrotic areas to adjacent spared lung with an increase in vascular capacitance and vessel volume, the augmented negative intra-thoracic pressure during inspiration due to the lung stiffness with subsequent dilation effect on blood vessels and the development of pleuro-parenchymal and bronchial-pulmonary arterial anastomosis, ultimately leading to the increased PVV [76]. PVV signal might be related to vascular abnormalities (*i.e.* aspects of PVOD and PCH), which have been previously reported by histology studies [38, 44] in less-fibrotic areas and which could be the first pathological lesions in IPF preceding and/or leading to fibrogenesis [43].

Weatherley *et al*. [78] proposed a semiquantitative image measure of pulmonary perfusion based on the first pass of gadolinium-based contrast agent using dynamic contrast-enhanced magnetic resonance imaging (MRI) in a cohort of patients with IPF. These authors demonstrated an increased pulmonary transit time of contrast through the lung in regions of fibrosis, proportional to gas exchange worsening, related with physiological gas exchange variables (*e.g.* D_{LCO}) and with a progression over 6 months. A decreased first moment transit time in IPF patients with a functional impairment (assessed with FVC and/or D_{LCO}) was found [79]. If confirmed in larger studies, these findings might provide a new tool to assess early perfusion changes in the absence of detectable PH and early detection of disease progression [78–80].

Vascular effects of antifibrotic therapies and new pharmacological options with vascular-targeted activity

Pharmacological treatment of IPF currently relies on antifibrotic drugs (pirfenidone and nintedanib) that can slow the rate FVC decline [81–83]. However, these treatments do not stop progression and come with substantial adverse effects.

Current antifibrotic therapies and new treatment options under investigation have vascular-targeted pharmacological effects (table 1). Whether they add to antifibrotic activity in the treatment of IPF is largely unknown; however, endothelial targets may represent additional options to conventional profibrotic ones (*e.g.* collagen deposition). Pharmacological options with pleiotropic effect with concomitant vascular-directed activity might be promising in the treatment of the disease.

Pirfenidone is an antifibrotic and anti-inflammatory drug that decreases inflammation [84] and oxidative stress [85], regulates apoptosis [86] and has a biphasic effect on angiogenesis [87]. In rat models of PH, pirfenidone improves haemodynamics and vascular remodelling of lung arterioles by the inhibition of IL-1β and IL-18 cleavage in lung tissue. IL-1β and IL-18 are products of the inflammasome NLRP3 (NLR family pyrin domain containing 3) activation, a component of the innate immune system strongly linked to vascular cells senescence and remodelling [88–90]. Further studies are needed to confirm these findings in humans with IPF.

Nintedanib is a multitarget tyrosine kinase inhibitor. It competitively blocks the kinase activity of several receptors, including VEGFR 1–3; PDGFR-α and -β; and FGFR 1–3 [91], thus inhibiting proliferation, migration and transformation of lung fibroblasts [92, 93]. Several anti-angiogenetic activities of nintedanib have been demonstrated. Nintedanib inhibits the proliferation of pericytes and vascular smooth muscle cells (endothelial and perivascular cells) in tumour tissues [92, 93]. In murine models of pulmonary fibrosis, nintedanib inhibits EndMT [93], reduces vascular proliferation and normalises the distorted microvascular architecture by increasing intervascular distances and reducing vessels diameters [94]. In a recent bioinformatic study, Landi *et al*. [95] highlighted different molecular pathways targeted by nintedanib, showing a positive effect of the drug on intercellular adhesions, regulating vascular permeability and an indirect effect on microRNA activity (*e.g.* miR-34a-5p), regulating endothelial function. In murine models of PH, nintedanib improved right ventricular contractility, decreased right ventricular dilatation and reduced right ventricular hypertrophy and collagen content. However, it did not inhibit the proliferation of pulmonary microvascular ECs, thus, not reversing pulmonary vascular remodelling [96]. Future studies are needed to assess whether these anti-angiogenic effects may add to the antifibrotic activity in patients with IPF.

Pulmonary vasodilators in the treatment of IPF and PH-IPF

Approved specific pulmonary vasodilators for PAH target three pathways: prostacyclin, nitric oxide and angiotensin pathway [14]. Many studies tried to demonstrate the efficacy of these drugs in ILD/IPF, mostly failing to meet a variety of primary and secondary end-points [97]. The spectrum of pulmonary vascular involvement was present in variable shares according to the studies. Some include ILD/IPF populations in which a pulmonary vascular phenotype was hypothesised by the presence of specific clinical features (*e.g.* markedly reduced D_{LCO} or high supplemental oxygen requirements) [98–100]. However, most clinical trials assessed PH directly through RHC or indirectly by echocardiographic findings. In some cases, trials were interrupted due to a high number of adverse events, including death, in the intervention arm [101, 102]. Overall, an inaccurate population selection, both in terms of phenotype (*e.g.* presence of emphysema) or the choice of specific subgroups with consequential difficulties in enrolment (*e.g.* a specific group of IPF-PH patients with RHC-confirmed diagnosis), different criteria to define PH (such as the absence of mandated RHC) and possibly the wrong choice of end-points for the trial time duration can explain their failure [97–99, 101–108]. The best end-point for clinical trials on pulmonary vascular diseases is a matter of debate [97, 109, 110] (table 2). Studies on pulmonary vasodilators in the treatment of IPF and PH-IPF,

TABLE 1 New drugs under investigation in the treatment of idiopathic pulmonary fibrosis (IPF) with vascular-targeted pharmacological effects

Drug	Trial name/Clinical Trials.gov identifier	Phase	Status	Estimated completion date	Route of administration	Main mechanism of action	Main pharmacological activity	Vascular-targeted pharmacological activity
Anlotinib [92, 115, 116]	NCT05828953	2	Recruiting	July 2024	Oral	Multitargeted tyrosine kinase inhibitor (VEGFR; PDGFR; EGFR; FGFR)	Inhibition of proliferation of pulmonary fibroblasts and apoptosis of fibroblasts promotion	Angiogenesis, proliferation and survival of endothelial and perivascular cells inhibition
BBT-877 [117–121]	NCT05483907	2	Recruiting	December 2024	Oral	Autotaxin inhibitor (LPA production inhibition)	Inhibition of fibroblast recruitment and fibroblast resistance to apoptosis	Vascular leak reduction. Endothelial barrier function promotion. Vascular permeability reduction
BDL-0409 (Cudetaxestat) [117–121]	RESPIRARE/ NCT05373914	2	Active, not yet recruiting	March 2024	Oral	Autotaxin inhibitor (LPA production inhibition)	Inhibition of fibroblast recruitment and fibroblast resistance to apoptosis	Vascular leak reduction. Endothelial barrier function promotion. Vascular permeability reduction
BMS-986278 [117–121]	ALOFT/NCT06003426	3	Recruiting	October 2026	Oral	LPA receptor 1 antagonist	Inhibition of fibroblast recruitment and fibroblast resistance to apoptosis	Vascular leak reduction. Endothelial barrier function promotion. Vascular permeability reduction
C21 [122–124]	NCT04533022	2	Active, not yet recruiting	March 2024	Oral	Angiotensin II receptor type-2 agonist	Alveolar repair and maintenance of alveolar integrity	Vasodilatation
CSL312 [125, 126]	NCT05130970	2	Recruiting	January 2024	Intravenous	Humanised anti-FXIIa monoclonal antibody	Inhibition of IL-6 production and fibroblast migration	Intrinsic coagulation pathway balance Vascular permeability reduction
HZN-825 [117–121]	NCT05032066	2	Active, not yet recruiting	July 2025	Oral	LPA receptor 1 antagonist	Inhibition of fibroblast recruitment and fibroblast resistance to apoptosis	Vascular leak reduction. Endothelial barrier function promotion. Vascular permeability reduction
Ifetroban [127, 128]	NCT05571059	2	Active, not yet recruiting	December 2026	Oral	TBXA2R antagonist (inhibition of TXA2 PGD2 signalling pathways)	Inhibition of profibrotic signalling (antifibrotic effect)	Inhibition of platelets aggregation and vascular smooth muscle cells constriction
NIP292 [129]	NCT04720443	1	Completed		Oral		Anti-inflammatory, antifibrotic activity	Expansion of blood vessels, and repair of vascular endothelial damage
Treprostinil [113, 114]	TETON/ NCT04708782	3	Recruiting	June 2025	Inhaled	Analogue of prostacyclin	Vasodilation of pulmonary and systemic arteries, platelet aggregation inhibition; antifibrotic effects through the activation of EP_2, DP_1 and PPAR	Vasodilation of pulmonary and systemic arteries and inhibition of platelet aggregation
TTI-101 [130]	REVERT-IPF/ NCT05671835	2	Recruiting	March 2025	Oral	Protein STAT3 inhibition	Reduction of inflammatory cell migration, fibroblast proliferation and differentiation into myofibroblasts and extracellular matrix deposition	VEGF-induced vascular permeability reduction

VEGFR: vascular endothelial growth factor receptors; PDGFR: platelet-derived growth factor receptor; EGFR: epidermal growth factor receptor; FGFR: fibroblast growth factor receptor, LPA: lysophosphatidic acid; IL: interleukin; TBXA2R: thromboxane A2 receptor; TXA2: thromboxane A2; PGD2: prostaglandin D2; EP_2: prostaglandin E receptor 2; DP_1: prostaglandin D receptor 1; PPAR: peroxisome proliferator-activated receptors; STAT3: signal transducer and activator of transcription 3.

TABLE 2 Advantages and disadvantages of common pulmonary vascular disease end-points in patients with interstitial lung disease (ILD)

End-point	Advantages	Disadvantages	Major applicable pathology	
			Vasculature	Interstitium
Functional end-points				
6MWT	- Simple, inexpensive, validated - 6MWD is a well-established prognostic marker in PAH and IPF - 6MWT provides additional clinically relevant variables (*e.g.* oxygen desaturation) - Best suited for single agent, placebo-controlled study	- Conflicting data regarding correlation between changes in 6MWD and longer-term outcomes - Subjectivity: relies on patient's effort - Ceiling effect - Less sensitive in studies on add on therapies	✓	✓
Exercise capacity (CPET)	- Reflects physiology - Well-established prognostic marker in PH and IPF	- Requires specific expertise - More time consuming than 6MWT	✓	✓
Lung function	- FVC is a well-established marker of disease progression and prognosis in IPF, being the most widely used primary end-point in IPF trials - D_{LCO} reflects PH-ILD pathophysiology as marker of alveolar-capillary membrane integrity	- Not formally validated as surrogate end-points in PH - D_{LCO} more useful when assessed relatively to markers of fibrosis progression (*i.e.* FVC/D_{LCO})	✓ (D_{LCO})	✓ (FVC and D_{LCO})
Functional class (NYHA, WHO-FC)	- Reflects disease severity and exercise tolerance - Well-established prognostic marker in PH - Useful in composite end-points	- Interobserver variability - Limited sensitivity to change - Imprecise	✓	✓
Accelerometry/actigraphy	- Accurately reflects daily levels of physical activity - More sensitive to change than 6MWT	- Not formally validated as surrogate end-point - Requires consistency and engagement from study subjects	✓	✓
Supportive end-points				
Haemodynamic parameters (*e.g.* PVR)	- PVR is a well-established prognostic marker in PH-ILD	- Changes in haemodynamic parameters were only partially associated with treatment effect in PAH trials - Invasive procedure	✓	
Biomarkers (NT-pro-BNP or BNP)	- Correlated with morbidity and mortality	- Not formally validated as surrogate end-point	✓	
Supplemental oxygen needs	- Patient centric end-point with well-established prognostic value in PH and IPF - Useful in early phase of disease (*e.g.* initiation of O_2 supplementation) - Reflects disease severity - Useful in composite end-points	- Not formally validated as surrogate end-point - Requires standardisation of criteria for initiating or changing supplementation	✓	✓
Patient-centred end-points				
PROs	- Mirrors the beneficial effect of improving a functional outcome on patient's experience - Many questionnaires already validated in cardiorespiratory diseases	- No standardised approach to PROs - Many PROs are symptom but not disease specific	✓	✓
Survival-related end-points				
Hospitalisation	- Well-established prognostic implications in IPF - Implications for patients and also healthcare resource utilisation	- The role of cardiorespiratory *versus* all-cause hospitalisation is less clear - Different criteria/thresholds across countries - Clinical meaning of ED visits less defined	✓	✓

Continued

TABLE 2 Continued

End-point	Advantages	Disadvantages	Major applicable pathology	
			Vasculature	Interstitium
Lung transplantation	- Traditionally utilised in composite end-point with mortality	- Variability across regions and countries - Available only for fit candidates	✓	✓
Time to clinical worsening/ composite end-points (*i.e.* combination of two or more clinically meaningful outcomes)	- Increased number of events in a given group of patients - Include multiple domains of disease progression - Combination might identify a beneficial effect of study drug - May include quality of life implications (patient-centredness)	- Ideal combinations of which end-points to include is unclear - Different end-points might need to be weighted - Showing improvement in time to clinical worsening requires large sample sizes - May miss clinical improvement	✓	✓
Mortality	- Highly meaningful end-point in PH-ILD	- The role of cardiorespiratory *versus* all-cause is less clear - Requires longer follow-up and larger sample sizes	✓	✓

6MWT: 6-min walk test; PVR: pulmonary vascular resistance; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; 6MWD: 6-min walk distance; IPF: idiopathic pulmonary fibrosis; CPET: cardiopulmonary exercise test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NYHA: New York Heart Association; WHO-FC: World Health Organization functional class; NT-pro-BNP: N-terminal pro B-type natriuretic peptide; PRO: patient-reported outcome; ED: emergency department.

including at least a subgroup of patients with instrumental suspect or definite diagnosis of PH (echocardiography and/or RHC) are summarised in table 3.

Promising data have recently emerged. The INCREASE trial was the largest randomised controlled study targeting PH-ILD, testing the efficacy and safety of inhaled treprostinil [111]. In a population of 326 ILD patients, 28.2% suffered from IPF. The study met its primary end-point of change in the 6-min walk distance at 16 weeks, beyond multiple secondary end-points such as time to clinical worsening, change in the NT-pro-BNP and 6-min walk distance at 12 and 15 weeks. Serious adverse events were not more incident in the treprostinil than in the placebo arm; interestingly, the incidence of acute exacerbations of the underlying disease was lower in the treatment group. Moreover, there were no significant treatment-related changes in pulse oximetry or need for supplemental oxygen, a theoretical risk of pulmonary vasodilators in patients with substantial lung fibrosis. A *post hoc* analysis suggested that patients in the treprostinil arm had an improvement in FVC at 16 weeks, which was even more relevant in patients with IPF [112]. These results suggest that treprostinil might have independent antifibrotic properties beyond traditional vasodilatory effects; moreover, the inhaled delivery might have a specific role due to targeted deposition of drug at the disease site, rapid onset of action, and limited side effects compared with oral administration [113]. A randomised, double-blind, placebo-controlled, phase III study of the efficacy and safety of inhaled treprostinil in patients with IPF is underway [113, 114] (table 1).

Conclusions

Vasculature plays a key role in the natural history of IPF. Microvascular disarrangements are detectable from the early phases of disease. The development of PH in a subgroup of patients represents an advanced phenotype in the spectrum of the disease and is related to a worse prognosis. Pulmonary vascular volume has recently emerged as a novel CT pattern and a predictor of mortality, independent of PH and correlated with lung function variables.

New treatment options with a concomitant vascular activity might be promising in the treatment of the disease.

Questions for future research

- Future studies should confirm the role of pulmonary vascular volume at CT and novel pulmonary perfusion techniques (*e.g.* dynamic contrast-enhanced MRI) as new tools to assess early perfusion changes in the absence of detectable PH and early detection of disease progression.
- Endothelial targets of pharmacological therapies of IPF may represent additional options to conventional profibrotics (*e.g.* collagen deposition). Future research should evaluate whether pharmacological options

TABLE 3 Summary of studies on pulmonary vasodilators for the treatment of idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH)-IPF

Investigator/year (study name) [ref.]	Study design	Enrolled patients with ILD (IPF)	PH assessment	Drug(s)	End-points	Outcomes
Olschewski/1999 [131]	PCS	8 (1)	RHC	Inhaled NO, *i.v.* epoprostenol, inhaled iloprost	Changes in mPAP and PVR[§]	Significant decrease in mPAP and PVR
Ghofrani/2002 [132]	RCT	16 (7)	RHC	Inhaled NO+oral sildenafil or *i.v.* epoprostenol (randomised)	Changes in PVR (primary)	Significant decrease in PVR for both drugs
Krowka/2007 [103]	RCT	51 (51)	RHC or Echocardiography	Inhaled iloprost *versus* placebo	Safety (primary) Changes in 6MWD and NYHA functional class (vascular)	Similar incidence of AEs between groups No significant changes in 6MWD and NYHA class
Chapman/2009 [133]	RCS	25 (NS)	RHC	Oral sildenafil	Changes in mean PVR, mPAP and 6MWD[§]	Significant increase in 6MWD and decrease in mPAP No changes in PVR
Corte/2010 [134]	RCS	15 (1)	Echocardiography	Oral sildenafil	Changes in 6MWD, BNP and RV systolic pressure at echocardiography[§]	Significant increase in 6MWD, significant decrease in BNP, no changes in RV systolic pressure
Raghu/2012 (ARTEMIS-IPF) [102]	RCT	492 (492)[#]	RHC	Oral ambrisentan *versus* placebo	IPF progression (all-cause mortality, respiratory hospitalisation or decrease in lung function) (primary)	Increased risk of IPF progression
Hoeper/2013 [135]	PCS	22 (13)	RHC	Oral riociguat	Safety (primary) Changes in CO, PVR, mPAP and 6MWD (vascular)	Overall low incidence of AE Significant increase in CO and 6MWD; significant decrease in PVR; no effect on mPAP
Saggar/2014 [136]	PCS	15 (8)	RHC	*i.v.* or *s.c.* treprostinil	Changes in mPAP, PVR, CI and 6MWD[§]	Significant decrease in mPAP, PVR and increase in CI Significant increase in 6MWD
Corte/2014 (BPHIT) [104]	RCT	60 (NS)	RHC	Oral bosentan *versus* placebo	Changes in PVR index (primary)	No change in PVRi
Zimmerman/2014 [137]	RCS	10 (6)	RHC	Oral sildenafil or tadalafil	Changes in CI, PVR, mPAP and 6MWD[§]	Significant increase in CI and decrease in PVR No changes in mPAP and 6MWD
Kolb/2018 (INSTAGE) [100]	RCT	274 (274)[¶]	Echocardiography	Oral nintedanib+sildenafil *versus* nintedanib+placebo	Changes in 6MWD (primary)	No change in 6MWD
Nathan/2019 (RISE-IIP) [101]	RCT	147 (103)	RHC	Oral riociguat *versus* placebo	Changes in SGRQ (primary)	No change in SGRQ
Nathan/2020 [99]	RCT	41 (30)	Echocardiography or RHC	Inhaled NO *versus* placebo	Changes in activity levels through actigraphy (primary) Changes in 6MWD (vascular)	Significant increase in moderate-vigorous physical activity No change in 6MWD
Waxman/2021 (INCREASE) [111]	RCT	326 (92)	RHC	Inhaled treprostinil *versus* placebo	Changes in 6MWD (primary) Changes in NT-pro-BNP (vascular)	Significant increase in 6MWD Significant decrease in NT-pro-BNP
Nathan/2021 [112]	RCT (*post hoc* analysis)	326 (92)	RHC	Inhaled treprostinil *versus* placebo	Changes in FVC (primary)	Significant increase in FVC
King/2022 [105]	RCT	44 (31)[+]	Echocardiography	Inhaled NO *versus* placebo	Survival (primary) Changes in mPAP, CO, PVR, TAPSE and 6MWD (vascular)	Better survival No significant changes in mPAP, CO, PVR Significant decrease in TAPSE and 6MWD
Dawes/2023 [138]	RCS	128 (74)	RHC	Sildenafil, tadalafil	Changes in mPAP and PVR[§]	Significant decrease in mPAP and PVR

ILD: interstitial lung disease; RCT: randomised controlled trial; RCS: retrospective cohort study; PCS: prospective cohort study; NS: not specified; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; NO: nitric oxide; 6MWD: 6-min walk distance; AEs: adverse effects; NYHA: New York Heart Association; BNP: brain natriuretic peptide; RV: right ventricle; CO: cardiac output; CI: cardiac index; PVRi: pulmonary vascular resistance index; WHO-FC: World Health Organization functional class; SGRQ: St George's Respiratory Questionnaire; NT-pro-BNP: N-terminal pro B-type natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; FVC: forced vital capacity. [#]: only 54 patients with established PH by RHC; [¶]: only 117 patients with suspected PH by echocardiography; [+]: only 27 patients with intermediate or high probability of PH by echocardiography; [§]: no formal primary end-point declared.

with pleiotropic effect with concomitant vascular-directed activity might be effective in the treatment of the disease.

- Future research should assess the presence of antifibrotic properties of inhaled treprostinil beyond traditional vasodilatory effects, which could potentially make it the preferred pharmacological option for patients with PH-IPF.

Provenance: Submitted article, peer reviewed.

Conflict of interest: G. Sotgiu is an associate editor of this journal. The other authors have nothing to disclose.

References

1 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.

2 Martinez FJ, Collard HR, Pardo A, *et al.* Idiopathic pulmonary fibrosis. *Nat Rev Dis Primer* 2017; 3: 17074.

3 Ley B, Collard HR, King TEJ. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.

4 Mondoni M, Alfano F, Varone F, *et al.* Observational, multicenter study on the efficacy, tolerability, and safety of nintedanib in patients with idiopathic pulmonary fibrosis older than 80 years. *Respir Int Rev Thorac Dis* 2023; 102: 25–33.

5 Sgalla G, Iovene B, Calvello M, *et al.* Idiopathic pulmonary fibrosis: pathogenesis and management. *Respir Res* 2018; 19: 32.

6 Barratt S, Millar A. Vascular remodelling in the pathogenesis of idiopathic pulmonary fibrosis. *QJM Mon J Assoc Physicians* 2014; 107: 515–519.

7 Fließer E, Lins T, Berg JL, *et al.* The endothelium in lung fibrosis: a core signalling hub in disease pathogenesis? *Am J Physiol Cell Physiol* 2023; 325: C2–C16.

8 King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. *Lancet Respir Med* 2017; 5: 72–84.

9 Hoeper MM, Humbert M, Souza R, *et al.* A global view of pulmonary hypertension. *Lancet Respir Med* 2016; 4: 306–322.

10 Ruffenach G, Hong J, Vaillancourt M, *et al.* Pulmonary hypertension secondary to pulmonary fibrosis: clinical data, histopathology and molecular insights. *Respir Res* 2020; 21: 303.

11 Raghu G, Amatto VC, Behr J, *et al.* Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* 2015; 46: 1113–1130.

12 Nathan SD, Shlobin OA, Ahmad S, *et al.* Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respir Int Rev Thorac Dis* 2008; 76: 288–294.

13 Raghu G, Nathan SD, Behr J, *et al.* Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. *Eur Respir J* 2015; 46: 1370–1377.

14 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.

15 Rahaghi FF, Kolaitis NA, Adegunsoye A, *et al.* Screening strategies for pulmonary hypertension in patients with interstitial lung disease: a multidisciplinary Delphi study. *Chest* 2022; 162: 145–155.

16 Luppi F, Kalluri M, Faverio P, *et al.* Idiopathic pulmonary fibrosis beyond the lung: understanding disease mechanisms to improve diagnosis and management. *Respir Res* 2021; 22: 109.

17 Zisman DA, Ross DJ, Belperio JA, *et al.* Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Med* 2007; 101: 2153–2159.

18 Molgat-Seon Y, Schaeffer MR, Ryerson CJ, *et al.* Exercise pathophysiology in interstitial lung disease. *Clin Chest Med* 2019; 40: 405–420.

19 Gille T, Laveneziana P. Cardiopulmonary exercise testing in interstitial lung diseases and the value of ventilatory efficiency. *Eur Respir Rev* 2021; 30: 200355.

20 Zhai Z, Murphy K, Tighe H, *et al.* Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2011; 140: 1284–1291.

21 Armstrong HF, Thirapatarapong W, Dussault NE, *et al.* Distinguishing pulmonary hypertension in interstitial lung disease by ventilation and perfusion defects measured by cardiopulmonary exercise testing. *Respir Int Rev Thorac Dis* 2013; 86: 407–413.

22 Armstrong HF, Schulze PC, Bacchetta M, *et al.* Impact of pulmonary hypertension on exercise performance in patients with interstitial lung disease undergoing evaluation for lung transplantation. *Respirol Carlton Vic* 2014; 19: 675–682.

23 Boutou AK, Pitsiou GG, Trigonis I, *et al.* Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. *Respirol Carlton Vic* 2011; 16: 451–458.

24 Nathan SD, Chandel A, Wang Y, *et al.* Derivation and validation of a noninvasive prediction tool to identify pulmonary hypertension in patients with IPF: evolution of the model FORD. *J Heart Lung Transplant* 2024; 43: 547–553.
25 Gaikwad AV, Lu W, Dey S, *et al.* Vascular remodelling in idiopathic pulmonary fibrosis patients and its detrimental effect on lung physiology: potential role of endothelial-to-mesenchymal transition. *ERJ Open Res* 2022; 8: 00571-2021.
26 Gaikwad AV, Lu W, Dey S, *et al.* Endothelial-to-mesenchymal transition: a precursor to pulmonary arterial remodelling in patients with idiopathic pulmonary fibrosis. *ERJ Open Res* 2023; 9: 00487-2022.
27 Phan THG, Paliogiannis P, Nasrallah GK, *et al.* Emerging cellular and molecular determinants of idiopathic pulmonary fibrosis. *Cell Mol Life Sci* 2021; 78: 2031–2057.
28 Ng B, Dong J, D'Agostino G, *et al.* Interleukin-11 is a therapeutic target in idiopathic pulmonary fibrosis. *Sci Transl Med* 2019; 11: eaaw1237.
29 Milara J, Roger I, Montero P, *et al.* IL-11 system participates in pulmonary artery remodelling and hypertension in pulmonary fibrosis. *Respir Res* 2022; 23: 313.
30 Zhao W, Wang L, Yang J, *et al.* Endothelial cell-derived MMP19 promotes pulmonary fibrosis by inducing E(nd)MT and monocyte infiltration. *Cell Commun Signal* 2023; 21: 56.
31 Turner-Warwick M. Precapillary systemic-pulmonary anastomoses. *Thorax* 1963; 18: 225–237.
32 Ebina M, Shimizukawa M, Shibata N, *et al.* Heterogeneous increase in CD34-positive alveolar capillaries in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; 169: 1203–1208.
33 Renzoni EA, Walsh DA, Salmon M, *et al.* Interstitial vascularity in fibrosing alveolitis. *Am J Respir Crit Care Med* 2003; 167: 438–443.
34 Farkas L, Gauldie J, Voelkel NF, *et al.* Pulmonary hypertension and idiopathic pulmonary fibrosis: a tale of angiogenesis, apoptosis, and growth factors. *Am J Respir Cell Mol Biol* 2011; 45: 1–15.
35 Magro CM, Waldman WJ, Knight DA, *et al.* Idiopathic pulmonary fibrosis related to endothelial injury and antiendothelial cell antibodies. *Hum Immunol* 2006; 67: 284–297.
36 Keane MP, Arenberg DA, Lynch JP, *et al.* The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. *J Immunol* 1997; 159: 1437–1443.
37 Nathan SD, Noble PW, Tuder RM. Idiopathic pulmonary fibrosis and pulmonary hypertension: connecting the dots. *Am J Respir Crit Care Med* 2007; 175: 875–880.
38 Colombat M, Mal H, Groussard O, *et al.* Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: Histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. *Hum Pathol* 2007; 38: 60–65.
39 Parra ER, David YR, da Costa LRS, *et al.* Heterogeneous remodelling of lung vessels in idiopathic pulmonary fibrosis. *Lung* 2005; 183: 291–300.
40 McKeown S, Richter AG, O'Kane C, *et al.* MMP expression and abnormal lung permeability are important determinants of outcome in IPF. *Eur Respir J* 2009; 33: 77–84.
41 Jayant G, Kuperberg S, Somnay K, *et al.* The role of sphingolipids in regulating vascular permeability in idiopathic pulmonary fibrosis. *Biomedicines* 2023; 11: 1728.
42 Gaikwad AV, Eapen MS, McAlinden KD, *et al.* Endothelial to mesenchymal transition (EndMT) and vascular remodelling in pulmonary hypertension and idiopathic pulmonary fibrosis. *Expert Rev Respir Med* 2020; 14: 1027–1043.
43 Puxeddu E, Cavalli F, Pezzuto G, *et al.* Impact of pulmonary vascular volume on mortality in IPF: is it time to reconsider the role of vasculature in disease pathogenesis and progression? *Eur Respir J* 2017; 49: 1602345.
44 Kim K-H, Maldonado F, Ryu JH, *et al.* Iron deposition and increased alveolar septal capillary density in nonfibrotic lung tissue are associated with pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Res* 2010; 11: 37.
45 Sangiuolo F, Puxeddu E, Pezzuto G, *et al.* HFE gene variants and iron-induced oxygen radical generation in idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 483–490.
46 Puxeddu E, Comandini A, Cavalli F, *et al.* Iron laden macrophages in idiopathic pulmonary fibrosis: the telltale of occult alveolar haemorrhage? *Pulm Pharmacol Ther* 2014; 28: 35–40.
47 Milara J, Ballester B, Morell A, *et al.* JAK2 mediates lung fibrosis, pulmonary vascular remodelling and hypertension in idiopathic pulmonary fibrosis: an experimental study. *Thorax* 2018; 73: 519–529.
48 Milara J, Hernandez G, Ballester B, *et al.* The JAK2 pathway is activated in idiopathic pulmonary fibrosis. *Respir Res* 2018; 19: 24.
49 Sakao S, Tanabe N, Tatsumi K. Hypoxic pulmonary vasoconstriction and the diffusing capacity in pulmonary hypertension secondary to idiopathic pulmonary fibrosis. *J Am Heart Assoc* 2019; 8: e013310.
50 Marshall BE, Marshall C. A model for hypoxic constriction of the pulmonary circulation. *J Appl Physiol* 1988; 64: 68–77.
51 Sakao S, Taraseviciene-Stewart L, Lee JD, *et al.* Initial apoptosis is followed by increased proliferation of apoptosis-resistant endothelial cells. *FASEB J* 2005; 19: 1178–1180.

52 Kylhammar D, Rådegran G. The principal pathways involved in the *in vivo* modulation of hypoxic pulmonary vasoconstriction, pulmonary arterial remodelling and pulmonary hypertension. *Acta Physiol* 2017; 219: 728–756.
53 Post JM, Hume JR, Archer SL, *et al.* Direct role for potassium channel inhibition in hypoxic pulmonary vasoconstriction. *Am J Physiol* 1992; 262: C882–C890.
54 McMurtry IF, Davidson AB, Reeves JT, *et al.* Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. *Circ Res* 1976; 38: 99–104.
55 Dunham-Snary KJ, Wu D, Sykes EA, *et al.* Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. *Chest* 2017; 151: 181–192.
56 Mura M, Anraku M, Yun Z, *et al.* Gene expression profiling in the lungs of patients with pulmonary hypertension associated with pulmonary fibrosis. *Chest* 2012; 141: 661–673.
57 Tirelli C, Pesenti C, Miozzo M, *et al.* The genetic and epigenetic footprint in idiopathic pulmonary fibrosis and familial pulmonary fibrosis: a state-of-the-art review. *Diagnostics* 2022; 12: 3107.
58 Pardo A, Selman M. Matrix metalloproteases in aberrant fibrotic tissue remodelling. *Proc Am Thorac Soc* 2006; 3: 383–388.
59 Rosas IO, Richards TJ, Konishi K, *et al.* MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med* 2008; 5: e93.
60 Dhont S, Zwaenepoel B, Vandecasteele E, *et al.* Pulmonary hypertension in interstitial lung disease: an area of unmet clinical need. *ERJ Open Res* 2022; 8: 00272-2022.
61 Collum SD, Amione-Guerra J, Cruz-Solbes AS, *et al.* Pulmonary hypertension associated with idiopathic pulmonary fibrosis: current and future perspectives. *Can Respir J* 2017; 2017: 1430350.
62 Yu PB, Deng DY, Beppu H, *et al.* Bone morphogenetic protein (BMP) type II receptor is required for BMP-mediated growth arrest and differentiation in pulmonary artery smooth muscle cells. *J Biol Chem* 2008; 283: 3877–3888.
63 Newman JH, Phillips JA, Loyd JE. Narrative review: the enigma of pulmonary arterial hypertension: new insights from genetic studies. *Ann Intern Med* 2008; 148: 278–283.
64 Gajecki D, Gawrys J, Szahidewicz-Krupska E, *et al.* Novel molecular mechanisms of pulmonary hypertension: a search for biomarkers and novel drug targets-from bench to bed site. *Oxid Med Cell Longev* 2020; 2020: 7265487.
65 Li W, Dunmore BJ, Morrell NW. Bone morphogenetic protein type II receptor mutations causing protein misfolding in heritable pulmonary arterial hypertension. *Proc Am Thorac Soc* 2010; 7: 395–398.
66 Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonary fibrosis. *Annu Rev Pathol* 2014; 9: 157–179.
67 Willis BC, Borok Z. TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease. *Am J Physiol Lung Cell Mol Physiol* 2007; 293: L525–L534.
68 Steiner MK, Syrkina OL, Kolliputi N, *et al.* Interleukin-6 overexpression induces pulmonary hypertension. *Circ Res* 2009; 104: 236–244.
69 Chen N-Y, D Collum S, Luo F, *et al.* Macrophage bone morphogenic protein receptor 2 depletion in idiopathic pulmonary fibrosis and Group III pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2016; 311: L238–L254.
70 Olsson KM, Hoeper MM, Pausch C, *et al.* Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry. *Eur Respir J* 2021; 58: 2101483.
71 Nathan SD, Tehrani B, Zhao Q, *et al.* Pulmonary vascular dysfunction without pulmonary hypertension: a distinct phenotype in idiopathic pulmonary fibrosis. *Pulm Circ* 2024; 14: e12311.
72 Guazzi M. Use of TAPSE/PASP ratio in pulmonary arterial hypertension: an easy shortcut in a congested road. *Int J Cardiol* 2018; 266: 242–244.
73 D'Andrea A, Stanziola AA, Saggar R, *et al.* Right ventricular functional reserve in early-stage idiopathic pulmonary fibrosis: an exercise two-dimensional speckle tracking Doppler echocardiography study. *Chest* 2019; 155: 297–306.
74 Santoro C, Buonauro A, Canora A, *et al.* Non-invasive assessment of right ventricle to arterial coupling for prognosis stratification of fibrotic interstitial lung diseases. *J Clin Med* 2022; 11: 6115.
75 Jacob J, Pienn M, Payer C, *et al.* Quantitative CT-derived vessel metrics in idiopathic pulmonary fibrosis: a structure-function study. *Respirol Carlton Vic* 2019; 24: 445–452.
76 Jacob J, Nicholson AG, Wells AU, *et al.* Impact of pulmonary vascular volume on mortality in IPF: is it time to reconsider the role of vasculature in disease pathogenesis and progression? *Eur Respir J* 2017; 49: 1602524.
77 Wu W-J, Huang W-M, Liang C-H, *et al.* Pulmonary vascular volume is associated with DLCO and fibrotic score in idiopathic pulmonary fibrosis: an observational study. *BMC Med Imaging* 2022; 22: 76.
78 Weatherley ND, Eaden JA, Hughes PJC, *et al.* Quantification of pulmonary perfusion in idiopathic pulmonary fibrosis with first pass dynamic contrast-enhanced perfusion MRI. *Thorax* 2021; 76: 144–151.

79 Torres LA, Lee KE, Barton GP, *et al.* Dynamic contrast enhanced MRI for the evaluation of lung perfusion in idiopathic pulmonary fibrosis. *Eur Respir J* 2022; 60: 2102058.
80 Ciet P. MRI in interstitial lung disease (M-ILD): a momentum to innovate lung diagnostic. *Thorax* 2021; 76: 108–108.
81 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.
82 King TE, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
83 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
84 Ferrara F, Granata G, Pelliccia C, *et al.* The added value of pirfenidone to fight inflammation and fibrotic state induced by SARS-CoV-2: anti-inflammatory and anti-fibrotic therapy could solve the lung complications of the infection? *Eur J Clin Pharmacol* 2020; 76: 1615–1618.
85 Du Y, Zhu P, Wang X, *et al.* Pirfenidone alleviates lipopolysaccharide-induced lung injury by accentuating BAP31 regulation of ER stress and mitochondrial injury. *J Autoimmun* 2020; 112: 102464.
86 Nakazato H, Oku H, Yamane S, *et al.* A novel anti-fibrotic agent pirfenidone suppresses tumour necrosis factor-alpha at the translational level. *Eur J Pharmacol* 2002; 446: 177–185.
87 Gan D, Cheng W, Ke L, *et al.* Biphasic effect of pirfenidone on angiogenesis. *Front Pharmacol* 2021; 12: 804327.
88 Mavrogiannis E, Hagdorn QAJ, Bazioti V, *et al.* Pirfenidone ameliorates pulmonary arterial pressure and neointimal remodelling in experimental pulmonary arterial hypertension by suppressing NLRP3 inflammasome activation. *Pulm Circ* 2022; 12: e12101.
89 Li Y, Li H, Liu S, *et al.* Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. *Mol Immunol* 2018; 99: 134–144.
90 Romero A, Dongil P, Valencia I, *et al.* Pharmacological blockade of NLRP3 Inflammasome/IL-1β-positive loop mitigates endothelial cell senescence and dysfunction. *Aging Dis* 2022; 13: 284–297.
91 Wollin L, Wex E, Pautsch A, *et al.* Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1434–1445.
92 Wind S, Schmid U, Freiwald M, *et al.* Clinical pharmacokinetics and pharmacodynamics of Nintedanib. *Clin Pharmacokinet* 2019; 58: 1131–1147.
93 Yu W-K, Chen W-C, Su VY-F, *et al.* Nintedanib inhibits endothelial mesenchymal transition in bleomycin-induced pulmonary fibrosis via focal adhesion kinase activity reduction. *Int J Mol Sci* 2022; 23: 8193.
94 Ackermann M, Kim YO, Wagner WL, *et al.* Effects of nintedanib on the microvascular architecture in a lung fibrosis model. *Angiogenesis* 2017; 20: 359–372.
95 Landi C, Carleo A, Vantaggiato L, *et al.* Common molecular pathways targeted by nintedanib in cancer and IPF: a bioinformatic study. *Pulm Pharmacol Ther* 2020; 64: 101941.
96 Rol N, de Raaf MA, Sun XQ, *et al.* Nintedanib improves cardiac fibrosis but leaves pulmonary vascular remodelling unaltered in experimental pulmonary hypertension. *Cardiovasc Res* 2019; 115: 432–439.
97 Nathan SD, Fernandes P, Psotka M, *et al.* Pulmonary hypertension in interstitial lung disease: clinical trial design and end-points: a consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative-Group 3 Pulmonary Hypertension. *Pulm Circ* 2022; 12: e12178.
98 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.
99 Nathan SD, Flaherty KR, Glassberg MK, *et al.* A randomized, double-blind, placebo-controlled study of pulsed, inhaled nitric oxide in subjects at risk of pulmonary hypertension associated with pulmonary fibrosis. *Chest* 2020; 158: 637–645.
100 Kolb M, Raghu G, Wells AU, *et al.* Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2018; 379: 1722–1731.
101 Nathan SD, Behr J, Collard HR, *et al.* Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *Lancet Respir Med* 2019; 7: 780–790.
102 Raghu G, Behr J, Brown KK, *et al.* Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med* 2013; 158: 641–649.
103 Krowka MJ, Ahmad S, Andrade JA de, *et al.* A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of iloprost inhalation in adults with abnormal pulmonary arterial pressure and exercise limitation associated with idiopathic pulmonary fibrosis. *Chest* 2007; 132: 633A.
104 Corte TJ, Keir GJ, Dimopoulos K, *et al.* Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2014; 190: 208–217.
105 King CS, Flaherty KR, Glassberg MK, *et al.* A Phase-2 exploratory randomized controlled trial of INOpulse in patients with fibrotic interstitial lung disease requiring oxygen. *Ann Am Thorac Soc* 2022; 19: 594–602.
106 King TE, Brown KK, Raghu G, *et al.* BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 92–99.

107 Raghu G, Million-Rousseau R, Morganti A, *et al.* Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *Eur Respir J* 2013; 42: 1622–1632.
108 Behr J, Nathan SD, Wuyts WA, *et al.* Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; 9: 85–95.
109 Hemnes A, Rothman AMK, Swift AJ, *et al.* Role of biomarkers in evaluation, treatment and clinical studies of pulmonary arterial hypertension. *Pulm Circ* 2020; 10: 2045894020957234.
110 Caccamo M, Harrell FE, Hemnes AR. Evolution and optimization of clinical trial endpoints and design in pulmonary arterial hypertension. *Pulm Circ* 2023; 13: e12271.
111 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.
112 Nathan SD, Waxman A, Rajagopal S, *et al.* Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a *post-hoc* analysis of the INCREASE study. *Lancet Respir Med* 2021; 9: 1266–1274.
113 Kolb M, Orfanos SE, Lambers C, *et al.* The antifibrotic effects of inhaled treprostinil: an emerging option for ILD. *Adv Ther* 2022; 39: 3881–3895.
114 Nathan SD, Behr J, Cottin V, *et al.* Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis. *BMJ Open Respir Res* 2022; 9: e001310.
115 Chen W, Zhang J, Zhong W, *et al.* Anlotinib inhibits PFKFB3-driven glycolysis in myofibroblasts to reverse pulmonary fibrosis. *Front Pharmacol* 2021; 12: 744826.
116 Ruan H, Lv Z, Liu S, *et al.* Anlotinib attenuated bleomycin-induced pulmonary fibrosis *via* the TGF-β1 signalling pathway. *J Pharm Pharmacol* 2020; 72: 44–55.
117 Tager AM, LaCamera P, Shea BS, *et al.* The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med* 2008; 14: 45–54.
118 Corte TJ, Lancaster L, Swigris JJ, *et al.* Phase 2 trial design of BMS-986278, a lysophosphatidic acid receptor 1 (LPA1) antagonist, in patients with idiopathic pulmonary fibrosis (IPF) or progressive fibrotic interstitial lung disease (PF-ILD). *BMJ Open Respir Res* 2021; 8: e001026.
119 Luo Y-L, Li Y, Zhou W, *et al.* Inhibition of LPA-LPAR1 and VEGF-VEGFR2 signaling in IPF treatment. *Drug Des Devel Ther* 2023; 17: 2679–2690.
120 Shea BS, Tager AM. Role of the lysophospholipid mediators lysophosphatidic acid and sphingosine 1-phosphate in lung fibrosis. *Proc Am Thorac Soc* 2012; 9: 102–110.
121 Song Y, Hudson K, Ye Z, *et al.* Pharmacokinects study to evaluate drug-drug interactions (DDI) between hzn-825 and pirfenidone/nintedanib. *Chest* 2023; 164: A126–A127.
122 Matavelli LC, Siragy HM. AT2 receptor activities and pathophysiological implications. *J Cardiovasc Pharmacol* 2015; 65: 226–232.
123 Bruce E, Shenoy V, Rathinasabapathy A, *et al.* Selective activation of angiotensin AT2 receptors attenuates progression of pulmonary hypertension and inhibits cardiopulmonary fibrosis. *Br J Pharmacol* 2015; 172: 2219–2231.
124 Vicore pharma. Buloxibutid (C21) – IPF. Date last accessed: 3 September 2024. Date last updated 2023. https://vicorepharma.com/our-programs/rare-lung-diseases/c21-ipf-fibrosis/
125 Jaffar J, McMillan L, Wilson N, *et al.* Coagulation factor-XII induces interleukin-6 by primary lung fibroblasts: a role in idiopathic pulmonary fibrosis? *Am J Physiol Lung Cell Mol Physiol* 2022; 322: L258–L272.
126 McKenzie A, Roberts A, Malandkar S, *et al.* A phase I, first-in-human, randomized dose-escalation study of anti-activated factor XII monoclonal antibody garadacimab. *Clin Transl Sci* 2022; 15: 626–637.
127 Furue A, Hattori K, Hosono K, *et al.* Inhibition of TP signalling promotes endometriosis growth and neovascularization. *Mol Med Rep* 2023; 28: 192.
128 Suzuki T, Kropski JA, Chen J, *et al.* Thromboxane-prostanoid receptor signaling drives persistent fibroblast activation in pulmonary fibrosis. *Am J Respir Crit Care Med* 2022; 206: 596–607.
129 CR Pharma. A safety, tolerability, and pharmacokinetic study of NIP292 in healthy normal subjects. Date last accessed: 3 September 2023. Date last updated: 24 March 2023. https://clinicaltrials.gov/study/NCT04720443
130 Wang L, Astone M, Alam SK, *et al.* Suppressing STAT3 activity protects the endothelial barrier from VEGF-mediated vascular permeability. *Dis Model Mech* 2021; 14: dmm049029.
131 Olschewski H, Ghofrani HA, Walmrath D, *et al.* Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med* 1999; 160: 600–607.
132 Ghofrani HA, Wiedemann R, Rose F, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; 136: 515–522.
133 Chapman TH, Wilde M, Sheth A, *et al.* Sildenafil therapy in secondary pulmonary hypertension: Is there benefit in prolonged use? *Vascul Pharmacol* 2009; 51: 90–95.
134 Corte TJ, Gatzoulis MA, Parfitt L, *et al.* The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease. *Respirol Carlton Vic* 2010; 15: 1226–1232.

135 Hoeper MM, Halank M, Wilkens H, *et al.* Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *Eur Respir J* 2013; 41: 853–860.
136 Saggar R, Khanna D, Vaidya A, *et al.* Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. *Thorax* 2014; 69: 123–129.
137 Zimmermann GS, von Wulffen W, Huppmann P, *et al.* Haemodynamic changes in pulmonary hypertension in patients with interstitial lung disease treated with PDE-5 inhibitors. *Respirol Carlton Vic* 2014; 19: 700–706.
138 Dawes TJW, McCabe C, Dimopoulos K, *et al.* Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: a Bayesian retrospective observational cohort study. *Respirology* 2023; 28: 262–272.