ERS International Congress 2021: highlights from the Pulmonary Vascular Diseases Assembly

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Shareable abstract (@ERSpublications)
This article summarises communications from #ERSCongress 2021 on pulmonary embolism diagnosis and treatment, PAH and CTEPH during the COVID-19 pandemic and beyond, novelties in post-capillary PH and in PH associated with respiratory diseases https://bit.ly/3ASDO21

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Abstract

This article aims to summarise the latest research presented at the virtual 2021 European Respiratory Society (ERS) International Congress in the field of pulmonary vascular disease. In light of the current guidelines and proceedings, knowledge gaps are addressed and the newest findings of the various forms of pulmonary hypertension as well as key points on pulmonary embolism are discussed.

Despite the comprehensive coverage of the guidelines for pulmonary embolism at previous conferences, discussions about controversies in the diagnosis and treatment of this condition in specific cases were debated and are addressed in the first section of this article.

We then report on an interesting pro–con debate about the current classification of pulmonary hypertension. We further report on presentations on Group 3 pulmonary hypertension, with research exploring pathogenesis, phenotyping, diagnosis and treatment; important contributions on the diagnosis of post-capillary pulmonary hypertension are also included.

Finally, we summarise the latest evidence presented on pulmonary vascular disease and COVID-19 and a statement on the new imaging guidelines for pulmonary vascular disease from the Fleischner Society.

Pulmonary embolism and related controversies

After the publication of the Guidelines for the diagnosis and management of acute pulmonary embolism developed by the European Society of Cardiology (ESC) in September 2019, and more recently the position paper on follow-up after acute pulmonary embolism (PE) from the ESC working group on pulmonary hypertension and right ventricular function, topics of particular importance were discussed in several sessions at the ERS 2021 international congress [1–3]. A better insight into the modalities of interventional treatment was provided. Furthermore, previously unresolved questions dealing with the treatment of certain groups of patients, such as patients with malignant diseases and pregnant women, have been explained in more detail. Finally, the sessions focused on the management of subsegmental PE as well as a general reference on monitoring patients after the acute phase of the disease.

Interventional treatment in the intermediate–high risk group

In the four-tiered risk stratification of patients with PE based on the risk of early mortality, the intermediate- to high-risk group presents the strongest uncertainties. Luke Howard summarised recent findings and current knowledge regarding therapeutic strategies for this patient group. The published Pulmonary Embolism THrOmbolysis (PEITHO) trial showed that tenecteplase reduced the composite outcome (death or haemodynamic decompensation within 7 days after randomisation), but at the cost of more extracranial bleeding (6.3% *versus* 1.2%; p<0.001) and stroke (2.4% *versus* 0.2%, p=0.003) than in the placebo group [4]. Because of this unfavourable risk–benefit ratio and unchanged all-cause 30-day mortality, fibrinolysis in intermediate risk PE is not recommended by the ERS/ESC guidelines [1, 2].

According to the recommendations of the Pulmonary Embolism Response Team (PERT) Consortium, it is emphasised that in patients with indication for systemic thrombolysis who at the same time have relative contraindication for this type of therapy interventional treatment procedure, especially catheter-directed thrombolysis or a reduced dose of systemic thrombolysis, should be considered [5]. One of the studies that was a cornerstone for the PERT's recommendations is the MOderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial [6], which showed that a reduced dose of alteplase (*i.e.* 50 mg) is safe and effective in the treatment of intermediate risk PE. Nonetheless, there is accumulating evidence in favour of local therapy, particularly catheter-directed thrombolysis: ULTIMA [7], SEATTLE II [8], OPTALYSE PE [9], PERFECT [10] and SUNSET sPE trial [11] have shown its positive effects on right ventricular function and on thrombus burden in comparison with unfractionated heparin (UFH) therapy in patients with intermediate- to high-risk PE, and a single arm study found similar benefits for the right to left ventricular ratio [12]. The contribution of ultrasound to local thrombolysis and the optimal dose of thrombolytics remain controversial, in addition to which patients will benefit most from it.

Pulmonary embolism in cancer, pregnancy and post-partum

Cancer-associated thrombosis accounts for 20% of all venous thromboembolism (VTE) [13]. According to the talk by Manuel Monreal, the approach to treatment of these patients with anticoagulation has undergone significant changes over the past decade, whereby recent studies are giving advantage to treatment with direct oral anticoagulants (DOACs). A Cochrane meta-analysis by Kahale *et al.* [14] showed that low molecular weight heparin (LMWH) therapy, compared to vitamin K antagonists, resulted in a lower rate of recurrent VTE with similar bleeding risk. According to the ESC Guidelines, LMWH is a recommended therapy after VTE for a minimum of 6 months [2]. Yet, recent trials comparing DOACs *versus* LMWH provide data that justify the use of apixaban, edoxaban and rivaroxaban in patients with cancer-associated thrombosis [15].

Another issue that requires special consideration is the occurrence of recurrent VTE in patients with ongoing anticoagulation. Le Gal *et al*. [16] proposed an assessment of the probability of recurrent PE based on findings of imaging examinations including computed tomography pulmonary angiography (CTPA), compression ultrasonography (CUS) of the lower extremity and ventilation/perfusion lung scan. The most important contributing factors for recurrent VTE are non-compliance to therapy and cancer [17]. Data from the Registro Informatizado de la Enfermedad TromboEmbólica venosa (RIETE) unequivocally indicate an association between the site of cancer and the rate of recurrent VTE, as well as the risk of bleeding under anticoagulant therapy: rate of recurrent VTE and major bleeding were similar in patients who suffer from breast and colorectal cancer; recurrent VTE was more common than bleeding in patients with lung cancer, while in patients with prostate cancer bleeding exceeded recurrent VTE [18]. Data from the RIETE registry suggest that individualised therapy for VTE is likely to be associated with better outcomes.

Fionnuala Ni Aile covered the topic lung embolism in pregnancy and post-partum. VTE is one of the leading causes of maternal morbidity and mortality [19]. The ESC Guidelines have provided a diagnostic algorithm that aims to diagnose this condition while minimising radiation exposure [2]. Of special

importance in this algorithm, but also an integral part of the pregnancy-adapted YEARS algorithm, is the CUS of the lower extremity. Implementation of the YEARS algorithm reduces the need for CTPA by 30 to 60% depending on the trimester. In patients with a high clinical suspicion for PE or deep vein thrombosis (DVT) who have a positive proximal CUS, anticoagulant therapy can be started automatically without additional imaging methods [20]. An unresolved issue is the prophylactic dose of LMWH in pregnant women who have previously had a VTE. The trial HIGHLOW [21] is underway: the goal of the study is to provide data on the incidence of post-partum haemorrhage, risk of VTE, delivery outcomes and the degree of healthcare services utilisation among pregnant women – comparing the groups with LMWH prophylactic *versus* therapeutic dose.

Home treatment of low-risk pulmonary embolism and subsegmental pulmonary embolism

Current ERS/ESC guidelines for the management of PE [2] recommend the use of clinically validated scores, the HESTIA criteria [22], PESI [23] and simplified Pulmonary Embolism Severity Index [24] (sPESI), to stratify the risk of patients with PE in the initial phase. Olivier Sanchez pointed out that home treatment of PE is suitable in patients with low-risk PE (around 30%) and discussed results of the HOME-PE trial of 1975 normotensive PE patients randomised to a triaging strategy for home treatment based on HESTIA criteria *versus* sPESI [25]. Patients were eligible for outpatient care if the sPESI score was 0 or all 11 HESTIA criteria were negative; otherwise, patients were hospitalised. Both scores were equally safe and efficient in identifying candidates for home treatment. A greater proportion of patients were eligible for home care using the sPESI score (48.4%) compared with the HESTIA (39.4%), but the HESTIA score was more applicable and less frequently overruled by the physician in charge. According to Becattini *et al*. [26] and the current ERS/ESC guidelines for PE, ruling out right ventricular dysfunction might identify very low-risk patients. Interestingly, in the HOME-PE trial none of the patients with right ventricular dysfunction experienced worse outcomes compared to those without right ventricular dysfunction.

Management of subsegmental PE

According to Behnood Bikdeli the therapeutic approach to subsegmental PE (SSPE) remains controversial, because of the non-uniform definition and the overdiagnosis of this condition [27]. Based on the Delphi analysis of experts, SSPE is defined as a contrast defect in a subsegmental artery visible in at least two subsequent axial slices of 1 mm or less [28]. With the aim of reducing overdiagnosis in the interpretation of CTPA, it is necessary to pay attention to the quality of the image and possible artefacts, as well as the analysis of lung parenchyma and airways, in order to exclude false positive findings [29]. Mortality associated with SSPE is low, but the risk of recurrence is not lower compared to patients with central PE. Initiation of anticoagulant therapy is recommended if SSPE occurs in patients with a previous thromboembolic event, antiphospholipid syndrome, pregnancy, cancer or proximal DVT [28].

Follow-up of pulmonary embolism

The importance of follow-up after an acute thromboembolic event was highlighted by Frederikus Klok. The type and length of anticoagulant therapy, as well as bleeding risk factors, must be well assessed and periodically monitored; when comorbidities are adequately treated, a lower risk of bleeding can be achieved [30, 31]. In patients in whom the cause of PE has not been identified, previously so-called unprovoked embolism, the diagnosis of cancer is made in about 5% in the following 12 months [32]. Basic workup including medical history, physical examination, blood tests and chest radiographs is recommended, and age- and sex-specific testing can be done in accordance with national guidelines and local practice [33]. Thrombophilia tests are indicated only if a positive finding would be of clinical significance [34]. Recommendations regarding sports and travel after PE are also topics on which clearer recommendations are needed: an upcoming publication by Klok *et al*. should further clarify these questions.

Pro–con debate: the current classification of pulmonary hypertension meets clinical practice

The current classification of pulmonary hypertension (PH) has many strengths for its use in clinical practice, highlighted by David Montani, but also limitations, especially for certain forms of PH, underlined by Harm Jan Bogaard.

The first classification of PH dates back to 1973, and it has evolved greatly over time: the current classification of PH in five groups was updated at the 6th World Pulmonary Hypertension Symposium in Nice in 2018 [35]. Classifications are necessary in the clinic and in research to standardise the definitions of diseases and the management of patients and to open new avenues of research. David Montani explained that the current classification of PH is well suited to the clinic because it meets five criteria that can be expected from a good clinical classification:

1) Be based on evidence and be proposed by experts: the classification is based on the 2015 ESC/ERS guidelines established by experts in pulmonology and cardiology, paediatricians and other specialists [36] and on the work done before and during the 6th World Symposium of 2018 [35].

2) Be simple and understandable: the classification is accessible to non-specialists and helps to transmit current knowledge in the field of PH to the medical community.

3) Be useful to the clinician to guide the management of patients: the five groups have common phenotypes and pathophysiology with algorithms specific to each group (*i.e.* targeting endothelial dysfunction in pulmonary arterial hypertension (PAH)), which helps the management and communication with the patients (*i.e.* no indication for PAH treatment in group 2 or 3). In addition, the classification is a tool to identify populations at risk of PH (patients with systemic sclerosis, portal hypertension, HIV, sickle cell disease), specific forms of PH such as veno-occlusive disease and is a tool of pharmacovigilance for the identification of drugs and toxins that may cause PAH.

4) Be widely accepted and widespread in the world.

5) Be flexible and adaptive: the classification is regularly revised and updated to adapt to new knowledge and clinical practice. For example, PAH responding to calcium channel blockers was differentiated from idiopathic PAH (IPAH) in the last classification to underline their specific management.

In his argument, HJ Bogaard highlighted the usefulness and widespread use of the PH classification in the clinic, but he emphasised several limitations. First, outside of groups 1 and 4, the classification is not very detailed and has no therapeutic impact for groups 2 and 3 of PH, although they represent the majority of PH cases. In addition, within the same group, *i.e.* in idiopathic PAH, there are significant differences in phenotypes and severity, resulting in different treatments; however, the classification does not reflect the heterogeneity of phenotypes. Furthermore, certain phenotypes remain difficult to classify, such as PH in older patients, pre-capillary PH in smokers with low diffusing capacity of lungs for carbon monoxide (D_{LCO}) and normal thoracic CT scan and respiratory volumes, nitric oxide responders not responding to calcium channel blockers and patients with sickle cell disease. Some patients may also have PH that can fit into two groups, or they might present comorbidities which could attribute the pulmonary vascular disease to another group, and it is up to the clinician to decide on the most likely cause of PH. Finally, the current classification does not consider certain biological features such as inflammation, cell hyperproliferation, metabolic anomalies and oxidative stress, which may be relevant: phenotyping the patients according to these findings could be useful for their management. The PH classification could thus be improved by pursuing research on these sub-phenotypes, developing biological or molecular biomarkers to recognise new ones, identifying responders to vasodilator treatments in groups 2 and 3, and building clinical trials with new treatments targeting these sub-phenotypes.

During the discussion, the two experts agreed on the general usefulness of this classification, in particular for non-experts in PH, but also on the need to go further in the identification of new sub-phenotypes beyond the five groups.

Pulmonary hypertension due to lung diseases and/or hypoxia

PH in the context of lung disease is one of the most common forms of PH, although reliable estimates are lacking because of the few clinical indications for right heart catheterisation (RHC), the gold standard for PH diagnosis. Once considered as a broadly homogeneous group of diseases, in which the pulmonary vascular derangement arose as a consequence of hypoxic vasoconstriction, recent advances have outlined differences in genetic, clinical, functional and haemodynamic characteristics of patients with PH associated with COPD, interstitial lung disease (ILD) and other lung diseases.

Pathogenesis, pathology and phenotypes

To better characterise the pathogenesis of pulmonary vascular impairment in the different lung diseases, several authors have presented interesting works at the ERS 2021 congress.

In recent years, three independent studies found an association between a D_{LCO} below 45% and a poor prognosis in PH [37–39]. There are PAH subtypes in which D_{LCO} tends to be low, such as pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis or scleroderma-associated PAH. Additionally, PH due to emphysema or ILD also present with lower D_{LCO}. In contrast, most of IPAH patients show relatively preserved gas exchange and a mildly impaired D_{LCO} suggesting that the alveolocapillary unit remains largely intact [40]. Karen Olsson discussed a subtype of idiopathic PAH,

mostly presenting in elderly patients with a smoking history, characterised by a low D_{LCO} and marked hypoxaemia in the absence of parenchymal lung disease. Hoeper and Vonk-Noordegraaf previously described that tobacco smoke might cause direct damage to the alveolo-capillary unit leading to a vanishing capillary syndrome [41–43]. In this line, Karen Olsson showed the results of a cluster analysis from the COMPERA registry to determine IPAH phenotypes [44] based on age, sex, D_{LCO} <45% *versus* ⩾45%, smoking status and presence of comorbidities (obesity, hypertension, coronary heart disease and diabetes mellitus). Three clusters were identified: Cluster 1, named "classic IPAH" (n=106; 12.6%), was mostly composed of younger, non-smoking females without comorbidities and with D_{LCO} ⩾45%; Cluster 2, named "heart failure with preserved ejection fraction (HFpEF)-like" (n=301; 35.8%) was predominantly composed of older, non-smoking females with a few comorbidities and D_{LCO} ⩾45%; and Cluster 3, named "cardiopulmonary phenotype" (n=434; 51.6%) was the most frequent, composed of older smoking males with frequent comorbidities and low D_{LCO}. Patients in Cluster 1 had a better response to PAH treatment and survival than patients in the two other clusters. In summary, lower D_{LCO} in pulmonary vascular disease is associated with impaired response to PAH therapy and worse prognosis (figure 1).

Bhattarai *et al.* [45] have assessed in detail the early arterial changes found in COPD patients that could be preceding the establishment of PH. They considered four groups: COPD patients who were current smokers, COPD patients who were ex-smokers, patients with small airways disease and smokers with normal lung function; specimens from the four groups were compared with pulmonary arteries of control subjects. They found that all study groups had a reduced number of pulmonary arteries compared to control subjects and that COPD patients who were still smoking presented the highest increase in arterial wall thickness, which affected most prominently the intimal layer and reversed slightly when they stopped smoking. Interestingly, parameters of airflow obstruction and small airways calibre correlated with arterial wall thickness, possibly suggesting a dynamic interaction between the two anatomical structures, which needs to be further explored. In the same line, Gaikwad *et al.* [46] presented another study by the same group that assessed pulmonary arterial remodelling in idiopathic pulmonary fibrosis (IPF) patients compared to control subjects, observing a reduction in the number of arteries of size 300–1000 µm, as well significantly increased arterial thickness; the deposition of elastin in the extracellular matrix was a clear contributor of the increased thickness. To elucidate the mechanism of these alterations, Gaikwad and co-authors also assessed the presence of mesenchymal markers S100A4 and vimentin proteins in the arterial wall, finding them increased in IPF patients and thereby suggesting that the pulmonary arterial walls might be undergoing endothelial to mesenchymal transition. These interesting histological findings should be confirmed with 3D-reconstruction imaging techniques to further assess vessel density and remodelling.

The observation that COPD patients with severe PH present distinctive pulmonary function test (PFT) features, such as severe hypoxaemia and greatly reduced D_{LCO} despite milder airflow obstruction, was made over 15 years ago [47]. To assess the determinants of hypoxaemia in patients with COPD and severe PH, Piccari *et al.* [48] used the multiple inert gas elimination technique (MIGET) during the diagnostic

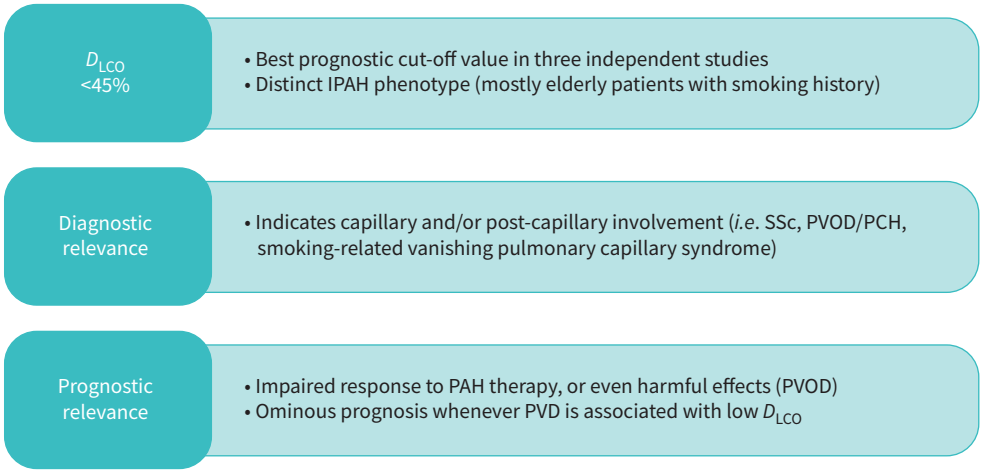

FIGURE 1 Low diffusing capacity of lungs for carbon monoxide (D_{LCO}) in patients with pulmonary vascular disease (PVD) (courtesy of Karen Olssen). IPAH: idiopathic pulmonary arterial hypertension; SSc: systemic sclerosis; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; PAH: pulmonary arterial hypertension.

RHC of COPD patients with suspected severe PH [49] and compared the results with historical COPD patients without PH and with mild–moderate PH who had been similarly studied. Besides the known PFT features, patients with COPD and severe PH presented greater ventilation/perfusion (V'_A/Q') mismatch and increased proportion of blood flow to areas with low ventilation or shunt; they presented also with lower mixed venous blood oxygen pressure (P_{vO_2}) as a result of right ventricular failure. They concluded that in patients with COPD and severe PH, hypoxaemia results from several factors such as severe V'_A/Q' mismatch and right ventricular failure; thus, pulmonary vascular alterations play a fundamental role in the profound gas exchange impairment found in these patients.

Diagnosis

There are clinical and physiological indicators of PH in ILD. An increased dyspnoea despite preserved lung volumes, low oxygenation and need for oxygen supplementation or high flow rates, rapid oxygen desaturation even in mild exercise, low D_{LCO} and low transfer coefficient of the lung for carbon monoxide (K_{CO}) and hyperventilation (low P_{aCO_2}) to maintain oxygenation are signs that increase the likelihood of PH [50, 51]. Katerina Antoniou (Greece) highlighted that noninvasive screening for PH in ILD patients is sufficient in most clinical scenarios, whereas RHC should be restricted to patients in which exercise limitation cannot be fully explained by lung function anomalies in case the patient is enrolled in a clinical trial or to lung transplant candidates.

The diagnostic workup in PH is often at first a process of elimination of more prevalent forms [52]. As a contribution to this, Saunders *et al*. [53] presented an intriguing study on the possibility to detect lung disease during cardiac magnetic resonance (CMR) in the workup for suspected PH, using CMR metric lung T_1, a noninvasive, non-ionising marker of lung parenchymal health that is sensitive to changes in both lung tissue and lung perfusion. Using a single-slice, inspiratory Look-Locker T1 mapping acquisition [54] and comparing the T_1 images from 82 patients with suspected PH and 10 healthy volunteers with computed tomography (CT) scans, previously assessed by radiologists as showing no lung disease, fibrosis, emphysema, hypoattenuation, consolidation or ground glass, they found that T_1 was indeed able to identify patients with lung disease (n=18) from those with other forms of PH (n=53), and that within patients with lung disease a lower T_1 was correlated with the presence of emphysema. Thus, they suggest that with a short additional acquisition during a CMR, the suspicion of lung disease could be assessed and potentially orient the diagnostic process towards group 3 PH.

Treatment

According to the PH guidelines and the statement from the 6th World Symposium on Pulmonary Hypertension, adjunctive therapies such as oxygen therapy when indicated, pulmonary rehabilitation, diuretics and stabilisation of the underlying lung disease remain the cornerstones of treatment. The use of PAH therapies in group 3 PH is controversial, and therapeutic decisions should be made at experienced PH centres and patients should be enrolled in clinical trials [36, 49]. The clinical trials of pulmonary vasodilator therapy in PH-IPF have largely been disappointing, although recent breakthroughs have reopened the debate [55].

The results of clinical trials and retrospective studies examining the role of sildenafil in PH-ILD are inconclusive. The STEP-IPF trial compared sildenafil with placebo in a population of patients with advanced IPF enriched for the presence of PH by means of reduced D_{LCO}. Although the study failed to demonstrate a difference in the primary end-point of a $\geqslant$20% increase in 6-min walk test (6MWT) distance, sildenafil improved a number of secondary end-points, including quality-of-life measures, arterial oxygen saturation and D_{LCO} [56].

On this note, Dawes *et al*. [57] retrospectively analysed the outcome of 183 patients with group 3 PH (67% of which with ILD-associated PH, PH-ILD) attended during the last 20 years at the Royal Brompton Hospital (London, UK) and found a transplant-free survival benefit of a little over a year (2.33 *versus* 1.09 years) in ILD patients treated with sildenafil compared to those not treated; the benefit was largest in younger males with normal tricuspid annular plane systolic excursion (TAPSE) and high pulmonary vascular resistance (PVR). This is in contrast with the STEP-IPF which did not observe statistically significant differences in death or acute exacerbation in advanced IPF patients; however, pulmonary haemodynamics were not assessed in the study [56]. Thus, further trials could explore the efficacy of phosphodiesterase-5-inhibitors (PDE5-i) in ILD patients with an established diagnosis of PH, following the retrospective analysis by Dawes and colleagues.

The INSTAGE study, a randomised controlled trial combining sildenafil with the antifibrotic agent nintedanib in patients with IPF enriched for the presence of PH, failed to replicate the quality-of-life

improvement achieved with sildenafil in the STEP-IPF trial. However, the combination of sildenafil plus nintedanib demonstrated a statistically significant reduction in the combined end-point of death or absolute decline in forced vital capacity (FVC) <5% [58]. A phase IIb study to assess the efficacy and safety of sildenafil added to pirfenidone in patients with advanced IPF and at risk for PH showed no benefit on disease progression [59]. As underlined by Vincent Cottin, the available evidence suggests that the use of sildenafil in PH-ILD is unlikely to be harmful and may be beneficial.

The randomised, placebo-controlled study to evaluate safety and effectiveness of ambrisentan in IPF (ARTEMIS-IPF) study was terminated early due to lack of efficacy and potential harm after enrolment of nearly 500 patients [60]. The RISE-IIP trial, a phase IIb study of riociguat in patients with idiopathic interstitial pneumonias with RHC-confirmed PH was terminated early for increased rates of serious adverse events and death in the treatment group. The study also failed to demonstrate improvement in 6MWT distance in patients treated with riociguat [61]. On the basis of these data, ambrisentan and riociguat should not be used in patients with PH-ILD.

The INCREASE study, which compared inhaled treprostinil with placebo in 326 patients with PH-ILD achieved its primary end-point in the treprostinil arm increasing 6MWT distance with improvements in secondary end-points, such as N-terminal pro-brain natriuretic peptide and time to clinical worsening [62]. A *post hoc* analysis with the aim of characterising the effects of inhaled treprostinil on FVC revealed an improvement in the treatment arm, especially in patients with IPF and other idiopathic interstitial pneumonias [63]. The various trials mentioned are summarised in table 1.

Post-capillary PH

Most of the current scores to distinguish between pre- and post-capillary PH were developed by expert centres but lack external validation. The OPTICS score is a refined version of the previously developed Jacobs' left heart failure risk score, which uses a combination of clinical data, ECG and echocardiographic variables (figure 2) [64]. HJ Bogaard discussed the results of the external validation of the OPTICS score in a prospective cohort from 12 community hospitals. Using a cut-off value of >104, the OPTICS score had a positive predictive value of 100% for detection of post-capillary PH. Interestingly, in the same cohort, a

TABLE 1 Overview of trials with targeted pulmonary hypertension (PH) medication in interstitial lung diseases mentioned in this article

Trial	Subjects n	Study type	Drugs	Patient population	Duration	Primary end-point result	Other outcomes
STEP-IPF (2010) [56]	180	RCT	Sildenafil *versus* placebo		12 weeks	No improvement in 6MWT	No difference in death or exacerbation Improvement in QoL
Dawes *et al.* (2021) [57]	183	Retrospective	PDE-5 *versus* no treatment	Group 3 PH (67% ILD-PH)	Median follow-up 1.6 years	Transplant-free survival 2.33 *versus* 1.09 years	
INSTAGE (2018) [58]	247	RCT	Sildefanil +nintedanib *versus* placebo+nintedanib	IPF+PH	24 weeks	No improvement in QoL	Reduction of death/ decline in FVC
Behr *et al.* (2021) [59]	247	RCT	Sildenafil +pirfenidone *versus* placebo +pirfenidone	IPF+risk of PH	52 weeks	No benefit for disease progression/death	
Artemis-IPF (2013) [81]	68	RCT	Ambrisentan *versus* placebo	IPF	Terminated early	Lack of efficacy and potential harm (more hospitalisation)	
RISE-IIP (2019) [61]	147	RCT	Riociguat *versus* placebo	IIP+PH	Terminated early	Increased SAE and death in patients with riociguat	
INCREASE (2021) [62]	326	RCT	Treprostinil inhalative *versus* placebo	ILD-PH	16 weeks	Increase in 6MWT	Improvement NT-proBNP, time to clinical worsening

RCT: randomised controlled trial; 6MWT: 6-min walk test; QoL: quality of life; PDE-5: phosphodiesterase-5; ILD: interstitial lung disease; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; SAE: serious adverse event; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Clinical variable	Values	Points
Obesity	Body mass index >30 kg·m^{-2}	22
Medical history of		
Diabetes mellitus	Medical history of diabetes mellitus	26
Atrial fibrillation	Paroxysmal or persistent	21
Dyslipidaemia	Non-fasting total cholesterol >5 mmol·L^{-1}; HDL-C <1.0 mmol·L^{-1} ; LDL-C >3 mmol·L^{-1}	17
Valvular surgery	Mitral or aortic valvular surgery in medical history without residual left valvular heart disease (less than mild on echocardiography)	56
ECG		
SV1+RV6 per mm	Sum of s wave in V1 and r wave in V6 on ECG (in mm)	1× (SV1+RV6)
Echocardiography		
Left atrial dilation	Left atrial volume above 34 mL·m^{-2}	21

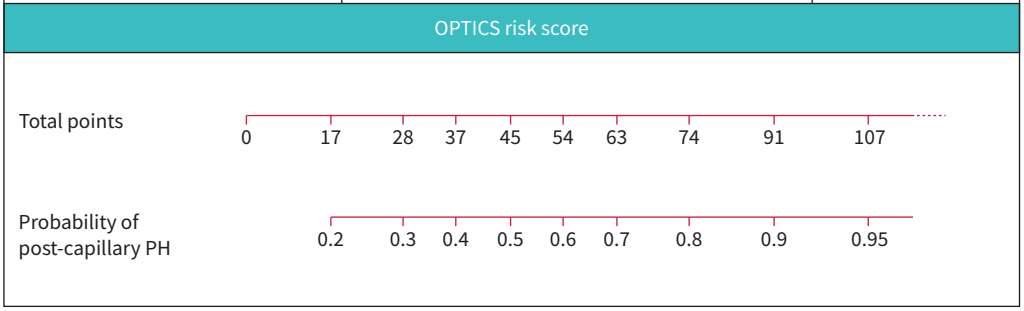

FIGURE 2 OPTICS risk score. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SV1: s wave in V1 ECG lead; RV6: r wave in V6 ECG lead; PH: pulmonary hypertension.

high probability of HFpEF assessed by the H_2FPEF score [65] did not exclude the presence of pre-capillary PH. Consequently, the OPTICS score might help to avoid unnecessary invasive procedures by predicting elevated pulmonary artery wedge pressure in PH patients without clear signs of left heart disease.

Portopulmonary hypertension

Laurent Savale discussed interesting novelties in portopulmonary hypertension (PoPH). PoPH is the concomitant presence of PAH and portal hypertension in patients with or without cirrhosis. PAH can develop in 2 to 6% of patients with portal hypertension and results from complex pathophysiological interactions between the portal and pulmonary circulation. Based on the high prevalence of cirrhosis, it is likely that PoPH remains underdiagnosed in many countries. In large PH registries, patients with PoPH represent 5 to 15% of patients with PAH, with the highest prevalence observed in the French registry, up to 20% of patients with PAH. According to data from the French registry, survival of patients with PoPH is highly influenced by the severity of the underlying liver disease. In terms of treatment, the current PH guidelines state that the algorithm for the management of patients with PAH can be cautiously applied to those patients, considering the severity of PAH, the severity of the liver disease and the possibility of liver transplantation. Indeed, the management of patients with PoPH is complex and must be based on a multidisciplinary approach, in particular for liver transplant candidates. PAH medications seem particularly efficacious in terms of haemodynamic improvement. However, patients with PoPH are usually excluded from the main randomised controlled trials (RCTs). There is a single RCT, the PORTICO study, that showed that macitentan decreased PVR by 35% after 12 weeks, without significant change in exercise capacity, and the treatment was well tolerated [66]. Most of the patients from the French registry (n=637) were treated with monotherapy. Interestingly, the effect of monotherapy on PVR was similar with a PDE-5i (−37%) and with an endothelin-receptor antagonist (ERA) (−40%). In patients with PoPH, initial combination therapy of an ERA and a PDE-5 inhibitor resulted in marked haemodynamic improvement, reaching a decrease in PVR of about 60% [67].

Finally, PoPH is usually a contraindication to liver transplantation. However, survival of patients with PoPH who underwent liver transplantation was better than non-transplanted patients, including those with mild cirrhosis [67]. The use of PAH drugs allows liver transplantation to be considered in selected patients, those who achieve sufficient improvement in haemodynamics, with a mean pulmonary arterial pressure <35 mmHg and/or PVR <3 WU. Those haemodynamic criteria allowing liver transplantation might be reached in at least 80% of PoPH patients after treatment with PAH medications [68]. Finally, normalisation in pulmonary haemodynamics is an achievable goal by combining PAH medications and liver transplantation in selected patients. Patients with PoPH who underwent liver transplantation no longer progress and have excellent long-term outcomes [67].

Pulmonary hypertension in the COVID-19 pandemic and beyond

COVID-19 pandemic and pulmonary hypertension

The COVID-19 pandemic greatly affected patients' life including patients living with PH. Montani *et al*. [69] presented a national retrospective cohort study from the French PH registry. Data from 211 pre-capillary PH patients suffering from SARS-CoV-2 infection were collected: 40% were outpatients, 32% were hospitalised in a conventional ward and 28% in an intensive care unit. Acute PE was diagnosed in five cases. Overall and in-hospital mortality was 25% and 41%, respectively. Non-survivors were significantly older, predominantly males and with comorbidities. No worsening of PH was noticed for survivors after the COVID-19 infection.

Baratto *et al*. [70] reported an observational analysis of the impact of the COVID-19 lockdown on exercise capacity in 63 patients with stable PAH. A comparison of the pooled 6MWT distances between three pre-lockdown and one post-lockdown visits showed a significant reduction of 6MWT distance of 14 m (p=0.004).

These findings, among others presented in this session, illustrate the consequent impact of the COVID-19 pandemic on potentially frail patients living with PH, and highlight the need for a comprehensive patient support throughout this difficult period.

Also noteworthy

Traditionally, vitamin K antagonists have been the mainstay of anticoagulant treatment in PAH and CTEPH but DOACs are now increasingly used [71–73]. A small study by Bokan *et al*. [74] investigated the choice of anticoagulant therapy after PE as a risk factor for CTEPH severity. Among 21 CTEPH patients over a 2-year period, DOACs were prescribed in 71.4% of cases (more frequently apixaban, followed by rivaroxaban and edoxaban) compared with 29% of cases treated with vitamin K antagonists (phenprocoumon). The choice of anticoagulant did not show any statistically significant effect on any selected parameters related to CTEPH severity. These results need confirmation in a larger trial.

In a "real life" randomised crossover study, Schneider *et al*. [75] investigated exercise performance and hypoxia-related health effects in 28 stable patients with PH during a high-altitude stay. Symptom-limited constant work-rate exercise test time reduced from 24 min to 17 min after >3 h at 2500 m of altitude, with similar dyspnoea level. Heart rate and tricuspid regurgitation pressure gradient were higher at altitude, but the slope of the relationship between the regurgitation pressure and cardiac output during exercise was similar at both levels. Short-time exposure to hypoxia was well tolerated for most patients with PH.

Imaging of pulmonary hypertension in adults: a position paper from the Fleischner Society

The Fleishner society published this year a position paper on imaging of PH in adults [76]. David Kiely gave an overview of the novelties included in this statement paper in the session *Clinical challenges beyond guidelines*, with a focus on magnetic resonance imaging (MRI) in PH. Although RHC will remain mandatory in the diagnostic algorithm for the necessary distinction between pre- and post-capillary PH, MRI should play an increasingly important role in patient monitoring in the coming years. Cardiac MRI is promising for the noninvasive follow-up of PH patients, as it provides a comprehensive evaluation of the heart with quantification of right ventricular volumes, mass and function, which are critical for PH prognosis [77]. In addition, innovative MRI techniques allow an increasingly precise evaluation of pulmonary haemodynamics and lung perfusion [78–80].

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References

1 Konstantinides SV, Meyer G, Becattini C, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020; 41: 543–603.

2 Konstantinides SV, Meyer G, Becattini C, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2020; 41: 543–603.

3 Klok FA, Ageno W, Ay C, *et al.* Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. *Eur Heart J* 2021; 42: 3146–3157.

4 Meyer G, Vicaut E, Danays T, *et al.* Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014; 370: 1402–1411.

5 Rivera-Lebron B, McDaniel M, Ahrar K, *et al.* Diagnosis, treatment and follow up of acute pulmonary embolism: consensus practice from the PERT Consortium. *Clin Appl Thromb Hemost* 2019; 25: 1076029619853037.

6 Sharifi M, Bay C, Skrocki L, *et al.* Moderate pulmonary embolism treated with thrombolysis (from the 'MOPETT' Trial). *Am J Cardiol* 2013; 111: 273–277.

7 Kucher N, Boekstegers P, Muller OJ, *et al.* Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014; 129: 479–486.

8 Piazza G, Hohlfelder B, Jaff MR, *et al.* A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv* 2015; 8: 1382–1392.

9 Tapson VF, Sterling K, Jones N, *et al.* A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. *JACC Cardiovasc Interv* 2018; 11: 1401–1410.

10 Kuo WT, Banerjee A, Kim PS, *et al.* Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest* 2015; 148: 667–673.

11 Avgerinos ED, Jaber W, Lacomis J, *et al.* Randomized trial comparing standard *versus* ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE Trial. *JACC Cardiovasc Interv* 2021; 14: 1364–1373.

12 Sista AK, Horowitz JM, Tapson VF, *et al.* Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. *JACC Cardiovasc Interv* 2021; 14: 319–329.

13 Fernandes CJ, Morinaga LTK, Alves JL Jr, *et al.* Cancer-associated thrombosis: the when, how and why. *Eur Respir Rev* 2019; 28: 180119.
14 Kahale LA, Hakoum MB, Tsolakian IG, *et al.* Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev* 2018; 6: CD006650.
15 Mosarla RC, Vaduganathan M, Qamar A, *et al.* Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol* 2019; 73: 1336–1349.
16 Le Gal G, Kovacs MJ, Carrier M, *et al.* Validation of a diagnostic approach to exclude recurrent venous thromboembolism. *J Thromb Haemost* 2009; 7: 752–759.
17 Ainle FN, Kevane B. Which patients are at high risk of recurrent venous thromboembolism (deep vein thrombosis and pulmonary embolism)? *Hematology Am Soc Hematol Educ Program* 2020; 2020: 201–212.
18 Mahe I, Chidiac J, Bertoletti L, *et al.* The clinical course of venous thromboembolism may differ according to cancer site. *Am J Med* 2017; 130: 337–347.
19 Bates SM, Rajasekhar A, Middeldorp S, *et al.* American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv* 2018; 2: 3317–3359.
20 van der Pol LM, Tromeur C, Bistervels IM, *et al.* Pregnancy-adapted YEARS algorithm for diagnosis of suspected pulmonary embolism. *N Engl J Med* 2019; 380: 1139–1149.
21 Bleker SM, Buchmuller A, Chauleur C, *et al.* Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomised trial of two doses. *Thromb Res* 2016; 144: 62–68.
22 Zondag W, Hiddinga BI, Crobach MJ, *et al.* Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. *Eur Respir J* 2013; 41: 588–592.
23 Aujesky D, Obrosky DS, Stone RA, *et al.* Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005; 172: 1041–1046.
24 Jimenez D, Aujesky D, Moores L, *et al.* Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010; 170: 1383–1389.
25 Roy PM, Penaloza A, Hugli O, *et al.* Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. *Eur Heart J* 2021; 42: 3146–3157.
26 Becattini C, Maraziti G, Vinson DR, *et al.* Right ventricle assessment in patients with pulmonary embolism at low risk for death based on clinical models: an individual patient data meta-analysis. *Eur Heart J* 2021; 42: 3190–3199.
27 Hutchinson BD, Navin P, Marom EM, *et al.* Overdiagnosis of pulmonary embolism by pulmonary CT angiography. *Am J Roentgenol* 2015; 205: 271–277.
28 den Exter PL, Kroft LJM, Gonsalves C, *et al.* Establishing diagnostic criteria and treatment of subsegmental pulmonary embolism: a Delphi analysis of experts. *Res Pract Thromb Haemost* 2020; 4: 1251–1261.
29 Miller WT Jr, Marinari LA, Barbosa E Jr, *et al.* Small pulmonary artery defects are not reliable indicators of pulmonary embolism. *Ann Am Thorac Soc* 2015; 12: 1022–1029.
30 Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. *Blood* 2020; 135: 724–734.
31 Boon G, Bogaard HJ, Klok FA. Essential aspects of the follow-up after acute pulmonary embolism: an illustrated review. *Res Pract Thromb Haemost* 2020; 4: 958–968.
32 van Es N, Le Gal G, Otten HM, *et al.* Screening for occult cancer in patients with unprovoked venous thromboembolism: a systematic review and meta-analysis of individual patient data. *Ann Intern Med* 2017; 167: 410–417.
33 Khan F, Rahman A, Carrier M. Occult cancer detection in venous thromboembolism: the past, the present, and the future. *Res Pract Thromb Haemost* 2017; 1: 9–13.
34 Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. *N Engl J Med* 2018; 379: 1290.
35 Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.
36 Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
37 Hoeper MM, Meyer K, Rademacher J, *et al.* Diffusion capacity and mortality in patients with pulmonary hypertension due to heart failure with preserved ejection fraction. *JACC Heart Fail* 2016; 4: 441–449.
38 Lewis RA, Thompson AAR, Billings CG, *et al.* Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2020; 55: 2000041.

39 Trip P, Nossent EJ, de Man FS, *et al.* Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. *Eur Respir J* 2013; 42: 1575–1585.
40 Sun XG, Hansen JE, Oudiz RJ, *et al.* Pulmonary function in primary pulmonary hypertension. *J Am Coll Cardiol* 2003; 41: 1028–1035.
41 Hoeper MM, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? *Lancet Respir Med* 2017; 5: 676–678.
42 Keusch S, Hildenbrand FF, Bollmann T, *et al.* Tobacco smoke exposure in pulmonary arterial and thromboembolic pulmonary hypertension. *Respiration* 2014; 88: 38–45.
43 Schiess R, Senn O, Fischler M, *et al.* Tobacco smoke: a risk factor for pulmonary arterial hypertension? A case-control study. *Chest* 2010; 138: 1086–1092.
44 Hoeper MM, Pausch C, Grunig E, *et al.* Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. *J Heart Lung Transplant* 2020; 39: 1435–1444.
45 Bhattarai P, Lu W, Markos J, *et al.* Increased arterial remodelling in smokers and mild-moderate COPD patients are indicative of potential early onset of pulmonary hypertension. *Eur Respir J* 2021; 58: OA1216.
46 Gaikwad A, Lu W, Dey S, *et al.* Arterial remodelling in patients with idiopathic pulmonary fibrosis (IPF) and the possible role of endothelial to mesenchymal transition (EndMT). *Eur Respir J* 2021; 58: Suppl. 65, OA1222.
47 Chaouat A, Bugnet AS, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.
48 Piccari L, Blanco I, Torralba Y, *et al.* Gas exchange impairment in COPD with severe pulmonary hypertension. *Eur Respir J* 2021; 58: Suppl. 65, PA1926.
49 Nathan SD, Barbera JA, Gaine SP, *et al.* Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019; 53: 1801914.
50 King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. *Curr Opin Pulm Med* 2019; 25: 459–467.
51 Behr J, Nathan SD. Pulmonary hypertension in interstitial lung disease: screening, diagnosis and treatment. *Curr Opin Pulm Med* 2021; 27: 396–404.
52 Frost A, Badesch D, Gibbs JSR, *et al.* Diagnosis of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801904.
53 Swift A, Saunders L, Capener D, *et al.* MRI metric lung parenchyma T1 indicates lung pathology in patients with pulmonary hypertension. *Eur Respir J* 2021; 58: Suppl. 65, PA1934.
54 Saunders LC, Eaden JA, Bianchi SM, *et al.* Free breathing lung T1 mapping using image registration in patients with idiopathic pulmonary fibrosis. *Magn Reson Med* 2020; 84: 3088–3102.
55 Shioleno AM, Ruopp NF. Group 3 pulmonary hypertension: a review of diagnostics and clinical trials. *Clin Chest Med* 2021; 42: 59–70.
56 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.
57 Dawes T, Dimopoulas KD, Mccabe C, *et al.* Survival effects of pulmonary vasodilators in group 3 pulmonary hypertension. *Eur Respir J* 2021; 58: Suppl. 65, OA177.
58 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.
59 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.
60 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.
61 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.
62 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.
63 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.
64 Jansen SMA, Huis In 't Veld AE, Jacobs W, *et al.* Noninvasive prediction of elevated wedge pressure in pulmonary hypertension patients without clear signs of left-sided heart disease: external validation of the OPTICS risk score. *J Am Heart Assoc* 2020; 9: e015992.
65 Suzuki S, Kaikita K, Yamamoto E, *et al.* H2 FPEF score for predicting future heart failure in stable outpatients with cardiovascular risk factors. *ESC Heart Fail* 2020; 7: 65–74.
66 Sitbon O, Bosch J, Cottreel E, *et al.* Macitentan for the treatment of portopulmonary hypertension (PORTICO): a multicentre, randomised, double-blind, placebo-controlled, phase 4 trial. *Lancet Respir Med* 2019; 7: 594–604.

67 Savale L, Guimas M, Ebstein N, *et al.* Portopulmonary hypertension in the current era of pulmonary hypertension management. *J Hepatol* 2020; 73: 130–139.

68 Savale L, Sattler C, Coilly A, *et al.* Long-term outcome in liver transplantation candidates with portopulmonary hypertension. *Hepatology* 2017; 65: 1683–1692.

69 Montani D, Certain M-C, Savale L, *et al.* Late Breaking Abstract – COVID-19 in patients with pulmonary hypertension: a national prospective cohort study. *Eur Respir J* 2021; 58: Suppl. 65, PA3606.

70 Baratto C, Caravita S, Dewachter C, *et al.* Impact of 3-months COVID-19 lockdown on exercise capacity in stable pulmonary arterial hypertension. *Eur Respir J* 2021; 58: Suppl. 65, PA3589.

71 Delcroix M, Torbicki A, Gopalan D, *et al.* ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2021; 57: 2002828.

72 Bunclark K, Newnham M, Chiu YD, *et al.* A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost* 2020; 18: 114–122.

73 Humbert M, Simonneau G, Pittrow D, *et al.* Safety of riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension with concomitant novel oral anticoagulants or vitamin K antagonist use: data from the EXPERT Registry. *Am J Respir Crit Care Med* 2021; 201: A6043.

74 Bokan A, Staehler G, Kempa AT, *et al.* Type of anticoagulant therapy as a risk factor for the severity of chronic thromboembolic pulmonary hypertension. *J Thromb Haemost* 2021; 58: Suppl. 65, PA3593.

75 Schneider SR, Mayer LC, Lichtblau M, *et al.* Effect of a daytrip to altitude (2500 m) on exercise performance in pulmonary hypertension – randomized cross-over trial. *ERJ Open Res* 2021: 7: 00314-2021.

76 Remy-Jardin M, Ryerson CJ, Schiebler ML, *et al.* Imaging of pulmonary hypertension in adults: a position paper from the Fleischner Society. *Eur Respir J* 2021; 57: 2004455.

77 Wessels JN, de Man FS, Vonk Noordegraaf A. The use of magnetic resonance imaging in pulmonary hypertension: why are we still waiting? *Eur Respir Rev* 2020; 29: 200139.

78 Rajaram S, Swift AJ, Telfer A, *et al.* 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax* 2013; 68: 677–678.

79 Reiter U, Kovacs G, Reiter C, *et al.* MR 4D flow-based mean pulmonary arterial pressure tracking in pulmonary hypertension. *Eur Radiol* 2021; 31: 1883–1893.

80 Kiely DG, Levin D, Hassoun P, *et al.* EXPRESS: statement on imaging and pulmonary hypertension from the Pulmonary Vascular Research Institute (PVRI). *Pulm Circ* 2019: 9: 2045894019841990.

81 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.