Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease with a variable natural history. Pulmonary hypertension (PH) is frequently found in patients with IPF and is associated with an almost 3-fold increase in the risk of death. Pulmonary hypoxic vasoconstriction plays an important role in the pathogenesis of PH in IPF (PH-IPF), although it has become clear that it is not the only mechanism involved. While invasive right heart catheterization is the gold standard modality of hemodynamic assessment, there has been increasing interest in noninvasive testing, such as Doppler echocardiogram, as complementary methods of assessing right ventricular function in these patients. While the expanding array of pharmacologic options for the treatment of pulmonary arterial hypertension has engendered increased interest in the application of these therapies for PH-IPF, supportive evidence for benefit is lacking.

Key Words—pulmonary fibrosis, idiopathic pulmonary fibrosis, pulmonary hypertension, pulmonary vascular disease, interstitial lung disease
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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia of unknown etiology, limited to the lungs and associated with the histopathologic and/or radiographic pattern of usual interstitial pneumonia.1,2 IPF is the most common idiopathic interstitial pneumonia with an incidence of 7 to 16 per 100,000 cases and a prevalence of 14 to 43 per 100,000 persons.3,4 IPF is a fatal lung disease with a variable natural history and a median survival of 2.5 to 5 years.5,6 Pulmonary hypertension (PH) is a well recognized complication of IPF, and when present, it is associated with an almost 3-fold increase in the risk of death.7,8 This review will summarize the current knowledge of the epidemiology, pathophysiology, diagnostic methods, clinical implications, and possible treatments of PH in IPF.

DEFINITION AND EPIDEMIOLOGY
The Fifth Symposium on PH held in 2013 in Nice, France, classifies PH associated with IPF in “Group 3: Pulmonary hypertension due to lung disease and/or hypoxemia,” differentiating this from other etiologies of PH.9 PH is defined as resting mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg as assessed by right heart catheterization (RHC). PH should be differentiated from pulmonary arterial hypertension (PAH), hemodynamically defined as mPAP of ≥25 mm Hg in the presence of a normal pulmonary capillary wedge pressure (PCWP) on resting RHC.9 It has not been established which hemodynamic definition is suitable for patients with PH-IPF. In a series of 70 patients with IPF, a receiver operating curve (ROC) analysis suggested mPAP cutoff of 17 was the best predictor for mortality10; however, this has not been validated in another cohort.

There have been several publications on the incidence of PH-IPF, reporting ranges from 20% to 42% (Table 1). Several factors account for this wide incidence range. The first factor is the lack of a standardized definition for PH-IPF. Some studies used the criteria for PH and others the PAH definition. The second factor is the diagnostic method used for the PH diagnosis. While most studies used hemodynamic measurement as assessed by RHC, some included patients with PH defined by pulmonary artery systolic pressure (PASP) on echocardiograms. Finally, most studies were performed in patients being worked up for lung transplantation, since these patients routinely undergo RHC as part of their transplant evaluation. Although lung transplant is the only treatment available for IPF, the selected subgroup that receives evaluation is not representative of the overall IPF population. Using cohorts that consist of a younger IPF population with fewer comorbidities might underestimate the “true” incidence of PH-IPF. Furthermore, the timing of evaluation for PH-IPF may affect the prevalence. It has been shown that at an earlier IPF stage hemodynamics might be normal or just mildly abnormal. Use of data from patients with more advanced disease undergoing transplant evaluation may overestimate the incidence of PH-IPF, and even in the setting of advanced disease PH progression is ongoing. A study of IPF patients awaiting lung transplantation using serial RHC data showed progressive development of PH from time of initial transplant evaluation (38.6%) to time of transplant (86.4%).11

When PH is present in patients with IPF, it is generally mild to moderate. In a retrospective study of 135 patients with IPF, those with PH-IPF (defined by mPAP ≥25 mm Hg and PCWP <15 mm Hg) had mPAP of 31±6 mm Hg and mean pulmonary vascular resistance (PVR) of 5±2 Wood units.12 Fourteen patients (11%) had moderate to severe right ventricular (RV) dysfunction on echocardiogram.12 However, a minority of patients with advanced lung disease have severe PH, in which the PAP is higher than expected, and those are sometimes referred to as “out of pro-
portion” PH. A definition for “out of proportion” PH has not yet been established or included in the diagnostic criteria for Group 3 PH.

PATHOGENESIS

The histopathologic hallmark of IPF includes heterogeneous areas of fibrosis with architectural distortion. The fibrotic zones are composed mainly of dense collagen, with scattered subepithelial foci of proliferating fibroblasts and myofibroblasts (fibroblast foci). Progressive parenchymal fibrosis then leads to pulmonary vascular destruction, the initial pathologic mechanism of PH-IPF (Figure 1, top left, A, and top right, B). Vessel ablation in areas of dense fibrosis contributes to reduction of capillary density, impaired gas exchange, and elevated PVR. However, occlusive venopathy and vascular remodeling have been found in nonfibrotic lung areas, suggesting mechanisms other than extension of fibrosis and vascular obliteration contribute to the development of PH-IPF (Figure 1, bottom left, C, and bottom right, D).

Chronic alveolar hypoxia leads to subsequent pulmonary vascular remodeling and pulmonary artery (PA) vasoconstriction, also playing a major role in the development of PH-IPF. Vessels show intimal proliferation and medial thickening of muscular pulmonary arteries and pulmonary veins. This leads to neovascularization and a redistribution of microvessels within the pulmonary interstitium. New vessels differ morphologically from normal arteries and arterioles by lacking an elastin layer, which reduces vascular compliance.

Further vascular remodeling is due to overexpression of inflammatory mediators (cytokines and growth factors). In general, leukotrienes promote fibrosis, whereas prostaglandin E2 (PGE2) opposes fibrogenic responses. There is an imbalance of these factors in IPF, which favors the production of 5-lipoxygenase (a profibrotic leukotriene), and upregulation of tumor necrosis factor (TNF-α), platelet-derived growth factor (PDGF), and fibroblast growth factor, all of which mediate lung fibrosis and vascular remodeling. There is also evidence of decreased levels of PGE2 in bronchoalveolar lavage in patients with IPF. Decreased levels of PGE2 may increase expression of TNF-α and transforming growth factor (TGF)-β, responsible for collagen deposition. Finally, genetic overexpression of the vasoconstrictor endothelin-1 (ET-1) causes pulmonary fibrosis in mice. ET-1 is highly expressed in lung tissue, bronchoalveolar lavage fluid, and serum from patients with IPF and concomitant PH. This evidence provided the rationale for performing clinical trials using prostacyclin.
and endothelin receptor antagonists in patients with IPF-PH.

Comorbidities, both pulmonary and nonpulmonary, frequently exist in IPF (Figure 2). These comorbidities, such as coronary artery disease, systolic or diastolic left ventricular dysfunction, obstructive sleep apnea, and recurrent venous thromboembolic events may contribute to the development of PH in patients with IPF.20 When present, they may contribute to increased mortality and should be addressed therapeutically as indicated.

**DIAGNOSIS**

PH-IPF symptoms are nonspecific and overlap with symptoms of IPF, making the diagnosis extremely challenging. These include resting or exertional shortness of breath, fatigue, weakness, palpitations, chest discomfort, and light-headedness or syncope. Cardiac examination may reveal an accentuated or loud P2 component of the second heart sound, a fixed split of the second heart sound (consistent with pulmonic insufficiency), and a holosystolic tricuspid regurgitation murmur. Other physical examination signs may include RV heave, jugular venous distention, and pedal edema. These findings represent progressive RV dilation and hypertrophy leading to increased right atrial pressure, and are consistent with a more advanced disease stage.

Clinical suspicion for PH-IPF should be high in the setting of progressive exercise limitation despite stable pulmonary function testing and/or parenchymal fibrosis on a chest computed tomography (CT) scan. Once other etiologies have been ruled out (such as pulmonary embolism), these symptoms should alert a physician to possible presence of PH-IPF and may justify pursuing further diagnostic testing.

**Imaging**

Chest radiography (CXR) may reveal cardiomegaly and enlargement of the pulmonary arteries. Although these findings might indicate presence of PH, they are nonspecific, and normal radiographic findings do not rule out PH.13 Chest CT findings suggestive of PH include enlargement of the pulmonary trunk (PA diameter >29 mm), RV dilation, and ratio of the main PA to ascending aorta diameter (ratio >1).21 However, a study of 65 patients with IPF failed to demonstrate a correlation between mPAP on RHC and main PA diameter or fibrosis score on CT scan.22

**Pulmonary Function Testing**

Pulmonary function test (PFT) values are fundamental in establishing the diagnosis and severity of IPF. A restrictive pattern is typically seen in PFTs of IPF patients. There is no significant difference in the forced vital capacity (FVC) and total lung capacity (TLC) of IPF patients with and without PH.7,23 However, percentage of predicted lung diffusion capacity for carbon monoxide (DLCO %) is significantly lower in those with PH-IPF (31±10% vs 38±11%; P=0.04).7 A DLCO <30% has been shown to be associated with a 2-fold higher prevalence of PH-IPF.23 Similarly, a FVC %/DLCO % ratio >1.5 was associated with an almost 2-fold increased risk of PH-IPF.23 The combination of DLCO <40% together with the need for supplemental oxygen predicted presence of PH-IPF with a sensitivity and specificity of 65% and 94.1%, respectively.7 However, none of these associations has been sufficiently robust to serve as a diagnostic predictor of PH-IPF.

**Exercise Capacity**

Performance on a 6-minute walk test (6MWT) is a key component in the evaluation of IPF. Mean distance walked (144±66 vs 366±82 m; P<0.001) and the pulse oximetry saturation (SpO2) nadir (80±4% vs 88±4%; P<0.001) during the 6MWT was found to be significantly lower in PH-IPF in a recent study of patients with advanced IPF.7 Exercise desaturation to <85% had a sensitivity and specificity of 100% and 61.9%, respectively, for associated PH.24 Also, failure of the heart rate to fall 1 minute after a 6MWT was found to predict presence of PH in patients with IPF (OR 4.0, 95% 1.17-13.69, P=0.02).25

The impact of PH on gas exchange and exercise capacity was evaluated in a study of patients with pulmonary fibrosis undergoing cardiopulmonary exercise testing.26 Patients with PH showed a significantly impaired exercise tolerance, worsened ventilatory efficiency, and increased dyspnea.

**Biomarkers**

Circulating levels of B-type natriuretic peptide (BNP) have been used as a prognostic biomarker for PAH.27 It has been shown that plasma BNP levels are higher in patients with fibrotic lung...
Bernoulli equation is applied to calculate measured PASP by RHC.24 Between estimated PASP by DE and that measurement of PASP was possible in a group of patients with IPF, showing the mean TAPSE varies between 2.3 and 2.6 cm, with a TAPSE of 2.0 cm likely representing the lowest acceptable normal value.32 In PAH, a TAPSE <1.8 cm was associated with greater RV dysfunction, lower cardiac index, and higher mortality.35 In 134 patients with IPF, the mean TAPSE was 2.1 cm with a significantly lower TAPSE (1.8 cm vs 2.1 cm; P=0.01) in those with moderate to severe RV dysfunction.12 TAPSE was associated with stroke volume and inversely associated with PVR, independent of age, sex, race, height, weight, and FVC.12

Dilation of the RV in presence of normal size left ventricle (LV) strongly suggests increased RV afterload. Direct measurement of the RV-to-LV diameter ratio (RV:LV) assesses the relationship between the RV and the LV, and has been used to indicate presence of PH. In IPF patients, the mean RV:LV diameter ratio was 0.9±0.3 and a ratio ≥1 was significantly correlated with increased PVR, independent of age, sex, race, height, weight, and FVC.12 Therefore, echocardiographic measures of RV structure and function, particularly presence of RV dilation, RV dysfunction, and RV:LV diameter ratio >1, may suggest presence of PH-IPF and strong consideration should be given to pursue RHC.

**Right Heart Catheterization**

RHC is the gold standard modality for hemodynamic assessment of PH-IPF. It will confirm the diagnosis and establish its severity. At this time, RHC is not routinely recommended in patients with IPF. Current indications for RHC in chronic lung disease include: proper diagnosis of PH in candidates for transplantation; suspected “out of proportion” PH, potentially amenable to be enrolled in randomized controlled clinical trials with PAH drug therapy; frequent episodes of RV failure; and inconclusive echocardiographic study in cases with a high level of suspicion.13,34 RHC can also demonstrate presence of diastolic dysfunction, which can frequently cause PH and imparts different implications in management (aggressive diuresis, blood pressure control, etc). Moreover, RHC can provide important prognostic information that can be used in patient counseling and possibly other therapeutic considerations for a disease with no current available treatment.

**CLINICAL IMPLICATIONS**

IPF has a median survival of 2.5 to 5 years.5,6 Presence of PH-IPF is a poor prognostic factor and is associated with a 3-fold increased risk of death, independent of age, race, FVC percentage, 6-minute walk distance (6MWD), and other covariates, (HR 3.6; 95% CI 1.8-7.1; P=0.0004).8 In one study, PH was present in 52.4% of IPF nonsurvivors compared to only 24.1% of survivors (P=0.008).7 The 1-year mortality rate of IPF patients with PH was 28% compared to 5.5% in those without PH (P=0.002) (Figure 3).7 In one study, DLCO <40% predicted mortality in IPF patients (RR 2.70; 95%
CI 1.46-4.99). However, in another study, while FVC and DLCO were lower in nonsurvivors, they did not independently predict outcomes, suggesting that rapid clinical deterioration with right heart failure may occur unrelated to progression of underlying parenchymal process. In IPF, 6MWD was a better predictor of mortality than FVC, and a 6MWD <207 m was associated with a greater than 4-fold mortality rate (RR 4.7; 95% CI 2.5-8.9; \( P<0.0001 \)). Similarly, heart rate recovery after 6MWT was found to predict survival in patients with IPF without PH. In addition, BNP has also been identified as a risk factor for death independent of lung functional impairment or hypoxemia in IPF patients.

We have shown that increasing RV:LV diameter ratio, moderate to severe right atrial and RV dilation and moderate to severe RV dysfunction detected by DE were associated with an increased risk of death, independent of covariates (including age, sex, race, height, weight, and FVC) in patients with IPF being evaluated for lung transplantation (Table 2). Moreover, RV:LV diameter ratio and RV dysfunction predicted adverse outcomes independently of the presence of PH-IPF or the level of the PVR. The presence of an increased RV:LV diameter ratio might represent an early anatomical change in response to higher PVR prior to the development of frank RV failure, and could directly contribute to adverse outcome. This suggests that right sided heart structure and function may provide complementary information in identifying a population of patients with IPF who are at increased risk of death.

Focusing on hemodynamics, Lettieri et al showed a linear correlation between mPAP and outcomes, with higher pressures associated with a greater risk of mortality (HR 1.09; CI 1.02-1.16). In our study, higher mPAP was also possibly associated with reduced survival but did not reach statistical significance. Higher PVR was associated with 30% increased risk for overall mortality (HR per 1 Wood unit increase = 1.3; 95% CI 1.1-1.5; \( P=0.001 \)). Right atrial pressure, cardiac output, and stroke volume were not associated with the risk of death (Table 2). Preoperative mPAP >35 mm Hg has also been associated with increased mortality at 3 months after lung transplantation.

**MANAGEMENT**

There are limited data on the treatment of PH-IPF. Oxygen therapy for correction of hypoxemia decreases mortality in chronic obstructive pulmonary disease but such findings have not been demonstrated or systematically evaluated in IPF. However, given that hypoxic vasoconstriction plays an important role in the pathogenesis of PH-IPF, the use of oxygen to maintain resting and exertional arterial oxygen saturation above 90% is recommended. There is a growing interest in the potential benefit of PAH-specific therapies in PH-IPF (Table 3). Olschewski et al investigated the acute effects of inhaled nitric oxide (iNO), inhaled and intravenous prostacyclin (epoprostenol and iloprost, respectively), and calcium channel blockers (CCB) in a pilot, open-label study of patients with pulmonary fibrosis of various causes with associated PH (1 had IPF). All 4 drugs decreased mPAP and PVR; epoprostenol worsened oxygenation by increasing the ventilation/perfusion (V/Q) mismatch; and epoprostenol and CCB caused hypotension. Similarly, Ghofrani et al examined the acute effects of a single dose of iNO, epoprostenol, or sildenafil in 16 patients with PH associated with pulmonary fibrosis (7 with IPF). All improved PVR, while only epoprostenol affected V/Q mismatch and worsened hypoxemia. The largest prospective prosta-cyclin study in PH-IPF was published in abstract form, included 51 patients with PH-IPF, and showed no difference

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**Table 2. Cox Proportional Hazards Models for Echocardiographic and Hemodynamic Predictors of Mortality in Idiopathic Pulmonary Fibrosis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
<th>Censored at Lung Transplantation†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>( P ) Value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV:LV ≥1</td>
<td>3.8 1.5-9.7</td>
<td>0.006</td>
<td>4.5 1.7-11.9</td>
</tr>
<tr>
<td>TAPSE &lt;1.6 cm</td>
<td>2.0 1.0-3.7</td>
<td>0.05</td>
<td>1.9 1.0-3.7</td>
</tr>
<tr>
<td>Moderate to severe right atrial dilation</td>
<td>2.4 1.2-4.7</td>
<td>0.009</td>
<td>2.9 1.4-5.9</td>
</tr>
<tr>
<td>Moderate to severe RV dilation</td>
<td>2.6 1.4-4.6</td>
<td>0.001</td>
<td>2.7 1.4-5.4</td>
</tr>
<tr>
<td>Moderate to severe RV dysfunction</td>
<td>4.9 2.5-9.6</td>
<td>&lt;0.001</td>
<td>5.5 2.6-11.5</td>
</tr>
<tr>
<td>PASP, for 5 mm Hg increase</td>
<td>1.1 1.1-1.2</td>
<td>&lt;0.001</td>
<td>1.2 1.1-1.3</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure, for 1 mm Hg increase</td>
<td>0.9 0.9-1.0</td>
<td>0.34</td>
<td>0.9 0.9-1.0</td>
</tr>
<tr>
<td>mPAP, for 10 mm Hg increase</td>
<td>1.3 1.0-1.7</td>
<td>0.06</td>
<td>1.3 1.0-1.8</td>
</tr>
<tr>
<td>PVR, for 1 Wood unit increase</td>
<td>1.3 1.1-1.4</td>
<td>&lt;0.001</td>
<td>1.3 1.1-1.5</td>
</tr>
<tr>
<td>Cardiac output, for 1 L/min decrease</td>
<td>1.1 0.9-1.4</td>
<td>0.31</td>
<td>1.2 0.9-1.5</td>
</tr>
<tr>
<td>Stroke volume, for 10 mL decrease</td>
<td>1.1 1.0-1.2</td>
<td>0.18</td>
<td>1.1 0.9-1.3</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race/ethnicity, height, weight, FVC, and transplant status
†Adjusted for age, sex, race/ethnicity, height, weight, FVC

Adapted from Rivera-Lebron et al, 2013.
in the 6MWD or oxygenation with 12 weeks of inhaled iloprost.42

Endothelin receptor blockers have also been studied in IPF. Bosentan Use in Interstitial Lung Disease-1 (BUILD-1),43 a double-blind placebo-controlled trial, investigated the use of bosentan in 158 IPF patients. No significant improvement in 6MWD was observed after 12 months; however, there was a trend toward delaying time to death or disease progression with therapy. Subsequently, BUILD-3 evaluated 616 patients with mild, biopsy-proven IPF, but did not show delay in time to death or disease progression. Most recently, ARTEMIS-IPF examined the use of ambrisentan in IPF. This study was terminated early for futility, as ambrisentan was not effective in treating IPF and may have been associated with an increased risk of disease progression and respiratory hospitalizations. It is important to note that these 3 studies were not designed to study patients with PH-IPF, as their inclusion criteria were based on presence of IPF. A subset of 21 patients with PH associated with ILD in ARIES-3 demonstrated no improvement in 6MWD.

Collard et al performed an open-label study of 14 patients with PH-IPF, and demonstrated a significant improvement in 6MWD after 3 months of the phosphodiesterase inhibitor sildenafil. The Sildenafil Trial of Exercise Performance in IPF (STEP-IPF),48 a placebo-controlled trial of sildenafil in 180 patients with IPF without hemodynamically diagnosed PH, failed to meet its primary endpoint of a greater than 20% improvement in 6MWD at 12 and 24 weeks. It did show improvement in dyspnea and quality of life. Interestingly, a recent post-hoc analysis of STEP-IPF showed that the subgroup of patients with echocardiographic evidence of RV dysfunction had better preservation of exercise capacity, while subjects without RV dysfunction did not respond to therapy.49 This might indicate that subjects with RV dysfunction have a greater degree of circulatory limitation to exercise, and are thus apt to functionally improve in response to RV afterload reducing treatment. To determine the effect of PAH therapies on patients with PH-IPF, future studies of PH therapy may need to be focused on IPF subgroups with the combination of significantly elevated PVR and RV dysfunction, as these subjects may have greater capacity to improve.

Riociguat is the first member of a new class of vasodilating agents known as soluble guanylate cyclase stimulators that

<table>
<thead>
<tr>
<th>Author/Journal/Year</th>
<th>Drug Group</th>
<th>PH Definition</th>
<th>N</th>
<th>Study Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olschewski,40 AJRCCM 1999</td>
<td>iNO, IV epoprostenol, inhaled iloprost, CCB</td>
<td>Pulm fibrosis</td>
<td>8 (IPF=1)</td>
<td>Open label</td>
<td>All ↓ PVR, mPAP Epo ↓ O2 CCB ↓ BP</td>
</tr>
<tr>
<td>Ghofrani,41 Lancet 2002</td>
<td>iNO, IV epoprostenol or sildenafil</td>
<td>Pulm fibrosis</td>
<td>16 (IPF=7)</td>
<td>Open label</td>
<td>All ↓ PVR, Epo ↓ O2 Sildenafil ↑ O₂</td>
</tr>
<tr>
<td>Krowka,42 Chest [abstract] 2007</td>
<td>Inhaled iloprost</td>
<td>IPF</td>
<td>51</td>
<td>DB-RCT</td>
<td>No change in 6MWT, exercise O₂, WHO class in 12 weeks</td>
</tr>
<tr>
<td>King,43 AJRCCM 2008 BUILD-1</td>
<td>Bosentan</td>
<td>IPF</td>
<td>158</td>
<td>DB-RCT</td>
<td>No change in 6MWD at 12 months. Trend toward delaying time to death or disease progression</td>
</tr>
<tr>
<td>King,44 AJRCCM 2011 BUILD-3</td>
<td>Bosentan</td>
<td>IPF mild, biopsy proven</td>
<td>616</td>
<td>DB-RCT</td>
<td>No delay in time to death or disease progression</td>
</tr>
<tr>
<td>Raghu,45 Annals 2013 ARTEMIS-IPF</td>
<td>Ambrisentan</td>
<td>IPF</td>
<td>494</td>
<td>DB-RCT</td>
<td>Stopped early for lack of efficacy and possible ↑ risk of disease progression</td>
</tr>
<tr>
<td>Collard,47 Chest 2007</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>14</td>
<td>Open label-RCT</td>
<td>57% improved 6MWD of 20% at 3 months</td>
</tr>
<tr>
<td>IPFnet,48 NEJM 2010 STEP-IPF</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>180</td>
<td>DB-RCT</td>
<td>Did not meet 20% change in 6MWD at 12 or 24 weeks. Improvement in sob and QoL</td>
</tr>
<tr>
<td>Han,49 Chest 2013 (STEP-IPF post-hoc analysis)</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>119</td>
<td>DB-RCT</td>
<td>Improved preservation of 6MWD</td>
</tr>
</tbody>
</table>

Adapted from Nathan, 2009.55
cause vasodilation in both nitric oxide-dependent and independent pathways. Riociguat was investigated in a pilot, open-label study of 22 ILD-associated PH subjects (13 with IPF) with the primary endpoints of safety and tolerability.60 In this study, patients had mPAP >30 mm Hg (mean ± SD 40±10 mm Hg) and PVR >400 dyns·cm⁻⁵ (mean ± SD 656±201 dyns·cm⁻⁵). It showed improvement in 6MWD, cardiac output, and PVR, and no change in mPAP at 12 weeks. Arterial partial pressure of oxygen (PaO₂) decreased by 7±12 mm Hg at 12 weeks, suggesting presence of V/Q mismatch.

In summary, these studies present conflicting results with the use of PAH-specific agents in this population. Several factors may account for this. Some studies included patients with various diffuse fibrotic lung diseases, and response to PAH-specific therapy may differ between different groups. Other studies did not require PH for enrollment or relied on echocardiographic estimates of PASP as a surrogate for PH definition. Moreover, specific IPF patient subgroups most likely to benefit from vasodilator therapy have not been properly identified and studied. Finally, appropriate trial design and endpoints have not been determined for this entity.

Current guidelines discourage the use of PAH-specific therapy in IPF patients.1,3,5,6 Benefit of PAH-specific drugs in patients with PH-IPF has not been proven. Prospective, randomized, placebo-controlled trials evaluating IPF patients with hemodynamically proven PH and/or evidence of right heart failure by echocardiogram need to be completed before these therapies can be universally endorsed and adopted. Appropriate patient subgroups will need to be identified and targeted (eg, disproportionate PH), in whom PH likely contributes significantly to exercise limitation and morbidity. Moreover, appropriate trial endpoints will need to be agreed upon.

Finally, lung transplantation should be considered in the appropriate IPF patients with progressive lung disease. Five-year post-transplantation survival in IPF patients is estimated to be at 50% to 56%.1 Presence of PH does not preclude lung transplantation and is associated with increased mortality while awaiting transplantation. The current Lung Allocation Scoring system of the United Network for Organ Sharing increases priority for patients with PH in the setting of parenchymal lung disease.51 However, presence of PH also affects post-transplant outcomes with increased risk of primary graft dysfunction,52 perioperative mortality, and postoperative mortality.53

CONCLUSION
In conclusion, PH is a common complication of IPF. The diagnosis of PH-IPF is challenging, as symptoms are nonspecific. Presence of clinical deterioration without progression of underlying parenchymal lung disease justifies further diagnostic testing. Echocardiographic findings of RV dysfunction, RV dilatation, and increased RV:LV diameter ratio may suggest presence of PH-IPF. RHC is the gold standard for the diagnosis of PH-IPF, and should be considered when it is likely to influence clinical decision making. Presence of PH-IPF is associated with increased risk of mortality and worse outcome. Therapeutic considerations may include treatment of hypoxemia, treatment of underlying comorbid conditions, and lung transplantation. The application of PAH-specific therapies for PH-IPF is of uncertain benefit and needs further evaluation.

References
18. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary


