IPF: From Pathogenesis to cure

PH in IPF what to do: ERA, PDE5 inhibitors or palliation?

Rome 9-10th May 2014

Sergio Harari
U.O. di Pneumologia e UTIR
Servizio di Emodinamica e Fisiopatologia Respiratoria
Ospedale San Giuseppe - Milano
1. Pulmonary Arterial Hypertension

- Idiopathic PAH
- Disorders of the respiratory system and hypoxemia
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Sleep disorders
  - Alveolar hypoventilation
  - Chronic exposure to high altitude
  - Others...

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- COPD
- Interstitial lung disease
- Others pulmonary diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear or multifactorial mechanisms

1: Hematologic disorders, myeloproliferative disorders, splenectomy
2: Systemic disorders: vasculitis, sarcoidosis, PLCH, LAM, neurofibromatosis
3: Metabolic disorders: GD, thyroid disorders, glycogen storage disease
4: Others: tumoral obstruction, fibrosing mediastinitis, dyalisis
Disorders of the respiratory system and hypoxemia

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognosis factor and not require specific therapeutic intervention (except oxygen therapy)
- Medial hypertrophy and mild intimal fibrosis
Treatment of hypoxic pulmonary hypertension

- Efficacy of vasodilators has never been demonstrated
- Long-term oxygen therapy improves survival in COPD
  - 24 H > 12 H (NOTT study 1981)
  - 15 H > 0 H (BMRC study 1981)
  - Survival improvement due to $O_2$ is associated with minor changes in PAP
- Beneficial effects of drugs in a subgroup of patients with severe PH?
The prevalence of PH in patients with ILD varies greatly as a function of the underlying disease and the diagnostic mode used to identify PH.

The most extensive data have been published in IPF.
Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatment

How frequent is it?
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>N</th>
<th>Diagnosis</th>
<th>Definition of PH</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leutche et al.</td>
<td>2004</td>
<td>IPF</td>
<td>28</td>
<td>RHC</td>
<td>mPAP &gt; 35 mmHg</td>
<td>21.4</td>
</tr>
<tr>
<td>Nadrous et al.</td>
<td>2005</td>
<td>IPF</td>
<td>88</td>
<td>Echo</td>
<td>sPAP &gt; 35 mmHg, sPAP &gt; 50 mmHg</td>
<td>84, 31</td>
</tr>
<tr>
<td>Hamada et al.</td>
<td>2007</td>
<td>IPF</td>
<td>70</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>8.1</td>
</tr>
<tr>
<td>Zisman et al.</td>
<td>2007</td>
<td>IPF</td>
<td>65</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>41.5</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>2007</td>
<td>IPF</td>
<td>41</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg, PCWP ≤ 15 mmHg</td>
<td>20</td>
</tr>
<tr>
<td>Shorr et al.</td>
<td>2007</td>
<td>IPF</td>
<td>2.5</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>46.1</td>
</tr>
<tr>
<td>Nathan et al.</td>
<td>2008</td>
<td>IPF</td>
<td>118</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>40.7</td>
</tr>
<tr>
<td>Song et al.</td>
<td>2009</td>
<td>IPF</td>
<td>131</td>
<td>Echo</td>
<td>sPAP &gt; 40 mmHg</td>
<td>25</td>
</tr>
<tr>
<td>Minai et al.</td>
<td>2009</td>
<td>IPF</td>
<td>148</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg, mPAP &gt; 40 mmHg</td>
<td>45.9, 14.2</td>
</tr>
<tr>
<td>Kimura et al.</td>
<td>2012</td>
<td>IPF</td>
<td>101</td>
<td>RHC</td>
<td>mPAP &gt; 20 mmHg</td>
<td>34.6</td>
</tr>
</tbody>
</table>
The incidence and prevalence of PH in IPF remain unclear, with widely varying estimates. The differences reflect:

- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities
Out-of-Proportion PH
Nice definitions 2013

COPD/IPF/CPFE without PH : mPAP <25mmHg

COPD/IPF/CPFE with PH mPAP >25mmHg;

COPD/IPF/CPFE with severe PH
mPAP >35mmHg or mPAP >25mmHg with low cardiac index (CI <2.0 l/min/m2)
Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatment

Does it affect the prognosis of IPF?
### Pulmonary hypertension in IPF

<table>
<thead>
<tr>
<th>88 patients with IPF</th>
<th>PASP 0-35 mmHg (n=14)</th>
<th>PASP 36-50 mmHg (n=47)</th>
<th>PASP &gt;50 mmHg (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>4.8y</td>
<td>4.1y</td>
<td>0.7y</td>
</tr>
<tr>
<td>1 year survival</td>
<td>100%</td>
<td>79%</td>
<td>44%</td>
</tr>
<tr>
<td>3 year survival</td>
<td>64%</td>
<td>61%</td>
<td>32%</td>
</tr>
</tbody>
</table>

### Pulmonary hypertension in IPF

<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP ≤ 25 mmHg (n= 10)</th>
<th>MAP &gt; 25 mmHg (n= 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPAP, mmHg</strong></td>
<td>18.2 ± 3.6</td>
<td>29.8 ± 5.1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>6MWT distance, m</strong></td>
<td>365.9 ± 81.8</td>
<td>143.5 ± 65.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>SpO2 nadir on 6MWT, %</strong></td>
<td>88.0 ± 3.5</td>
<td>80.1 ± 3.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Mortality rate, %</strong></td>
<td>37.5</td>
<td>70.0</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883
Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883

In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF. PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications.
The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients.
Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis

**How can we investigate these patients?**
PH in IPF patients is more frequent when the underlying fibrosis is severe (secondary PH).

However, PH may occur in milder disease, raising the possibility of therapeutic intervention.

Thus, screening IPF patients for the early identification of PH is essential.
Correlates of PH in IPF

- it appears that PH may not correlate with lung volumes in patients with IPF
- factors aside from progressive fibrosis are responsible for PH in IPF
- pulmonary artery remodeling might play a more relevant role than vasoconstriction, yet the two pathogenetic processes might be intimately interrelated
Assessment of PH in IPF

Patients with IPF should be evaluated for PH when:

- The symptoms are more severe than one would expect from lung function data (dyspnea and fatigue are symptoms of IPF as well as PH)
- When signs of right heart failure develop
- If clinical deterioration is not matched by a decline in pulmonary function
- Profound hypoxemia, and a low DLCO are indicators of PH
## Recommendation for PH due to lung diseases

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class#</th>
<th>Level(f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>RHC is recommended for a definite diagnosis of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

**Once PH is suspected, patients should be evaluated by echocardiography**

<table>
<thead>
<tr>
<th>Should be enrolled in RCTs targeting PAH specific drugs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

# class of recommendations
\(f\) level of evidence
The main findings of this study are:
1. Noninvasive diagnostic tests such as echocardiogram, 6MWT distance, DSP, and SpO2 perform poorly in detecting PH in IPF patients.
2. The diagnostic accuracy of the echocardiogram for the detection of PAH exceeds that of the other variables, with a sensitivity of 72% and a positive predictive value of 62%.
3. The prevalence of PH in our cohort of patients with IPF was 43%.

Modrykamien AM et al. Respir Care 2010; 55: 584
The effect of diffuse pulmonary fibrosis on the reliability of CT signs of pulmonary hypertension

**Conclusion:** PA dilatation occurs in the absence of PH in patients with pulmonary fibrosis and is therefore an unreliable sign of PH in these patients.

Transverse CT scan shows dilatated main PA (diameter 35.23 mm) in 53-year-old patient with IPF and normal PAP.

Radiology; 2008; 249:1042-9
### Statement

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class #</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>RHC is recommended for a definite diagnosis of PH due to lung diseases</strong></td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

*Given the limitations of echocardiography, RHC remains the standard for the diagnosis of PH*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class #</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with “out of proportion” PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatment

Therapeutic options for PH in IPF are limited
## Statement

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class#</th>
<th>Levelf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>RHC is recommended for a definite diagnosis of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

The benefit of reversing intermittent hypoxia (at night or on exercise) is unclear and needs further study
STEP-IPF - Sildenafil in IPF

- Prospective, randomized, clinical trial: to evaluate effectiveness of sildenafil at improving breathing function, exercise capacity and QoL in patients with advanced IPF

- **Primary endpoint:** Change in 6-MWD (defined as ≥ 20% improvement or ≤ 20% improvement)

**STEP-IPF Results**

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Placebo</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20% improvement in 6MWD</td>
<td>9/89 (10%)</td>
<td>6/91 (7%)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

- No significant change in **6MWD** at 12 or 24 weeks
- No difference in mortality or acute exacerbations after 12 or 24 weeks
- **QOL**
  - Improvement with treatment on St. George’s Respiratory Questionnaire \(P = 0.01\)
  - No improvement on SF-36 or EQ-5D tests
- **Dyspnea**
  - Improvement with treatment on SOB Questionnaire \(P = 0.006\)
  - No improvement on Borg Dyspnea Index after walk test
- **Gas exchange** at 12 weeks
  - Improvement in \(DL_{CO}\) \(P = 0.04\)
  - Improvement in arterial oxygen saturation \(P = 0.05\)
- Serious adverse events were similar in the two study groups.

Sildenafil in IPF with Right-sided Ventricular Dysfunction
A substudy of STEP-IPF

- Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n  56; placebo, n  63)

- Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.

- Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD,

- St. George’s Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.
Sildenafil in IPF with Right-sided Ventricular Dysfunctional A substudy of STEP-IPF

Change in 6MWD at 12 weeks by treatment and presence of RVSD

Change in SGRQ total score at 12 weeks by treatment and presence of RVSD

Patients with any evidence of RVSD treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo.

Treatment with sildenafil in subjects with RVSD resulted in a significantly lower SGRQ total score.
ARTEMIS STUDIES
Study design

**AMBRISSENTAN-IPF** (mPAP <25 mmHg)
- Ambrisentan (n= 400) 10 mg/d
- PBO (n= 200)

**AMBRISSENTAN-PH** (mPAP > 25 mmHg)
- Ambrisentan (n= 400→40) 10 mg/d
- PBO (n=200→25)

Primary endpoint Change in % predicted FVC and DLCO at 12 months

Primary endpoint Change in 6MWT at 12 months

Ambrisentan PH-IPF trial was interrupted prematurely because of a lack of superior activity of the experimental arm (unpublished data)
Objective: To determine whether ambrisentan, an ETA receptor–selective antagonist, reduces the rate of IPF progression.

Design: Randomized, double-blind, placebo-controlled, event driven trial (ClinicalTrials.gov: NCT00768300)

Participants: Patients with IPF aged 40 to 80 years with minimal or no honeycombing on HRCT

Intervention: Ambrisentan, 10 mg/d, or placebo

Measurements: Time to disease progression, defined as death, respiratory hospitalization, or a categorical decrease in lung function.

Conclusion: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations.
Out-of-proportion pulmonary hypertension
A paradigm for rare diseases

..we can highlight some of the limitations of this study design, which have also been observed in other studies.

First, patients who were deemed eligible for enrollment included not only those with a PAP > 35 mm Hg, but also subjects with a mean PAP > 25 mm Hg.

Second, the 6-MWD, which is a non validated and probably misleading test, was chosen as the primary end point.

This test has not yet been validated as a useful screen for PH in IPF, and its prognostic significance is still unknown.

Harari S. Chest, 2012; 145: 1087
Out-of-proportion pulmonary hypertension
A paradigm for rare diseases

Out-of-proportion PH is a gray area of medicine that needs further clarification on some issues.

First of all, we need to clarify whether a mean PAP of 35 mm Hg is the adequate value to define this category of patients, or whether another cutoff should be selected.

Secondly, we need to clarify if we should consider only patients with minor pulmonary function abnormalities and moderate to severe PH as potential candidates for PH therapies.

Harari S. Chest, 2012; 145: 1087
Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial


<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>n (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Non-specific interstitial lung disease</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

**Pulmonary function**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC % pred</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>67 ± 20</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>67 ± 17</td>
</tr>
<tr>
<td>Dlco * mmol·min⁻¹·kPa⁻¹</td>
<td>2.7 ± 1.5</td>
</tr>
</tbody>
</table>

**Haemodynamics and blood gases**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure mmHg</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Pulmonary vascular resistance dyn·s⁻¹·cm⁻⁵</td>
<td>656 ± 201</td>
</tr>
<tr>
<td>Cardiac output L·min⁻¹</td>
<td>4.3 ± 1.4</td>
</tr>
<tr>
<td>Systolic blood pressure* mmHg</td>
<td>136 ± 16</td>
</tr>
<tr>
<td>Heart rate* beats per minute</td>
<td>78 ± 14</td>
</tr>
<tr>
<td>SPO₂ %</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>SvO₂ %</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>PaCO₂ mmHg</td>
<td>39 ± 7</td>
</tr>
</tbody>
</table>
**Objective:** to assess the safety, tolerability and preliminary efficacy of riociguat, in patients with PH-ILD

**Design:** open-label, uncontrolled pilot trial

**Intervention:** patients received oral riociguat (1.0–2.5 mg three times daily) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15)

**Conclusions:** Riociguat was well tolerated by most patients and improved cardiac output and PVR, but not mPAP. Further studies are necessary to evaluate the safety and efficacy of riociguat in patients with PH-ILD.
Pulmonary rare diseases
Ospedale San Giuseppe Experience (2001-2012)
Tot. 996 patients

IPF 363 pz

- Sarcoidosis
- BOOP
- LAM
- PLCH
- Pulmonary hypertension
- Others IIP
- IPF
- Vasculitides
### RHC and 6MWD in IPF

<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP ≤ 25 mmHg (n=17)</th>
<th>MAP &gt; 25 mmHg (n=13)</th>
<th>MAP &gt; 35 mmHg (n=4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP, mmHg</td>
<td>19.4 ± 3.6</td>
<td>32.4 ± 6</td>
<td>40.5 ± 2.6</td>
<td>NA</td>
</tr>
<tr>
<td>6MWT distance, m</td>
<td>222.0 ± 118.5</td>
<td>222.3 ± 118.5</td>
<td>203.7 ± 128.3</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>FVC, %</td>
<td>51.6 ± 13.8*</td>
<td>63.8 ± 16*</td>
<td>56.0 ± 6.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>58.3 ± 16.3</td>
<td>65.8 ± 18.8</td>
<td>55.2 ± 3.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>31.4 ± 9.6</td>
<td>24.2 ± 13.0</td>
<td>29.0 ± 7.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CI, l/min/m2</td>
<td>3.4 ± 0.55*</td>
<td>2.9 ± 0.7*</td>
<td>2.8 ± 0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVR, wood units</td>
<td>3.5 ± 1.1*</td>
<td>6.9 ± 1.4*</td>
<td>10.3 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with - without PH or with out of proportion PH.

6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.

Kimura M et al. Respiration 2012
PH in CPFE

PH is frequent in patients with the CPFE syndrome, with 47% of patients with estimated systolic right ventricular pressure ≥45 mmHg at echocardiography.

The risk of developing pulmonary hypertension is much higher in CPFE than in IPF without emphysema.

The prognosis of CPFE is worse than that of IPF without emphysema, an outcome determined by severe pulmonary hypertension and not only by the presence of associated emphysema.
PH in patients with CPFE

A retrospective multicentre study was conducted in 40 patients (38 males; age 68 ± 9 yrs; 39 smokers) Dyspnoea was functional class II in 15%, III in 55% and IV in 30%. 6-min walk distance was 244±126 m. FVC was 86 ± 18%, FEV1 78 ± 19%, and DLCO 28 ± 16% of predicted. PaO2 on room air was 56 ± 12 mmHg). Mean pulmonary artery pressure was 40 ± 9 mmHg, cardiac index 2.5 ± 0.7 and pulmonary vascular resistance 521 ± 205.

Cottin V et al Eur Respir J 2010; 35; 105
1-yr survival was 60%.

Higher pulmonary vascular resistance, higher heart rate, lower cardiac index and lower carbon monoxide diffusion transfer were associated with shorter survival.

**Conclusion:** Patients with CPFE and PH confirmed by RHC have a dismal prognosis despite moderately altered lung volumes and flows and moderately severe haemodynamic parameters.
Although the efficacy of drugs specifically indicated in pulmonary arterial hypertension has not been demonstrated in patients with pulmonary parenchymal disorders and associated out-of-proportion pulmonary hypertension, a large number of patients from the present study were treated off-label on an individual basis, thereby providing some preliminary information on the efficacy and safety of pulmonary hypertension therapy in this condition.

No significant effect of treatment was found on survival.
ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class#</th>
<th>Levelf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>RHC is recommended for a definite diagnosis of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Patients with “out of proportion” PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
**ESC/ERS GUIDELINES**

**Guidelines for the diagnosis and treatment of pulmonary hypertension**

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Class#</th>
<th>Levelf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>RHC is recommended for a definite diagnosis of PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Patients with &quot;out of proportion&quot; PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
The Question: PH in IPF what to do: ERA, PDE5 inhibitors or palliation?

The Answer: Palliation- oxygen therapy, diuretics, etc.. We need well designed clinical trial to evaluate response to therapy of selected IPF population of patients