Idiopathic Pulmonary Fibrosis: State-of-the-Art Evaluation and Management: Comorbidities in IPF

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Steven Nathan, MBBCh, FCCP
Grant monies (from industry related sources): Actelion, Boehringer Ingelheim, FibroGen, Gilead, InterMune, Sanofi-Aventis, and United Therapeutics
Advisory committee, speakers bureau and consultant fees from Actelion, Bayer, CSL Behring, Gilead, GeNO, InterMune, and United Therapeutics
Learning Objectives

• Discuss the diagnosis and management of IPF comorbidities
Caveolin, EGFs, MMP1, 2, 7, 9, CXCL12
TGF-β, α-FAP, TNF-α
PDGF, IFN-δ, CTGF, IL-13
Endothelin
Caveolin, EGFs, MMP1,2,7,9, CXCL12, TGF-β, FAP, TNF-α, PDGF, IFN-γ, CTGF, IL-13, Endothelin
**Pulmonary**

- Pulmonary vascular
  - Pulmonary embolus
  - Pulmonary hypertension
- Parenchymal
  - COPD
  - Lung cancer
  - Infectious-aspergillomas
- Other
  - Sleep apnea

**Extra-pulmonary**

- Cardiac:
  - CAD
  - Diastolic heart failure
- GI:
  - GERD
  - Nutrition
- Psychiatric
  - Anxiety
  - Depression
- Musculoskeletal
  - Deconditioning
- Endocrine
  - Hypogonadism
  - Diabetes
IPF with severe PH (mPAP = 61 mmHg)
Pulmonary hypertension in IPF is associated with:
A. The degree of restriction on PFTs
B. The CT fibrosis score
C. Worse survival
D. The amount of concomitant emphysema
Prevalence of PH in IPF

- Munich 2004: 28%
- IFH 2008: 41%
- UCLA 2007: 42%
- UNOS 2007: 46%
- Mayo 2008: 45%
- Mayo 2005: 84%
- Cleveland Clinic 2009: 46%
- Artemis IPF 2011: 14%
IPF: Distribution of mPAPs

Mean Pulmonary Artery Pressure: Prognostic Value in IPF

**Graph:**
- **n = 54** (Yes, mPap > 25 mm Hg)
- **n = 25** (No, mPap ≤ 25 mm Hg)

**Cumulative Probability to Survival**

### Years to Event

- **0.0**
- **0.2**
- **0.4**
- **0.6**
- **0.8**
- **1.0**

- **P < 0.001**

**References:**

Chest. 2006;129:746-752.
IPF Survival stratified by sPAP (N=88)

Chest. 2005;128:2393-2399
**PH in IPF: Impact on 6MWT**

<table>
<thead>
<tr>
<th></th>
<th>mPAP ≤ 25 mm Hg (N = 24)</th>
<th>mPAP &gt; 25 mm Hg (N = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD (m)</td>
<td>366 ± 82</td>
<td>144 ± 66</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO₂ nadir (%)</td>
<td>88 ± 4</td>
<td>80 ± 4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Chest. 2006;129:746-752.*
## PH in IPF: No correlation with Restriction

<table>
<thead>
<tr>
<th>FVC range</th>
<th>N</th>
<th>FVC%</th>
<th>DL\textsubscript{CO}%</th>
<th>mPAP (mmHg)</th>
<th>Patients with PH</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 70%</td>
<td>16</td>
<td>80.4</td>
<td>43.2</td>
<td>29.7</td>
<td>10</td>
<td>62.5</td>
</tr>
<tr>
<td>60-69%</td>
<td>26</td>
<td>63.1</td>
<td>41.1</td>
<td>22.1</td>
<td>7</td>
<td>26.9</td>
</tr>
<tr>
<td>50-59%</td>
<td>23</td>
<td>54.6</td>
<td>31.1</td>
<td>23.2</td>
<td>10</td>
<td>43.5</td>
</tr>
<tr>
<td>40-49%</td>
<td>31</td>
<td>44.8</td>
<td>32.5</td>
<td>22.9</td>
<td>13</td>
<td>41.9</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>22</td>
<td>32.0</td>
<td>22.1</td>
<td>21.6</td>
<td>8</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*Chest. 2007;131:657-663.*
When to Suspect PH in IPF

• PFTs
  – $D_{LCO} < 40\%$
• 6MWT
  – Distance
  – $SpO_2$ nadir
  – Pulse rate recovery
• BNP
• Echocardiography
Echocardiography does not accurately predict PH in IPF

N = 110, idiopathic pulmonary fibrosis patients with both echo and RHC. Comparison of RVSP by echo to PASP by RHC

IPF and PH: What Is the Limiting Factor?

Breathing Limitation

Vasoactive Therapies

Parenchymal Disease  Pulmonary Hypertension
## Case Series and Trials of Therapy for PH in IPF

<table>
<thead>
<tr>
<th>Type of Lung Disease</th>
<th>Investigator /Sponsor</th>
<th>Type of Study</th>
<th>N</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Fibrosis</td>
<td>Ghofrani</td>
<td>RCT open label</td>
<td>16</td>
<td>Sildenafil, iNO, epoprostenol</td>
<td>Sildenafil improved pulmonary hemo’s and gas exchange</td>
</tr>
<tr>
<td>IPF, CTD, Sarcoid</td>
<td>Minai</td>
<td>Case series</td>
<td>19</td>
<td>IV Epoprostenol, Bosentan</td>
<td>Improvement in NYHA/WHO Class and 6-MWT</td>
</tr>
<tr>
<td>IPF</td>
<td>Collard</td>
<td>Open label prospective trial</td>
<td>14</td>
<td>Sildenafil</td>
<td>57% had significant increase in 6MWT</td>
</tr>
<tr>
<td>IPF</td>
<td>Cotherix</td>
<td>RCT-phase II</td>
<td>51</td>
<td>Inhaled iloprost</td>
<td>No improvement in 6-MWT, NYHA/WHO Class</td>
</tr>
<tr>
<td>IPF</td>
<td>Jackson</td>
<td>RCT</td>
<td>29</td>
<td>Sildenafil</td>
<td>No Δ in 6MWT or Borg score</td>
</tr>
<tr>
<td>IPF</td>
<td>IPFnet</td>
<td>RCT-phase II</td>
<td>170</td>
<td>Sildenafil</td>
<td>6MWT</td>
</tr>
<tr>
<td>IPF</td>
<td>Gilead</td>
<td>RCT-phase III</td>
<td>220</td>
<td>Ambrisentan</td>
<td>6MWT/mortality**Stopped Jan 2011 for lack of efficacy &amp; ?harm</td>
</tr>
<tr>
<td>ILD</td>
<td>Hoeper</td>
<td>Open label</td>
<td>22</td>
<td>Riociguat</td>
<td>PVR ↓18% 6MWT ↑26 meters</td>
</tr>
</tbody>
</table>

*Modified from Eur Respir Mono 2012;57:1-13*
Step Study: ? Proof of concept

Table 2. Change in Prespecified Secondary Outcomes at 12 Weeks.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sildenafil (N=89)</th>
<th>Placebo (N=91)</th>
<th>Absolute Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea score on Borg Dyspnea Index after walk test</td>
<td>0.04 (-0.30 to 0.37)</td>
<td>0.37 (0.04 to 0.70)</td>
<td>-0.34 (-0.81 to 0.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>Shortness of Breath Questionnaire</td>
<td>0.22 (-3.10 to 3.54)</td>
<td>6.81 (3.53 to 10.08)</td>
<td>-6.58 (-11.25 to -1.92)</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>-1.64 (-3.91 to -0.64)</td>
<td>2.45 (0.17 to 4.72)</td>
<td>-1.81 (-4.56 to 0.95)</td>
<td>0.17</td>
</tr>
<tr>
<td>Symptoms score</td>
<td>-3.58 (-7.02 to -0.13)</td>
<td>2.35 (-1.30 to 5.61)</td>
<td>-3.31 (-7.22 to -0.39)</td>
<td>0.01</td>
</tr>
<tr>
<td>Activity score</td>
<td>-1.15 (-3.68 to 1.38)</td>
<td>2.49 (0.00 to 4.99)</td>
<td>-1.64 (-7.20 to -0.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Impacts score (social function)</td>
<td>-0.88 (-3.78 to 2.02)</td>
<td>2.82 (-0.03 to 5.67)</td>
<td>-3.70 (-7.76 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>SF-36§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregate physical score</td>
<td>-0.51 (-3.86 to 0.83)</td>
<td>-0.35 (-1.68 to 0.99)</td>
<td>-0.16 (-2.06 to 1.73)</td>
<td>0.65</td>
</tr>
<tr>
<td>Aggregate mental score</td>
<td>1.30 (-0.59 to 3.18)</td>
<td>3.02 (1.15 to 4.89)</td>
<td>-1.72 (-4.38 to 0.93)</td>
<td>0.31</td>
</tr>
<tr>
<td>Bodily vitality</td>
<td>0.21 (-2.13 to 1.71)</td>
<td>1.97 (0.08 to 3.85)</td>
<td>-1.76 (-4.58 to 0.07)</td>
<td>0.05</td>
</tr>
<tr>
<td>General</td>
<td>-0.04 (-2.52 to 2.46)</td>
<td>-0.21 (-2.57 to 2.14)</td>
<td>0.17 (-0.48 to 1.83)</td>
<td>0.68</td>
</tr>
<tr>
<td>Mental</td>
<td>-1.61 (-5.16 to 1.67)</td>
<td>-3.76 (-6.92 to 0.16)</td>
<td>2.15 (-1.19 to 5.50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Physical</td>
<td>0.12 (-2.93 to 3.17)</td>
<td>-2.24 (-5.48 to 1.02)</td>
<td>2.36 (0.12 to 4.60)</td>
<td>0.57</td>
</tr>
<tr>
<td>Role-physical score</td>
<td>0.57 (-3.96 to 4.11)</td>
<td>-3.82 (-7.67 to -2.01)</td>
<td>4.40 (-0.42 to 9.25)</td>
<td>0.08</td>
</tr>
<tr>
<td>Role-mental score</td>
<td>-0.87 (-2.89 to 0.10)</td>
<td>-2.01 (-4.98 to -0.08)</td>
<td>1.14 (-1.82 to 3.10)</td>
<td>0.41</td>
</tr>
<tr>
<td>Social functioning score</td>
<td>0.72 (-3.06 to 1.57)</td>
<td>-2.71 (-4.97 to -0.46)</td>
<td>3.44 (0.25 to 6.63)</td>
<td>0.11</td>
</tr>
<tr>
<td>Vitality score</td>
<td>0.02 (-1.70 to 1.73)</td>
<td>-0.17 (-2.76 to 2.37)</td>
<td>0.19 (-0.54 to 0.43)</td>
<td>0.37</td>
</tr>
<tr>
<td>Score on EQ-5D</td>
<td>-0.01 (-0.06 to 0.04)</td>
<td>-0.03 (-0.08 to 0.01)</td>
<td>0.02 (-0.04 to 0.08)</td>
<td>0.54</td>
</tr>
<tr>
<td>Self-report questionnaire</td>
<td>-0.01 (-1.10 to 0.40)</td>
<td>-1.34 (-1.54 to 0.13)</td>
<td>1.33 (-2.73 to 5.37)</td>
<td></td>
</tr>
<tr>
<td>Visual-analogue scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity (% of predicted value)</td>
<td>-0.97 (-2.00 to 0.06)</td>
<td>-1.29 (-2.30 to -0.28)</td>
<td>0.32 (-1.18 to 1.83)</td>
<td>0.64</td>
</tr>
<tr>
<td>Carbon monoxide diffusion capacity (% of predicted value)</td>
<td>0.20 (-1.00 to 1.40)</td>
<td>0.27 (-1.07 to 1.63)</td>
<td>0.07 (-1.95 to 1.99)</td>
<td>0.41</td>
</tr>
<tr>
<td>Partial pressure of nitrogen (mm Hg)</td>
<td>-0.10 (-0.50 to 0.30)</td>
<td>-0.05 (0.05 to 0.30)</td>
<td>0.05 (-0.75 to 0.85)</td>
<td>0.68</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide (mm Hg)</td>
<td>-0.01 (-0.51 to 0.50)</td>
<td>-0.02 (0.53 to 0.51)</td>
<td>0.01 (-1.03 to 1.05)</td>
<td>0.94</td>
</tr>
<tr>
<td>Alveolar-arterial gradient (mm Hg)</td>
<td>0.41 (-1.54 to 2.37)</td>
<td>2.95 (0.99 to 4.93)</td>
<td>-2.54 (-5.31 to 0.23)</td>
<td>0.05</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>-0.17 (-1.02 to 0.69)</td>
<td>-1.38 (-2.23 to -0.52)</td>
<td>1.21 (0.00 to 2.42)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Adjustment variables in the linear mixed models included baseline measurements of age, sex, race, height, and carbon monoxide diffusion capacity. The estimated change is for the 12-week period. EQ-5D denotes EuroQol Group 5 Dimension, and SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey.
†This value is the absolute difference between the sildenafil group and the placebo group in the change from baseline.
‡A higher score indicates worse function.
§A higher score indicates better function.

Table 3. Death and Acute Exacerbation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil (N=89)</th>
<th>Placebo (N=91)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause — no (%) in 12 wk*</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Acute exacerbations — no (%) in 12 wk*</td>
<td>24 wk</td>
<td>3 (3)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>All patients — no (%)</td>
<td>28 wk</td>
<td>4 (5)</td>
<td>11 (13)</td>
</tr>
</tbody>
</table>

Percentages of deaths are based on data from Kaplan–Meier analysis and were calculated as 1 minus the Kaplan–Meier survival rate. The numbers at risk in the sildenafil group were 84 at 12 weeks, 73 at 24 weeks, and 57 at 28 weeks; the numbers at risk in the placebo group were 85 at 12 weeks, 71 at 24 weeks, and 50 at 28 weeks.
Question 1

Pulmonary hypertension in IPF is associated with:
A. The degree of restriction on PFTs
B. The CT fibrosis score
C. Worse survival √
D. The amount of concomitant emphysema
Question 2

Therapy for GERD in patients with IPF
A. Is associated with slower rate of loss of lung function
B. Should only be instituted in those patients with symptomatic disease
C. Has not been shown to be associated with improved outcomes
D. Is ineffective because of bile acid reflux
Gastroesophageal Reflux Disease (GERD)

• Symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity or lung
• Association with IPF
  – Contribution to IPF pathology unknown
• Common in patients with IPF
  – Clinically silent in the majority of cases
• May have nonacid components (alkaline GERD)

IPF and GERD

IPF and GERD: More Than ILD

![Graph showing percent of total time pH < 4 in supine position for IPF and control patients in distal and proximal esophagus.](image-url)

Supine position

GERD

- Acid GERD prevalent in IPF (87%)
- 47% experience classic GERD symptoms
- GERD and IPF severities not correlated:

\[ \text{DL}_{\text{CO}} \quad \text{FVC} \]

\[ \text{Eur Respir J. 2006;27:136-142.} \]
IPF and GERD

• Diagnosis
  – Ba swallow
  – Esophageal manometry
  – 24 hour pH probe
  – BAL
    ➢ Pepsin, bile acids

• Treatment
  – PPIs
  – Nissen fundoplication
Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials

Joyce S Lee, Harold R Collard, Kevin J Anstrom, Fernando J Martinez, Imre Noth, Rhonda S Roberts, Eric Yow, Ganesh Raghu, for the IPFnet Investigators

Summary
Background Abnormal acid gastro-oesophageal reflux is common in patients with idiopathic pulmonary fibrosis (IPF) and is considered a risk factor for development of IPF. Retrospective studies have shown improved outcomes in patients given anti-acid treatment. The aim of this study was to investigate the association between anti-acid treatment and disease progression in IPF.

Methods In an analysis of data from three randomised controlled trials, we identified patients with IPF assigned to receive placebo. Case report forms had been designed to prospectively obtain data about diagnosis and treatment of abnormal acid gastro-oesophageal reflux in each trial. The primary outcome was estimated change in forced vital capacity (FVC) at 30 weeks (mean follow-up) in patients who were and were not using a proton-pump inhibitor or histamine-receptor-2 (H2) blocker.

Findings Of the 242 patients randomly assigned to the placebo groups of the three trials, 124 (51%) were taking a proton-pump inhibitor or H2 blocker at enrolment. After adjustment for sex, baseline FVC as a percentage of predicted, and baseline diffusing capacity of the lung for carbon monoxide as a percentage of predicted, patients taking anti-acid treatment at baseline had a smaller decrease in FVC at 30 weeks (−0·06 L, 95% CI −0·11 to −0·01) than did those not taking anti-acid treatment (−0·12 L, −0·17 to −0·08; difference 0·07 L, 95% CI 0·0 to 0·14; p=0·05).

Interpretation Anti-acid treatment could be beneficial in patients with IPF, and abnormal acid gastro-oesophageal reflux seems to contribute to disease progression. Controlled clinical trials of anti-acid treatments are now needed.

Funding National Institutes of Health.
IPF: Change in FVC on PPI/H$_2$ blocker vs. not

* Rate of change adjusted for sex, FVC, DLco

Lancet Respir Med 2013:1:369-76
GERD Treatment and Survival

![Graph showing survival analysis for taking and not taking GERD medications](image)

HR = 0.51, p value < 0.01

Question 2

Therapy for GERD in patients with IPF

A. Is associated with slower rate of loss of lung function
B. Should only be instituted in those patients with symptomatic disease
C. Has not been shown to be associated with improved outcomes
D. Is ineffective because of bile acid reflux

√
Sleep Disruption is Common in IPF

• Nocturnal hypoxemia is common
  – Associated with
    ➢ significant sleep disruption,
    ➢ decreased energy levels
    ➢ impaired physical functioning
  – Daytime SpO₂ is a strong predictor of nocturnal SpO₂
  – Daytime spirometric measures are poor predictors of nocturnal hypoxia
  – Potential palliative benefit of nocturnal or continuous oxygen therapy in IPF patients has not been studied

OSA Is Common in IPF

- 55 subjects with IPF
- Sleep apnea evaluation
  - Epworth Sleepiness Scale
  - Sleep Apnea Scale of Sleep Disorders
  - Nocturnal polysomnography
- Findings that did not correlate with OSA
  - Spirometry
  - Lung volume
  - DL_{CO}
  - ESS


AHI: apnea-hypopnea index
Sleep in IPF Patients

OSA-hypopnea syndrome (OSAHS)

- 34 newly diagnosed IPF patients, therapy naive
- Overnight polysomnography
- TLC might predispose IPF patients in sleep disordered breathing

\[ P = 0.03, r = -0.38 \]

Cardiovascular Disease in IPF

- ↑ Acute coronary syndrome, angina, DVT
- ↑ CAD
- Congestive heart failure (CHF) and coronary artery disease (CAD) ≈1/3 deaths in IPF

Association between IPF and Vascular Disease

**Figure 1.** The cumulative incidence of first-time acute coronary syndromes in people with idiopathic pulmonary fibrosis (IPF) and control subjects during the follow-up period.

**Table 2. Incident Cardiovascular Outcomes**

<table>
<thead>
<tr>
<th>Incident cardiovascular outcomes*</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndromes</td>
<td>3.14 (2.02–4.87)</td>
</tr>
<tr>
<td>Angina</td>
<td>1.23 (0.79–1.89)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.55 (0.95–2.54)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>3.39 (1.57–7.28)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.60 (0.98–2.62)</td>
</tr>
</tbody>
</table>

*Case and control subjects were not matched, so the number of cases in each group is different.

Definition of abbreviations:
- **RR:** Relative risk
- **CI:** Confidence interval

Cumulative Incidence of IHD is Higher With IPF

Nelson-Aalen cumulative hazard estimates

- General population controls
- Incident cases of IPF

Influence of CAD on IPF Mortality

IPF mortality: from IPF or with IPF?


Olson et al. Am J Respir Crit Care Med 2007;176:277-284
IPF survival by age

King et al. Am J Respir Crit Care Med 2001;164:1171-1181
Key Messages

• IPF is a disease of the elderly that is frequently associated with comorbidities
• Comorbidities may have morbidity as well as possibly mortality implications
• An awareness and high index of suspicion for common comorbidities is important in the global management of patients with IPF