BPCO: dalle novità patogenetiche alla terapia

Gianna Camiciottoli

Dip. Di Scienze Biomediche, Sperimentali e Cliniche “Mario Serio”

Università degli Studi di Firenze

Firenze, 11 novembre 2016
Conflict of interest disclosure

X I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.

I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:
Small Airways Disease
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction
- Loss of alveolar attachments
- Decrease of elastic recoil

Airflow limitation
- Both mechanisms concur to determine the overall severity of COPD
- Their relative predominance determines the clinical phenotype of COPD
COPD Phenotypes

Airway tree

Pathology of the airways in COPD

<table>
<thead>
<tr>
<th></th>
<th>Bronchitis</th>
<th>Bronchiolitis</th>
<th>Emphysema</th>
</tr>
</thead>
</table>
COPD (Chronic obstructive pulmonary disease) Phenotypes

Conducting airways:
- Trachea
- Bronchi
- Bronchioles
- Terminal bronchioles
- Transitional bronchioles

Acinar airways:
- Respiratory bronchioles
- Alveolar ducts
- Alveolar sacs

Image A shows a diagram of the airway structures, while Image B and Image C depict microscopic views.
«I find it a step backward to grade the severity of COPD solely by the FEV1. COPD consists of two (or more) separate diseases, chronic bronchitis and emphysema. Each of these has its own pathophysiology and therefore management. To lump them together is misleading.»

John B West. *Am J Respir Crit Care Med* 2013
Beyond airflow limitation: another look at COPD

M. Pistolesi

Thorax January 2009 Vol 64 No 1

- Regardless of expiratory airflow limitation, the different pathological changes seen in vivo by HRCT are brought by people with different body habits.
- The words “expiratory airflow limitation” expresses our present inaccuracy in differentiating increased airway resistance from increased lung compliance.
- Let us jump over the hindering barrier of airflow limitation and explore the COPD world beyond.
“Progress toward specific treatments for COPD might be accelerated by moving beyond measurements of airflow limitation to the precise diagnosis of the specific targets responsible for the airflow limitation.”

“This step will require precise, safe, non-invasive quantitative methods of diagnosis that will allow both the airway-obstructive and emphysema phenotypes to serve as measurable endpoints in clinical trials.”
Quantitative CT

- Mean Lung attenuation
- % area with attenuation values below a predetermined threshold
- Bronchial wall thickness
- Cross sectional area of blood vessels
COPD

%LAA-950

AWT-Pi10 (mm)

n=100 learning set

Principal Component Analysis

CT1 is proportional to the difference of the original variables (%LAA-950 minus AWT-Pi10) and reflects then the prevalent mechanism of airflow obstruction (airways or emphysema CT phenotype).

CT2 is proportional to the sum of the original variables (%LAA-950 plus AWT-Pi10) and reflects then the overall CT severity of COPD.

CT1 is proportional to the difference of the original variables (%LAA-950 minus AWT-Pi10) and reflects then the prevalent mechanism of airflow obstruction (airways or emphysema CT phenotype).
The models derived from the learning set of 100 patients were ten fold cross-validated and trained to estimate CT1 and CT2 in the prospective set of 373 patients.
Prospective validation

CT1 = (-0.018 x DLCO%) + (-0.580 x purulent sputum*) + (0.011 x TLC%) + 0.324

CT2 = (-0.030 x FEV1/VC) + (0.775 x purulent sputum*) + (0.013 x FRC%) - 0.575

- Sputum purulence
- FEV1/VC
- TLC%
- FRC%
- DLCO%

n = 373
testing set
(patients who did not undergo CT)
Prospective validation

COPD severity and phenotype

n=373

testing set

very severe

severe

moderate

mild

FEV1/VC: 45%
FRC: 132%
DLCO: 78%

n=73

FEV1/VC: 36%
FRC: 162%
DLCO: 49%

n=143

FEV1/VC: 60%
FRC: 100%
DLCO: 88%

n=77

FEV1/VC: 52%
FRC: 118%
DLCO: 61%

absent/occasional 0.30
chronic/purulent -0.41
chronic/non-purulent 0.07
CT classification versus GOLD 2015 classification

- **COPD Phenotypes**
  - CT classification versus GOLD 2015 classification

**Symptoms**
- Purulent sputum
- $\text{FEV}_1/\text{VC}$
- TLC%
- FRC%
- DLCO%

**Risk of Hospitalization**
- mMRC 0-1
- CAT < 10
- mMRC > 2
- CAT ≥ 10

**Exacerbation History**
- mMRC/CAT
- $\text{FEV}_1\%$
- Exacerbation history
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined COPD Assessment

Risk
(GOLD Classification of Airflow Limitation)

3
(C)

4
(D)

Symptoms

mMRC 0-1
CAT < 10

1
(B)

2
< 2

Risk

Hospitalization

(Exacerbation history)

≥ 2

1

mMRC ≥ 2
CAT ≥ 10

(A)
### Manage Stable COPD: Pharmacologic Therapy

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>First choice</th>
<th>Second choice</th>
<th>Alternative Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA</td>
<td>PDE4-inh. SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS and LAMA or ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Phenotype: a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes: symptoms, exacerbations, response to therapy, rate of disease progression, or death

Patients with COPD often present with comorbid diseases, including cardiovascular disease, metabolic syndrome, osteoporosis, depression, and skeletal muscle wasting and dysfunction
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined COPD Assessment

<table>
<thead>
<tr>
<th>Risk (GOLD Classification of Airflow Limitation)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>(C) mMRC 0-1 CAT &lt; 10</td>
</tr>
<tr>
<td>3</td>
<td>(D) mMRC ≥ 2 CAT ≥ 10</td>
</tr>
<tr>
<td>2</td>
<td>≥ 2 Hospitalization History</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

(A) mMRC 0-1 CAT < 10
(B) mMRC ≥ 2 CAT ≥ 10
(C) mMRC 0-1 CAT < 10
(D) mMRC ≥ 2 CAT ≥ 10
Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification

<table>
<thead>
<tr>
<th>Symptoms (mMRC score)</th>
<th>mMRC-defined</th>
<th>CAT-defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>mMRC 0–1</td>
<td>43%</td>
<td>7%</td>
</tr>
<tr>
<td>mMRC ≥2</td>
<td>25%</td>
<td>61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Exacerbation history</th>
<th>GOLD classification of airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>22%</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>C</td>
<td>&gt;2</td>
<td>65%</td>
</tr>
<tr>
<td>D</td>
<td>&gt;2</td>
<td>35%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms (CAT score)</th>
<th>CAT-defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT &lt;10</td>
<td>12%</td>
</tr>
<tr>
<td>CAT ≥10</td>
<td>88%</td>
</tr>
</tbody>
</table>

Price BD et al. Inter J COPD 2014
Combined COPD Assessment

<table>
<thead>
<tr>
<th>Risk (GOLD Classification of Airflow Limitation)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>mMRC 0-1</td>
</tr>
<tr>
<td>3</td>
<td>mMRC 0-1</td>
</tr>
<tr>
<td>2</td>
<td>mMRC 0-1</td>
</tr>
<tr>
<td>1</td>
<td>mMRC 0-1</td>
</tr>
</tbody>
</table>

- (A): mMRC 0-1, CAT < 10
- (B): mMRC ≥ 2, CAT ≥ 10
- (C): mMRC 0-1, CAT ≥ 10
- (D): mMRC ≥ 2, CAT < 10

Risk:

- 1: No exacerbation history
- ≥ 2: ≥ 2 exacerbation history

Hospitalization

Exacerbation history
Phenotype: a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes: symptoms, exacerbations, response to therapy, rate of disease progression, or death

Patients with COPD often present with comorbid diseases, including cardiovascular disease, metabolic syndrome, osteoporosis, depression, and skeletal muscle wasting and dysfunction.
## Characteristics Compared between Emphysema-Predominant and Airway-Predominant COPD Subject Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emphysema-Predominant COPD (n = 75)*</th>
<th>Airway-Predominant COPD (n = 174)*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.4 ± 8.0</td>
<td>63.7 ± 9.1</td>
<td>.13</td>
</tr>
<tr>
<td>No. of female subjects</td>
<td>35 (47)</td>
<td>42 (24)</td>
<td>.10</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>53.5 ± 22.4</td>
<td>53.4 ± 42.9</td>
<td>.95</td>
</tr>
<tr>
<td>No. of COPD exacerbations per year</td>
<td>1.1 ± 1.4</td>
<td>0.8 ± 1.4</td>
<td>.10</td>
</tr>
<tr>
<td>FEV(_1) percent predicted</td>
<td>29.3 ± 13.1</td>
<td>51.9 ± 21.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire total score</td>
<td>49.2 ± 16.4</td>
<td>40.7 ± 19.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MMRC dyspnea scale score</td>
<td>2.8 ± 1.2</td>
<td>2.2 ± 1.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Six-minute walk distance (m)</td>
<td>291.3 ± 115.1</td>
<td>324.2 ± 140.8</td>
<td>.03</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>22.7 ± 4.0</td>
<td>30.7 ± 6.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BODE score</td>
<td>5.1 ± 1.8</td>
<td>3.0 ± 2.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>9.3 ± 29.2</td>
<td>12.1 ± 32.7</td>
<td>.35</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9.3 ± 29.3</td>
<td>19.5 ± 39.8</td>
<td>.03</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>28.0 ± 45.2</td>
<td>7.8 ± 26.4</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Data from COPD Gene study. Han MK et al. *Radiology* 2011
### TABLE 2. CHARACTERISTICS OF SUBJECTS WITH COPD CLASSIFIED BY ANNUAL RATES OF DECLINE IN FEV₁ DURING THE FOLLOW-UP

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>All Patients (N = 261)</th>
<th>Rapid Decliners (N = 65)</th>
<th>Slow Decliners (N = 131)</th>
<th>Sustainers (N = 65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous smoker, N (%)</td>
<td>40 (15)</td>
<td>4 (6)</td>
<td>24 (18)</td>
<td>12 (19)</td>
<td>0.21</td>
</tr>
<tr>
<td>Intermittent smoker, N (%)</td>
<td>40 (15)</td>
<td>12 (19)</td>
<td>18 (14)</td>
<td>10 (15)</td>
<td>0.21</td>
</tr>
<tr>
<td>Former smoker, N (%)</td>
<td>181 (69)</td>
<td>49 (75)</td>
<td>89 (68)</td>
<td>43 (66)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Exacerbation (events/person/yr)‡**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 261)</th>
<th>Rapid Decliners (N = 65)</th>
<th>Slow Decliners (N = 131)</th>
<th>Sustainers (N = 65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom definition</td>
<td>0.22 ± 0.39</td>
<td>0.19 ± 0.33</td>
<td>0.24 ± 0.44</td>
<td>0.22 ± 0.33</td>
<td>0.64</td>
</tr>
<tr>
<td>Prescription change</td>
<td>0.17 ± 0.33</td>
<td>0.15 ± 0.32</td>
<td>0.18 ± 0.36</td>
<td>0.18 ± 0.28</td>
<td>0.87</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>0.06 ± 0.20</td>
<td>0.07 ± 0.21</td>
<td>0.06 ± 0.23</td>
<td>0.05 ± 0.11</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**Medication for COPD (%)‡**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 261)</th>
<th>Rapid Decliners (N = 65)</th>
<th>Slow Decliners (N = 131)</th>
<th>Sustainers (N = 65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medication</td>
<td>190 (73)</td>
<td>51 (78)</td>
<td>97 (74)</td>
<td>42 (65)</td>
<td>0.19</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>135 (52)</td>
<td>36 (55)</td>
<td>71 (54)</td>
<td>28 (43)</td>
<td>0.27</td>
</tr>
<tr>
<td>β-Receptor agonists</td>
<td>92 (35)</td>
<td>23 (35)</td>
<td>47 (36)</td>
<td>22 (34)</td>
<td>0.96</td>
</tr>
<tr>
<td>Theophylline</td>
<td>116 (44)</td>
<td>32 (49)</td>
<td>58 (44)</td>
<td>26 (40)</td>
<td>0.57</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>36 (14)</td>
<td>10 (15)</td>
<td>18 (14)</td>
<td>8 (12)</td>
<td>0.88</td>
</tr>
</tbody>
</table>
COPD Phenotypes

Exacerbation severity
- Mild: treated at home
- Severe: emergency room or hospitalized

Clinical manifestation
- Dyspnoea (D)
- Sputum (S)
- Dyspnoea + sputum (D+S)

Exacerbations Frequency
- Not frequent: <2 /year
- Frequent: ≥2 /year

68% 32%
18%
58%
24%
23%
77%

CT1 and CT2 classification versus exacerbation
Bigazzi F et al, European Respiratory Journal Sep 2014, 44 (Suppl 58) P571
CT1 and CT2 classification versus COPD Phenotypes

<table>
<thead>
<tr>
<th>Phenotype CT1</th>
<th>&lt;2</th>
<th>≥2</th>
<th>mild</th>
<th>severe</th>
<th>D</th>
<th>S</th>
<th>D+S</th>
</tr>
</thead>
<tbody>
<tr>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity CT2</th>
<th>p&lt;0.01</th>
<th>p&lt;0.05</th>
<th>p&lt;0.01</th>
<th>p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

p<0.01 indicates statistical significance.
Exacerbation severity
Mild: treated at home
Severe: emergency room or hospitalized

Clinical manifestation
- Dyspnoea (D) 24%
- Sputum (S) 58%
- Dyspnoea + sputum (D+S) 18%

Exacerbations Frequency
- Not frequent: <2/year 58%
- Frequent: ≥2/year 42%

1/3 are frequent exacerbators at 3-year follow-up
1/16 have severe exacerbations at 3-year follow-up

-notch study, Bigazzi F et al, European Respiratory Journal (Suppl), on line first October 2016.
Conclusions

• Exacerbations are an index of clinical and functional impairment in COPD

• Exacerbation frequency and severity are not related to predominant phenotype as assessed by quantitative CT while could be considered as an index of disease severity

• The so-called “frequent exacerbator” and “severe exacerbator” are not stable phenotypes and these clinical characteristics cannot be taken into account to personalize therapy in patients with COPD
Phenotype: a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes: symptoms, exacerbations, response to therapy, rate of disease progression, or death.

Patients with COPD often present with comorbid diseases, including cardiovascular disease, metabolic syndrome, osteoporosis, depression, and skeletal muscle wasting and dysfunction.
Annual Change in Pulmonary Function and Clinical Phenotype in Chronic Obstructive Pulmonary Disease

### TABLE 1. CHARACTERISTICS OF SUBJECTS WITH COPD CLASSIFIED BY ANNUAL RATES OF DECLINE IN FEV$_1$ AT BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Rapid Decliners ($N = 65$)</th>
<th>Slow Decliners ($N = 131$)</th>
<th>Sustainers ($N = 65$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>69 ± 6</td>
<td>70 ± 8</td>
<td>68 ± 9</td>
<td>0.11</td>
</tr>
<tr>
<td>Female sex, N (%)</td>
<td>1 (1.5)</td>
<td>10 (7.6)</td>
<td>4 (6.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>21 ± 3*</td>
<td>22 ± 3</td>
<td>23 ± 4</td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td>Current smoker at entry, N (%)</td>
<td>13 (20)</td>
<td>40 (31)</td>
<td>20 (31)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking index at entry, pack-years</td>
<td>67 ± 27</td>
<td>64 ± 33</td>
<td>55 ± 25</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronchodilator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.58 ± 0.65</td>
<td>1.55 ± 0.67</td>
<td>1.70 ± 0.73</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>57 ± 22</td>
<td>58 ± 22</td>
<td>61 ± 24</td>
<td>0.59</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>95 ± 19</td>
<td>92 ± 20</td>
<td>92 ± 23</td>
<td>0.70</td>
</tr>
<tr>
<td>Postbronchodilator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.76 ± 0.62</td>
<td>1.71 ± 0.66</td>
<td>1.84 ± 0.67</td>
<td>0.42</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>64 ± 21</td>
<td>64 ± 22</td>
<td>66 ± 23</td>
<td>0.74</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>103 ± 17</td>
<td>100 ± 19</td>
<td>99 ± 22</td>
<td>0.47</td>
</tr>
<tr>
<td>Reversibility of FEV$_1$, %</td>
<td>0.50 ± 0.13</td>
<td>0.51 ± 0.12</td>
<td>0.53 ± 0.13</td>
<td>0.20</td>
</tr>
<tr>
<td>Reversibility of FEV$_1$, ml</td>
<td>176 ± 152</td>
<td>167 ± 121</td>
<td>148 ± 141</td>
<td>0.47</td>
</tr>
<tr>
<td>$Dl_{CO}$, mmol/min/mm Hg</td>
<td>11.2 ± 5.2$^f$</td>
<td>12 ± 4.6$^*$</td>
<td>14 ± 4 $^*$</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>$Kco$, mmol/min/mm Hg/L</td>
<td>2.5 ± 1.2$^f$</td>
<td>2.8 ± 1$^f$</td>
<td>3.3 ± 1$^f$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Patient-reported outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis, N (%)</td>
<td>7 (11)</td>
<td>11 (8)</td>
<td>11 (17)</td>
<td>0.20</td>
</tr>
<tr>
<td>MRC dyspnea score, ≥2 (%)</td>
<td>56 (86)</td>
<td>111 (85)</td>
<td>52 (80)</td>
<td>0.59</td>
</tr>
<tr>
<td>SGRO total score</td>
<td>31 ± 17</td>
<td>32 ± 17</td>
<td>31 ± 19</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood neutrophil count, cells/mm$^3$</td>
<td>3,597 (2,759–4,601)</td>
<td>3,342 (2,704–3,953)</td>
<td>3,534 (2,893–4,287)</td>
<td>0.13</td>
</tr>
<tr>
<td>Blood eosinophil count, cells/mm$^3$</td>
<td>120 (80–221)</td>
<td>169 (94–248)$^*$</td>
<td>233 (131–353)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Serum total IgE, IU/ml</td>
<td>62 (19–153)</td>
<td>73 (19–184)</td>
<td>86 (27–216)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Phenotype: a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes: symptoms, exacerbations, response to therapy, rate of disease progression, or death

Patients with COPD often present with comorbid diseases, including cardiovascular disease, metabolic syndrome, osteoporosis, depression, and skeletal muscle wasting and dysfunction
Prevalence of comorbidities according to predominant phenotype and severity of chronic obstructive pulmonary disease

Gianna Camiciottoli¹,²
Francesca Bigazzi¹
Chiara Magni¹
Viola Bonti¹
Stefano Diciotti³
Maurizio Bartolucci⁴
Mario Mascalchi⁵
Massimo Pistolesi¹

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International Journal of COPD
14 September 2016
A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Key exclusion criteria were a history of asthma, a COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, use of supplemental oxygen for more than 12 hours per day, and the presence of a coexisting illness that could preclude participation in the study or interfere with the study results. The protocol was approved by the ethics committee at each center, and all patients provided written informed consent.
Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

- Idiopathic arterial hypertension (IAH),
- Ischemic heart disease (IHD),
- Heart failure (HF)
- Peripheral vascular disease (PVD),
- Diabetes (D),
- Osteoporosis (O)
- Anxious depressive syndrome (ADS)

Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

Table 1: Anthropometric and functional data in patients with COPD according to phenotypes and severity of the disease

<table>
<thead>
<tr>
<th></th>
<th>COPD (n=412)</th>
<th>Predominant airway disease (n=222)</th>
<th>Predominant emphysema (n=190)</th>
<th>P-value</th>
<th>Mild COPD (n=284)</th>
<th>Severe COPD (n=128)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>299/113</td>
<td>174/48</td>
<td>125/65</td>
<td></td>
<td>195/89</td>
<td>104/24</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>70±9</td>
<td>71±8</td>
<td>69±9</td>
<td>≤0.05</td>
<td>70±9</td>
<td>69±8</td>
<td>ns</td>
</tr>
<tr>
<td>p/y</td>
<td>46±27</td>
<td>45±29</td>
<td>48±25</td>
<td>ns</td>
<td>45±28</td>
<td>50±24</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>26±5</td>
<td>28±5</td>
<td>25±4</td>
<td>≤0.0001</td>
<td>27±5</td>
<td>25±4</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>69±25</td>
<td>76±23</td>
<td>61±26</td>
<td>≤0.0001</td>
<td>79±22</td>
<td>48±19</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>FEV₁/VC (%)</td>
<td>52±14</td>
<td>57±11</td>
<td>46±14</td>
<td>≤0.0001</td>
<td>58±11</td>
<td>39±12</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>FRC (%)</td>
<td>120±31</td>
<td>110±25</td>
<td>132±32</td>
<td>≤0.0001</td>
<td>107±21</td>
<td>150±29</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>105±17</td>
<td>100±16</td>
<td>110±16</td>
<td>≤0.0001</td>
<td>100±15</td>
<td>116±15</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>DL&lt;sub&gt;CO&lt;/sub&gt; (%)</td>
<td>76±23</td>
<td>89±16</td>
<td>61±16</td>
<td>≤0.0001</td>
<td>81±21</td>
<td>66±22</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD.
Abbreviations: BMI, body mass index (weight/height²); COPD, chronic obstructive pulmonary disease; DL<sub>CO</sub> %, diffusing capacity of lung for carbon monoxide (% of predicted); FEV₁, forced expiratory volume in 1 second (% of predicted); FEV₁/VC%, FEV₁–vital capacity ratio; FRC%, functional residual capacity (% of predicted); ns, nonsignificant; p/y, number of daily cigarettes × number of years/20; SD, standard deviation; TLC%, total lung capacity (% of predicted).

Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

Figure 1 Prevalence of comorbidities in 412 outpatients with COPD. Abbreviations: ADS, anxious depressive syndrome; com, comorbidities; COPD, chronic obstructive pulmonary disease; D, diabetes; HF, heart failure; IAH, idiopathic arterial hypertension; IHHD, ischemic heart disease; O, osteoporosis; PVD, peripheral vascular disease.

Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

Prevalence of comorbidities according to predominant Phenotype and Severity of COPD

Figure 5: Prevalence of cardiovascular comorbidities in 412 outpatients according to mild or severe grade of COPD and according to the predominant phenotype.

Notes: *P<0.05; ***P<0.0001.

Conclusion

Understanding the association between comorbidities and phenotypes of COPD is critical, especially in patients with mild disease. The increased prevalence of comorbidities among patients with COPD has several relevant practical aspects: first of all, the need for an early diagnosis of COPD. Increasing knowledge on links between COPD and comorbidities could provide innovative treatment strategies and it would assign each patient with COPD targeted therapies according to their personalized profile of phenotype, severity, and comorbidity.

COPD

CT classification versus GOLD 2015 classification

- Purulent sputum
- FEV₁/VC
- TLC%
- FRC%
- DLCO%

- mMRC/CAT
- FEV₁%
- Exacerbation history

Symptoms

Risk

(GOLD Classification of Airflow Limitation)

Hospitalization

Exacerbation history

COPD Phenotypes

CT classification versus GOLD 2015 classification

CT2 predicted

CT1 predicted

A B C D
COPD Phenotypes

**GOLD D**

- **Absent sputum**
  - FEV$_1$ 19%, FEV$_1$/VC 26, TLC 151%, RV 312%, RV/TLC 79%
  - FRC 132%, DLCO 19%
  - mMRC 4
  - CAT20
  - Hospitalized

- **Purulent sputum**
  - FEV$_1$ 50%, FEV$_1$/VC 63, TLC 83%, RV 102%, RV/TLC 43%
  - FRC 90%, DLCO 77%
  - Peripheral oedema
  - mMRC 2
  - CAT20
  - Hospitalized
CT classification versus Comorbidities

COPD Phenotypes

CT1 = (-0.018 \times DLCO\%) + (-0.580 \times \text{purulent sputum}^*) + (0.011 \times TLC\%) + 0.324

CT2 = (-0.030 \times FEV1/VC) + (0.775 \times \text{purulent sputum}^*) + (0.013 \times FRC\%) - 0.575
Chronic bronchitis/Bronchiolitis

Small airway disease

Emphysema

ICS +
LABA+
LAMA+
PDE4Inh

ICS +
LAMA
and/or
LABA

LABA +
LAMA

LAMA
and/or
LABA

Personalized therapy

COPD

Chronic bronchitis/Bronchiolitis

Emphysema

severity
COPD

- Mortality
- Disease progression
- Lung function
- Symptoms: cough, sputum production, and dyspnoea
- Exercise tolerance
- Exacerbations
- Disability
- Health status and quality of life

Individualisation of treatment choices in COPD

Present COPD pharmacological treatments

- LABA;
- LAMA;
- LABA + LAMA;
- LABA + ICS;
- LABA + LAMA + ICS;
- LABA + roflumilast;
- LAMA + roflumilast

Expected benefits

Expected risks

- Pneumonia
- Tuberculosis
- Skin bruising
- Osteoporosis or fractures
- Muscle dysfunction
- Nutritional impairment
- Cataract
- Diabetes
- Tremour
- Cardiovascular events
- Neuropsychological effects
- Gastrointestinal symptoms

Prescott G Woodruff, Alvar Agusti, Nicolas Roche, Dave Singh, Fernando J Martinez

Lancet 2015
La terapia personalizzata della BPCO

- La terapia della BPCO non dovrebbe basarsi soltanto sui sintomi, la frequenza di riacutizzazioni ed il FEV1.
- Ciascun paziente dovrebbe essere sottoposto ad una valutazione clinica e funzionale completa allo scopo di identificare il meccanismo fisiopatologico predominante alla base dell’ostruzione.
- Tale identificazione è essenziale per indirizzare la terapia alle differenti presentazioni cliniche di ciascun paziente.