What is the best way of assessing disease progression in COPD?

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David Geffen School of Medicine at UCLA
COPD: Definition (GOLD, 2001-11)*

- A disease state characterized by airflow limitation that
  - is not fully reversible
  - is usually progressive
  - is associated with an abnormal inflammatory response of the lungs to noxious particles or gases

* http://www.goldcopd.com
## Classification of Severity of Airflow Obstruction (GOLD)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild COPD</td>
<td>• FEV₁/FVC $&lt; 70%$ (for stages I-IV)</td>
</tr>
<tr>
<td></td>
<td>• FEV₁ $\geq 80%$ predicted</td>
</tr>
<tr>
<td></td>
<td>• with or w/o chronic symptoms</td>
</tr>
<tr>
<td>II: Moderate COPD</td>
<td>• 50% $\leq$ FEV₁ $&lt; 80%$ predicted</td>
</tr>
<tr>
<td></td>
<td>• with or w/o chronic symptoms</td>
</tr>
<tr>
<td>III: Severe COPD</td>
<td>• 30% $\leq$ FEV₁ $&lt; 50%$ predicted</td>
</tr>
<tr>
<td></td>
<td>• with or w/o chronic symptoms</td>
</tr>
<tr>
<td>IV: Very severe COPD</td>
<td>• 30% $\geq$ FEV₁ predicted or $&lt;50%$ pred plus chronic respiratory failure*</td>
</tr>
</tbody>
</table>

* respiratory failure: PaO₂ $< 60$ mm Hg with or w/o PaCO₂ $> 50$ mm Hg
New COPD Classification Scheme

GROUP C - High Risk, Less Symptoms

GROUP D - High Risk, More Symptoms

GROUP A - Low Risk, Less Symptoms

GROUP B - Low Risk, More Symptoms

Symptoms (mMRC or CAT score)

RISK

GOLD Classification of Airflow Limitation

mMRC 0-1 CAT <10

mMRC ≥2 CAT ≥10

Exacerbation history

GOLD 2011 (www.goldcopd.org)
COPD: Definition (ATS/ERS, 2004-11)*

- A preventable and treatable disease state that
  - is characterized by airflow limitation that is not fully reversible
  - is usually progressive
  - is associated with an abnormal inflammatory response of the lungs to noxious particles or gases
  - also produces significant systemic consequences

* http://www.copd-ats-ers.org
COPD is a progressive disease defined by an accelerated annual decline in FEV\textsubscript{1}.

Fletcher C. *BMJ* 1977;1:1645-1648
Clinical Course of COPD

COPD

- Expiratory Flow Limitation
- Air Trapping
- Hyperinflation

Breathlessness

- Exacerbations
- Deconditioning
- Reduced Exercise Capacity

Inactivity

- Poor Health-Related Quality of Life

Disability  Disease progression  Death

Decramer M. Eur Respir Rev 2006
COPD: A Multicomponent Disease

Mucociliary dysfunction
- Mucus hypersecretion
- Reduced mucociliary transport
- Mucosal damage
- Increased numbers of inflammatory cells/activation:
  - CD8+ T-lymphocytes
  - Monocytes/macrophages
  - Neutrophils
  - Mast cells
- Elevated inflammatory mediators: IL-8, TNF-α, LTB-4, and oxidants
- Protease/anti-protease imbalance

Airway inflammation
- Loss of alveolar attachments
- Loss of elastic recoil
- Increased smooth muscle contraction

Structural changes
- Goblet cell hyperplasia/metaplasia
- Mucous gland hypertrophy
- Increased smooth muscle mass
- Airway fibrosis
- Alveolar destruction

Systemic component
- Poor nutritional status
- Reduced BMI
- Impaired skeletal muscle
- Weakness
- Wasting

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- Alveolar destruction

Systemic component
- Poor nutritional status
- Reduced BMI
- Impaired skeletal muscle
- Weakness
- Wasting
Small airways are the major site of pathology in COPD

Barnes PJ
NEJM
2004;
350:2635-7
Progressive small airways pathology

Adapted from Hogg et al. N Engl J Med 2004
Relationship between $FEV_1$ and degree of luminal occlusion by mucus

Inflammation in small airways at different stages of COPD severity

Small airway wall thickness at different stages of COPD severity

HRCT Evidence of Emphysema

Note the large air-filled spaces in the lung
Measurements of airway wall thickness

Hasegawa et al., AJRCCM 2006
Computer-generated Lung Attenuation Curve
CT Density Mask
for Evaluation of Emphysema

Courtesy of Jonathan Goldin, MD, David Geffen School of Medicine at UCLA
Annual $\Delta$ in CT lung density in emphysema due to AAT deficiency*; comparison with $\Delta$ in FEV$_1$

*$N = 77$

$r = 0.316; p = 0.007$

Dirksen A et al. ERJ 2009; 33:1345-53
Natural history of COPD: Rate of lung function decline vs. rate of symptom increase

Asymptomatic
Lung function normal
Lung function reduced

FEV₁ (% of Predicted)
100
50
20

Axis of Progression
Symptoms
Mild
Severe

Correlation coefficients* between annual changes in FEV$_1$ % pred and in various clinical parameters†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ total</td>
<td>-0.44*</td>
</tr>
<tr>
<td>CRQ total</td>
<td>0.33*</td>
</tr>
<tr>
<td>mMRC (dyspnea)</td>
<td>-0.37*</td>
</tr>
<tr>
<td>HADS (anxiety)</td>
<td>-0.12</td>
</tr>
<tr>
<td>HADS (depression)</td>
<td>-0.26*</td>
</tr>
<tr>
<td>Peak O$_2$ consumption</td>
<td>-0.21*</td>
</tr>
</tbody>
</table>

*Pearson †Mixed effects models  (covariates: age & smoking [fixed]; time [random])

Oga et al. Respir Med 2007

N=137 male COPD patients followed for 5 yrs; mean baseline FEV1 50% pred
Relationship between exercise performance (6WMD) and COPD severity defined by FEV1

Biomarkers may play in identifying risk, monitoring disease progression, projecting outcomes and serving as surrogate endpoints in COPD.
Definition of a “biomarker”

• “Any biochemical feature, molecule or material (cells, tissue) – or physiologic or radiographic feature - that can be measured in the body or its products, and which can reflect the disease process or predict its outcome.”¹

• A suitable biomarker should be reproducible, sensitive, specific, easy and cheap to determine and should present a high predictive values”²

¹Tzouvelekis et al. Respir Res 2005; ²Barnes et al. AJRCCM 2006
Examples of biomarkers

• Induced sputum
  - Neutrophils, CD8\(^+\) cells, Tc1 cells, eosinophils, macrophages
  - Soluble inflammatory markers in fluid phase
    - MPO, NE, ECP, IL-8, LTB-4, GRO-\(\alpha\), MCP-1, GM-CSF, TNF-\(\alpha\)

• Exhaled breath condensate
  - CO, NO, pentane, ethane, H\(_2\)O\(_2\), 8-isoprostane, IL-6, LTB-4

• Peripheral blood samples for protein or mRNA
  - Neutrophilic superoxide, CRP, fibrinogen, elastin-derived peptides, Clara cell protein, surfactant protein D

• Urine
  - Urinary desmosine, 8-isoprostane, 8-OH-deoxyguanosineTxB2
Biomarkers in BAL & Bronchial Biopsies

- Alveolar macrophages, neutrophils, CD8 lymphs, eos
- Apoptosis mediators
- Histone deacetylases
- IL-6, IL-8, MPO, GRO-a, GSH, CXCR 1 & 2
- Collagenase 1 and 2 (MMP-1, MMP-8) and gelatinases A and B (MMP-2, MMP-9)
- TGF-β and tissue inhibitors of MMP (TIMPP)
- STAT-4 (transcription factor signal transducer & activator of transcription)
- Nuclear factor-κB (NFκB)
The promise of ECLIPSE, SPIROMICS and COPD Gene

- **ECLIPSE**
  - Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (N = 2180 COPD and 343 smoking & 223 nonsmoking controls followed for 3 yrs)

- **SPIROMICS**
  - Subpopulations and Intermediate Outcome Measures in COPD Study (N = 2400 COPD and 600 & 200 nonsmoking controls followed for 3 yrs)

- **COPD Gene**
  - Aims to find genetic risk factors (using GWAS) within phenotypes defined by HRCT, clinical & physiological factors that are associated with the development of COPD (N = 12,000 current or ex-smokers with COPD – GOLD Stages 2-4 - and without COPD)
## Effects of biomarkers on FEV\textsubscript{1} in ECLIPSE

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Effect on Baseline FEV\textsubscript{1} (ml)</th>
<th>P Value*</th>
<th>Effect on Annual Rate of Change in FEV\textsubscript{1} (ml/yr)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>-93±10.6</td>
<td>&lt;0.001</td>
<td>-1±2.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>0±10.0</td>
<td>&gt;0.99</td>
<td>1±2.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>20±9.9</td>
<td>0.04</td>
<td>-2±2.0</td>
<td>0.36</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1±9.9</td>
<td>0.89</td>
<td>0±1.8</td>
<td>0.84</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-23±10.3</td>
<td>0.037</td>
<td>4±2.1</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>CC-16</strong></td>
<td><strong>33±10.8</strong></td>
<td><strong>0.002</strong></td>
<td><strong>4±2.2</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Surfactant protein D</td>
<td>0±10.3</td>
<td>0.96</td>
<td>-3±2.1</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SE.
† Effects are per increase of 1 SD in the values of the individual biomarkers (i.e., a change of 1 SD in the level of the biomarker resulted in a specific effect on FEV\textsubscript{1}). CC-16 denotes Clara cell protein 16, and TNF-α tumor necrosis factor alpha.
‡ P values were not corrected for multiple testing.
What factors influence or modify the progression of COPD as defined by the annual rate of decline in FEV$_1$?
Impact of baseline factors on FEV$_1$ rate of decline (Yr 1-5) in the Lung Health Study*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Increment or Comparison</th>
<th>Estimated Effect (% pred)</th>
<th>SEE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log mch reactivity, %/mg/ml</td>
<td>+0.5</td>
<td>-0.35</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>+10</td>
<td>-0.20</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>+10</td>
<td>-0.05</td>
<td>0.02</td>
<td>0.020</td>
</tr>
<tr>
<td>FEV$_1$ % pred</td>
<td>+10</td>
<td>+0.07</td>
<td>0.03</td>
<td>0.031</td>
</tr>
<tr>
<td>Bronchodilator response, %</td>
<td>+5</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.176</td>
</tr>
<tr>
<td>Gender</td>
<td>F vs. M</td>
<td>+0.03</td>
<td>0.06</td>
<td>0.584</td>
</tr>
</tbody>
</table>

*multivariate linear regression analysis (PROC GLM)

Scanlon et al. AJRCCM 2000
Smoking cessation slows the accelerated decline in FEV$_1$ in COPD (observational study)

Fletcher C. BMJ 1977;1:1645-1648
Early Smoking Cessation
Recovery of $FEV_1$ to Non-smoker Levels
Among Quitters <30 Years Old

Framingham Offspring Cohort*

*N = 1578 NS; 754 CS; 1633 other smokers
(N’s for men and women combined)

Kohansal et al. AJRCCM 2009; 180:3-10
Impact of air pollution and smoking on the annual rate of decline of FEV$_1$ over 5 yrs in men

Tashkin et al. UCLA Population Studies of COPD
Am J Respir Crit Care Med 1994; 149:1209-17
COPD Exacerbations Hasten Decline in Lung Function

Mean $\Delta$ FEV1 (ml/year) vs. Physician visits per year for lower respiratory illnesses

COPD Exacerbations Hasten Decline in Lung Function


Infrequent exacerbators (n = 16)
FEV$_1$ change = 32 ml/year

Frequent exacerbators (n = 16)
FEV$_1$ change = 40 ml/year
Association between exacerbation frequency and annual rates of change in spirometry & HRQoL*

<table>
<thead>
<tr>
<th>Exacerbation Rate</th>
<th>0</th>
<th>&gt;0-1</th>
<th>&gt;1-2</th>
<th>&gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BD FEV₁, ml/y</td>
<td>-40</td>
<td>-41</td>
<td>-43</td>
<td>-48</td>
</tr>
<tr>
<td>SGRQ total score, y⁻¹</td>
<td>0.72</td>
<td>1.16</td>
<td>1.44</td>
<td>1.99</td>
</tr>
<tr>
<td>Hospitalized Exacerbation Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-BD FEV₁, ml/y</td>
<td>-41</td>
<td>-45</td>
<td>-57</td>
<td>-59</td>
</tr>
<tr>
<td>SGRQ total score, y⁻¹</td>
<td>0.95</td>
<td>1.70</td>
<td>3.34</td>
<td>4.22</td>
</tr>
</tbody>
</table>

*UPLIFT (placebo group only)  
Halpin et al. Int J COPD 2012
Genes associated with different phenotypes of COPD and with asthma

<table>
<thead>
<tr>
<th>Gene</th>
<th>FEV$_1$ Decline</th>
<th>COPD: Lung Function</th>
<th>COPD: CT Emphysema</th>
<th>CT: Airway Wall Thickening</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRB2</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CHRNA3</td>
<td>NT</td>
<td>*</td>
<td>+</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>EPHX1</td>
<td>+*</td>
<td>+</td>
<td>+†</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>GSTP1</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>HMOX1</td>
<td>+*</td>
<td>—</td>
<td>+</td>
<td>NT</td>
<td>—</td>
</tr>
<tr>
<td>SERPINE2</td>
<td>NT</td>
<td>*</td>
<td>+</td>
<td>NT</td>
<td>—</td>
</tr>
<tr>
<td>TGFB1</td>
<td>—</td>
<td>+</td>
<td>#</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TNFα</td>
<td>—</td>
<td>+</td>
<td>#</td>
<td>NT</td>
<td>+</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; NT = not tested.

* Replicated genetic finding.
† Loose replication because different Reference SNP (rs) numbers were associated.
# Marginally associated, likely due to small sample sizes.

Data from References 59–61, 70, 71.

Postma et al. AJRCCM 2011
Can interventions modify the course of COPD as defined by the annual rate of decline in FEV$_1$?
Schematic illustration of effects of an intervention on disease progression

Halpin D & Tashkin DP. J COPD 2009; 6:211-25
Smoking cessation slows disease progression: Interventional study

Anthonisen et al. AJRCCM 2002;166:675-9
ICS Alone Do **Not** Modify COPD Natural History

As summarized by MacNee and Calverley, *Thorax* 2003;58:261-5.

Values represent mean annual declines in $\text{FEV}_1$, ml

CCLS = Copenhagen City Lung Study
*Lancet* 1999;353:1819-23
EUROSCOP = European Respiratory Society Study of COPD
ISOLDE = Inhaled Steroids in Obstructive Lung Disease
*BMJ* 2000;320:1297-1303,
LHS2 = Lung Health Study 2
Lack of Effect of ICS on FEV$_1$ Decline
Soriano et al. Chest 2007; 131:682-9

Data from 7 RCTs:
LHS II (1057)
CCLS (239)
ISOLDE (520)
EUROSCOP (1029)
TRISTAN (515)
Szafranski (248)
Calverley 2 (303)
Total N = 3911
Adjusted means* & rate of decline in post-BD FEV₁ over 3 yrs for SFC, SAL, FP and Placebo treatment

*Random coefficient model

*p<0.003

Celli et al. AJRCCM 2008, 332-8
N-acetylcysteine Trial: BRONCUS

Change in FEV₁

Exacerbation Rate

<table>
<thead>
<tr>
<th></th>
<th>Rate (Events/yr)</th>
<th>StDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC</td>
<td>1.25</td>
<td>1.35</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.31</td>
<td>1.39</td>
</tr>
<tr>
<td>HR</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>

NAC is ineffective at prevention of deterioration in lung function and prevention of exacerbations in patients with COPD

Tiotropium reduces the rate of pre-bronchodilator FEV$_1$ decline in a 1-yr study

Anzueto et al. Pulm Pharm Ther 2005; 18:75-81

* $p=0.005$ tiotropium versus placebo (mean regression slopes)
UPLIFT Trial: Study Design

Run in 2 weeks

Treatment period 4 years (48 month)

30 days follow-up

Offer: 4-week smoking cessation program

Tiotropium qd

All previously prescribed respiratory medications and adaptation to medical needs (except inhaled anticholinergics)

Placebo qd

Stop: Tiotropium qd
Start: Ipratropium qid

Day 1
Randomization

Day 30

Every 6 months

4 years End of trial

End of follow up

Screening
Spirometry

Day 1
Spirometry + SGRQ

Day 30
Spirometry

Every 6 months
Spirometry + SGRQ

4 years End of trial
Spirometry + SGRQ

End of follow up
Spirometry

Vital status
Decramer et al. COPD 2004
Tiotropium does not influence the rate of decline in pre- or post-bronchodilator FEV\(_1\) over 4 Years

Tashkin et al., NEJM 2008

*P<0.0001 vs. control. Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements.
Baseline trough FEV\(_1\) (observed mean) = 1.116 (trough), 1.347 (peak). Patients with ≥3 acceptable PFTs after day 30 were included in the analysis.
Tiotropium does not influence the rate of decline in pre- or post-bronchodilator FEV₁ over 4 Years

*P<0.0001 vs. control. Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements.
Baseline trough FEV₁ (observed mean) = 1.116 (trough), 1.347 (peak). Patients with ≥3 acceptable PFTs after day 30 were included in the analysis.

Tashkin et al., NEJM 2008
Baseline and On Treatment* Respiratory Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Tiotropium (n = 2986)</th>
<th>Control (n = 3006)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>On Treatment</td>
</tr>
<tr>
<td>Any respiratory medication</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>Short-acting anticholinergic</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>Short-acting beta-agonist</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>Long-acting beta-agonist*</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Inhaled steroid*</td>
<td>62</td>
<td>74</td>
</tr>
<tr>
<td>Theophylline</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Supplemental O₂</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

*Used alone or in combination
+ At any time during treatment including short-term treatment of exacerbations
## Annual Decline in Post-Bronchodilator FEV$_1$ in Major Long-Term COPD Trials

<table>
<thead>
<tr>
<th>Study (Duration) (order: year of publication)</th>
<th>Current smokers</th>
<th>Baseline FEV$_1$ % predicted</th>
<th>Study drug</th>
<th>Annual decline in FEV$_1$ (mL/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Study drug</td>
</tr>
<tr>
<td><strong>EUROSCOP (3 years)</strong></td>
<td>100%</td>
<td>~ 79%</td>
<td>Budesonide</td>
<td>57</td>
</tr>
<tr>
<td><strong>ISOLDE (3 years)</strong></td>
<td>36 – 39%</td>
<td>~ 50%</td>
<td>Fluticasone</td>
<td>50</td>
</tr>
<tr>
<td><strong>LHS II (3.3 years)</strong></td>
<td>90%</td>
<td>~ 68%</td>
<td>Triamcinolone</td>
<td>44</td>
</tr>
<tr>
<td><strong>BRONCUS (3 years)</strong></td>
<td>41- 51%</td>
<td>~ 57%</td>
<td>NAC</td>
<td>54</td>
</tr>
<tr>
<td><strong>TORCH (3 years) post hoc analysis</strong></td>
<td>43%</td>
<td>~ 48%</td>
<td>S/F/SFC</td>
<td>42/42/39</td>
</tr>
<tr>
<td><strong>UPLIFT (3 years)</strong></td>
<td>30%</td>
<td>~ 47%</td>
<td>Tiotropium</td>
<td>37</td>
</tr>
<tr>
<td><strong>UPLIFT (4 years)</strong></td>
<td>30%</td>
<td>~ 47%</td>
<td>Tiotropium</td>
<td>40</td>
</tr>
</tbody>
</table>

* All respiratory medications permitted throughout the trial, other than inhaled anticholinergics
## Rate of Decline in FEV$_1$

**No Baseline LABA or ICS**

Mean slope from day 30 until completion of double-blind treatment

- treated set with ≥3 post-randomization measurements

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium (mL/yr)</th>
<th>Control (mL/yr)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SE)</td>
<td>n</td>
</tr>
<tr>
<td>Pre-bronch</td>
<td>789</td>
<td>33 (2)</td>
<td>767</td>
</tr>
<tr>
<td>Post-bronch</td>
<td>787</td>
<td>40 (3)</td>
<td>764</td>
</tr>
</tbody>
</table>

Tashkin et al., NEJM 2008
### Model of Slopes According to Time On or Off ICS/LABA

<table>
<thead>
<tr>
<th></th>
<th>Pre-bronchodilator FEV$_1$</th>
<th></th>
<th>Post-bronchodilator FEV$_1$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON (mL/yr)</td>
<td>OFF (mL/yr)</td>
<td>ON (mL/yr)</td>
<td>OFF (mL/yr)</td>
</tr>
<tr>
<td>Tiotropium (n=2561)</td>
<td>29 (2)</td>
<td>33 (3)</td>
<td>40 (2)</td>
<td>39 (3)</td>
</tr>
<tr>
<td>Control (n=2422)</td>
<td>28 (2)</td>
<td>39 (3)</td>
<td>40 (2)</td>
<td>49 (3)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.52</td>
<td>0.13</td>
<td>0.93</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Advantage:** Use all data points, results interpretable, off ICS/LABA patients comparable to TORCH

*Tashkin et al., NEJM 2008*
Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial

Trooster T, Celli B, Lystig T, Kesten S, Mehra S, Tashkin DP, Drecamer M; Uplift Investigators Collaborators

Rate of Decline in $\text{FEV}_1$ in Maintenance-Naïve Patients

Rate of decline in post-BD $\text{FEV}_1$:

$42 \text{ ml/yr (Tiotropium)} \quad \text{vs} \quad 53 \text{ ml/yr (Placebo)}$

$P<0.05$ at all time points

A high % of the total UPLIFT population had GOLD Stage II COPD at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tiotropium (n = 2986)</th>
<th>Control (n = 3006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>65 ± 8</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Body Mass Index*</td>
<td>26 ± 5</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Smoking history (pack-yrs)*</td>
<td>49 ± 28</td>
<td>48 ± 28</td>
</tr>
<tr>
<td>GOLD stage (II / III / IV) (%)</td>
<td>46 / 44 / 8</td>
<td>45 / 44 / 9</td>
</tr>
<tr>
<td>SGRQ total score (units)*</td>
<td>46 ± 17</td>
<td>46 ± 17</td>
</tr>
</tbody>
</table>

*Mean ± SD
Rate of decline in postbronchodilator FEV$_1$ in relation to disease severity and tiotropium treatment

\[ \Delta=6 \ (3) \quad P=0.02 \]

\[ \Delta=0 \ (3) \quad P=0.87 \]

\[ \Delta=-9 \ (7) \quad P=0.24 \]

\( P=0.08 \) for subgroup by treatment interaction

TORCH decline in post-bronchodilator FEV$_1$ by GOLD stage

Mean rate of decline in FEV1 by GOLD stage (ECLIPSE study)

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>Mean Rate of Decline (± SE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>II (Moderate)</td>
<td>35 ± 1 ml/yr</td>
</tr>
<tr>
<td>III (Severe)</td>
<td>33 ± 1 ml/yr</td>
</tr>
<tr>
<td>IV (Very severe)</td>
<td>25 ± 2 ml/yr</td>
</tr>
</tbody>
</table>

*p=0.17 stage II vs. stage III; p<0.001 stage II vs. stage IV; p<009 for stage 3 vs. stage 4

Vestbo et al. NEJM 2011
Decline of FEV$_1$ with Age and Smoking History

FEV$_1$ (% of value at age 25)

Age (years)

Never smoked or not susceptible to smoke

Smoked regularly and susceptible to smoke

Disability

Death

Fletcher C. BMJ 1977;1:1645-1648
Rate of decline in FEV$_1$ in relation to degree of airflow obstruction is S-shaped*

Adapted from Drummond et al. AJRCCM 2012 * LHS data
COPD in young patients: A pre-specified analysis of the four-year trial of tiotropium (UPLIFT)

A.H. Morice a,*, B. Celli b, S. Kesten c, T. Lystig c, D. Tashkin d, M. Decramer e

a Cardiovascular and Respiratory Studies, Hull York Medicine School, University of Hull, Castle Hill Hospital,
Castle Road, Cottingham, East Yorkshire, HU16 5JQ, UK
b Brigham and Women’s Hospital, Boston, MA, USA
c Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
d David Geffen School of Medicine, UCLA, Los Angeles, CA, USA
e University of Leuven, Leuven, Belgium
Rate of Decline in FEV\textsubscript{1} in Patients < 50 Yrs of Age (N=356)

Post-bronchodilator FEV\textsubscript{1} decline: Tiotropium vs. control:
38 mL/yr vs. 58 mL/yr (\(p< 0.01\)) respectively

\[\Delta \text{20 mL/yr}\]

Mechanical stress triggers release of pro-fibrotic mediators from bronchial epithelium

Tiotropium inhibits LPS-induced neutrophilia in guinea pig cartilaginous & non-cartilaginous airways

Pera et al. ERJ 2011 [Epub 24 Feb]
Tiotropium inhibits LPS-induced goblet cell hyperplasia in guinea pig cartilaginous airways.

Pera et al. ERJ 2011 [Epub 24 Feb]
Acetylcholine-induced proliferation of fibroblasts and myofibroblasts in vitro is inhibited by tiotropium bromide

Distribution of individual annual rates of $\Delta$ in FEV$_1$ over 3-yr period in mod-very severe COPD* 

Vestbo et al. NEJM 2011

38% - $>$40 ml/yr decline
31% - 21-40 ml/yr decline
23% - 20 ml/yr decline to 20 ml/yr increase

*ECLIPSE study (N=2163)
Lung Volumes: Air-trapping and Hyperinflation in COPD

[Diagram showing comparison between normal lung volumes and COPD lung volumes, with labels for TLC, IRV, ERV, RV, FRC, and IC.]
Air-trapping and $\text{FEV}_1$

Linear component $p<0.0001$
Non-linear component $p=0.03$

Foglio et al Respir Med 2000;94:256
Hyperinflation and FEV\textsubscript{1}

Begin and Grassino ARRD 1991; 143: 905-912
Operating Lung Volumes at Rest & during Exercise

Normal

COPD

pre-dose

post-dose

Adapted from O’Donnell DE. AJRCCM 2001; 164:770-7
Correlations Between Dyspnea and Physiologic Function

- Inspiratory capacity
  - Exercise endurance
  - Exertional dyspnea

\[ P < .001 \]

Change in FVC over 4 yrs in UPLIFT

Tiotropium vs Control

Pre-Bronch FVC
Δ = +186 to 205 mL

Post-Bronch FVC
Δ = +31 to 65 mL

n=2519
n=2381
n=2498
n=2371

Day 30
(steady state)

Month

*P<0.0001 vs. control
†P<0.05 vs. control

Tashkin et al. NEJM 2008
Change in inspiratory capacity over 4 yrs

Celli et al. Respir Research 2012
Change in SGRQ over 3 yrs for each treatment

Calverley et al. NEJM 2007; 356:775-89

Graph showing the adjusted mean change in SGRQ total score over time for different treatments (Placebo, SAL, FP, SFC). The number of subjects and time points are also shown.

*p=0.057 vs placebo; †p<0.001 vs placebo; ††p<0.001 vs placebo, SAL and FP
Vertical bars are standard errors
Footnote: a decrease in SGRQ score indicates improvement
Quality of life over 4 yrs in UPLIFT

SGRQ Total Score (Units)

- Tiotropium (n = 2478)
- Control (n = 2337)

Improvement

SGRQ Total Score

* P<0.0001 vs. control. Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline SGRQ Total Score (observed mean) = 45.028. Patients with ≥2 acceptable SGRQ Total Scores after month 6 were included in the analysis.

Tashkin et al. NEJM 2008
Annual rate of pre- and post-BD FEV1 by quartiles in the UPLIFT trial

Pre-bronchodilator FEV1

Post-bronchodilator FEV1

Mean rate of change in FEV1 (ml/yr)

Rate of decline quartile

Q1  Q2  Q3  Q4

Q1  Q2  Q3  Q4

Tiotropium  Placebo

FEV1, forced expiratory volume in 1 second

Kesten et al. Respir Research 2011
Annual rates of decline in health status (SGRQ total score, units/yr) according to quartiles of rates of decline in post-bronchodilator FEV₁

SGRQ, St George’s Respiratory Questionnaire

Kesten et al. Respir Research 2011
Proportion of patients who died during treatment according to quartiles of rate of decline in post-bronchodilator FEV$_1$

*Hazard ratio (tiotropium vs placebo) estimated using Cox regression with treatment, rate of decline quartile, and rate of decline quartile by treatment interaction as covariates. Observations were censored at 1440 days.

Kesten et al. Respir Research 2011
Summary

• Question
  • Is the rate of decline in FEV\textsubscript{1} a useful objective parameter for tracking the course of the disease and its modification by therapeutic interventions?

• Answer – a qualified yes, since
  • It parallels the course of the disease as reflected by other measures, including small airways pathology, lung volumes and PROs, such as health status and exacerbation frequency
  • It is favorably modified by interventions, especially sustained smoking cessation, although the impact of pharmacotherapy is confounded by other factors, including concomitant medication, the level of disease severity and age