Recent Advances in the Management and Prevention of COPD Exacerbations

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To begin with...I am not this individual
Disclosures

FJM has been a member of advisory boards and/or consultant for AstraZeneca, Boehringer Ingelheim, Bridge Therapeutics, Chiesi, ConCert, Genentech, GlaxoSmithKline, Nitto, Novartis, Patara, Pearl, Proterrix Bio, Sunovion, Teva, Theravance, and Zambon.

He has been a member of steering committees for studies sponsored by Afferent/Merck, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Promedior, ProMetic, Respivant/Patara, Veracyte.

He has served on speaker’s bureaus or in continuing medical education activities sponsored by American College of Chest Physicians, AstraZeneca, Boehringer Ingelheim, Canadian Respiratory Network, Columbia University, Dartmouth University, France Foundation, GlaxoSmithKline, Inova Health System, Methodist Hospital, Miller Communications, National Association for Continuing Education, New York University, Novartis, PeerView, Potomac, Prime, Puerto Rican Respiratory Society, Rockpointe, University of Alabama Birmingham, UpToDate, WebMD/MedScape, Western Connecticut Health Network.

He has served on DSMBs for Biogen, Boehringer Ingelheim, Genentech and GSK.
Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?
COPD Exacerbations

Consequences

- ↓ quality of life\textsuperscript{1,2}
- ↑ loss of lung function\textsuperscript{2}
- ↑ hospitalization rate\textsuperscript{3}
- ↑ use of healthcare resources\textsuperscript{4}
- ↑ mortality\textsuperscript{2}

AECOPD are associated with decreased physical activity

AECOPD are associated with subsequent increased risk of CV event

Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?
Which of the following has been demonstrated to decrease AECOPD rates

- 1. ICS/LABA
- 2. LAMA
- 3. ICS/LABA/LAMA
- 4. Azithromycin
- 5. All of the above
Multiple agents have been shown to decrease exacerbation rates

- ICS
- LABA
- ICS/LABA
- LAMA
- LABA/LAMA
- Macrolides
- Vaccines

Walters JAE et al; Cochrane Database of Systematic Reviews; Art. No.: CD001390
Horita N et al, Cochrane Database of Systematic Reviews 2017; Art. No: CD012066
Exacerbation rates in Netherlands have decreased over the past 25 years.

Bischoff EWMA et al; *Br J Gen Pract* 2009; 59: 927-33
FLAME study design

Inclusion criteria:
- Post-bronch. FEV₁ 25–60% predicted (FEV₁/FVC ratio <0.7)
- ≥1 COPD exacerbation in previous 12 months
- Moderate-to-severe dyspnoea (mMRC >2)

Tiotropium mandatory

Population:
N = 3,362
FEV₁ 44.1% pred.
GOLD D [75%] / B [24%]
exacerbation history >2 [19%]
mMRC score = 2 [72%] / ≥3 [28%]

Primary endpoint
Non-inferiority on rate of all mild/moderate/severe exacerbations

1,580/4,942 excluded

FLAME: Probability of a first mild, moderate or severe exacerbation on treatment

- In a breathless patient population (mMRC≥2) with a prior exacerbation history, dual bronchodilation with QVA149 reduced the risk of all exacerbation types vs. salmeterol-fluticasone propionate

![Graph showing exacerbation probability over weeks]

**RR 0.83 (95% CI 0.75-0.91)**

IMPACT: InforMing the PAthway of COPD Treatment study design

Population: symptomatic and at risk of exacerbation (≥1 exacerbation in the past 12 months)

Key inclusion criteria:
- Age 40+ and COPD diagnosis (ATS/ERS definition)
- CAT ≥10
- FEV₁ <50% + ≥1 moderate/severe exacerbations in past year; OR FEV₁ ≥50% to <80% + ≥2 moderate exacerbations or ≥1 severe exacerbation in past year

Allowed inclusion of patients with co-morbidities such as:
- CV risk/disease
- Diabetes
- Prior history of asthma

Co-primary treatment comparisons (ITT population)
- Annual rate of moderate/severe exacerbations:
  - FF/UMEC/VI vs FF/VI
  - FF/UMEC/VI vs UMEC/VI

* For all combinations, delivered doses were as follows: FF (92 µg), UMEC (55 µg) and VI (22 µg); all treatments were administered via the ELLIPTA inhaler.
ICS/LABA decreased the rate of on-treatment moderate/severe exacerbations compared with LAMA/LABA.

![Graph showing the annual rate of moderate/severe exacerbations for UMEC/VI and FF/VI.](image)

- **UMEC/VI**
  - Annual rate: 1.21 (95% CI: 1.14, 1.29)
  - Reduction: 11.5% (95% CI: 1.02, 1.12) compared to FF/VI
  - Sample size: n=2069

- **FF/VI**
  - Annual rate: 1.07 (95% CI: 1.02, 1.12)
  - Sample size: n=4133

Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.

How can we attempt to compare FLAME with IMPACT?

<table>
<thead>
<tr>
<th>Baseline COPD medications, n (%)</th>
<th>FF/UMEC/VI (n=4151)</th>
<th>FF/VI (n=4134)</th>
<th>UMEC/VI (n=2070)</th>
<th>Overall (N=10355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS + LABA + LAMA</td>
<td>1672 (40%)</td>
<td>1647 (40%)</td>
<td>864 (42%)</td>
<td>4183 (40%)</td>
</tr>
<tr>
<td>ICS + LABA</td>
<td>1354 (33%)</td>
<td>1340 (32%)</td>
<td>647 (31%)</td>
<td>3341 (32%)</td>
</tr>
<tr>
<td>LABA + LAMA</td>
<td>389 (9%)</td>
<td>349 (8%)</td>
<td>196 (9%)</td>
<td>934 (9%)</td>
</tr>
<tr>
<td>LAMA</td>
<td>304 (7%)</td>
<td>365 (9%)</td>
<td>162 (8%)</td>
<td>831 (8%)</td>
</tr>
</tbody>
</table>

* These were the most common baseline combinations; treatment combinations may have included phosphodiesterase-4 inhibitor and/or a xanthine.

ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist.
AECOPD rates in IMPACT by prior exacerbation history or baseline therapy

![Diagram showing AECOPD rates in IMPACT by prior exacerbation history or baseline therapy.](image)

*Between day of screening -3 days and date of screening (inclusive); **p<0.05 in favour of FF/VI;
†post hoc analysis
CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Lipson DA, et al. ERS 2018; Poster PA4384
LABA/LAMA/ICS reduces moderate/severe exacerbations compared with individual dual combinations in same device

Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/Vi, 4134 patients treated with FF/Vi and 2070 patients treated with UMEC/Vi.

ICS is associated with improved all-cause mortality (on-treatment data) in IMPACT\textsuperscript{1,2}.

Relative risk reduction:

- FF/UMEC/VI vs UMEC/VI: 42.1\%, HR 0.58 (95% CI: 0.38, 0.88), \(p=0.011\)
- FF/VI vs UMEC/VI: 38.7\%, HR 0.61 (95% CI: 0.40, 0.93), \(p=0.022\)

Number of subjects at risk:

<table>
<thead>
<tr>
<th></th>
<th>FF/UMEC/VI</th>
<th>FF/VI</th>
<th>UMEC/VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>4151</td>
<td>4134</td>
<td>2070</td>
</tr>
<tr>
<td>56</td>
<td>4082</td>
<td>3984</td>
<td>1993</td>
</tr>
<tr>
<td>84</td>
<td>3968</td>
<td>3798</td>
<td>1880</td>
</tr>
<tr>
<td>112</td>
<td>3898</td>
<td>3694</td>
<td>1820</td>
</tr>
<tr>
<td>140</td>
<td>3838</td>
<td>3619</td>
<td>1769</td>
</tr>
<tr>
<td>168</td>
<td>3752</td>
<td>3496</td>
<td>1713</td>
</tr>
<tr>
<td>196</td>
<td>3714</td>
<td>3443</td>
<td>1685</td>
</tr>
<tr>
<td>224</td>
<td>3690</td>
<td>3391</td>
<td>1656</td>
</tr>
<tr>
<td>252</td>
<td>3613</td>
<td>3291</td>
<td>1612</td>
</tr>
<tr>
<td>280</td>
<td>3581</td>
<td>3258</td>
<td>1595</td>
</tr>
<tr>
<td>308</td>
<td>3545</td>
<td>3230</td>
<td>1578</td>
</tr>
<tr>
<td>336</td>
<td>3486</td>
<td>3182</td>
<td>1548</td>
</tr>
<tr>
<td>364</td>
<td>3454</td>
<td>3152</td>
<td>1531</td>
</tr>
</tbody>
</table>

EVOLUTION OF ROFLUMILAST PROGRAM
IDENTIFICATION OF TARGET PATIENT POPULATION

Subgroup analyses of early Phase III Studies M2-111, M2-112

Hypothesis Generation

Confirmatory 1-yr Pivotal Studies M2-124, M2-125
- Severe/very severe patients
- History of chronic cough and sputum
- History of exacerbations
In the primary analysis (Poisson regression, ITT), roflumilast reduced the rate of moderate or severe exacerbations by 13.2% (p=0.0529)

Rate ratio (95% CI)

Placebo: 0.927
Roflumilast: 0.805

0.868 (0.753–1.002)

CI: confidence interval; ITT: intention to treat
*Patients experiencing at least one exacerbation
Rate ratios, 95% CI and p-values are based on a Poisson regression analysis in the ITT population

MARTINEZ FJ ET AL. LANCET 2015; 385: 857-66
In patients receiving ICS/LABA/LAMA, roflumilast significantly reduced the rate of severe exacerbations

![Bar chart showing reduced rate of severe exacerbations in patients receiving roflumilast compared to placebo.](chart)

- **23.3%** reduction in severe exacerbations with roflumilast, p=0.0406
- **28.9%** reduction in severe exacerbations with roflumilast, p=0.2021

**Mean rate of COPD exacerbations per patient per year**

**Rate ratio (95% CI)**
- ICS/LABA/LAMA subgroup: 0.767 (0.595–0.989)
- ICS/LABA (no LAMA) subgroup: 0.711 (0.421–1.201)

**n**
- ICS/LABA/LAMA subgroup: 152
- ICS/LABA (no LAMA) subgroup: 40

*Patients experiencing at least one exacerbation; rate ratios, 95% CI and p-values are based on a negative binomial regression analysis in the ITT population.

**MARTINEZ FJ ET AL. LANCET 2015; 385: 857-66**
Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?
Benefit–risk balance should be tailored to individual patient characteristics

Individual presentation and underlying mechanisms
- Mortality
- Disease progression
- Lung function
- Symptoms: cough, sputum production, and dyspnea
- Exercise tolerance
- Exacerbations
- Disability
- Health status and quality of life

Individual risk factors and comorbidities
- Pneumonia
- Tuberculosis
- Skin bruising
- Osteoporosis or fractures
- Muscle dysfunction
- Nutritional impairment
- Cataract
- Diabetes
- Tremor
- Cardiovascular events
- Neuropsychological events
- Gastrointestinal symptoms

Individualization 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

71-year-old with 4-year history of exertional breathlessness, osteoporosis with *past compression fracture*, rheumatic fever, syringomyelia, and *past pneumonia*. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA.

He has experienced a hospitalization since your last visit.

His eosinophil count is 100.

**What is would be your therapy?**

1. LAMA/LABA
2. ICS/LABA
3. ICS/LABA + LAMA
4. LABA/LAMA + ICS
71-year-old with 4-year history of exertional breathlessness, osteoporosis with past compression fracture, rheumatic fever, syringomyelia, and past pneumonia. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA.

He has experienced a hospitalization since your last visit.

**His eosinophil count is 300.**

**What is would be your therapy?**

1. LAMA/LABA
2. ICS/LABA
3. ICS/LABA + LAMA
4. LABA/LAMA + ICS
ICS/LABA decreases AECOPD compared too LABA monotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Rate ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Fluticasone/salmeterol</td>
<td>-0.07</td>
<td>0.0734</td>
<td>13.4%</td>
<td>0.93 (0.81-1.03)</td>
<td>2003</td>
</tr>
<tr>
<td>TRISTAN</td>
<td>-0.13</td>
<td>0.044</td>
<td>16.0%</td>
<td>0.88 (0.81-0.93)</td>
<td>2004</td>
</tr>
<tr>
<td>TORCH</td>
<td>-0.4308</td>
<td>0.073</td>
<td>13.5%</td>
<td>0.65 (0.56-0.75)</td>
<td>2004</td>
</tr>
<tr>
<td>Kardos 2007</td>
<td>-0.3638</td>
<td>0.091</td>
<td>11.8%</td>
<td>0.70 (0.58-0.83)</td>
<td>2008</td>
</tr>
<tr>
<td>Ferguson 2008</td>
<td>-0.3624</td>
<td>0.091</td>
<td>11.8%</td>
<td>0.70 (0.58-0.83)</td>
<td>2009</td>
</tr>
<tr>
<td>Anzueto 2009</td>
<td>-0.3624</td>
<td>0.091</td>
<td>11.8%</td>
<td>0.70 (0.58-0.83)</td>
<td>2009</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.77 (0.66-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; χ² = 21.64, df = 4 (P = .0002); I² = 82%
Test for overall effect: z = 3.56 (P = .00004)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Rate ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.2 Budesonide/formoterol</td>
<td>-0.26</td>
<td>0.125</td>
<td>9.1%</td>
<td>0.77 (0.60-0.99)</td>
<td>2003</td>
</tr>
<tr>
<td>Szafranski 2003</td>
<td>-0.294</td>
<td>0.12</td>
<td>9.4%</td>
<td>0.75 (0.59-0.94)</td>
<td>2003</td>
</tr>
<tr>
<td>Calverley 2003</td>
<td>-0.2357</td>
<td>0.15</td>
<td>7.5%</td>
<td>0.79 (0.59-1.03)</td>
<td>2008</td>
</tr>
<tr>
<td>Taskin 2008</td>
<td>-0.4943</td>
<td>0.15</td>
<td>7.5%</td>
<td>0.61 (0.45-0.82)</td>
<td>2009</td>
</tr>
<tr>
<td>Rennard 2009</td>
<td>-0.4943</td>
<td>0.15</td>
<td>7.5%</td>
<td>0.61 (0.45-0.82)</td>
<td>2009</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.73 (0.64-0.83)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; χ² = 1.03, df = 3 (P = .60); I² = 0%
Test for overall effect: z = 4.66 (P < .00001)

Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Rate ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.02</td>
<td>0.2516</td>
<td>68%</td>
<td>0.76 (0.68-0.81)</td>
<td>2012</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; χ² = 25.18, df = 8 (P = .001); I² = 68%
Test for overall effect: z = 5.22 (P < .00001)
Test for subgroup differences: χ² = 0.24, df = 1 (P = .63), I² = 0%

EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risk of pneumonia with inhaled corticosteroid-containing medicines when used to treat COPD.

The PRAC review confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee’s view is that the benefits of inhaled corticosteroids continue to outweigh their risks.

14/07/2016 EMA/488280/2016
### Risk factors associated with CXR confirmed pneumonia in COPD patients treated with ICS

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≤64</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
</tr>
<tr>
<td><strong>Previous pneumonia</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td></td>
</tr>
<tr>
<td>≥25 kg/m²</td>
<td></td>
</tr>
<tr>
<td><strong>GOLD stage</strong></td>
<td></td>
</tr>
<tr>
<td>I &amp; II: FEV₁ ≥50% predicted</td>
<td></td>
</tr>
<tr>
<td>III: FEV₁ ≥30% – &lt;50% predicted</td>
<td></td>
</tr>
<tr>
<td>IV: FEV₁ &lt;30% predicted</td>
<td></td>
</tr>
</tbody>
</table>

Risk with VI 25 μg (n=818)
Risk with FF/VI 100/25 μg (n=806)


BMI, body mass index; CXR, chest x-ray; VI, vilanterol.

Risk factors associated with pneumonia was a secondary endpoint. The primary endpoint was the annual rate of moderate (requiring treatment with SCS and/or antibiotics) and severe (necessitating hospitalization) exacerbations.

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Eosinophil Count Associates in continuous fashion with Response to ICS/LABA compared with LABA Alone


Budesonide/formoterol vs LABA/LAMA (KRONOS) or LABA (SOPHOS)

PT010 (BGF) is in development and is not currently licensed for use in COPD
BGF: budesonide, glycopyrronium and formoterol fumarate; FEV₁, forced expiratory volume in 1 second; GFF, glycopyrronium and formoterol fumarate

Hanania N et al (ATS 2019)
71-year-old with 4-year history of exertional breathlessness, osteoporosis with past compression fracture, rheumatic fever, syringomyelia, and past pneumonia. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA/LABA.

He has experienced a hospitalization since your last visit.

His eosinophil count is 100.

What is would be your therapy?

1. LAMA/LABA
2. ICS/LABA
3. ICS/LABA/LAMA
4. Azithromycin
71-year-old with 4-year history of exertional breathlessness, osteoporosis with past compression fracture, rheumatic fever, syringomyelia, and past pneumonia. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA/LABA.

He has experienced a hospitalization since your last visit.

His eosinophil count is 300.

What is would be your therapy?

1. LAMA/LABA
2. ICS/LABA
3. ICS/LABA/LAMA
4. Azithromycin
Treatment of stable COPD

► Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (Figure 4.2).

► Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be needed.
THE Refined ABCD ASSESSMENT TOOL

Spirometrically Confirmed Diagnosis

Assessment of airflow limitation

Assessment of symptoms/risk of exacerbations

Post-bronchodilator FEV₁/FVC < 0.7

<table>
<thead>
<tr>
<th>Grade</th>
<th>FEV₁ (%) predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>≥ 80</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>50-79</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>30-49</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

Moderate or Severe Exacerbation History

≥2 or ≥ 1 leading to hospital admission

0 or 1 (not leading to hospital admission)

mMRC 0-1
CAT < 10

mMRC ≥ 2
CAT ≥ 10

Symptoms

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## Treatment of stable COPD

### INITIAL PHARMACOLOGICAL TREATMENT

<table>
<thead>
<tr>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization</td>
<td>LAMA or LAMA + LABA* or ICS + LABA**</td>
</tr>
<tr>
<td>0 or 1 moderate exacerbations (not leading to hospital admission)</td>
<td>*Consider if highly symptomatic (e.g. CAT &gt; 20) **Consider if eos ≥ 300</td>
</tr>
<tr>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>LAMA</td>
<td>A Long Acting Bronchodilator (LABA or LAMA)</td>
</tr>
<tr>
<td>A Bronchodilator</td>
<td></td>
</tr>
<tr>
<td>mMRC 0-1 CAT &lt; 10</td>
<td>mMRC ≥ 2 CAT ≥ 10</td>
</tr>
</tbody>
</table>

**FIGURE 4.1**

**Definition of abbreviations:** eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT: ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   ✓ Place patient in box corresponding to current treatment & follow indications
   ✓ Assess response, adjust and review
   ✓ These recommendations do not depend on the ABCD assessment at diagnosis

---

EXACERBATIONS

- LABA or LAMA
- LABA + LAMA
- LABA + ICS
- LABA + LAMA + ICS
- Rofumilast
  - FEV₁ < 50% & chronic bronchitis
- Azithromycin

eos = blood eosinophil count (cells/µL)
* Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization
** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

FIGURE 4.3

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A 63 year old man has known severe COPD (FEV1 40% predicted), no chronic sputum production, CAD (S/P PCI two years ago and 2 acute exacerbations two years ago. Since that time he has been remarkably stable while on inhaled LAMA/LABA/ICS.

He has CAT of 20 and mMRC of 2.

His eosinophil count is 300.

What would you do therapeutically at this point?

1. Prescribe chronic azithromycin (MWF)
2. Add roflumilast
3. No change in therapy
4. Discontinue ICS
5. Discontinue the LAMA
ICS Withdrawal – controversy continues

**POINT:**
Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 (30% ≤ FEV₁ < 50% Predicted) COPD? Yes

*James D. Chalmers, MD, PhD*
*Dundee, Scotland*

**COUNTERPOINT:**
Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 (30% ≤ FEV₁ < 50% Predicted) COPD? No

*Ian D. Pavord, FMedSci*
*Oxford, England*

Chalmers JD  *Chest* 2018; 153: 778-82
Pavord ID. *Chest* 2018; 153: 782-4
Withdrawal of Inhaled Glucocorticoids

A. Moderate or Severe COPD Exacerbation

- Hazard ratio, 1.06 (95% CI, 0.94–1.19)
- P = 0.35 by Wald’s chi-square test

B. Primary End Point and Sensitivity Analyses

- Primary end point
  - Hazard ratio: 0.94, 1.06, 1.19
- Primary end point including exacerbations on open-label therapy
  - Hazard ratio: 0.95, 1.06, 1.19
- Primary end point excluding baseline FEV₁ covariate
  - Hazard ratio: 0.93, 1.05, 1.18

Magnussen et al, NEJM 2014; 371: 1285-94
Withdrawal of Inhaled Glucocorticoids

C Severe COPD Exacerbation

Hazard ratio, 1.20 (95% CI, 0.98–1.48)  
P=0.08 by Wald’s chi-square test

D Change from Baseline in Trough FEV₁

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>IGC continuation</th>
<th>IGC withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGC continuation</td>
<td>1223 1135 1114 1077 970</td>
<td></td>
</tr>
<tr>
<td>IGC withdrawal</td>
<td>1218 1135 1092 1058 935</td>
<td></td>
</tr>
</tbody>
</table>

Magnussen et al, NEJM 2014; 371: 1285-94
Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial

**WISDOM post-hoc analysis: ICS withdrawal only increased exacerbation risk in patients with ≥2 prior exacerbations and elevated blood eosinophils**

<table>
<thead>
<tr>
<th>1 exacerbation per year</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=1454)</td>
<td>1.14</td>
</tr>
<tr>
<td>Baseline blood eosinophils</td>
<td></td>
</tr>
<tr>
<td>&lt;150/µL (n=664)</td>
<td>1.11</td>
</tr>
<tr>
<td>≥150/µL (n=750)</td>
<td>1.22</td>
</tr>
<tr>
<td>&lt;300/µL (n=1,121)</td>
<td>1.11</td>
</tr>
<tr>
<td>≥300/µL (n=293)</td>
<td>1.45</td>
</tr>
<tr>
<td>&lt;400/µL (n=1,253)</td>
<td>1.16</td>
</tr>
<tr>
<td>≥400/µL (n=161)</td>
<td>1.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>≥2 exacerbations per year</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=841)</td>
<td>1.07</td>
</tr>
<tr>
<td>Baseline blood eosinophils</td>
<td></td>
</tr>
<tr>
<td>&lt;150/µL (n=403)</td>
<td>1.02</td>
</tr>
<tr>
<td>≥150/µL (n=421)</td>
<td>1.19</td>
</tr>
<tr>
<td>&lt;300/µL (n=669)</td>
<td>0.99</td>
</tr>
<tr>
<td>≥300/µL (n=155)</td>
<td>1.75</td>
</tr>
<tr>
<td>&lt;400/µL (n=738)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥400/µL (n=86)</td>
<td>2.96</td>
</tr>
<tr>
<td>&lt;150/µL (n=403)</td>
<td>1.02</td>
</tr>
<tr>
<td>≥150/µL to &lt;300/µL (n=266)</td>
<td>0.99</td>
</tr>
<tr>
<td>≥300/µL to &lt;400/µL (n=69)</td>
<td>1.05</td>
</tr>
<tr>
<td>≥400/µL (n=86)</td>
<td>2.96</td>
</tr>
</tbody>
</table>

Total study population = 2,485

Calverley PMA, et al. Am J Respir Crit Care Med 2017
The primary objective was to demonstrate non-inferiority of IND/GLY versus TIO+SFC on change from baseline in post-dose trough FEV1 after 26 weeks of treatment.

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT: ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   ✓ Place patient in box corresponding to current treatment & follow indications
   ✓ Assess response, adjust and review
   ✓ These recommendations do not depend on the ABCD assessment at diagnosis

**EXACERBATIONS**

LABA or LAMA

LABA + LAMA

LABA + LAMA + ICS

LABA + ICS

**eos**

- eos = blood eosinophil count (cells/μL)
- * Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization
- ** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

Roflumilast

FEV₁ < 50% & chronic bronchitis

Azithromycin

In former smokers

FIGURE 4.3

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Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?
Progression from clinical phenotypes to biological endotypes

Woodruff PG et al; *Lancet* 2015; 385: 1789-98
AECOPD can be biologically ‘clustered’

Bafadhel M et al; AJRCCM 2011; 184: 662-71
Blood eosinophils at stable state associate with eosinophilic AECOPD

<table>
<thead>
<tr>
<th>99 subjects included in the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 subjects in RE group</td>
</tr>
<tr>
<td>26 subjects had at least one exacerbation during year 1 (78 exacerbations in total)</td>
</tr>
<tr>
<td>16 subjects in IE group</td>
</tr>
<tr>
<td>13 subjects had at least one exacerbation during year 1 (29 exacerbations in total)</td>
</tr>
<tr>
<td>57 subjects in PE group</td>
</tr>
<tr>
<td>48 subjects had at least one exacerbation during year 1 (161 exacerbations in total)</td>
</tr>
</tbody>
</table>

OR eosinophilic AECOPD 11.16; 95% CI 5.26-23.68

Kim VL et al; ERJ 2017; 50: 1700853
Mepolizumab has intriguing effect on AECOPD

RA 0.82 (0.68-0.98)
RA 0.98 (0.85-1.12)
RA 0.80 (0.65-0.98)
RA 0.86 (0.70-1.05)

Pavord ID et al; NEJM 2017 (on line as doi: 10.1056/NEJMoa1708208)
Roflumilast Response is Particularly Evident in COPD Patients with distinct phenotypes

So ... in conclusion

- AECOPD remain a major event in the natural history of COPD patients
- Reducing AECOPD risk remains a major component of therapeutic paradigms
- Pharmacotherapy can decrease AECOPD risk
- Pharmacotherapy should be tailored to the patient based on clinical and biomarker characteristics
- The future will utilize a better understanding of AECOPD biology to further improve personalized management strategies