New directions in COPD
Congress highlights from the ERS 2019 in Madrid
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Objectives
Objectives

The 2019 European Respiratory Society (ERS) annual congress was held in Madrid, Spain, from 28 September – 2 October, welcoming over 20,000 delegates from around the world.

New concepts were presented and discussed, including: advances in pharmacologic treatments, the appropriate use of ICS therapy, treatment of exacerbations, as well as new insights on pulmonary rehabilitation, exercise capacity in patients with COPD and co-morbidities of COPD.

Objectives of this report

• Inform interested healthcare professionals about the main COPD topics of discussion and highlights from the ERS 2019.

• Provide expert viewpoints on the clinical relevance of the new data for daily practice.

Focus of this report

This report particularly focuses on symptoms and treatment, exacerbations, the role of eosinophils in guiding therapy, inhalers and inhalation, physical activity, and co-morbidities.
Symptoms
Detecting early-stage COPD with forced oscillation technique

- A study (n=2,297 COPD patients and n=4,416 controls) assessed the ability of forced oscillation technique (FOT) to detect COPD at an early stage, as an alternative to spirometry.
- A combination of five FOT parameters was shown to perform best at detecting early COPD and small airway limitation:
  - Z5
  - Fres
  - R5-R20
  - Rp
  - X5
- In conclusion, FOT may be a meaningful alternative to spirometry to detect COPD.

### Table: Performance of FOT Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD Detection</th>
<th>Detection of Airflow Limitation in Small Airways</th>
<th>Distinguishing COPD GOLD 1 Stage from Non-COPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity (%)</td>
<td>64.90</td>
<td>62.80</td>
<td>56.80</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>79.30</td>
<td>70.70</td>
<td>71.60</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>61.83</td>
<td>82.47</td>
<td>19.65</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>81.20</td>
<td>51.27</td>
<td>97.43</td>
</tr>
</tbody>
</table>

FOT, forced oscillation technique
R5, respiratory resistance at 5 Hz
R20, respiratory resistance at 20 Hz
X5, respiratory reactance at 5 Hz
Fres, resonant frequency
Z5, respiratory impedance

Gao L et al. ERS 2019:PA2631.
Refining COPD phenotyping and its therapeutic implications

The effect of dual LAMA/LABA bronchodilator therapy (tiotropium/olodaterol, T/O) was compared to LABA monotherapy (formoterol, F) in an 8-week cross-over study aimed at refining phenotyping in COPD patients (n=66) by evaluating the use of plethysmography, impulse oscillometry (IOS) and multiple breath washout (MBW)

IOS: Peripheral resistance and ventilation heterogeneity (VH) clusters were identified

- Abnormal frequency dependence of resistance (D5-20, 55 ± 45%) and reactance area (Ax, 1.65 ± 1.60)
- Global VH was elevated to 10.2 ± 2.0
- Acinar phase-III slopes with an increase of 0.34 ± 0.21 L-1 resembled VH

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Gender differences in COPD phenotyping

Emphysema phenotyping in men vs women

A study of 112 COPD patients (GOLD 1-4, 29% female, 71% male) found:

• Significant correlation between residual volume ((RV) Spearman’s rho $\rho=0.377, p=0.001$) and FEV$_1$ ($\rho=-0.344, P=0.002$) with low attenuation volume (LAV %) in male, but not female patients

• A significant correlation between single breath diffusion capacity of the lungs for carbon monoxide corrected for haemoglobin, in females (DLCOcSB) with LAV % ($\rho=-0.731, p<0.001$)

• Inclusion of a cut-off value for the female, but not the male, group of the cohort raised the sensitivity to 92.3%, and the specificity to 87.5% — suggesting the need for new parameters to be further evaluated in a larger female population

COPD phenotype in women

A study of 166 COPD cases (86 men and 80 women) aimed to assess the differences of COPD characteristics based on gender

• mMRC dyspnoea results showed no significant differences between gender

• A significant difference was observed between the male and female gender for classification in stage 1, 2 and 4 according to GOLD 2018 ($p<0.001$)

• Particularly in rural areas, COPD is more frequently caused by wood vs tobacco exposure

• The findings may explain a female-specific COPD phenotype, characterised by increased prevalence of comorbidities, age and BMI vs males ($p<0.005$)


<table>
<thead>
<tr>
<th>Characteristics of COPD study population</th>
<th>Tobacco smoking</th>
<th>Wood smoke</th>
<th>BMI (kg/m$^2$)</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>100%</td>
<td>0%</td>
<td>23.5% ±5</td>
<td>32.5%</td>
</tr>
<tr>
<td>75%</td>
<td></td>
<td></td>
<td>25% ±7</td>
<td></td>
</tr>
<tr>
<td>28.8% ±7</td>
<td></td>
<td></td>
<td></td>
<td>52.5%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAV%, low attenuation volume percent
mMRC, Modified Medical Research Council
BMI, body mass index
Systemic and airway inflammation in COPD

High blood neutrophil count (BNC) could serve as an indicator of mortality and exacerbation risk in COPD (n=7,220; 10 years mean follow up)¹

Mortality rate was 80% higher in the high BNC group (vs normal; p<0.001)

- Elevated baseline BNC (>6000 cells/µL)
- Normal baseline BNC (<6000 cells/µL)

Mortality rate per 100 person years
- Elevated baseline BNC: 13.8
- Normal baseline BNC: 7.4

Exacerbation rate and severity were higher in the high BNC group (vs normal; p<0.001)

- Elevated baseline BNC (>6000 cells/µL)
- Normal baseline BNC (<6000 cells/µL)

Number of exacerbations/year
- Elevated baseline BNC: 1.7
- Normal baseline BNC: 1.3

Dynamic hyperinflation is associated with systemic and airway inflammation in COPD²

- Patients with dynamic hyperinflation, i.e. an increase in end-expiratory lung volume (EELV) during progressive exercise test, had higher levels of inflammatory biomarkers such as IL-1β, IL-6 and IL-8 (p<0.001) in plasma (systemic inflammation) and exhaled breath condensate (airway inflammation)

EXACT-PRO correlates with FEV₁ and systemic but not airway inflammation markers³

EXACT-PRO, a 14-items symptoms diary to measure exacerbation frequency, was significantly correlated with:

- COPD symptoms and health status: CAT (p<0.0001), SGRQ (p<0.0001), MRC (p<0.0001) and FEV₁ (p=0.007)
- Systemic inflammatory markers: neutrophil-to-lymphocyte ratio (p=0.03) and blood neutrophils (p=0.006)

No significant correlations were observed with airway inflammation markers

¹ Lonergan M et al. ERS 2019:PA3371.
² Aguilar M et al. ERS 2019:PA2039.
³ Youssaf AJ et al. ERS 2019:PA2592.

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Relevance of serial Age, Dyspnoea, and airflow Obstruction (ADO) scoring in COPD

ADO scores (Age, Dyspnoea, and Airflow Obstruction) were assessed in 4,804 primary care patients with COPD in the UK.

Although ADO scores did not change for most patients over time, factors like smoking and BMI were associated with change in ADO scores:

- Smoker, underweight or depressed patients had a more rapid progression
- Overweight and obese patients had a less rapid progression

One-time ADO assessments are helpful for defining treatment options and in communicating risk to patients.

Serial ADO assessments, particularly in patients who are smokers, underweight or depressed, can identify cases with worsening risk and update prognosis.

Baseline and increase in ADO score over time

| Mean baseline ADO score (0 to 14) | 7.4 (SD=2.1) |
| Annual increase in ADO score (2005–2014) | 0.187 points (95% CI: 0.174, 0.200); 6.7% with at least 1 point |

Factors associated with change in ADO score over time

**Smoking status**

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>β</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>0</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>0.0282</td>
<td>[0.0025, 0.0539]; p=0.032</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.0588</td>
<td>[0.0311, 0.0866]; p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Body mass index**

<table>
<thead>
<tr>
<th>Body mass index</th>
<th>β</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>0.0411</td>
<td>[–0.0175, 0.0996]; p=0.169</td>
<td></td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt;25)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight (25 to &lt;30)</td>
<td>–0.0347</td>
<td>[–0.0544, –0.0150]; p=0.001</td>
<td></td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>–0.0412</td>
<td>[–0.0625, –0.0198]; p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.0384</td>
<td>[0.0054, 0.0713]; p=0.022</td>
<td></td>
</tr>
</tbody>
</table>

Keene S et al. ERS 2019:OA1587.
Experts’ comments

• COPD in females needs to be considered differently to that in men. There seems to be different patterns of inflammation and damage in the female lung which should be further studied. And it is important to include a balanced male/female population in drug trials.

• Impulse Oscillometry (IOS) has the potential to improve the diagnosis of COPD and enable us to find truly early disease. Studies need to be performed to see if IOS changes with time and treatment.
Eosinophils
Blood eosinophil count as a guide in COPD treatment

Intra-patient and seasonal variability of blood eosinophil (B-Eos) counts

• Retrospective analyses (n=98) evaluated intra-patient variability of B-Eos according to 2019 GOLD guidelines\(^1\) (100 and 300 cell/µL)\(^2\)
  • Large standard deviations (SD, 15-846 cells/µL) and relative SDs within individual patients (5-658 cells/µL)
  • Many patients surpassed the cut-off values when measurement was performed at different time points
• Prospective analysis (n=36) assessed B-Eos counts over the year in COPD patients\(^3\)
  • No significant differences in absolute or relative B-Eos counts between the different seasons
  • However, small numerical increases were detected in the summer and autumn

B-Eos single measurement is not enough to guide COPD treatment\(^4\)

• GOLD 2019 recommends ICS-based management for COPD patients with B-Eos >300 cells/µL\(^1\)
  • However, there are conflicting data on the stability and reproducibility of B-Eos measurements
• A Finnish biobank study included clinically stable patients post-COPD diagnosis and assessed two B-Eos measurements*:
  • 49%: B-Eos persistently low (<150 cells/µL) to medium (≥150 - <300 cells/µL)
  • 7%: Consistently high B-Eos (≥ 300 cells/µL) to very high (≥400 cells/µL)
  • 44%: Unstable B-Eos (defined as change in B-Eos category during follow-up)
• Lack of stability in B-Eos casts doubts on its reliable use as a COPD biomarker

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1. GOLD 2019: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease
2. Van Rossem I et al. ERS 2019:PA2577.

*The two B-Eos measurements were separated by a minimum of 6 months and a maximum of 2 years.

B-Eos, blood eosinophils
ICS, inhaled corticosteroids
SD, standard deviation
Blood eosinophil (B-Eos) count and lung function decline in COPD patients

High B-Eos in frequent exacerbators is linked to lung function decline when not treated with ICS\(^1\)
- A study \((n=12,178)\) assessed whether the therapy level and B-Eos affect COPD exacerbations and lung decline
- Patients with frequent exacerbations, high B-Eos but not treated with ICS, showed a more rapid COPD progression compared to those on ICS therapy

<table>
<thead>
<tr>
<th>Patients with B-Eos ≥ 350 cells/μL (per exacerbation/year):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No ICS: FEV(_1) decline of 19.4 mL/year [95% CI: 12.0, 26.7]</td>
</tr>
<tr>
<td>• ICS: FEV(_1) decline of 4.3 mL/year [95% CI: 1.9, 6.7]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients treated with ICS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• B-Eos ≥ 450 cells/μL: FEV(_1) decline of 1 mL/year [95% CI: -2.5, 4.5]</td>
</tr>
<tr>
<td>• B-Eos 50-449 cells/μL: FEV(_1) decline of 6.8 mL/year [95% CI: 5.8, 8.0]</td>
</tr>
</tbody>
</table>

B-Eos as a marker of lung function decline in COPD\(^2\)
- A study \((n=676)\) assessed if elevated B-Eos (≥300 cells/μL) impact lung function over time
- Elevated baseline B-Eos (≥300 cells/μL) were associated with greater decline in FEV\(_1\) (49 mL/year vs 41 mL/year, \(p=0.004\)) and FVC (43 mL/year vs 36 mL/year, \(p=0.035\))
- FEV\(_1\)/FVC did not differ between the groups (B-Eos <300 cells/μL and ≥300 cells/μL)
- In an adjusted model, high B-Eos were still associated with greater decline in FEV\(_1\) (β-coefficient 8.2 mL/year [95% CI: 2.5, 14; \(p=0.005\)]) and FVC (β-coefficient 6.9 mL/year [95% CI: 0.09, 14; \(p=0.047\)])
- Results suggest a possible causal relationship between the B-Eos count and decline in lung function

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B-Eos, blood eosinophil
FEV\(_1\), forced expiratory volume in 1 second
FVC, forced vital capacity
ICS, inhaled corticosteroid

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## Predictive and protective features of high and low eosinophils

<table>
<thead>
<tr>
<th>Eosinopenia is associated with morbidity and mortality in COPD(^1)</th>
<th>Protective features of eosinophilia in COPD exacerbations(^2)</th>
<th>Relationships between COPD exacerbation treatment outcomes and biochemical indices(^3)</th>
</tr>
</thead>
</table>
| In a retrospective analysis (n=151), eosinopenia (reduction of circulating eosinophils) was associated with:  
  - Higher mortality  
  - Increased bacterial load  
  - More hospital admissions  
  Low eosinophil count in COPD patients could be used as a surrogate marker for morbidity and mortality in patients with COPD | Patients with non-eosinophilic COPD exacerbations (n=64) had worse clinical features compared to those with eosinophilic COPD exacerbations (n=30)  
  - Higher serum CRP levels (p=0.03)  
  - More respiratory acidosis (p=0.038)  
  - Consolidation on X-ray (p=0.02)  
  - Increased risk of readmission at 12 months (p=0.046) | A longitudinal exacerbation study (n=83) compared rates of symptom improvement to exacerbation treatment  
  - Increased CRP levels during exacerbation:  
    - Antibiotic treatment: Improved symptoms  
    - Systemic corticosteroids: Worsened cough and dyspnoea  
  - Increased eosinophils during exacerbation:  
    - Systemic corticosteroids: Improved cough, dyspnoea and sputum production, worsened sputum purulence  
    - Antibiotic treatment: Worsening of dyspnoea |


CRP, C-reactive protein
• Interpretation of eosinophils must be in the context of the clinical presentation whether at stable state or exacerbation

• There are clearly three types of categories of people with COPD and eosinophils: those that stay high (>300 cells/µL), those that stay low (<300 cells/µL) and those that are more variable. Understanding this for an individual patient may help then with appropriate prescription of treatment

• Eosinophils appear to be a good predictive marker of ICS response and subsequent prognosis in COPD, but a repeated measure is likely to give a more reliable indication than a single measure as we will then be sure if a patient stays steady high, steady low or be variable.

• Exogenous factors such as steroid use, presence of serious infection and allergen exposure may need to be taken into account when interpreting blood eosinophil levels.
Treatment

- Dual bronchodilation
- Appropriate use of ICS (including triple therapy)
- Other treatments
Dual bronchodilation
Comparative analysis of LAMA/LABA FDCs in patients with COPD

- A network meta-analyses (n=7,911) from 18 RCTs directly comparing efficacy (FEV₁, SGRQ, TDI) and safety (cardiovascular serious adverse events) of LAMA/LABA FDCs vs placebo or each other¹
- Combined efficacy and safety results reported via Improved Biodimensional SUCRA (IBiS) ranked the efficacy/safety profiles as follows (higher values meaning better treatment):¹²

T/O 5/5 μg >> GLY/IND 15.6/27.5 μg > UMEC/VI 62.5/25 μg = AB/FORM 400/12 μg > GLY/IND 50/110 μg > GLY/FORM 14.4/9.6 μg

Representation of the combined efficacy/safety IBiS score (Greater areas indicate a better efficacy/safety profile)¹²


Benefits of dual bronchodilation in patients with COPD

**Treatment**
- GLY/FORM 25/12 µg sDPI BID vs GLY 50 µg sDPI OD for 12 weeks

**Objective**
- Efficacy and safety of LAMA/LABA vs LABA in patients with moderate to severe COPD

**Outcomes**
- GLY/FORM was more effective than GLY in improving lung function and symptoms:
  - Trough FEV₁: 0.06L [95% CI: 0.00, 0.12; p<0.0001]
  - CAT score: -1.73 units [95% CI: -3.36, -0.10; p<0.05]
  - mMRC: -0.85 vs -0.65, both p<0.0001
  - Rescue medication use and change in CASIS score: both p<0.0001
- Both GLY/FORM and GLY were well tolerated

**Conclusion**
- GLY/FORM was more effective than GLY in improving lung function and symptoms

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**Randomised, prospective, open-label, comparative, parallel group, multi-centre study (n=365)**

**Randomised, double blind, placebo controlled, two-week crossover, single centre trial (n=48)**

**Treatment**
- GP/FORM 9/4.8 µg pMDI BID vs placebo

**Objective**
- Effect of LAMA/LABA on exercise tolerance during high intensity CWR cycle ergometry in patients with moderate to severe COPD

**Outcomes**
- • GP/FORM improved CWR endurance time vs placebo (383±184 seconds vs 328±116 seconds, p=0.013)
  - Increase in endurance time was greater, but not significant, in patients with severe COPD (GOLD 3 vs GOLD 1/2, 124±144 vs 34±144 seconds, p=0.076)

**Conclusion**
- GFF improved exercise tolerance in patients with COPD, especially in those with severe COPD

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**Abbreviations**
- BID, twice daily
- CM, correlation metric
- CAT, COPD Assessment Test
- sDPI, single-dose dry powder inhaler
- COPIS, COPD and asthma sleep impact scale
- FEV₁, forced expiratory volume in 1 second
- FVC, forced vital capacity
- GP/FORM, glycopyrrolate/formoterol fumarate
- LABA, long-acting beta-agonist
- LAMA, long-acting muscarinic antagonist
- mMRC, modified medical research council
- OD, once daily
- sDPI, single-dose dry powder inhaler
- VD/VT, dead space ventilation
- VQM, ventilation/perfusion match

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## The CLAIM study: the impact of LAMA/LABA in hyperinflated COPD patients

### Randomised, double-blind, single-centre, placebo-controlled, cross-over CLAIM study (n=62)

### Study details
- **Treatment**: GLY/IND 50/110 μg OD for 14 days followed by placebo or vice versa
- **Objective**: Impact of LAMA/LABA on pulmonary ventilation/perfusion match and regional ventilation dynamics in hyperinflated COPD patients

### Outcomes
At day 14, GLY/IND benefits vs placebo included:
- Ventilation/perfusion match (VQM) improved by 9.7% (p<0.0001)
- Perfusion improved by 8.2% (p=0.0489)
- Regional ventilation dynamics (measured by CM) improved by 6.2% (p<0.0001)

### Conclusion
GLY/IND improved VQM and regional ventilation dynamics in hyperinflated COPD patients

Voskrebzeniev A et al. ERS 2019: PA3381.
Improvement in dynamic lung hyperinflation with tiotropium/olodaterol treatment in Japanese patients

A study from the Shinshu University in Japan aimed:
To elucidate the effects of combined tiotropium/olodaterol (T/O) (Respimat®) on dynamic lung hyperinflation (DLH), 33 patients with mild-severe stable COPD were examined before and 8 weeks of treatment with T/O 5/5μg

Metronome-paced incremental hyperventilation (MPIH) method was used to quantify DLH following hyperventilation, with respiratory rate increased without exercise loading

T/O treatment significantly improved:
• DLH with incremental hyperventilation (from resting respiration rate to 40 bpm from inspiratory capacity (IC), p<0.05 for inter-group comparisons (before/after T/O treatment)
• FEV₁, CAT and 6MWD scores: FEV₁ at both 30 and 40 bpm from IC showed a significant correlation (r=0.44, p<0.05 and r=0.35, p<0.05, respectively)

This study suggests that T/O combination therapy is effective in reducing DLH, in addition to improvements in airflow obstruction, exercise tolerance and health status

Kawachi S et al. ERS 2019:PA3384.

Before T/O (mean ± SEM) After T/O (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Before T/O</th>
<th>After T/O</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>13.7 ± 1.4</td>
<td>10.8 ± 1.2*</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>460.2 ± 19.4</td>
<td>477.1 ± 18.4*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

IC, inspiratory capacity
MPHI, Metronome-paced incremental hyperventilation
IC, inspiratory capacity
FEV₁, forced expiratory volume in 1 second
CAT, COPD assessment test
DLH, dynamic lung hyperinflation
T/O, tiotropium/olodaterol
SEM, standard error of the mean
6MWD, 6-minute walk distance
Tiotropium/olodaterol improves lung function in treatment-naïve Japanese patients with COPD

In this 12-week prospective study, 80 treatment-naïve COPD patients in Japan were randomised to either T/O (5 µg / 5 µg) or tiotropium (5 µg) alone, and their effects on pulmonary function, dyspnoea, QoL and physical activity (PA) were studied.

T/O significantly improved FEV₁ and improved PA (as seen by a numerical decrease in the duration of the sedentary position (1.0 to 1.5 METs), and an increase in the duration of the activity (≥ 2.0 METs)) compared with tiotropium monotherapy.

**Takashi K et al. ERS 2019:PA2491.**
Tiotropium/olodaterol vs tiotropium reduced COPD exacerbations: pooled analysis of DYNAGITO® and TONADO® trials

This *post hoc* analysis included over 9,900 COPD patients receiving either tiotropium/olodaterol (T/O, 5/5 μg) or tiotropium (T, 5 μg) alone.

The following three subgroups were analysed:

- Low and high exacerbation history
- GOLD stage I–IV
- Baseline ICS use

Treatment with T/O vs T reduced the rate of moderate to severe COPD exacerbations:

- Regardless of exacerbation history
- In GOLD stage I/II and GOLD stage III patients
- In patients with baseline ICS use

### Moderate/severe exacerbations

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Rate ratio</th>
<th>95% CI</th>
<th>p value</th>
<th>Rate Ratio T/O vs T</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4,974 / 4,968</td>
<td>0.89</td>
<td>0.84, 0.95</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>0 to 1 moderate</td>
<td>2,983 / 2,956</td>
<td>0.90</td>
<td>0.82, 0.98</td>
<td>0.0179</td>
<td></td>
</tr>
<tr>
<td>mild exacerbations</td>
<td></td>
<td>0.89</td>
<td>0.81, 0.97</td>
<td>0.0074</td>
<td></td>
</tr>
<tr>
<td>≥2 moderate or ≥1</td>
<td>1,975 / 1,999</td>
<td>0.89</td>
<td>0.81, 0.97</td>
<td>0.0074</td>
<td></td>
</tr>
<tr>
<td>severe exacerbations</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### By GOLD stage

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Rate of events per patient-year (SE)</th>
<th>Rate ratio (95% CI)</th>
<th>Rate ratio T/O vs T</th>
</tr>
</thead>
<tbody>
<tr>
<td>By GOLD stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD stage I/II</td>
<td>1,974 / 1,877</td>
<td>0.60 (0.039)</td>
<td>0.49 (0.42)</td>
<td>0.82 (0.73, 0.92)</td>
</tr>
<tr>
<td>GOLD stage III</td>
<td>2,398 / 2,436</td>
<td>0.84 (0.032)</td>
<td>0.76 (0.032)</td>
<td>0.90 (0.82, 0.98)</td>
</tr>
<tr>
<td>GOLD stage IV</td>
<td>595 / 644</td>
<td>1.12 (0.056)</td>
<td>1.14 (0.056)</td>
<td>1.01 (0.88, 1.17)</td>
</tr>
</tbody>
</table>

Dual bronchodilation with tiotropium/olodaterol benefits COPD patients receiving only LAMA at baseline

Many COPD patients on monotherapy with LAMAs such as tiotropium (T) remain symptomatic. A pooled analysis of 4 clinical trials (TONADO® 1+2 and OTEMTO® 1+2) involving patients receiving only LAMA at baseline, a step up to tiotropium/olodaterol (T/O) dual therapy (vs tiotropium (T) only) significantly improved:

- **Lung function**
  Trough FEV₁ from baseline: 0.07 L [95% CI: 0.03, 0.12; p=0.0004]
- **Quality of life**
  SGRQ total score: −2.68 [95% CI: −5.06, −0.29; p=0.0280]
- **Dyspnoea**
  TDI score: 1.15 [95% CI: 0.56, 1.73; p=0.0001]

### Treatment differences in trough FEV₁ at week 12

<table>
<thead>
<tr>
<th></th>
<th>T/O (n=144)</th>
<th>T (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline in trough FEV₁ (L) ± SE</td>
<td>0.074</td>
<td>0.00</td>
</tr>
</tbody>
</table>

[95% CI: 0.033, 0.115; p=0.0004]

### Treatment differences in SGRQ total score at week 12

<table>
<thead>
<tr>
<th></th>
<th>T/O (n=141)</th>
<th>T (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline in SGRQ total score ± SE</td>
<td>−2.675</td>
<td>−0.00</td>
</tr>
</tbody>
</table>

[95% CI: −5.060, −0.291; p=0.0280]

### Treatment differences in TDI score at week 12

<table>
<thead>
<tr>
<th></th>
<th>T/O (n=140)</th>
<th>T (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline in TDI score ± SE</td>
<td>1.148</td>
<td>0.00</td>
</tr>
</tbody>
</table>

[95% CI: 0.564, 1.732; p=0.0001]
Assessment of physical functioning and satisfaction in an Italian cohort of COPD patients treated with tiotropium/olodaterol Respimat®

Changes in physical functioning and satisfaction were evaluated after approximately 6 weeks of treatment with tiotropium/olodaterol (T/O) Respimat® (patients receiving LAMA/LABA combinations in the 6 months prior to study entry were not included).

Self-reported physical function (PF-10) and general condition (PGE scores) improved and patients reported high satisfaction.

- Increase in PF-10 score of at least 10 points after six weeks was achieved for 52.5% of patients [95% CI: 46.5, 58.5]
- Based on PGE, most patients were in a satisfactory (50.7%) or good (39.9%) general condition.
- 86.3% of patients rated their overall satisfaction as very satisfied / satisfied / rather satisfied.

Therapeutic success (PF-10 ≥ 10 points from baseline) by GOLD stage

- GOLD A: 23%
- GOLD B: 60%
- GOLD C: 40%
- GOLD D: 65%

Patient overall satisfaction with treatment, inhalation and handling of Respimat® device at the end of the study

Pennisi A et al. ERS 2019:PA2511.
Experts’ comments

• New studies confirm and extend the positioning of LAMA/LABA as a potential initial step in pharmacological management of symptomatic COPD patients.
• Dual bronchodilators were more effective to single agents with regards to lung function, quality of life and breathlessness.
• The benefits of dual bronchodilators seem to be greatest, with regards to exacerbation, in mild and moderate disease when compared to more severe disease.
Appropriate use of ICS (including triple therapy)
Cost burden of ICS-containing regimens in COPD patients and patients’ perception of possible ICS withdrawal

In a study looking at the annual change in healthcare resource utilisation (HRU) and healthcare costs from baseline to follow-up in COPD patients with a history of 0–1 moderate exacerbation treatment initiation with ICS vs non-ICS therapy¹:

- ICS therapies were more often prescribed by non-pulmonologists
- In the ICS cohort, there was an additional burden of $125 per patient/year from baseline to follow-up
- When accounting for pneumonia, the additional cost burden increases to $370

Mild-to-moderate patients with COPD in general practice were interviewed (n=17) to assess their views of staged withdrawal of high-dose ICS prescribed outside of current guideline recommendations²:

- Many patients were unaware of the risks of using high-dose ICS and of the risk of side effects of high-dose ICS
- Most patients would be willing to reduce their dose of ICS or withdrawal from ICS if advised by their health care provider to do so, with explanation
- Proposed deprescribing should constitute detailed conversations between prescribers and patients

References:
Meta-analysis and systematic review showed single-inhaler triple therapy may increase the risk of pneumonia

7 studies investigating the clinical safety and efficacy of single inhaler triple therapy vs LABA/ICS, or vs LABA/ICS + LAMA as a multiple inhaler therapy, or vs LAMA/LABA, were analysed¹,²

Although there was a reduction in rate of moderate to severe exacerbation with single inhaler triple therapy vs LAMA/LABA and vs LABA/ICS, both LAMA/LABA and LABA/ICS therapies were better than single inhaler triple therapy in terms of improvement in FEV₁²

Moreover, the risk of pneumonia was significantly increased in single inhaler triple therapy vs LAMA/LABA (but not compared to LABA/ICS or single inhaler vs separate triple)¹,²

---

### Associations of triple therapy vs other treatment arms²

<table>
<thead>
<tr>
<th></th>
<th>Rate of moderate or severe exacerbation (RR [95% CI])</th>
<th>Change of FEV₁ (mean difference, [95% CI])</th>
<th>Risk of pneumonia (RR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single inhaler triple therapy vs LAMA/LABA</td>
<td>0.69 [0.55, 0.87]</td>
<td>Single inhaler triple therapy vs LAMA/LABA</td>
<td>0.03 [0.01, 0.06]</td>
</tr>
<tr>
<td>Single inhaler triple therapy vs LABA/ICS</td>
<td>0.80 [0.71, 0.90]</td>
<td>Single inhaler triple therapy vs LABA/ICS</td>
<td>0.10 [0.06, 0.14]</td>
</tr>
<tr>
<td>Single inhaler triple vs separate triple</td>
<td>0.97 [0.85, 1.10]</td>
<td>Single inhaler triple vs separate triple</td>
<td>0.01 [-0.01, 0.03]</td>
</tr>
<tr>
<td>Single inhaler triple therapy vs LAMA/ICS</td>
<td>1.38 [1.14, 1.67]</td>
<td>Single inhaler triple therapy vs LABA/ICS</td>
<td>1.24 [0.83, 1.85]</td>
</tr>
<tr>
<td>Single inhaler triple vs separate triple</td>
<td>0.88 [0.51, 1.52]</td>
<td></td>
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</tr>
</tbody>
</table>

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"Mild” COPD events were associated with worse outcomes

Post hoc analysis of the RISE* study showed “mild” COPD events (COPD symptom-related attacks) had a negative impact on health outcomes

COPD symptom-related attack defined as:
• worsening of ≥ 2 major symptoms (dyspnoea, sputum volume, and sputum colour / purulence)
or• worsening of 1 major symptom and ≥ 1 minor symptom (sore throat, colds, fever, cough, or wheeze);
coinciding with >2 or >4 puffs/day of short-acting β₂-agonists above baseline

Based on the results, the term “mild” may be misleading as symptom-related attacks were associated with poorer health outcomes and an increased risk of moderate/severe exacerbations

Ferguson G et al. ERS 2019:OA258.

Symptom-related attacks in COPD were associated with a significant:

- Decline in HRQoL
  - 4.11 mean difference†
  - 3.84 mean difference‡

- Decline in FEV₁
  - -0.083 L†
  - -0.098 L‡

- Risk of moderate / severe exacerbation
  - HR: 1.86; 95%CI: [1.39, 2.49]†
  - HR: 2.21; 95%CI: [1.48, 3.28]‡

“Mild” attacks may lead to worse outcomes

*Comparing the Efficacy of Symbicort® pMDI (Budesonide) and Formoterol Turbuhaler in Reducing Exacerbations in Patients With COPD
†>2 puffs/day above baseline
‡>4 puffs/day above baseline
CI, confidence interval; HRQoL, health related quality of life; HR, hazard ration
Eosinophil variability in COPD patients using inhaled corticosteroids

Patients with stable COPD (N=618) from two cohorts (Korean COPD Subtype Study and Seoul National University Airway Registry) were studied for longitudinal variability of blood eosinophils (B-Eos) on inhaled corticosteroids (ICS vs non-ICS)

In terms of the rate of moderate-to-severe acute exacerbations in the first year (events/year):

- **Non-ICS** therapy was significantly better in those with consistently low (B-Eos: < 250 cells/μL) or decreasing B-Eos (~70% of population)
- **ICS-containing** therapy was significantly better in those with consistently high (B-Eos: ≥ 250 cells/μL) or increasing B-Eos (~30% of population)

Yoon JK et al. ERS 2019:PA3372.
• Inhaled steroid therapy has been shown to reduce exacerbation rates and this effect may be predicted by an increase in blood eosinophils (B-Eos).

• The benefit of ICS increased as levels of B-Eos increase, but only a minority of patients have high levels of exacerbations and high levels of B-Eos.

• A single measurement of B-Eos may help predict which patients benefit from ICS.

• The use of ICS is not without risk. ICS treatment is associated with increased risk of pneumonia and furthermore, additional costs.

• ICS prescription should be given after a careful assessment of the risk and benefits for each patient.
Other treatments
CHF6001, a novel inhaled, selective PDE4i for COPD patients

Efficacy and safety¹

• 24-week, randomised PIONEER study (n=1130) compared CHF6001 vs budesonide or placebo on top of LABA therapy

• COPD patients (FEV₁, 30-70%) with a history of ≥1 moderate/severe exacerbation in the previous year were included

• Significant improvement (p<0.001) from baseline on TDI, SGRQ, E-RS and rescue use with all treatments (with no difference vs placebo)

• Trend towards reduction of moderate / severe exacerbations vs placebo (more pronounced in bronchitic patients with B-Eos count ≥0.15x10⁹/L)

• Good safety and tolerability with all doses

Impact on inflammatory markers²

• Randomised study (n=61) on effect of CHF6001 added to LAMA/LABA/ICS on inflammatory sputum and blood markers

• Moderate-to-severe COPD patients (FEV₁, 30%-70%)

• Significant impact on sputum (p<0.05) but not blood inflammatory markers

• ~2000-fold higher CHF6001 concentrations in sputum vs plasma

• Supports targeted effect in the lung while minimising systemic exposure

Efficacy of ensifentrine, a novel dual phosphodiesterase (PDE) 3 and 4 inhibitor

- Single dose study (n=37) evaluated the effect of ensifentrine, a novel dual PDE3/4 inhibitor, administered via DPI in patients with moderate to severe COPD
- Patients were randomised to either 150, 500, 1500, 3000 or 6000 µg ensifentrine or placebo, concomitant ICS was permitted
- Ensifentrine was well tolerated with no significant adverse events, heart or pulse rate similar to placebo and a linear, dose dependent PK
- Ensifentrine resulted in statistical and clinical meaningful, dose-dependent bronchodilation vs placebo

Change from baseline in average and peak FEV₁ over 4 hours

Rheault T et al. ERS 2019:OA265.
Benralizumab reduced eosinophilic inflammation in an ex vivo COPD model

- The effects of benralizumab on COPD inflammation were studied in an ex vivo bronchial mucosa model of smoke-induced COPD, with co-cultured eosinophils (Eos) and LPS-activated monocytes medium (MCM).
- Treatment with benralizumab led to a significant reduction in the IL-5 concentration in the first 14 days (p<0.005)
  - Control: 14.6 ± 3.2 pg/ml
  - Eos: 13.9 ± 4.2 pg/ml
  - Eos + MCM: 35.7 ± 5.9 pg/ml
  - Eos + MCM + benralizumab: 12.5 ± 4 pg/ml

Identifying COPD patients who benefitted from benralizumab

- Analysis of baseline factors to identify responders to benralizumab treatment in 3,910 patients (baseline B-Eos ≥220 cells/μL) randomised to placebo or benralizumab 30 mg or 100 mg for 56 weeks (GALATHEA/TERRANOVA studies)
- Patients on 100 mg benralizumab with:
  - a combination of prior triple inhaled therapy,
  - baseline B-Eos ≥220 cells/μL,
  - poor baseline lung function and
  - ≥3 exacerbations showed the greatest response (RR:0.70 [95% CI: 0.56, 0.88])


B-Eos, blood eosinophils
Eos, eosinophils
IL, interleukin
LPS, lipopolysaccharide
MCM, monocyte medium
RR, rate ratio

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RECONSIDER trial: Home initiation of chronic high-intensity non-invasive ventilation

- **RECONSIDER**, a randomised controlled trial (n=67), evaluated the efficacy of home initiation of NIV via telemedicine in stable hypercapnic COPD patients.
- Patients were randomised to either NIV initiation in hospital or at home using telemedicine.
- Home NIV initiation was equally effective as in-hospital NIV in terms of **daytime arterial carbon dioxide pressure (PaCO₂)** reduction at 6 months (both p<0.001).
- No difference with regards to HRQoL (adjusted mean difference 0.0 [95% CI: -0.4, 0.5]) between groups.
- Home NIV initiation reduced costs by over 50% vs in-hospital NIV (€3768 vs €8537, p<0.001).

**Graph:**
- **Home**
  - Baseline: 7.3±0.9 kPa
  - 6 months: 6.4±0.8 kPa
  - p<0.001
- **Hospital**
  - Baseline: 7.4±1.0 kPa
  - 6 months: 6.4±0.6 kPa
  - p<0.001

Adjusted mean difference in PaCO₂ change home vs in-hospital at 6 months: 0.04 kPa [95% CI: -0.31, 0.38]


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Experts’ comments

• The new PDE3/4 and PDE4 inhibitors have potential as bronchodilators in COPD via the inhaled route. This may well be on top of standard LAMA/LABA therapy.

• By using a simple biomarker/phenotype-led approach, it may be possible to predict who may benefit from anti-IL5 therapy in COPD.

• New data on the use of valvular volume reduction in COPD is leading us to an understanding of their mechanism of action and may well help define clearly those who may benefit.
Inhalation and inhalers
Poor inhaler technique is common in COPD

Critical handling errors with DPI, MDI and SMI (n=372)

- 48% of patients performed at least one critical handling error
- 35% presented incorrect positioning of the inhaler, 20% showed incorrect preparing/loading of the dose, 6% exhaled into the mouthpiece, 2% prepared the inhaler incorrectly
- At least one critical error was seen in 58% patients with MDI, 56% with SMI, 53% with mDPI and 46% with sDPI

Ability to use DPI vs MDI in Hong Kong Chinese patients with COPD (n=98)

- Fewer inhaler technique errors with DPI (Genuair®) vs MDI (Ellipta®) (p<0.001)
- Successful DPI inhalation was significantly associated with:
  - Higher PIFR (p<0.001 for Genuair® and p=0.003 for Ellipta®)
  - Higher AMT score (p=0.003 for Genuair® and p=0.04 for Ellipta®)

Association of inhalation errors with exacerbations (n=70)

- Poor inhalation technique was associated with
  - 4-fold increased risk of acute exacerbations (OR: 3.5 [95% CI: 1.1, 11.5; p=0.039])
  - Potentially avoidable antibiotic prescribing (OR: 3.8 [95% CI: 1.1, 13.6; p=0.038])

Inhaler errors and optimising inhaler use in elderly patients

Cognitive impairment could hinder proper inhaler use in elderly COPD and asthma patients

- In 75 in-patients (≥65 years of age), cognitive function assessed by mini-mental state examination (MMSE) and frontal assessment battery (FAB) was significantly lower in patients who used inhaler incorrectly (26.7%) vs those who used correctly (73.3%) (both p<0.001)
- MMSE and FAB cut-off points to predict incorrect users were determined: 22 for MMSE and 11 for FAB
- Reduced frontal lobe function (lower FAB) seems to hinder learning the proper inhaler technique

Repeat training can reduce inhaler errors in elderly inhaler users

A study (n=256, mean age 76.43 ± 6.13 years) assessed inhaler technique in patients who received previous inhaler training and used inhalers for at least three months
- Accuracy of inhaler use was low: only 24.7% of patients used inhalers correctly
- After retraining, the accuracy of inhaler use increased
- The most common error was ‘exhalation before inhalation’

Differences in adequate use ratio between inhaler types

<table>
<thead>
<tr>
<th>Inhaler</th>
<th>Before retraining</th>
<th>After retraining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evohaler®</td>
<td>38.7%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Respimat®</td>
<td>50.0%</td>
<td>86.1%</td>
</tr>
<tr>
<td>Turbohaler®</td>
<td>61.4%</td>
<td>74.3%</td>
</tr>
<tr>
<td>Ellipta®</td>
<td>60.8%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Breezhaler/Handihaler</td>
<td>43.2% p=0.026</td>
<td>65.3% p=0.129</td>
</tr>
</tbody>
</table>

1. Iwata Y et al. ERS 2019:PA687.
Improving medication delivery to the lungs by different aids

Patients (n=290) from four specialised clinics in central Denmark were assessed for inhaler technique

Results
- Female: 48%
- Age: 44-89 years
- FEV₁: 18%-84%
- Current smokers: 36%

47% of patients (who are already being treated) would benefit from an inhaler device change or correction to reach an optimal effect

Only 1% of patients were reluctant to change their device (n=3)

King K et al. ERS 2019 PA4199.
Peak inspiratory flow and DPI use in patients with COPD

- A cross-sectional study (n=109) in a Brazilian cohort aimed to evaluate the profile of inspiratory peak flow in COPD patients using two different DPI devices
- Mean inspiratory peak flow exceeded the cut-off (60 L/min) both in low and medium resistance (89.34 L/min and 68.05 L/min, respectively)
- Age, BMI, FEV₁, FVC, maximal expiratory pressure and maximal expiratory pressure influenced inspiratory peak flow (p<0.05)

Particle deposition in the respiratory tract

1. Inertial impaction
2. Sedimentation
3. Diffusion

BMI, body mass index
DPI, dry powder inhaler
Inhaled therapy in COPD: Does the device matter as much as the medication?

A recent survey of healthcare professionals (pulmonologists, primary care physicians and non-physician providers (n=513)) found the majority of HCPs consider medication class to be more important than device type (89% vs 11%)

However,

• Studies have also shown that drug efficacy is different for the same medication delivered via different device (e.g. in a study comparing fluticasone propionate/salmeterol xinafoate via pMDI vs DPI, treatment administered via pMDI resulted in a significantly lower rate of moderate/severe COPD exacerbations vs treatment administered via DPI (RR: 0.71 [95% CI: 0.54-0.93]))
• This is due to the amount of drug that effectively reaches the lung

Take-home message

• A combination of both drug and device make up the clinically effective dose

Patient-centric improvement of a soft mist inhaler

A reusable soft mist inhaler (reusable Respimat®)
The aim was to develop a reusable soft mist inhaler with improved usability, intended to be used with up to 6 cartridges¹
- The re-usable Respimat® inhaler was compared to the current inhaler and was rated to be easier to assemble
- Participants rated all cartridge exchange steps as “easy” or “very easy”
- The dose indicator and new cartridge counter were appreciated
- The reusable inhaler can be used safely and effective and is not vulnerable to potentially harmful use errors

These features are in-line with the “most important inhaler characteristics” according to asthma/COPD patients (n=452), namely²:
- Presence of dose counter
- Easy to use
- Able to see or hear when successful inhalation is achieved
- Quick to use
- Easy to carry
- Once-a-day dosing

¹ Meisenheimer M et al. ERS 2019:PA4227.
² Usmani OS. ERS 2019:3754 (oral presentation).

Automated clear base detachment process after 60 actuations

Cartridge lock triggers automated case lower part detachment
Adherence to COPD controller therapy in a real-life setting

Retrospective cohort study (n=43,337) to evaluate different patterns of adherence to COPD controller therapy:

- ICS
- LAMA
- LAMA+LABA
- LABA
- LABA+ICS
- LAMA+LABA

- Good adherence was defined as ≥80% of days covered per month by the prescription
- During the study, less than 30% of patients had good adherence to COPD controller therapy in general

In comparison to subjects with good adherence, patients with poor adherence:

- Were younger
- Had less severe COPD
- Were more likely to have gastroesophageal reflux disease
- Were more frequently smokers
- Were more likely to be depressed

Karimi L et al. ERS 2019:PA4192.

ICS, inhaled corticosteroid
LABA, long-acting beta-agonist
LAMA, long-acting muscarinic antagonist
Experts’ comments

- COPD patients have difficulties with adherence to medication.
- The choice of which inhaler to use is considered as important in COPD as any other airways disease. The patient’s inspiratory peak flow and ability to inhale are important factors when choosing an inhaler.
- Special consideration needs to be paid to the cognitive ability of COPD patients which may be compromised by age and the disease itself.
- At every patient contact, inhaler device training and education is essential and does improve adherence.
Diagnosing acute exacerbations of COPD (AECOPD)

Accuracy of diagnosis of AECOPD in an emergency room setting

- A causative diagnosis of AECOPD in the emergency room (ER) is often difficult due to multi-morbidities in smokers
- A study (n=119 smokers with acute respiratory symptoms) assessed accuracy of ER diagnosis vs post-hospitalisation diagnosis
- Results showed that diagnosis of AECOPD in ER is difficult, and often varies from diagnosis at respiratory ward due to frequently present concomitant heart failure (HF)

<table>
<thead>
<tr>
<th></th>
<th>Other</th>
<th>AECOPD</th>
<th>AECOPD+HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER diagnosis</td>
<td>36%</td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td>Respiratory ward</td>
<td>19%</td>
<td>41%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Diagnosis of AECOPD via a cough-centred, smartphone-based algorithm

- Evaluation of smartphone-based algorithm to detect COPD exacerbations via analysis of smartphone-reported:
  - Cough sounds
  - Patient-reported features (age, fever, acute cough)
- Reference diagnosis determined by expert clinicians:
  - Worsening symptoms of shortness of breath or cough and new lower-respiratory symptoms or acute fever history in a patient with COPD
- In comparison to the clinical reference diagnosis, the smartphone-based algorithm accurately predicted AECOPD in subjects with known COPD:
  - Patients ≥ 40 years: 82.1% positive per cent agreement (PPA), 91.0% negative per cent agreement (NPA)
  - Patients ≥ 65 years: 85.9% PPA, 88.9% NPA

1. Tiné M et al. ERS 2019:PA5220
2. Claxton S et al. ERS 2019:PA4278
DACCORD study: Frequent COPD exacerbations in real-life setting

2-year follow-up of 6,527 COPD patients on maintenance medication revealed:
• 7.1% were frequent exacerbators
• 17.3% were non-frequent exacerbators
• 75.6% were non-exacerbators

Although all patient groups showed a clinically improved CAT score after 2 years, the frequent exacerbators had the most marked improvement in MCID and absolute CAT difference
• Proportion of LABA- and/or LAMA-treated patients decreased
• Proportion of ICS-treated patients increased

<table>
<thead>
<tr>
<th></th>
<th>Non-exacerbators</th>
<th>Non-frequent exacerbators</th>
<th>Frequent exacerbators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>18.2 ± 7.5</td>
<td>21.8 ± 7.1</td>
<td>25.3 ± 6.9</td>
</tr>
<tr>
<td><strong>1st Year</strong></td>
<td>16.5 ± 7.5</td>
<td>18.9 ± 7.2</td>
<td>20.8 ± 7.2</td>
</tr>
<tr>
<td><strong>2nd Year</strong></td>
<td>16.2 ± 7.5</td>
<td>18.6 ± 7.1</td>
<td>19.5 ± 7.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1st Year</th>
<th>2nd Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCID improvement in CAT score</strong></td>
<td>50.4</td>
<td>60.9</td>
</tr>
<tr>
<td></td>
<td>53.6</td>
<td>62</td>
</tr>
</tbody>
</table>

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Predicting future exacerbation risk: Eosinophil counts alone do not seem to be enough

Previous studies showed contradictory results regarding the usefulness of eosinophil counts in predicting future exacerbations in patients with COPD

In the study population (N=7,743), there was no difference in exacerbation rate by baseline eosinophil count (stratified by ≤150 cells/μL; >150- ≤225 cells/μL; >225- ≤300 cells/μL; >300- ≤450 cells/μL; >450 cells/μL)

Patients with a high exacerbation history (defined as ≥2 exacerbations treated with antibiotics or systemic steroids in the previous year) had a higher exacerbation rate vs those with low exacerbation history (defined as ≤1 exacerbation treated with antibiotics or systemic steroids in the previous year)

Post hoc analysis of the DYNAGITO® trial

Furthermore, a pooled analysis of 16 clinical studies showed no relationship between exacerbation history and baseline blood eosinophil count

Pooled analysis of 24,103 patients

Regional analysis of COPD exacerbation rates in the DYNAGITO® trial

Post hoc analysis of DYNAGITO® (7,880 patients with COPD in 51 countries) examined rates of moderate and severe exacerbation as well as those leading to hospitalisation and grouped by region.

Wide variation in exacerbation rates across the different regions could be attributed to differences in:

- Healthcare systems
- Climate
- Culture
- Health-seeking behaviour
- Treatment availability
- Treatment compliance

Exacerbation treatment with both antibiotics and systemic corticosteroids was higher in most regions compared to treatment with either antibiotics or systemic corticosteroids alone.

Annualised rate of COPD exacerbations during treatment by region

Annualised rate of moderate/severe COPD exacerbations treated with antibiotics and/or systemic corticosteroids by region

*The pre-specified p<0.01 for the primary endpoint (annualised rate of moderate-to-severe COPD exacerbation) of the DYNAGITO® trial was not met.
The use of antibiotic therapy and COPD exacerbations

Prolonged macrolide maintenance therapy and COPD exacerbations

The COLUMBUS trial revealed 1-year azithromycin in patients with ≥3 exacerbations in previous year significantly lowered COPD exacerbations

According to retrospective cohort study using data from the Columbus Trial cohort (n=92), prolonged treatment with azithromycin beyond 1 year has no further beneficial effect

- Exacerbation frequency: 2.29 ±2.43 (treatment) vs 1.67 ±1.69 (control); p=0.577
- Time-to-first exacerbation: 138 days [IQR 91-222] (treatment) vs 168 [IQR 57-189] (control); p=0.11
- Number of hospital admissions: 0.56 ± 0.93 (treatment) vs 1.36 ±1.91 (control); p=0.307

Treatment without antibiotics was non-inferior to antibiotics in hospitalised COPD patients with non-purulent exacerbation

RCT in patients with non-purulent severe exacerbations of COPD comparing moxifloxacin 400 mg daily for 5 days (n=37) vs placebo (n=35)

- No significant differences in the length of hospital stay between the two groups (6 days in placebo vs 5 days in moxifloxacin group)
- Results suggest that for this outcome, the treatment without antibiotic is not inferior to antibiotics

• In the acute setting the diagnosis of AECOPD was not straightforward and heart failure is often co-existent.
• Clinicians should consider a standard test approach to AECOPD patients in order to fully risk assess and also pick phenotypes that may benefit from an individualised approach to treatment. This may include: Troponin, BNP, CRP and blood eosinophil count.
• Targeting treatment to the type of exacerbation has greatest potential for benefit, and reduction of harm from unwarranted medication use.
• There is enormous variability between regions as to how AECOPD are treated. This is not due to guidelines but to variable health care systems.
Physical activity and exercise tolerance
Benefits of completing and maintaining pulmonary rehabilitation regimes

Completing PR improves survival in COPD patients¹

- In a large cohort study (n=7092) unadjusted and cumulative mortality (adjusted for baseline gender, age, FEV₁, BMI, MRC dyspnoea grade, smoking status, co-morbidities, walking distance, home oxygen use, and hospitalisation in the last year) was higher for non-completers vs completers
  - Unadjusted: HR:1.54 [95% CI: 1.33, 1.78; p<0.001]
  - Adjusted: HR: 1.42 [95% CI: 1.20, 1.67; p<0.001]

Maintenance PR programme improved outcomes in obstructive lung disease patients²

- Prospective cohort study with 289 obstructive lung disease patients
- PR maintenance sessions (1–7 years):
  - 1 session/week of supervised exercise training
  - 8 sessions/year of therapeutic education
- The maintenance PR programme preserved the benefits of PR over several years
  - Effects of PR on exercise tolerance (6MWD) and quality of life (VQ11) were stable for 4 years (p<0.001)
  - Effect of PR effect on dyspnoea (MRC) was stable for at least 5 years (p<0.001)
- COPD patients in the PR maintenance programme showed a better survival probability than an age- and sex-matched general COPD population

Percent of COPD patients (n=7092)

<table>
<thead>
<tr>
<th></th>
<th>PR non-completers</th>
<th>PR completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
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</tbody>
</table>

Unadjusted mortality rate

<table>
<thead>
<tr>
<th></th>
<th>PR non-completers</th>
<th>PR completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>12.3%</td>
<td>8.3%</td>
</tr>
<tr>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
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</tr>
<tr>
<td>15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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CI, confidence interval
FEV₁, forced expiratory volume in 1 second
HR, hazard ratio
MRC, Medical Research Council scale
PR, pulmonary rehabilitation
VQ11, COPD specific HRQoL questionnaire

6MWD, 6-minute walk distance
BMI, body mass index
Home-based pulmonary rehabilitation in COPD

Systematic literature review on strategies to ensure sustained benefits in home-based PR

• Maintaining an exercise regime at home is important with emphasis on:
  • Endurance training – walking and using a portable cycle ergometer
  • Muscle strengthening – weight training, exercises against gravity, up and down stairs, resistance bands and sit-to-stand exercises
  • Strategies to improve long-term adherence includes the use of record diaries, pedometer, guidance books and contact via telephone

Effectiveness of home-based PR programmes

• In a randomised controlled trial (n=10), two home-based, low-cost PR programmes independently improved the number of steps on 6MST (p=0.006)

• Similar improvements were observed in a feasibility and effectiveness study with a 12-week minimal-resource community-based PR programme (n=77; CRD (including COPD) patients): mMRC (1 point), SGRQ (4 points), 1min-STS (3 repetitions), 6MW (25 m), Brief-BEST (4.9 points), HADS Anxiety and Depression scores (1.5 points)

• However, in a multicentre randomised controlled trial involving COPD patients (n=134) assessing long-term superiority of pulmonary tele-rehabilitation to conventional PR, no significant differences were observed in walking capacity (6MWD) and other outcome measures such as hospitalisation and mortality between the groups

Effectiveness of home-based PR programmes

<table>
<thead>
<tr>
<th></th>
<th>Educative group with a single educational session (n=5)</th>
<th>Supervised exercise group with eight physiotherapist sessions and home rehabilitation (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.8 ± 6.9</td>
<td>63.6 ± 3</td>
</tr>
<tr>
<td>FEV₁</td>
<td>42 ± 18</td>
<td>45 ± 22</td>
</tr>
<tr>
<td>6MST – pre-intervention (steps)</td>
<td>63 ± 10.3</td>
<td>59.6 ± 11.8</td>
</tr>
<tr>
<td>6MST – post-intervention (steps)</td>
<td>70 ± 12</td>
<td>63 ± 10</td>
</tr>
</tbody>
</table>

1min-STS, 1-minute sit-to-stand
6MST, 6-minute shuttle test
6MW, 6-minute walk distance
Brief-BEST, Balance Evaluation Systems Test
CRD, chronic respiratory disease
HADS, Hospital Anxiety and Depression Scale
mMRC, modified Medical Research Council scale

References:

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Cardiorespiratory responses during exercise in patients with COPD

Pulmonary rehabilitation (PR) in COPD patients ± heart failure (HF) 1

Analysis of data (n=7413) from the 2015 National COPD PR Audit dataset

- ISWT: COPD+HF (37.4m) vs COPD (59.3m) (p=0.047)
- 6MWT: Similar improvement between groups (p=0.79)
- CAT and CRQ: Significant, but similar (p≥0.05) improvement in both groups

PR improved exercise capacity, quality of life and symptom burden in adults with COPD as well as those with COPD and heart failure

Exercise induced dynamic hyperinflation and cardiovascular parameters 2

- Study (n=33; 20 men, 13 women) revealed that exercise induced dynamic hyperinflation negatively impacts cardiovascular parameters:
  - Significantly lower inspiratory capacity (DH 75.93±2.59 % SE vs Non-DH 128.80±6.38 % SE, p<0.001)
  - Significantly higher stroke volume (Stroke volume % max load: Non-DH 129.10±10.29 % SE vs DH 95.13±4.59 % SE p<0.01)
  - Significantly higher cardiac output (CO% max load: Non-DH 165.70±12.81 % SE vs DH 119.60±4.69 % SE, P<0.001)

Exercise training in patients with COPD

Resistance training with different intensities

A RCT of patients with COPD (n=27) showed:
- Low-load/high-repetition (LL/HR) compared with high-load/low-repetition (HL/LR) resistance training in patients with moderate to severe COPD
- Both improved
  - Dyspnoea (p=0.005)
  - Exercise capacity (p=0.023)
  - Muscle strength (p<0.001)
- SGRQ improved with LL/HR training (p=0.002) compared to HL/LR

Combining functional exercises with physical training

- 35 patients with COPD were randomised to either conventional training combined with a functional circuit vs conventional training alone
- The addition of functional circuit resulted in meaningful benefits in terms of body composition*
  - Increased musculoskeletal mass (25.70±6.93 vs 23.65±4.09, p=0.004) and protein mass (9.20±2.3 vs 8.51±1.34, p=0.016)
  - Decreased body fat mass (23.56±8.30 vs 30.97±11.95, p=0.017) and visceral fat area (101.96±29.12 vs 126.42±41.21, p=0.012)

Arm versus leg activity

- Systematic review and meta-analysis of 18 studies (n=423) showed:
  - Symptoms were dependent on intensity of activity performed
  - Physiological responses increased during leg- vs arm activities except during resistance training:
    - Oxygen consumption [VO₂]: 164mL/min
    - Tidal volume [VT]: 137 mL
    - Ventilation: 4.8 L/min
    - Ventilator reserve: 7% points
    - Workload: 20 watt

*Body composition parameters: musculoskeletal mass, protein mass, body fat mass, and visceral fat area; measured before and after training via bioimpedance measurements

New directions in exercise assessment and training

Clinically measured vs wrist accelerometer derived 6MWD

- In a cross-over RCT (n=52) the wrist accelerometer derived 6MWD correlated with the clinically measured 6MWD in patients with a history of respiratory symptoms during air pollution, but accelerometer derived 6MWD was consistently lower:
  - Measured mean 6MWD: 466m +/- 132m
  - Derived 6MWD: 423m +/- 143m
- Higher derived 6MWD was associated with:
  - Less symptoms
  - Lower disease impact
  - Increased activity
  - Improved overall score

Short-term exercise training in virtual reality

- A study (n=68) compared efficacy of a traditional PR programme + VR training vs PR programme + exercise capacity training in patients with COPD
- VR training was carried out with the Xbox360® console, along with the Kinect® motion sensor
- Both groups showed significant improvements in the Senior Fitness Test (SFT), with significant improvements in arm curl, chair stand and 6MWT in the PR+VR group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Within group second – first difference (± SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm curl [rep.]</td>
<td>TPR</td>
<td>1.35 (±0.47)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>4.65 (±0.47)</td>
<td>0.000</td>
</tr>
<tr>
<td>Chair stand [rep.]</td>
<td>TPR</td>
<td>0.82 (±0.4)</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>2.62 (±0.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>6-minute walk test [m]</td>
<td>TPR</td>
<td>16.24 (±6.47)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>35.47 (±6.47)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

2. Rutkowski S et al. ERS 2019:PA70.

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Experts’ comments

• It is essential to consider each individual patient’s barriers to doing pulmonary rehabilitation (PR), then either counter them directly and/or focus on the benefits and enabling factors.

• Completing a PR course is essential to achieve the benefits of PR. Furthermore, response to PR is associated with better outcomes.

• Follow on rehabilitation programmes are helpful to prolong the benefits of rehabilitation, but intensity and duration need to be clarified before a standard can be defined.

• New technologies for the assessment and delivery of PR are becoming available however, they must be carefully compared with current methods to clarify efficacy and meaning.

• We are beginning to understand which aspects of PR are important and effective and may be able to use this information to tailor/adapt course to be effective for all patients.
Co-morbidities
Cardiovascular risk & disease: Associations with poorer lung function & death

CV disease & mortality\(^1\)

- The NIVO study recruited patients ventilated for exacerbation of COPD complicated by respiratory acidaemia from 10 UK hospitals (n=733)
- An increasing burden of CVD* (defined by the number of CVDs present in an individual patient) is associated with an increase in mortality in patients with exacerbation of COPD requiring ventilation:
  - 1 CVD (n=218) \(\rightarrow\) 23.4% higher mortality
  - 2 CVDs (n=106) \(\rightarrow\) 20.8% higher mortality
  - 3 CVDs (n=46) \(\rightarrow\) 26.1% higher mortality
  - 3+ CVDs (n=18) \(\rightarrow\) 38.9% higher mortality

Cardiac biomarkers & outcomes of COPD exacerbations\(^2\)

- Cardiac biomarkers (NT-proBNP and troponin T) were measured in patients (n=176) admitted for COPD exacerbation
  - High NT-proBNP: >220pmol/L
  - High troponin T: >50ng/L
  - Patients with pulmonary embolism, valvular heart disease or acute heart failure were excluded, i.a.
  - Compared to patients with normal biomarker levels, patients with elevated cardiac biomarkers had a significant decrease in 1-year survival

<table>
<thead>
<tr>
<th>Cardiac biomarker status</th>
<th>1-year survival</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal NT-proBNP and troponin T (n=137; 78%)</td>
<td>reference group</td>
<td>1.00 [1.00, 1.00]</td>
</tr>
<tr>
<td>High NT-proBNP alone (n=19; 11%)</td>
<td>3.41</td>
<td>[1.2, 9.7]</td>
</tr>
<tr>
<td>High troponin T alone (n=7; 4%)</td>
<td>6.46</td>
<td>[1.82, 22.91]</td>
</tr>
<tr>
<td>Both high NT-proBNP and troponin T (n=12; 7%)</td>
<td>5.78</td>
<td>[2.03, 16.44]</td>
</tr>
</tbody>
</table>

1. Lane ND et al. ERS 2019:PA2655.
2. Shafuddin E et al. ERS 2019:PA4290.

* CVD in this cohort was defined as left ventricular systolic dysfunction, atrial fibrillation, ischaemic heart disease, stroke, or cor pulmonale
Frailty has negative impact on patients with COPD

Data from four studies which captured information on frailty in COPD showed that compared to non-frail patients with COPD, frail patients with COPD have:

- Worse physical ability\(^1\)
- Worse dyspnoea\(^2\)
- Significantly higher symptom burden\(^2,3\)
- Greater a fear of falling and a greater number of falls\(^3\)

However, frailty may\(^4\) or may not\(^3\) be associated with worse lung function, and therefore, should be assessed independently.

Frailty was evaluated early during admission for AECOPD (n=34) and defined according to Fried phenotype\(^5\):

- Frailty is highly prevalent in patients with COPD at time of exacerbation (46%), vs 19% in stable COPD and 10% in the general adult population.
- Frailty was associated with a 4.5-fold increased risk of readmission vs non-frail patients (p=0.008).

---

1. Johnston K et al. ERS 2019:PA575.
3. Neumannova K et al. ERS 2019:PA1207.
**COPD and lung cancer**

**COPD increased lung cancer risk irrespective of smoking status**

A large Korean national cohort study, with 11 years follow-up, found: incidence rate* [HR† (95% CI)] for lung cancer (n=338,548)

<table>
<thead>
<tr>
<th>COPD</th>
<th>Never smoker</th>
<th>Ever smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.5 [(reference)]</td>
<td>1.2 [1.97 (1.75, 2.21)]</td>
</tr>
<tr>
<td>Yes</td>
<td>3.0 [2.67 (2.09, 3.40)]</td>
<td>9.5 [6.19 (5.04, 7.61)]</td>
</tr>
</tbody>
</table>

COPD is a strong independent risk factor for lung cancer incidence in never smokers

Data from a retrospective study on patients with surgically-resected lung cancer show COPD is associated with an increase in recurrences, mortality and epidermoid carcinomas

Out of 208 patients who had undergone surgery for lung cancer, 75 had COPD and 133 were non-COPD patients

COPD patients had a 41% recurrence rate, compared to 31% of non-COPD patients

- Emphysema: 41% recurrence; 10% second tumour
- Chronic bronchitis: 60% recurrence; 4% second tumour

**Frequency of histological-types**

<table>
<thead>
<tr>
<th></th>
<th>Non-COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Others</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*per 1000 person-years
† HR: Hazard ratio modelled with death as a competing risk and with age as the time scale; adjusted for sex, body mass index (continuous) and Charlson comorbidity index

---

1. Park HY et al. ERS 2019;349:OA3288.
Bronchiectasis, *P. aeruginosa* and COPD: implications of their co-existence

<table>
<thead>
<tr>
<th>COPD was found to be present in 49.6% of never-smoker non-cystic fibrosis bronchiectasis patients¹</th>
<th>Similarly, the co-existence of COPD and bronchiectasis (BE) is associated with an increase in disease severity²</th>
<th>Presence of <em>Pseudomonas aeruginosa</em> is associated with an increased risk of severe exacerbations and death in COPD patients³</th>
</tr>
</thead>
</table>
| Retrospective analysis in never-smokers with non-cystic fibrosis bronchiectasis (n=121) revealed independent risk factors for co-existent COPD:  
  • Increased age  
  • Increased dyspnoea score (measured by mMRC)  
  • Greater number of affected lobes | In a prospective study (n=51), COPD+BE patients compared to BE-alone patients were:  
  • Older (p=0.028),  
  • Had worse dyspnoea (p=0.03),  
  • Lower FEV₁ (p<0.001), and  
  • Higher PCO₂ (p<0.001)  
  • COPD+BE patients had a higher rate of exacerbations (p=0.028) and *Pseudomonas aeruginosa* growth in sputum | In an observational cohort study on 22,053 COPD outpatients, *Pseudomonas aeruginosa* infection was associated with:  
  • Hospitalisation for exacerbation and all-cause death (HR: 2.8 [95%CI: 2.2, 3.6])  
  • All-cause death (HR: 2.7 [95%CI: 2.3–3.4])  
  The number of hospitalisation-demanding exacerbations doubled in *Pseudomonas*-positive patients after *Pseudomonas* isolation compared to before isolation (16.3 and 8.5 events/1000 days, respectively; p≤0.001) |

¹ Lee SJ & Lee JD. ERS 2019:PA2684.  
Chinese COPD clusters and their associations with clinical outcomes

Stable COPD patients with Chinese ethnicity (n=911) were recruited from tertiary respiratory clinics in Singapore, Malaysia, and Hong Kong.

Non-metric multi-dimensional scaling and subsequent hierarchical clustering were performed using clinical and microbiological data.

The study was the first to determine the clusters of Chinese patients with stable COPD and their associations with clinical outcomes.

Five unique clusters were characterised:
- Ex-tuberculosis
- Diabetic
- Low-comorbidity, low-risk
- Low-comorbidity, high-risk
- Cardiovascular

The cardiovascular cluster had the worst 2-year survival prognosis.

Tiew PY et al. ERS 2019:PA3897.
Experts’ comments

• CVD has a significant impact on COPD and vice versa. We need to be aware of this impact especially at the time of an exacerbation.

• In an ageing population there is an increase in frailty. This is made worse in COPD and a whole-patient approach is needed when assessing needs.

• Lung cancer occurs more in COPD patients and seems to recur more frequently as well. Both airways specialists and oncologists should use this data when treating and monitoring disease.

• Availability of high-resolution CT scans has led to the recognition of dual COPD and bronchiectasis pathologies. This is important due to the prognostic and treatment implications. A multi-professional approach will be essential.
Meet the consulting experts

Dr. Richard Russell
MBBS, FRCP, PhD
- Consultant Chest Physician
- Lymington New Forest Hospital, UK
- Director of West Hampshire Integrated Respiratory Service
- Senior Clinical Researcher, University of Oxford
- Honorary Senior Lecturer, Imperial College London
- Editor-in-Chief of the International Journal of COPD

Dr. Alice Turner
MBChB (Hons), MRCP, PGCE (MedEd), PhD
- Reader in respiratory medicine, University of Birmingham
- Honorary consultant respiratory physician, University Hospitals Birmingham NHS Foundation Trust
- Member of the British Thoracic Society specialist advisory group on COPD
- Member of the European Respiratory Society task force on alpha-1 antitrypsin deficiency (AATD)

Dr. Frits Franssen
MD, PhD
- Chest physician and interim medical director in CIRO, Horn, the Netherlands
- Respiratory consultant at Maastricht University Medical Center, the Netherlands
- Leading scientist on personalised medicine in COPD at CIRO
- Chair of European Respiratory Society group ‘rehabilitation and chronic care’
- Associate Editor of Respirology and Breathe
- Fellow of the European Respiratory Society
Disclosures

Dr. Richard Russell
Travel support
• Unattributed support for travel to a scientific conference from Boehringer Ingelheim and Chiesi UK

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Attended paid advisory boards for:
• AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis

No shares in the pharmaceutical industry or the tobacco industry.

Dr. Alice Turner
Travel support
• AstraZeneca, Chiesi

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• CSL Behring, pH Pharma, Vertex

No shares in the pharmaceutical industry or the tobacco industry.

Dr. Frits Franssen
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• Boehringer Ingelheim, TEVA

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Research grants:
• AstraZeneca, Novartis

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<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>Aclidinium bromide</td>
</tr>
<tr>
<td>AFD</td>
<td>Airway fractal dimension</td>
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<tr>
<td>AIC</td>
<td>Akaike information criteria</td>
</tr>
<tr>
<td>AMT</td>
<td>Abbreviated mental test</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>ACEPD</td>
<td>Acute exacerbation of COPD</td>
</tr>
<tr>
<td>B-Eos</td>
<td>Blood eosinophils</td>
</tr>
<tr>
<td>BIQ</td>
<td>BMI body mass index</td>
</tr>
<tr>
<td>BODE</td>
<td>Body mass index, airflow obstruction, dyspnoea and exercise capacity</td>
</tr>
<tr>
<td>Bpm</td>
<td>Breaths per minute</td>
</tr>
<tr>
<td>Brief-BEST</td>
<td>Brief Balance Evaluation Systems Test</td>
</tr>
<tr>
<td>CASIS</td>
<td>COPD and asthma sleep impact scale</td>
</tr>
<tr>
<td>CAT</td>
<td>COPD assessment test</td>
</tr>
<tr>
<td>CB</td>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td>Cl</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CM</td>
<td>Correlation metric</td>
</tr>
<tr>
<td>CON</td>
<td>Conventional concentric cycling</td>
</tr>
<tr>
<td>CPF</td>
<td>Cardiopulmonary exercise test</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CRQ</td>
<td>Chronic Respiratory Questionnaire</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>CWR</td>
<td>Constant work rate</td>
</tr>
<tr>
<td>DB</td>
<td>Dual bronchodilator</td>
</tr>
<tr>
<td>DH</td>
<td>Dynamic hyperinflation</td>
</tr>
<tr>
<td>DPI</td>
<td>Dry powder inhaler</td>
</tr>
<tr>
<td>DLH</td>
<td>Dynamic lung hyperinflation</td>
</tr>
<tr>
<td>DS-20</td>
<td>Oxytocin (NT)</td>
</tr>
<tr>
<td>ECC</td>
<td>Eccentric cycling</td>
</tr>
<tr>
<td>EELV</td>
<td>End-expiratory lung volume</td>
</tr>
<tr>
<td>EOS</td>
<td>Eosinophil / eosinophil count</td>
</tr>
<tr>
<td>ES</td>
<td>Emergency room</td>
</tr>
<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>EISWT</td>
<td>Endurance shuttle walk test</td>
</tr>
<tr>
<td>FAB</td>
<td>Frontal assessment battery</td>
</tr>
<tr>
<td>FDC</td>
<td>Forced dose combination</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FF</td>
<td>Fluticasone furoate</td>
</tr>
<tr>
<td>FOR</td>
<td>Formoterol fumarate</td>
</tr>
<tr>
<td>FOT</td>
<td>Forced oscillation technique</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GIPFORM</td>
<td>Glycoprotein/formoterol fumarate</td>
</tr>
<tr>
<td>GLY</td>
<td>Glycopyrronium</td>
</tr>
<tr>
<td>GLY/IND</td>
<td>Glycopyrrolate/indacaterol</td>
</tr>
<tr>
<td>GLYFORM</td>
<td>Glycopyrrolate/formoterol fumarate</td>
</tr>
<tr>
<td>GP</td>
<td>Glycoprotein</td>
</tr>
<tr>
<td>HAIDS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>HULR</td>
<td>High-load/repetiton</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>IC</td>
<td>Inspiratory capacity</td>
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<td>ICS</td>
<td>Inhaled corticosteroid</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<td>IRR</td>
<td>Incidence risk ratio</td>
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<td>ISWT</td>
<td>Incremental shuttle walk test</td>
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<td>LAV%</td>
<td>Low attenuation volume percent</td>
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<tr>
<td>LCI</td>
<td>Lung clearance index</td>
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<tr>
<td>LLHR</td>
<td>Low-load/high-repetiton</td>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharides</td>
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<tr>
<td>MOM</td>
<td>Monocyte medium</td>
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<tr>
<td>MDI</td>
<td>Metered-dose inhaler</td>
</tr>
<tr>
<td>mDP</td>
<td>Multi-dose dry powder inhaler</td>
</tr>
<tr>
<td>MECHA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
</tr>
<tr>
<td>M</td>
<td>Metabolic equivalent</td>
</tr>
<tr>
<td>MID</td>
<td>Minimal important difference</td>
</tr>
<tr>
<td>mMRC</td>
<td>Modified Medical Research Council scale</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state examination</td>
</tr>
<tr>
<td>MPH</td>
<td>Metronome-paced incremental hyperventilation</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>NHA</td>
<td>Nasal high-flow oxygen</td>
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<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>NPA</td>
<td>Negative per cent agreement</td>
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<tr>
<td>O</td>
<td>Olopatadine</td>
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<tr>
<td>OCS</td>
<td>Oral corticosteroid</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Daytime arterial carbon dioxide pressure</td>
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<tr>
<td>PAM</td>
<td>Patient activation measure</td>
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<td>PDE4</td>
<td>Phosphodiesterase 4</td>
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<td>PFT</td>
<td>Pulmonary function test</td>
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<tr>
<td>PIR</td>
<td>Peak inspiratory flow rate</td>
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<tr>
<td>P10</td>
<td>Square root of the wall area of a hypothetical 10 mm internal perimeter</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>pMDI</td>
<td>Pressurised metered-dose inhaler</td>
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<tr>
<td>PPA</td>
<td>Per cent agreement</td>
</tr>
<tr>
<td>PR</td>
<td>Pulmonary rehabilitation</td>
</tr>
<tr>
<td>prBNP</td>
<td>N-terminal (NT)-pro-hormone BNP</td>
</tr>
<tr>
<td>OD</td>
<td>Once daily</td>
</tr>
<tr>
<td>OXL</td>
<td>Quality of Life</td>
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<tr>
<td>LCT</td>
<td>Lung clearance test</td>
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<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>RS</td>
<td>Respiratory resistance at 5 Hz</td>
</tr>
<tr>
<td>R20</td>
<td>Respiratory resistance at 20 Hz</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<td>SDPI</td>
<td>Single-dose dry powder inhaler</td>
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<tr>
<td>SE</td>
<td>Standard error</td>
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<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
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<td>SFT</td>
<td>Senior fitness test</td>
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<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
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<tr>
<td>SIT</td>
<td>Single inhaler triple therapy</td>
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<tr>
<td>SUCRA</td>
<td>Surface Under the Cumulative Ranking Curve</td>
</tr>
<tr>
<td>TAC</td>
<td>Tiotropium</td>
</tr>
<tr>
<td>TCR</td>
<td>T-cell receptor</td>
</tr>
<tr>
<td>TDI</td>
<td>Transition dyspnoea index</td>
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<tr>
<td>TLC</td>
<td>Total lung capacity</td>
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<tr>
<td>TFC</td>
<td>Diffusing capacity of transfer factor of the lung for carbon monoxide</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
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<tr>
<td>T/O</td>
<td>Tiotropium/olodaterol</td>
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<tr>
<td>UMEC</td>
<td>Umeclidinium</td>
</tr>
<tr>
<td>UMEC/VI</td>
<td>Umeclidinium/vilanterol</td>
</tr>
<tr>
<td>V</td>
<td>Visit</td>
</tr>
<tr>
<td>VCD</td>
<td>Vocal cord dysfunction</td>
</tr>
<tr>
<td>VO2</td>
<td>Maximal oxygen uptake</td>
</tr>
<tr>
<td>VT</td>
<td>Tidal volume</td>
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<tr>
<td>VQVM</td>
<td>Ventilation/perfusion match</td>
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<td>VQ11</td>
<td>COPD-specific HRQoL questionnaire</td>
</tr>
<tr>
<td>VR</td>
<td>Virtual reality</td>
</tr>
<tr>
<td>WA%</td>
<td>Wall area percent of segmental airways</td>
</tr>
<tr>
<td>WK</td>
<td>Week</td>
</tr>
<tr>
<td>WR</td>
<td>Work rate</td>
</tr>
<tr>
<td>X5</td>
<td>Respiratory reactance at 5 Hz</td>
</tr>
<tr>
<td>ZS</td>
<td>Respiratory impedance</td>
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</table>

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Dr. Olaf Jöns

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