# Pharmacologic Prevention of AE-COPD

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# Contents

# Definition of AE-COPD

| Definitions of exacerbations of COPD | Reference |
|---|---|
| Chest illness severe enough to cause loss of time from work or force the patient to go to bed | Jones et al.[6] |
| Increase or onset of shortness of breath, sputum production and/or sputum purulence | Anthonisen et al.[7] |
| Worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapies | Paggiaro et al.[207] |
| An acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and necessitates a change in regular medication in a patient with underlying COPD | Rodriguez Roisin et al.[1] |
| An increase in any two major symptoms or increase in one major and one minor symptom on two consecutive days, the first of which was taken as the day of onset of exacerbation | Seemungal et al.[8] |
| A different definition that included not only the grading of symptoms, with dyspnoea being the dominant feature (>4 on a visual analogue scale) but also the measurement of respiratory rate (>24) and the addition of potential objective supporting criteria for exacerbation including oxygen desaturation ≤ 4% below that of stable state, elevated levels of circulating blood neutrophils or eosinophils (≥9000 neutrophils ·mm – or ≥2% blood eosinophils) and elevated C-reactive protein (≥10 mg $L^{-1}$) | Celli and Barnes[9] |
| Episodes of increasing respiratory symptoms, particularly dyspnoea, cough, sputum production and increased sputum purulence | Wedzicha et al.[2] |
| An acute worsening of respiratory symptoms that results in additional therapy | GOLD[4] |

- **Acute worsening of symptoms**

  : Increased dyspnea, coughing, increased sputum volume and sputum purulence

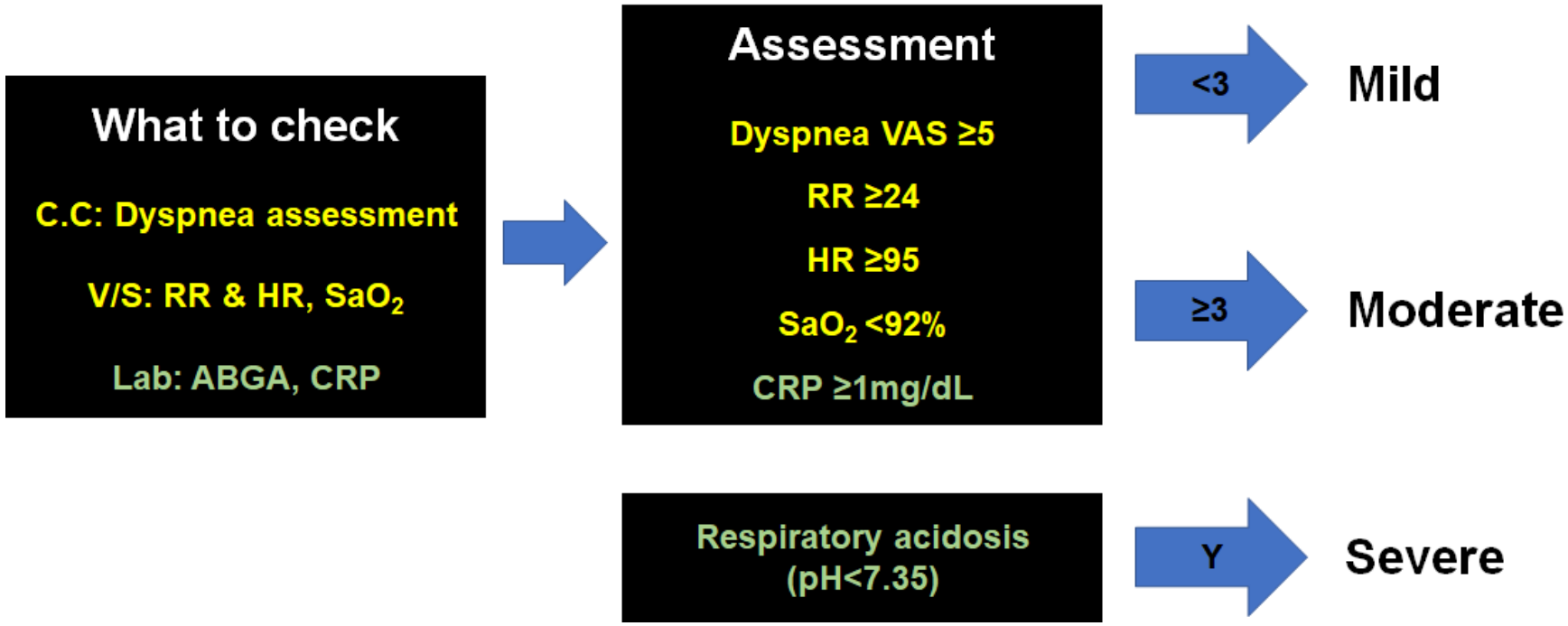
- **Requirement of additional therapy**

  : Hospital visit or admission

Respirology. 2021 Jun;26(6):532-551

# Severity of AE-COPD as point of care classification

| Severity | Criteria for judging severity |
|---|---|
| **Mild (default)** | • Dyspnea VAS <5<br>• RR <24 breaths/min<br>• HR <95 bpm<br>• Resting $SaO_2$ ≥92% breathing ambient air (or patient's usual oxygen prescription), AND change ≤3% (when known)<br>• CRP <10 mg/L (if obtained) |
| **Moderate (meets at least three of five*)** | • Dyspnea VAS ≥5<br>• RR ≥24 breaths/min<br>• HR ≥95 bpm<br>• Resting $SaO_2$ <92% breathing ambient air (or patient's usual oxygen prescription), AND/OR change >3% (when known)<br>• CRP ≥10 mg/L<br>If obtained, ABG may show hypoxemia ($PaO_2$ ≤60 mmHg) and/or hypercapnia ($PaCO_2$ >45 mmHg) but no acidosis |
| **Severe** | • ABG show hypercapnia and acidosis ($PaCO_2$ >45 mmHg and pH <7.35) |



# Severity of AE-COPD as patient outcome

- **Mild**

  : when **only symptoms** or treated with inhaled **short-acting bronchodilators**

- **Moderate**

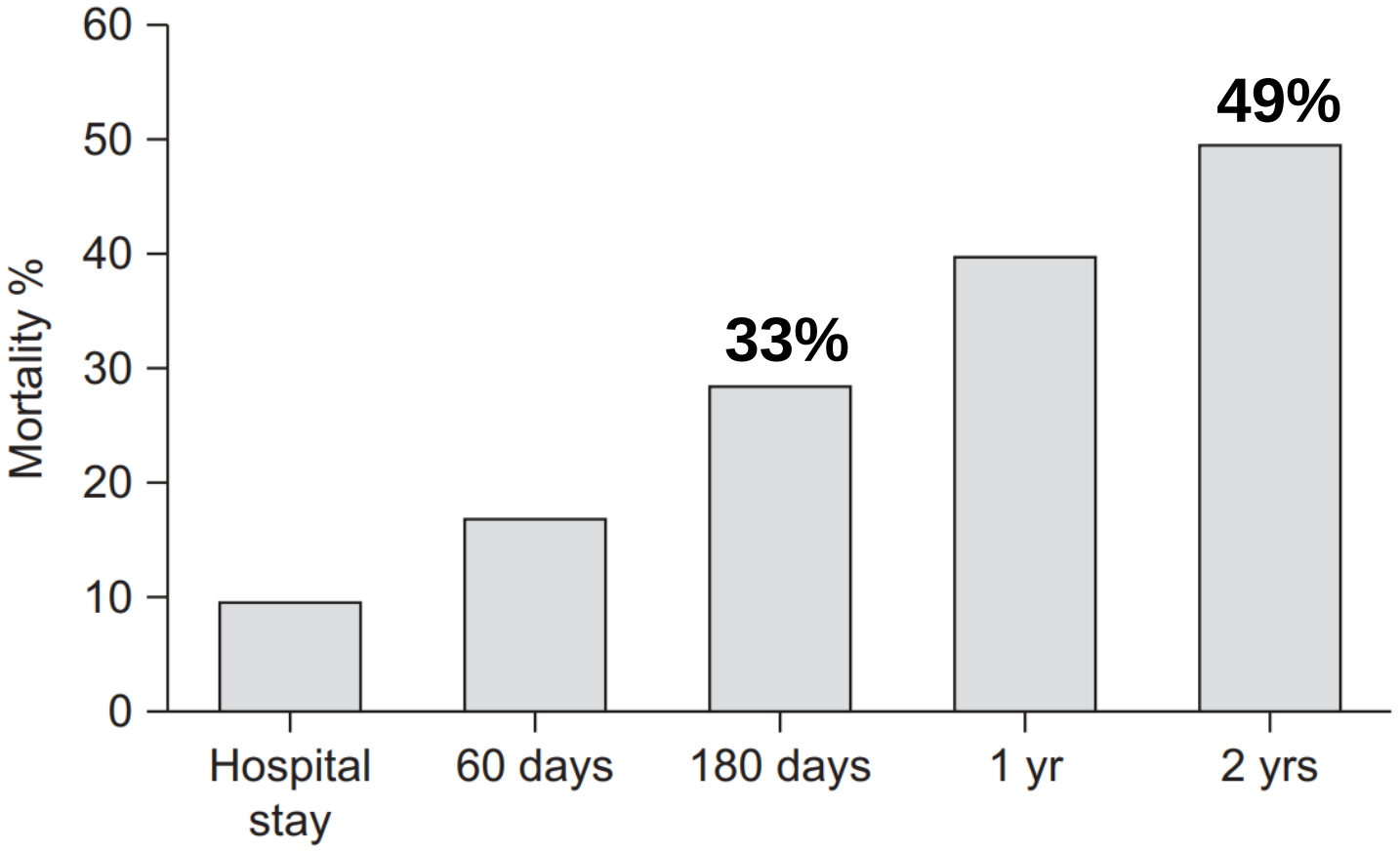
  : when the patient receives **antibiotics, systemic corticosteroids or both**

- **Severe**

  : when the patient visits an **emergency room** or is **hospitalized** due to the event

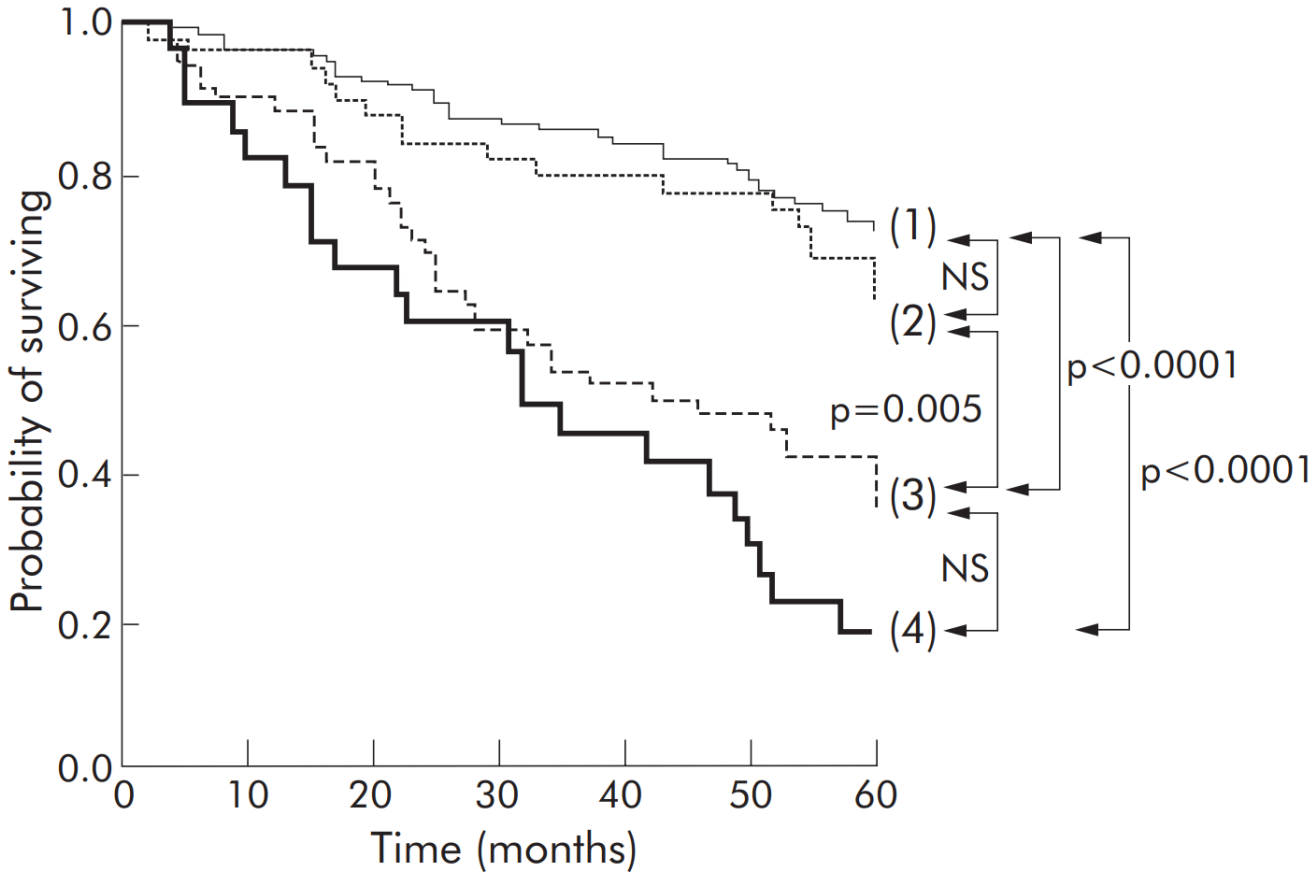
# Half of severe AE-COPD patients died in 2 years

- Severe (=hospitalized) AE-COPD patients




Eur Respir Rev. 2010 Jun;19(116):113-8.
Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 1):959-67.

# Poor prognosis after readmission




(1) NO acute exacerbation

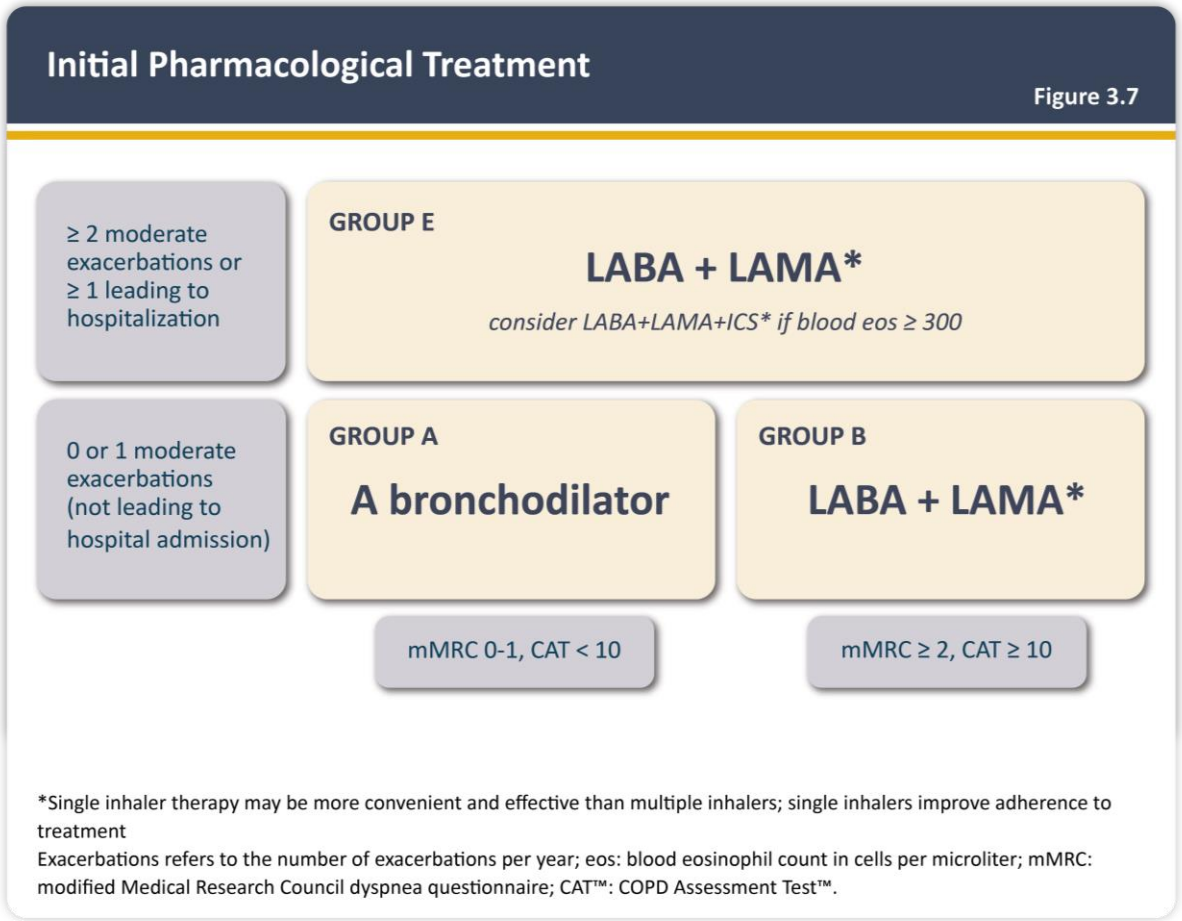
(2) Acute exacerbation without hospital admission

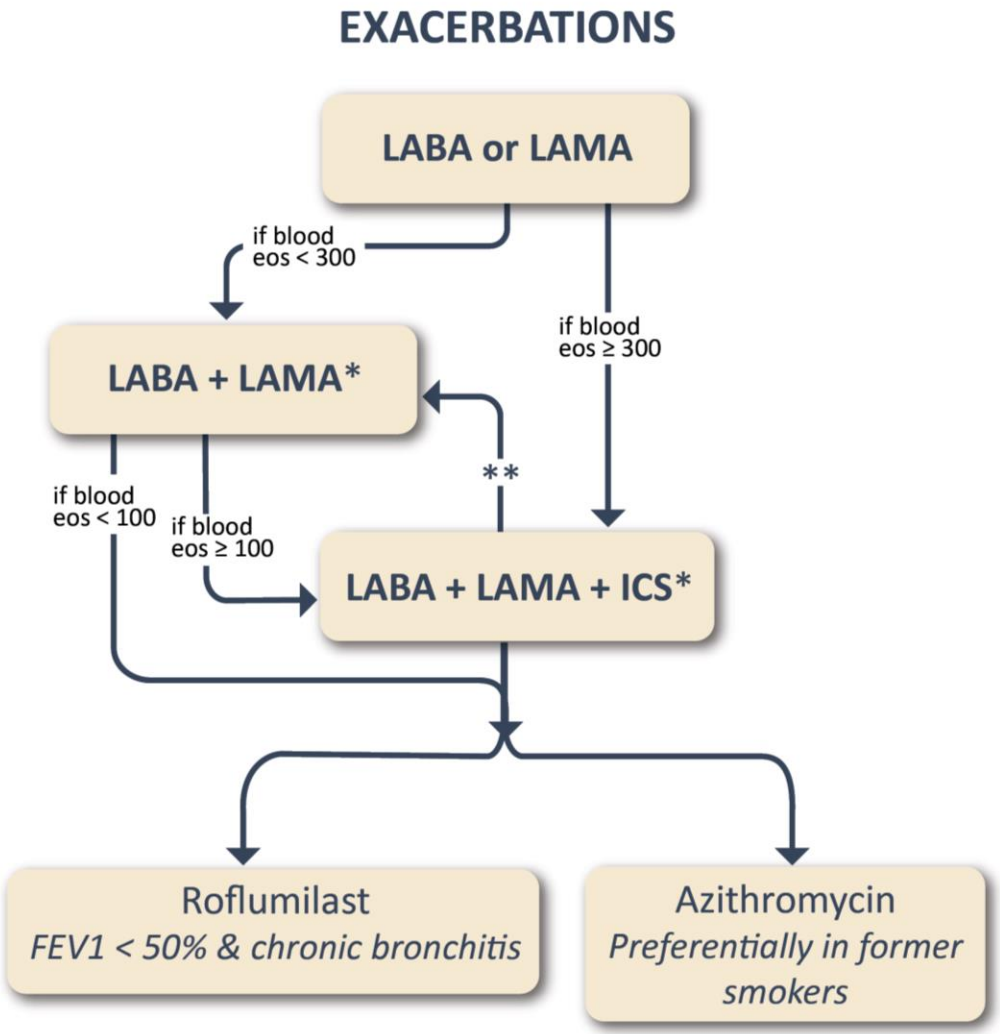
(3) Acute exacerbation **with hospital admission**

(4) Acute exacerbation **with readmission**

Thorax. 2005 Nov;60(11):925-31.

# Exacerbation prevention for stable COPD




GOLD report 2024

# TORCH trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

P: 40-80 YO, ≥10 PY, FEV1<60%, $FEV_1$/FVC≤0.7
I: SAL vs. FP vs. SAL/FP
C: PBO
O: Mortality
Duration: 3 yrs

**MtS AE: LABA, ICS/LABA > PBO**
**ICS/LABA > LABA or ICS**

| Efficacy analysis for exacerbation | | | | | | Rate Ratio (95% CI) | |
|---|---|---|---|---|---|---|---|
| Annual rate | | | | | | | |
| Moderate or severe | 1.13 | 0.97 | 0.93 | 0.85 | Combination therapy vs. placebo | 0.75 (0.69–0.81) | <0.001 |
| | | | | | Combination therapy vs. salmeterol | 0.88 (0.81–0.95) | 0.002 |
| | | | | | Combination therapy vs. fluticasone propionate | 0.91 (0.84–0.99) | 0.02 |
| | | | | | Salmeterol vs. placebo | 0.85 (0.78–0.93) | <0.001 |
| | | | | | Fluticasone propionate vs. placebo | 0.82 (0.76–0.89) | <0.001 |
| Requiring systemic corticosteroids | 0.80 | 0.64 | 0.52 | 0.46 | Combination therapy vs. placebo | 0.57 (0.51–0.64) | <0.001 |
| | | | | | Combination therapy vs. salmeterol | 0.71 (0.63–0.79) | <0.001 |
| | | | | | Combination therapy vs. fluticasone propionate | 0.87 (0.78–0.98) | 0.02 |
| | | | | | Salmeterol vs. placebo | 0.80 (0.72–0.90) | <0.001 |
| | | | | | Fluticasone propionate vs. placebo | 0.65 (0.58–0.73) | <0.001 |
| Severe (requiring hospitalization) | 0.19 | 0.16 | 0.17 | 0.16 | Combination therapy vs. placebo | 0.83 (0.71–0.98) | 0.03 |
| | | | | | Combination therapy vs. salmeterol | 1.02 (0.87–1.20) | 0.79 |
| | | | | | Combination therapy vs. fluticasone propionate | 0.95 (0.82–1.12) | 0.56 |
| | | | | | Salmeterol vs. placebo | 0.82 (0.69–0.96) | 0.02 |
| | | | | | Fluticasone propionate vs. placebo | 0.88 (0.74–1.03) | 0.10 |

N Engl J Med. 2007 Feb 22;356(8):775-89.

# UPLIFT trial

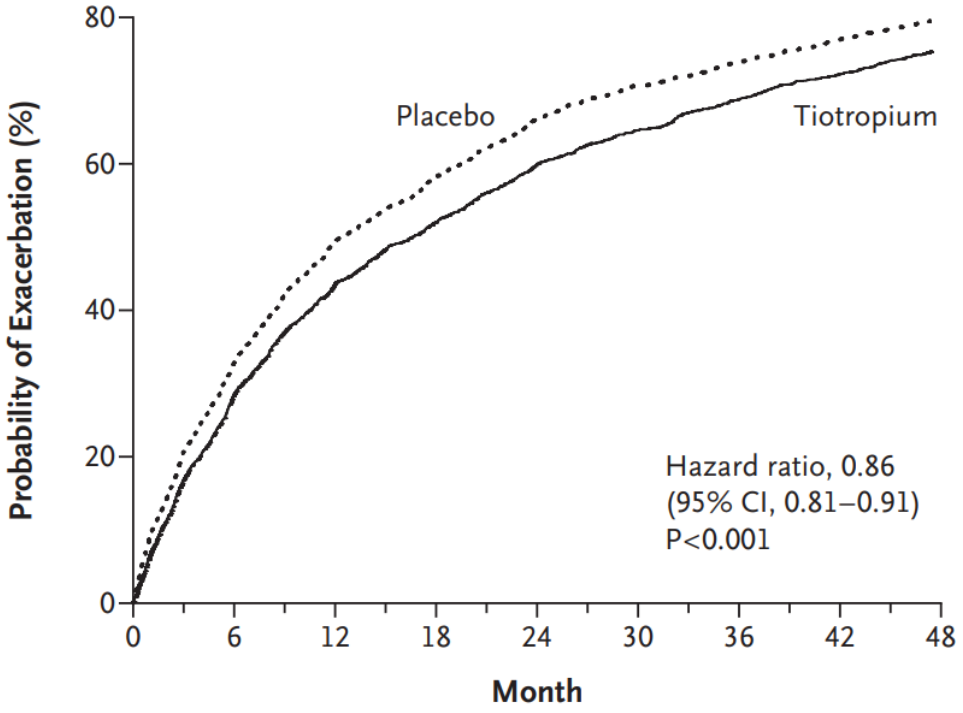
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

P: ≥40 YO, ≥10 PY, FEV1≤70%, $FEV_1$/FVC≤0.7
I: TIO
C: PBO
O: FEV1 decline
Duration: 4 yrs

**MtS AE: LAMA>PBO**




| Variable | Tiotropium | Placebo | Relative Risk for Tiotropium vs. Placebo (95% CI) | P Value |
|---|---|---|---|---|
| Exacerbation† | | | | |
| Per patient-year — no. | 0.73±0.02 | 0.85±0.02 | 0.86 (0.81–0.91) | <0.001 |
| Leading to hospitalization — no. per patient-year | 0.15±0.01 | 0.16±0.01 | 0.94 (0.82–1.07) | 0.34 |
| Days per patient-year | 12.11±0.32 | 13.64±0.35 | 0.89 (0.83–0.95) | 0.001 |
| Hospitalization days per patient-year | 3.17±0.17 | 3.13±0.17 | 1.01 (0.87–1.18) | 0.86 |
| Patients with exacerbation — no. (%)‡ | | | | |
| Total | 2001 (67.0) | 2049 (68.2) | NA | 0.35 |
| Leading to hospitalization | 759 (25.4) | 811 (27.0) | NA | 0.18 |

N Engl J Med. 2008 Oct 9;359(15):1543-54.

# Tie-COPD trial

ORIGINAL ARTICLE

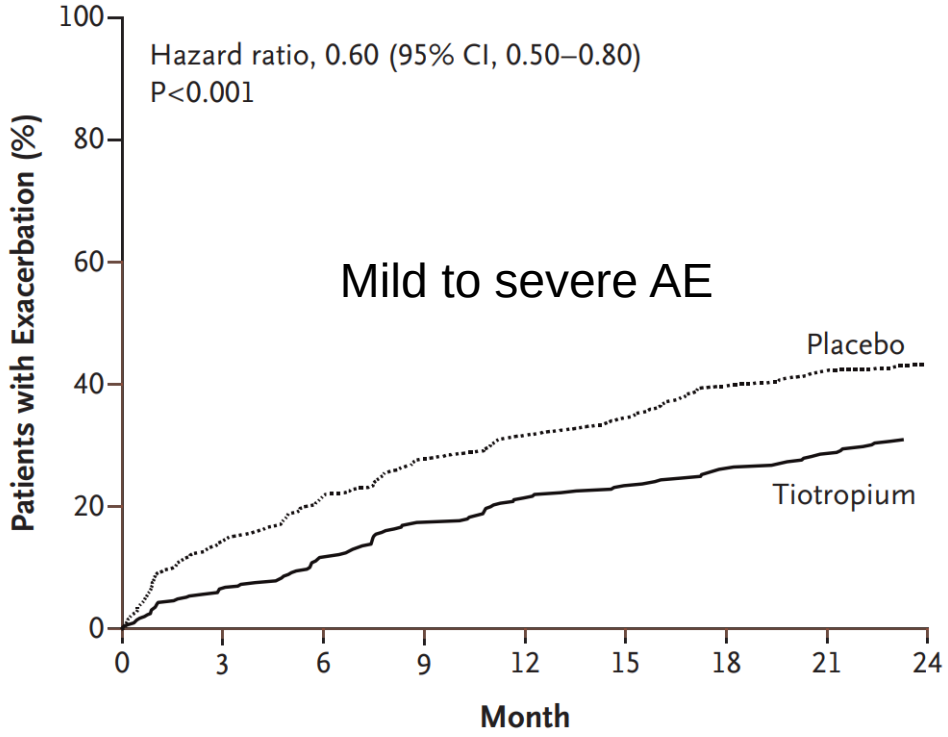
## Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

P: 40-85 YO, ≥10 PY, **FEV1>50%**, $FEV_1$/FVC<0.7
I: TIO
C: PBO
O: Change in FEV1 from baseline to 24 months
Duration: 2 yrs

**Any AE: LAMA>PBO**

Table 1. Characteristics of the Patients at Baseline (Full Analysis Set).*

| Characteristic | Placebo Group (N=383) | Tiotropium Group (N=388) | P Value† |
|---|---|---|---|
| GOLD stage — no. (%)** | | | 0.67 |
| 1 | 165 (43.1) | 173 (44.6) | |
| 2 | 218 (56.9) | 215 (55.4) | |
| CAT score†† | | | |
| Mean score | 6.8±5.9 | 7.4±6.2 | 0.18 |
| Distribution — no. (%) | | | 0.20 |
| <10 | 288 (75.2) | 276 (71.1) | |
| ≥10 | 95 (24.8) | 112 (28.9) | |
| mMRC dyspnea scale score‡‡ | | | |
| Mean score | 0.8±0.7 | 0.7±0.7 | 0.70 |
| Distribution — no. (%) | | | 0.96 |
| <2 | 339 (88.5) | 343 (88.4) | |
| ≥2 | 44 (11.5) | 45 (11.6) | |
| CCQ score§§ | 0.96±0.74 | 0.99±0.73 | 0.58 |




N Engl J Med. 2017 Sep 7;377(10):923-935.

# Tie-COPD trial

ORIGINAL ARTICLE

## Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

P: 40-85 YO, ≥10 PY, **FEV1>50%**, $FEV_1/FVC<0.7$
I: TIO
C: PBO
O: Change in FEV1 from baseline to 24 months
Duration: 2 yrs

**Table S12. Summary of AECOPD and COPD hospitalizations in subgroup stratified by CAT scores.***

| | Placebo | | Tiotropium | | Relative Risk for Tiotropium vs. Placebo | |
|---|---|---|---|---|---|---|
| **Variables** | **N** | **Mean (SE)** | **N** | **Mean (SE)** | **(95% CI)** | **P values** |
| CAT<10 | | | | | | |
| Exacerbation, no. per patient-year† | | | | | | |
| Total | 288 | 0.41±0.04 | 276 | 0.22±0.03 | 0.55(0.38 to 0.79) | 0.0013 |
| Moderate and over | 288 | 0.30±0.04 | 276 | 0.16±0.03 | 0.53(0.35 to 0.79) | 0.0017 |
| Hospitalization, per patient-year† | 278 | 0.05±0.01 | 268 | 0.02±0.01 | 0.33(0.11 to 0.95) | 0.0397 |
| CAT≥10 | | | | | | |
| Exacerbation, no. per patient-year† | | | | | | |
| Total | 95 | 0.82±0.14 | 112 | 0.37±0.08 | 0.46(0.27 to 0.77) | 0.0035 |
| Moderate and over | 95 | 0.66±0.12 | 112 | 0.29±0.07 | 0.44(0.25 to 0.77) | 0.0044 |
| Hospitalization, per patient-year† | 92 | 0.12±0.04 | 108 | 0.05±0.02 | 0.39(0.15 to 1.00) | 0.05 |
| Days of exacerbation per patient-year† | 92 | 6.97±1.11 | 108 | 3.38±0.66 | 0.49(0.30 to 0.80) | 0.0042 |
| Days of hospitalization per patient-year † | 92 | 1.43±0.47 | 108 | 0.59±0.26 | 0.41(0.14 to 1.22) | 0.11 |

**MtS AE: LAMA>PBO** (**even in less symptomatic patients**)

N Engl J Med. 2017 Sep 7;377(10):923-935.

# POET-COPD trial

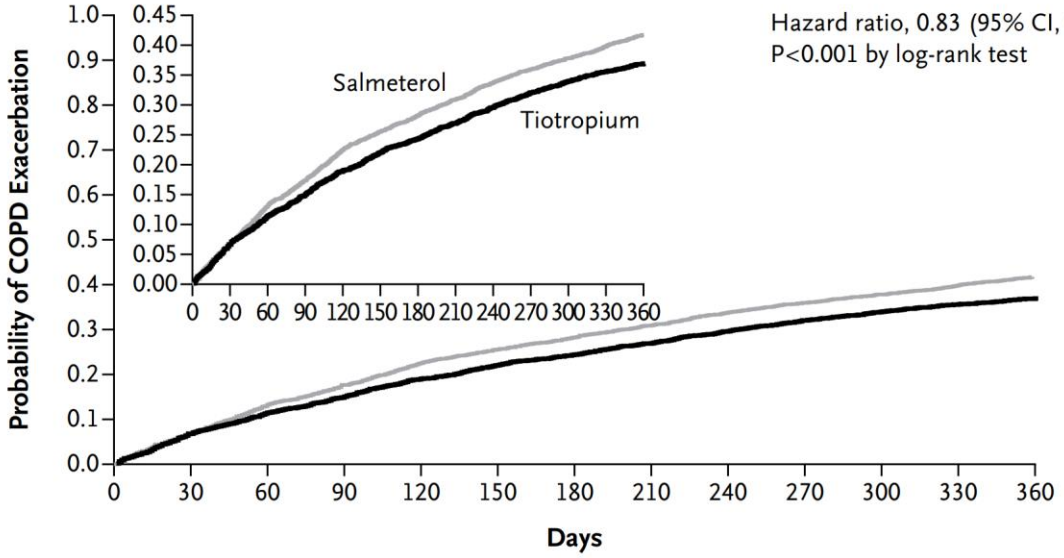
The NEW ENGLAND JOURNAL of MEDICINE

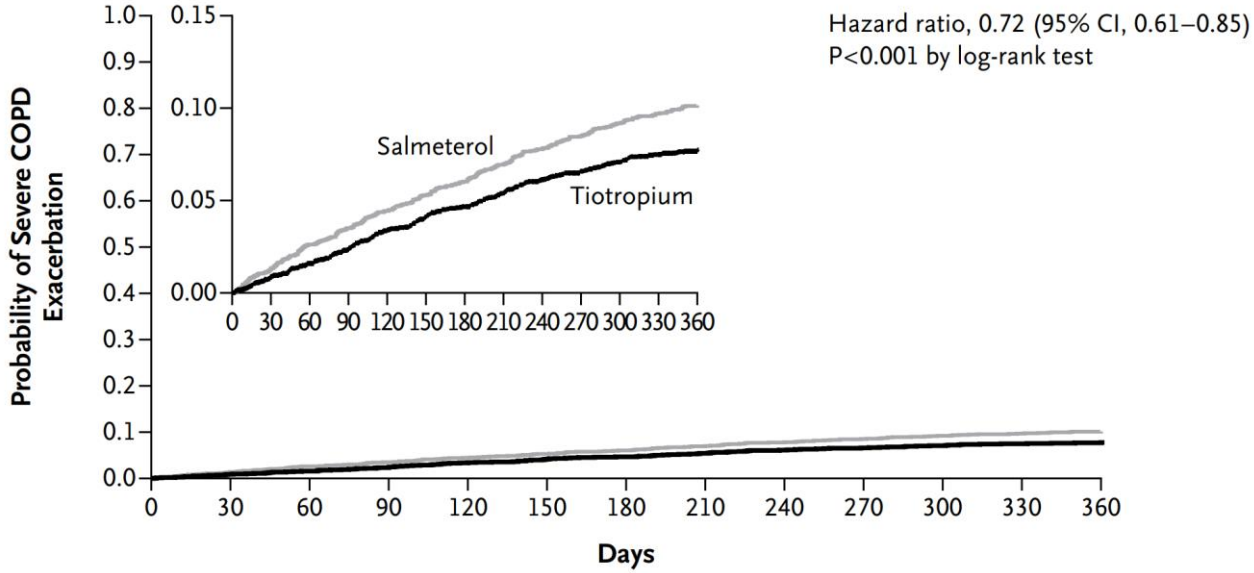
ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

P: 40-80 YO, ≥10 PY, FEV1≤70%, $FEV_1$/FVC≤0.7, **≥1 MtS AE**
I: TIO
C: SAL
O: Time to MtS AE
Duration: 1 yr

## MtS AE: LAMA>LABA (AE history)



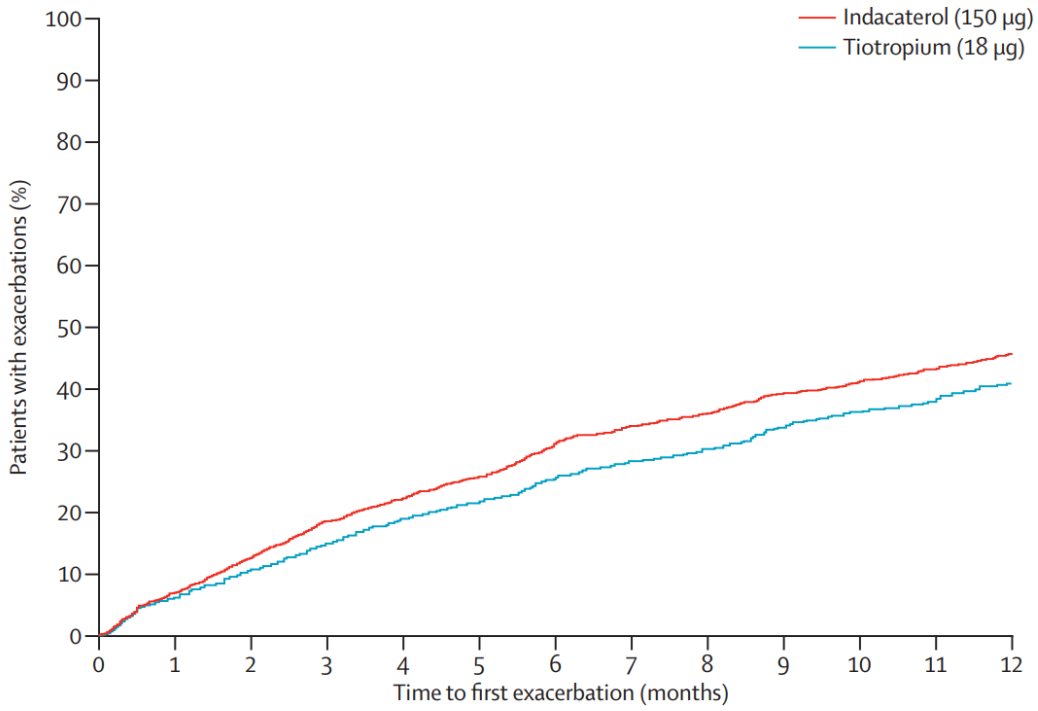

N Engl J Med. 2011 Mar 24;364(12):1093-1103.

# INVIGORATE trial

**Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study**

P: ≥40 YO, ≥10 PY, FEV1 30-50%, $FEV_1$/FVC<0.7, **≥1 MtS AE**
I: TIO
C: IND
O: Trough FEV1 at week 12
Duration: 1 yr

## MtS AE: LAMA>LABA (AE history)




The annualized rate of exacerbations was higher with indacaterol (n=1693) than it was with tiotropium (n=1689; 0·90 vs 0·73; rate ratio 1·24; 95% CI 1·12 to 1·37; p<0·0001)

Lancet Respir Med. 2013 Sep;1(7):524-33.

# INSPIRE trial

**The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide**

P: 40-80 YO, ≥10 PY, FEV1≤50%, $FEV_1$/FVC≤0.7, **≥1 MtS AE & mMRC ≥2**
I: SAL/FP
C: TIO
O: MtS AE rate
Duration: 1 yr

**MtS AE: LAMA ≒ ICS/LABA (AE history + Sx)**

| Variable | SFC 50/500 (*n* = 658) | Tiotropium (*n* = 665) | Rate Ratio* | 95% CI | *P* Value |
|---|---|---|---|---|---|
| | | Exacerbations (*mean no./yr*) | | | |
| HCU | 1.28 | 1.32 | 0.97 | 0.84 to 1.12 | 0.656 |
| Requiring oral corticosteroids | 0.69 | 0.85 | 0.81 | 0.67 to 0.99 | 0.039 |
| Requiring antibiotics | 0.97 | 0.82 | 1.19 | 1.02 to 1.38 | 0.028 |

Incidence of exacerbations requiring hospitalizations was 16% for SFC and 13% for tiotropium (P= 0.085)

Am J Respir Crit Care Med. 2008 Jan 1;177(1):19-26.

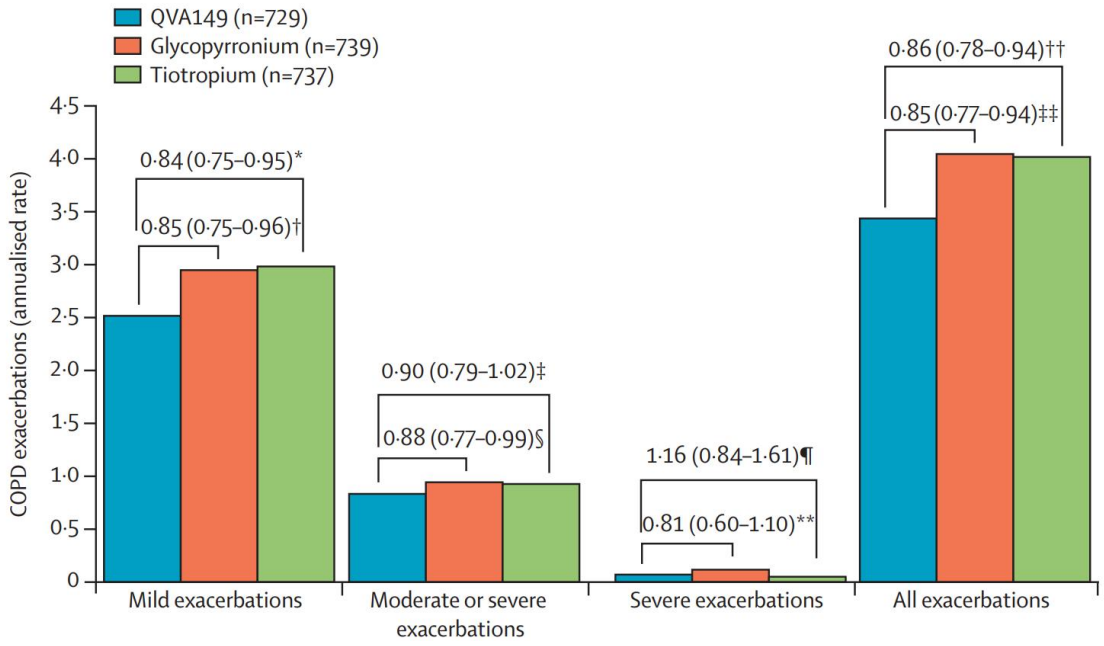
# SPARK trial

**Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study**

P: ≥40 YO, ≥10 PY, FEV1<50%, $FEV_1$/FVC≤0.7, **≥1 MtS AE**
I: IND/GLY
C: TIO, GLY
O: MtS AE rate
Duration: 64wk

## MtS AE: LABA/LAMA > LAMA (AE history)

| | QVA149 *vs* glycopyrronium | QVA149 *vs* tiotropium | Glycopyrronium *vs* tiotropium |
|---|---|---|---|
| Mild exacerbations | 0·85 (0·75–0·96; 0·0072) | 0·84 (0·75–0·95; 0·0052) | 0·99 (0·88–1·12; 0·90) |
| Moderate or severe exacerbations | 0·88 (0·77–0·99; 0·038) | 0·90 (0·79–1·02; 0·096) | 1·03 (0·91–1·16; 0·68) |
| Severe exacerbations | 0·81 (0·60–1·10; 0·18) | 1·16 (0·84–1·61; 0·36) | 1·43 (1·05–1·97; 0·025) |
| All exacerbations | 0·85 (0·77–0·94; 0·0012) | 0·86 (0·78–0·94; 0·0017) | 1·01 (0·91–1·11; 0·92) |



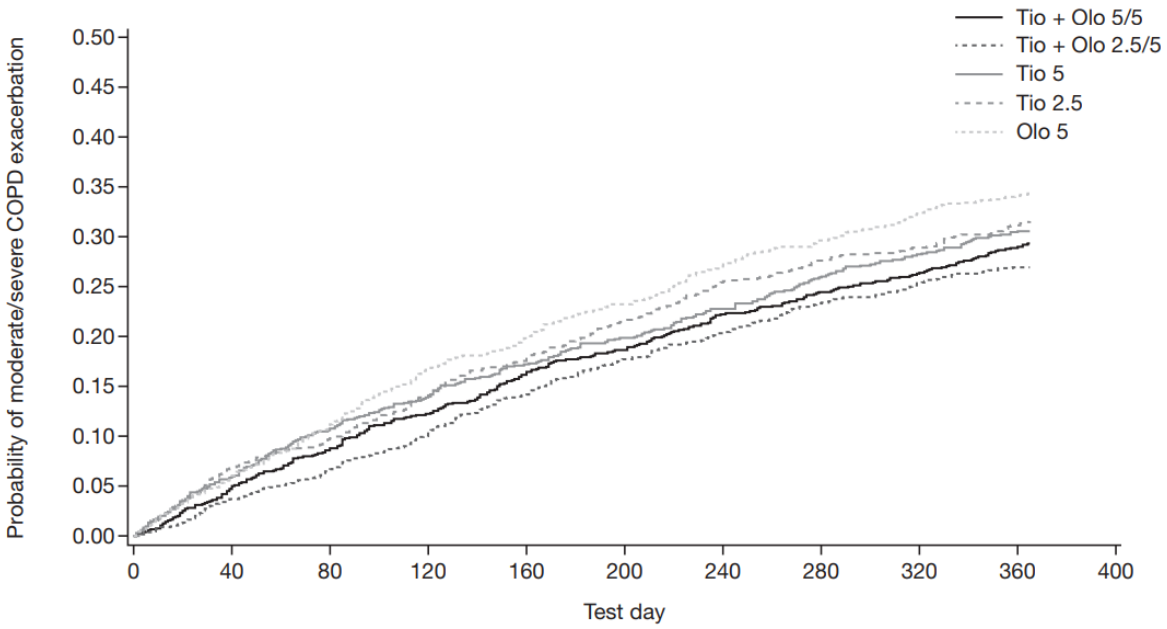

Lancet Respir Med. 2013 May;1(3):199-209.

# TONADO trial

**Tiotropium and olodaterol fixed-dose combination *versus* mono-components in COPD (GOLD 2–4)**

P: ≥40 YO, ≥10 PY, FEV1<80%, $FEV_1$/FVC≤0.7
I: TIO®/OLO
C: TIO®, OLO
O: FEV1 AUC0-3, Trough FEV1, SGRQ
Duration: 52wk

**MtS AE: LABA/LAMA > LABA, LAMA?**




?

| | Risk ratio | 95% CI | p-value |
|---|---|---|---|
| Tio + Olo 5/5 | | | |
| *versus* Olo 5 | 0.8340 | 0.7058, 0.9856 | 0.0332 |
| *versus* Tio 5 | 0.9247 | 0.7811, 1.0947 | 0.3631 |
| Tio + Olo 2.5/5 | | | |
| *versus* Olo 5 | 0.6865 | 0.5781, 0.8152 | <0.0001 |
| *versus* Tio 2.5 | 0.7608 | 0.6393, 0.9053 | 0.0021 |
| *versus* Tio 5 | 0.7611 | 0.6399, 0.9054 | 0.0021 |

Eur Respir J. 2015 Apr;45(4):969-79.

# DYNAGITO trial

**Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial**

P: ≥40 YO, ≥10 PY, FEV1<60%, $FEV_1$/FVC≤0.7, **≥1 MtS AE**
I: TIO®/OLO (5/5)
C: TIO®
O: MtS AE rate
Duration: 52wk

## MtS AE: LABA/LAMA > LAMA (AE history)

| | Adjusted rate of events per patient-year (95% CI) | | Rate ratio | 95% CI | p value |
|---|---|---|---|---|---|
| | Tiotropium–olodaterol group | Tiotropium group | | | |
| **Primary endpoint** | | | | | |
| Moderate and severe exacerbations | 0·90 (0·84–0·96)* | 0·97 (0·90–1·03)* | 0·93 | 0·85–1·02* (0·87–1·00)† | 0·0498 |
| **Other prespecified endpoints** | | | | | |
| Moderate and severe exacerbations | | | | | |
| Treated with antibiotics only | 0·27 (0·25-0·29) | 0·25 (0·23–0·27) | 1·07 | 0·96–1·20 | 0·21 |
| Treated with corticosteroids only | 0·14 (0·12–0·15) | 0·17 (0·15–0·19) | 0·80 | 0·68–0·94 | 0·0068 |
| Treated with antibiotics and corticosteroids in combination | 0·48 (0·45–0·52) | 0·53 (0·50–0·57) | 0·91 | 0·83–1·00 | 0·045 |
| Severe exacerbations | 0·24 (0·22–0·27) | 0·27 (0·25–0·30) | 0·89 | 0·78–1·02 | 0·090 |
| Exacerbations leading to hospitalisation | 0·18 (0·16–0·20) | 0·20 (0·18–0·22) | 0·89 | 0·76–1·03 | 0·13 |

Lancet Respir Med. 2018 May;6(5):337-344.

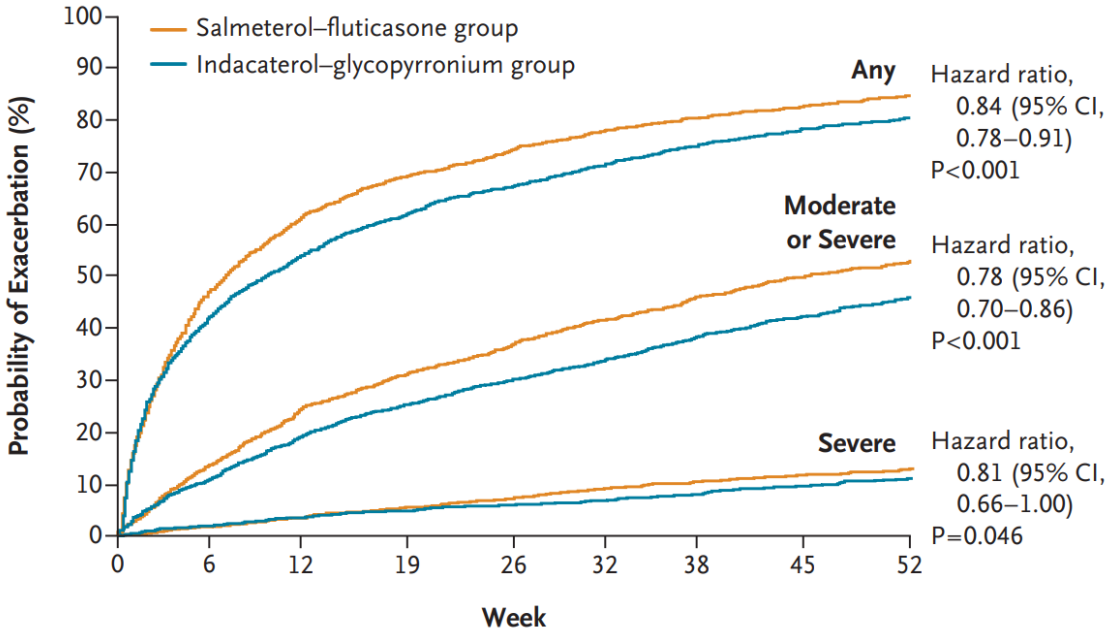
# FLAME trial

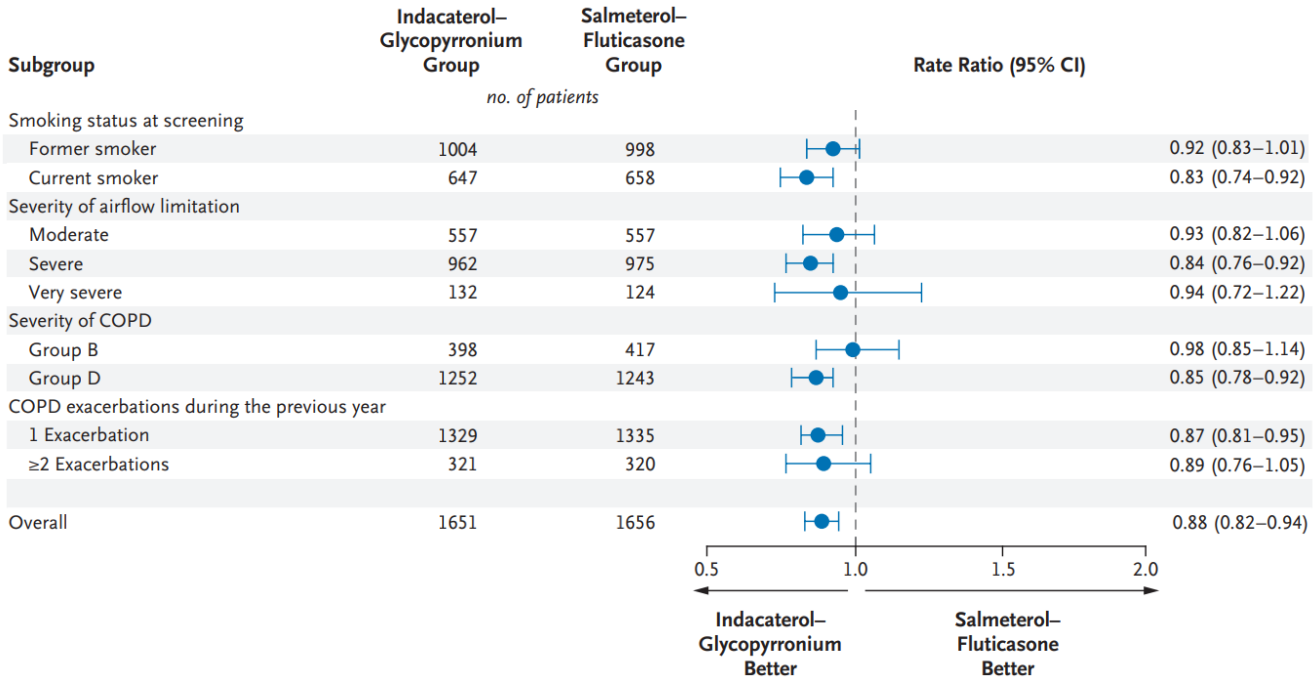
ORIGINAL ARTICLE

## Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

P: ≥40 YO, ≥10 PY, FEV1 25-60%, $FEV_1$/FVC≤0.7, **≥1 MtS AE, mMRC ≥2**
I: ING/GLY
C: FLU/SAL
O: MtS AE rate
Duration: 52wk

**MtS AE: LABA/LAMA > ICS/LABA (AE history + Sx)**



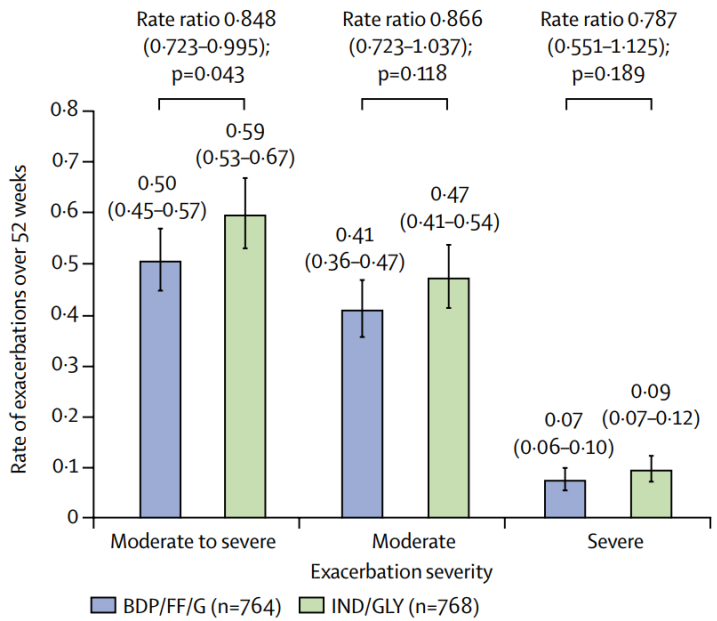



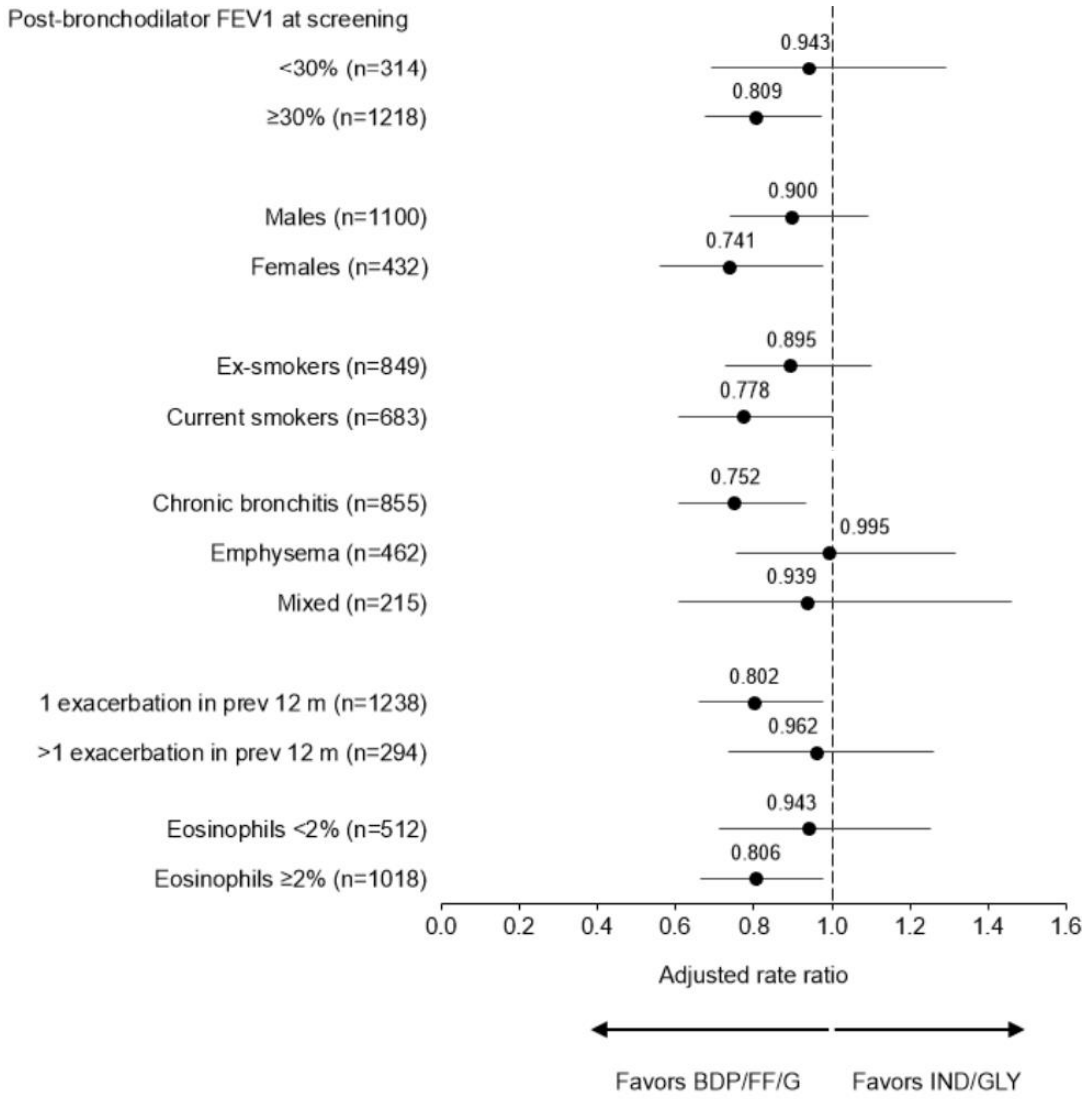

N Engl J Med. 2016 Jun 9;374(23):2222-34.

# TRIBUTE trial

**Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial**

P: ≥40 YO, Ever smoker, FEV1 <50%, $FEV_1$/FVC<0.7, **≥1 MtS AE, CAT ≥10**
I: BEC/FOR/GLY
C: IND/GLY
O: MtS AE rate
Duration: 52wk




**MtS AE: ICS/LABA/LAMA > LABA/LAMA (AE history + Sx)**

Lancet. 2018 Mar 17;391(10125):1076-1084.

# IMPACT trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 3, 2018 VOL. 378 NO. 18

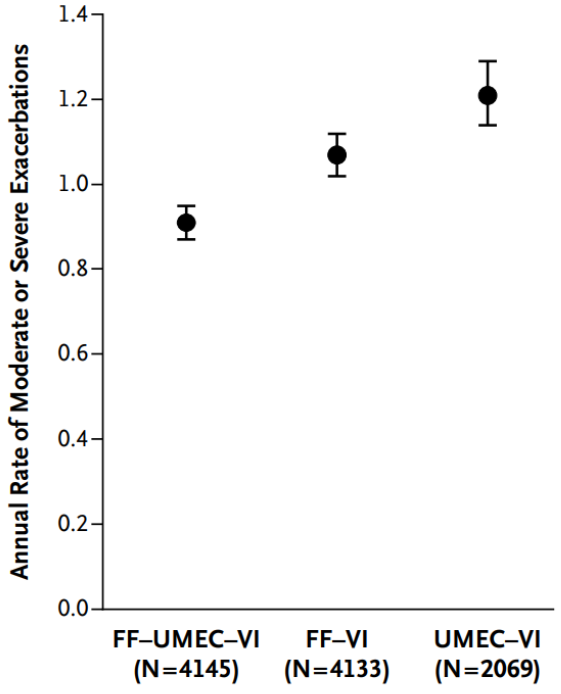
Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

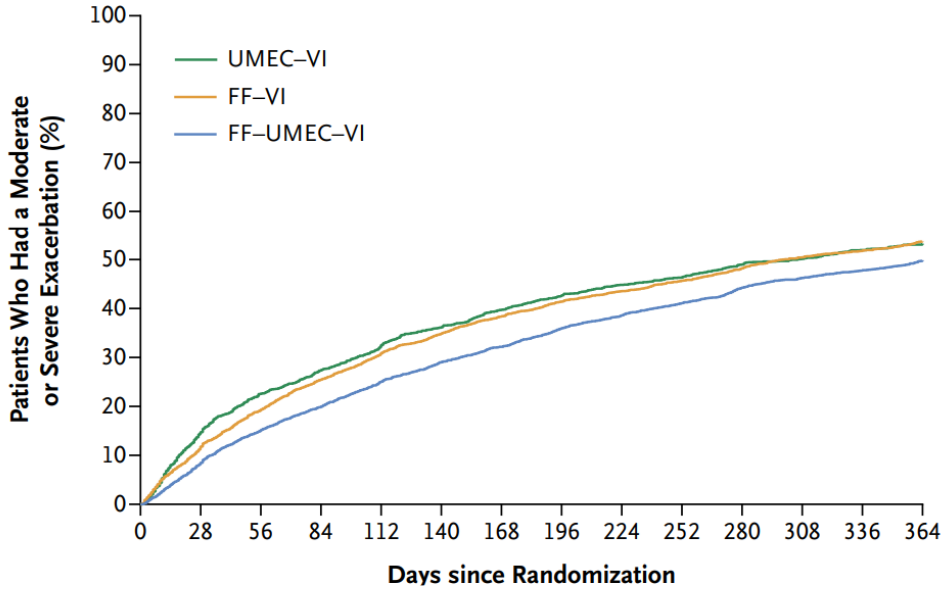
P: ≥40 YO, ≥10 PY, $FEV_1$/FVC<0.7, FEV1 <50% + **≥1 MtS AE** or FEV1 <50-80% + **≥2 M or 1 S AE**, **CAT ≥10**
I: UMEC/VIL/FF
C: FF/VIL, UMEC/VIL
O: MtS AE rate
Duration: 52wk

**MtS AE: ICS/LABA/LAMA > LABA/LAMA or ICS/LABA (AE history + Sx)**

**Triple vs. ICS/LABA**
RR=0.85 (0.80-0.90)

**Triple vs. LABA/LAMA**
RR=0.75 (0.70-0.81)




N Engl J Med. 2018 May 3;378(18):1671-1680.

# ETHOS trial

ORIGINAL ARTICLE

## Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

P: 40-80 YO, ≥10 PY, $FEV_1$/FVC<0.7, FEV1 25-65% + **≥1 MtS AE** or FEV1 ≥50% + **≥2 M or 1 S AE**, **CAT ≥10**
I: BUD (320ug / 160ug) /GLY/FOR
C: BUD (160ug) /FOR, GLY/FOR
O: MtS AE rate
Duration: 52wk

**MtS AE: ICS/LABA/LAMA > LABA/LAMA or ICS/LABA (AE history + Sx)**

| End Point | 320-μg–Budesonide Triple Therapy (N=2137) | 160-μg–Budesonide Triple Therapy (N=2121) | Glycopyrrolate–Formoterol (N=2120) | Budesonide–Formoterol (N=2131) |
|---|---|---|---|---|
| **Primary end point** | | | | |
| Primary analysis: model-estimated annual rate of moderate or severe COPD exacerbations | 1.08 | 1.07 | 1.42 | 1.24 |
| 320-μg–Budesonide triple therapy vs. comparators | | | | |
| Rate ratio for moderate or severe exacerbations (95% CI) | — | 1.00 (0.91–1.10) | 0.76 (0.69–0.83) | 0.87 (0.79–0.95) |
| P value† | | — | <0.001 | 0.003 |
| 160-μg–Budesonide triple therapy vs. comparators | | | | |
| Rate ratio for moderate or severe exacerbations (95% CI) | — | — | 0.75 (0.69–0.83) | 0.86 (0.79–0.95) |
| P value | | | <0.001 | 0.002 |

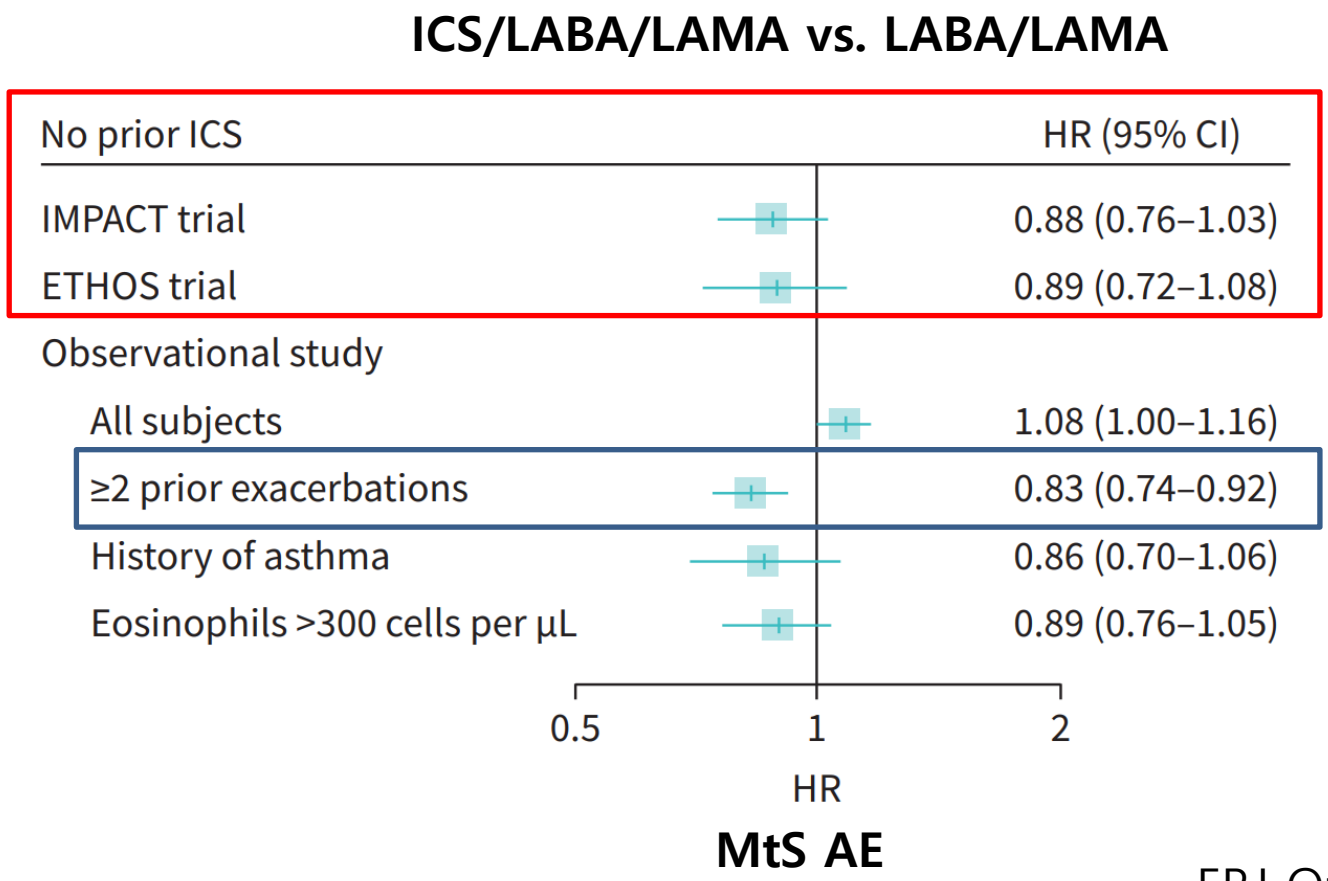
N Engl J Med. 2020 Jul 2;383(1):35-48.

# Comparison of TRIBUTE / IMPACT / ETHOS

| | TRIBUTE | IMPACT | ETHOS |
|---|---|---|---|
| **Intervention** | BEC/FOR/GLY | FLU/VIL/UMEC | BUD/FOR/GLY |
| **Device** | pMDI (Extrafine) | DPI | pMDI |
| **History of asthma** | Included | Included | Included |
| **Baseline ppFEV1** | 36% | 45% | 43% |
| **BDR** | 8.6% | 18% | 31% |
| **≥2 MtS exacerbation history** | 20% | 54% | 57% |
| **Blood eosinophil count** | 240/uL | 170/uL | 167/uL |
| **ICS discontinuation** | 65% | 70% | 80% |
| **Time to discontinuation of ICS** | 2-week run-in period | At randomization | At randomization |

# Triple therapy based on AE history

- COPD patients with **AE history** benefit from triple therapy compared to LABA/LAMA




ERJ Open Res. 2023 30;9(1):00615-2022

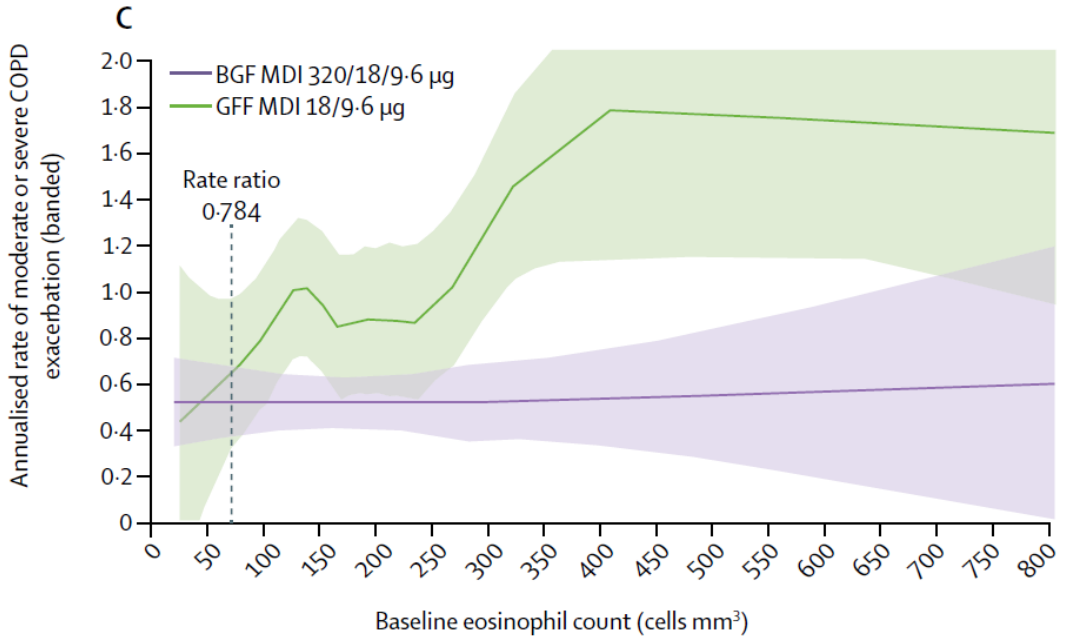
# KRONOS trial

## Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

P: 40-80 YO, ≥10 PY, $FEV_1$/FVC<0.7, FEV1 25-80%, **CAT ≥10**
I: BUD (320ug)/GLY/FOR
C: GLY/FOR, BUD (320ug)/FOR, Open BUD/FOR (DPI)
O: FEV1 $AUC_{0-4}$ at 24 wks, FEV1 change over 24 wks
Duration: 24wk

| | BGF MDI 320/18/9·6 µg (n=639) | GFF MDI 18/9·6 µg (n=625) | BFF MDI 320/9·6 µg (n=314) | Open-label BUD/FORM DPI 400/12 µg (n=318) |
|---|---|---|---|---|
| Moderate or severe COPD exacerbations in the past 12 months | | | | |
| 0 | 469 (73·4%) | 473 (75·7%) | 235 (74·8%) | 234 (73·6%) |
| 1 | 125 (19·6%) | 108 (17·3%) | 61 (19·4%) | 59 (18·6%) |
| ≥2 | 45 (7·0%) | 44 (7·0%) | 18 (5·7%) | 25 (7·9%) |

| | BGF MDI 320/18/9·6 µg | GFF MDI 18/9·6 µg | BFF MDI 320/9·6 µg | Open-label BUD/FORM DPI 400/12 µg |
|---|---|---|---|---|
| **Model-estimated rate of moderate or severe COPD exacerbations** | | | | |
| Number of patients | 639 | 625 | 314 | 318 |
| Rate, per year | 0·46 | 0·95 | 0·56 | 0·55 |
| Rate ratio (95% CI); p value* | NA | 0·48 (0·37 to 0·64); p<0·0001 | 0·82 (0·58 to 1·17); p=0·2792 | 0·83 (0·59 to 1·18); p=0·3120 |

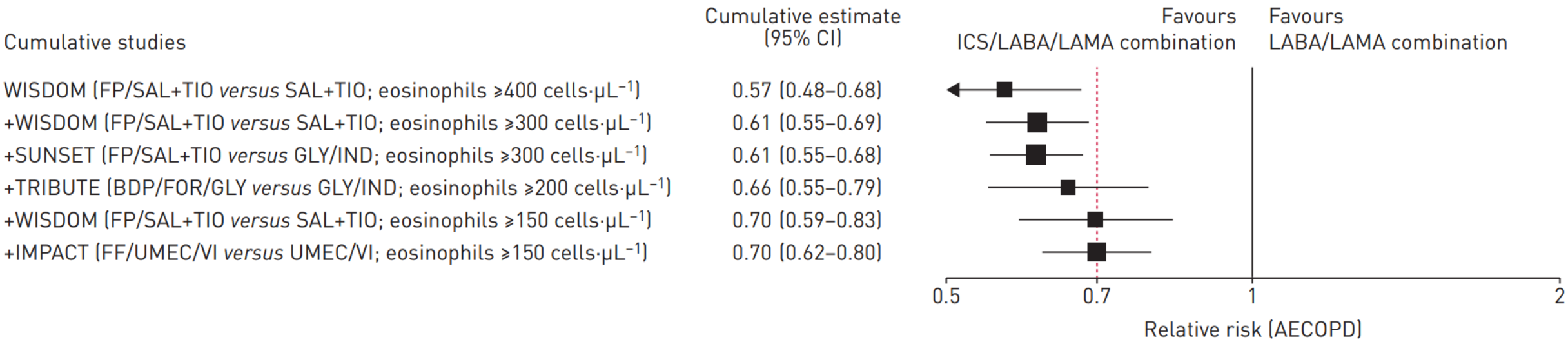



Lancet Respir Med. 2018 Oct;6(10):747-758.

# Triple therapy based on BEC

- COPD patients with **higher BEC** benefit from triple therapy compared to LABA/LAMA

## Meta-analysis




Eur Respir J. 2018 Dec 13;52(6):1801586.

# How do bronchodilators reduce AE?

**Most exacerbations** are considered to be of infectious etiology, leading to **increased small airway inflammation**

➔**The mechanisms** by which long-acting bronchodilators prevent exacerbations are **unclear**

**Many suggested mechanisms can be summarized as 3 categories**

1) Mucus clearance
2) Reduced inflammation
3) Better physical activity

# Current issues

- **COPD in never smoker**
- **COPD in the young**
- **Pre-COPD**
- **Early diagnosis (or screening) of COPD**

# Bronchiectasis with airway obstruction

## Tiotropium treatment for bronchiectasis: a randomised, placebo-controlled, crossover trial

P: Patients with **bronchiectasis** on HRCT, **$FEV_1/FVC<0.7$**,
≥1 MtS AE, **<20 pack-years**
I: Tiotropium handihaler (DPI)
C: Placebo
O: MtS AE rate
Duration: 26 weeks

**TABLE 1** Baseline characteristics

| | Sequence A: placebo–tiotropium (n=46) | Sequence B: tiotropium–placebo (n=44) |
|---|---|---|
| **Male** | 22 (48) | 12 (27) |
| **Age (years)** | 59.3±13.0 | 62.0±11.3 |
| **Smoking status** | | |
| Current/ex-smoker | 21 (46) | 16 (37) |
| Smoking history (pack-years)[#] | 6.0±5.7 | 6.0±5.3 |
| **Aetiology** | | |
| Idiopathic | 36 (78) | 31 (70) |
| Inflammatory bowel disease | 3 (7) | 2 (5) |
| Pink disease (infantile mercury exposure) | 0 (0) | 1 (2) |

Eur Respir J. 2022 Jun 9;59(6):2102184.

# Bronchiectasis with airway obstruction

**The annual rate of exacerbations**

- 2.17 per patient under tiotropium treatment
- 2.27 per patient under placebo
- **Rate ratio 0.96, 95% CI 0.72–1.27; p=0.77**

| | Placebo | Tiotropium | Difference in change adjusted for period (95% CI) | p-value |
|---|---|---|---|---|
| Exacerbation duration (days) | 19.6±14.6[#] | 21.7±16.9[#] | 2.4 (−1.5–6.2) | 0.49 |
| Time to first exacerbation (days) | 104 (80–136)[¶] | 74 (50–156)[¶] | 1.00 (0.68–1.46)[+] | 0.98 |

Eur Respir J. 2022 Jun 9;59(6):2102184.

# COPD in the young, Pre-COPD

## Future Steps for clinical trial

| | Young Patients with COPD | Pre-COPD |
|---|---|---|
| Potential outcomes to explore | • Rate of $FEV_1$ decline<br>• Time to first COPD exacerbation | • Time to onset of COPD<br>• Time to worsening in CAT (1 point) or SGRQ (4 points) |
| Study duration | • 3 yr | • 3–5 yr |
| Interim analysis at 6–12 mo (to assess dropping therapy arms and/or extending trial duration/ increase sample size) | • Rate of $FEV_1$ decline<br>• Time to first COPD exacerbation<br>• CAT change<br>• Composite outcomes* | • Rate of $FEV_1$ decline<br>• CAT change<br>• E-RS: COPD<br>• Others (impulse oscillometry and/or lung imaging: airways disease parameters; HCRU events; CompEx COPD)<br>• Composite outcomes* |
| Potential intervention arms | Currently approved medications for COPD | Currently approved medications for COPD as well as novel agents capable of modifying disease progression |
| Placebo control | No (as these are currently approved medications for airflow limitation with no age limits) | Yes (as these medications are not approved for this indication) |
| Study population as per the definition in the text (plus some other potential characteristics to consider in the study design to enrich the population studied) | • CAT score >10<br>• A respiratory HCRU event in 2 of the past 3 yr<br>• Biomarker enrichment† | • Individuals with NOCB symptoms as defined using the CAT or SGRQ<br>• A respiratory HCRU event in the past 24 mo<br>• Subjects with rapid $FEV_1$ decline<br>• Biomarker enrichment† |

Am J Respir Crit Care Med. 2022 Feb 1;205(3):275-287.

# RETHINC trial; Pre-COPD (Symptomatic smokers)

ORIGINAL ARTICLE

## Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function

P: Persons with ≥10 PY, **CAT ≥10, $FEV_1$/FVC>0.7**, FVC>70%
I: IND/GLY
C: PBO
O: Improvement of SGRQ score ≥4 points without treatment failure
Duration: 12wk

**Table 2. Efficacy Results for Continuous Outcomes.***

| Outcome | Treatment (N=227) | Placebo (N=244) |
|---|---|---|
| | Mean (95% CI) | |
| Change in questionnaire results from baseline to week 12 | | |
| SGRQ score | −7.7 (−9.4 to −5.9) | −8.9 (−10.6 to −7.2) |
| CAT score | −4.8 (−5.8 to −3.9) | −4.5 (−5.4 to −3.5) |
| TDI score† | 0.93 (0.59 to 1.27) | 0.92 (0.59 to 1.26) |
| Change in pulmonary function from baseline to week 12 | | |
| Inspiratory capacity — liters | 0.12 (0.07 to 0.18) | 0.02 (−0.03 to 0.08) |
| $FEV_1$ — liters | 0.04 (0.01 to 0.08) | −0.01 (−0.04 to 0.02) |
| Percent of predicted $FEV_1$ — percentage points | 2.48 (1.49 to 3.47) | −0.09 (−1.06 to 0.89) |
| $FEF_{25–75}$ — liters/sec | 0.07 (0.00 to 0.15) | −0.08 (−0.15 to 0.00) |
| $AUC_{0–3hr}$ for $FEV_1$ at week 12 — liters | 8.09 (7.99 to 8.20) | 7.82 (7.72 to 7.92) |
| Outcomes from daily diary — % of days | | |
| Any symptoms or use of albuterol | 67.0 (59.0 to 75.0) | 63.6 (55.7 to 71.5) |
| Shortness of breath | 30.7 (23.6 to 37.7) | 32.5 (25.6 to 39.4) |
| Chest tightness | 21.2 (15.0 to 27.4) | 23.5 (17.4 to 29.6) |
| Wheezing | 23.5 (17.8 to 29.2) | 24.3 (18.7 to 29.8) |
| Cough | 53.1 (45.9 to 60.2) | 48.0 (41.1 to 54.9) |
| Sputum | 45.1 (37.7 to 52.5) | 43.4 (36.1 to 50.6) |
| Use of albuterol | 9.3 (5.0 to 13.6) | 9.7 (5.5 to 14.0) |

**No difference in daily symptom worsening**

N Engl J Med. 2022 Sep 29;387(13):1173-1184.

# Mild COPD (GOLD stage I, $FEV_1$>80%)

- **No clinical trial only for mild COPD**

**MISTRAL Study**

In COPD patients **with AE history**

**TABLE 3** Number of exacerbations per patient per year according to chronic obstructive pulmonary disease (COPD) severity and exacerbation history at baseline, and ICS use during the trial

| | Tiotropium | Placebo | p-value |
|---|---|---|---|
| **COPD severity** | | | |
| $FEV_1$ >50% pred* | 1.21 (0.27) | 1.97 (0.50) | <0.01 |
| $FEV_1$ ⩽50% pred# | 1.83 (0.22) | 2.70 (0.35) | <0.05 |

Eur Respir J. 2006 Mar;27(3):547-55.

**Tie-COPD Study**

In COPD patients **with $FEV_1$>50%**

**Table S12. Summary of AECOPD and COPD hospitalizations in subgroup stratified by CAT scores.***

| | Placebo | | Tiotropium | | Relative Risk for Tiotropium vs. Placebo | |
|---|---|---|---|---|---|---|
| **Variables** | **N** | **Mean (SE)** | **N** | **Mean (SE)** | **(95% CI)** | **P values** |
| CAT<10 | | | | | | |
| Exacerbation, no. per patient-year† | | | | | | |
| Total | 288 | 0.41±0.04 | 276 | 0.22±0.03 | 0.55(0.38 to 0.79) | 0.0013 |
| Moderate and over | 288 | 0.30±0.04 | 276 | 0.16±0.03 | 0.53(0.35 to 0.79) | 0.0017 |
| Hospitalization, per patient-year† | 278 | 0.05±0.01 | 268 | 0.02±0.01 | 0.33(0.11 to 0.95) | 0.0397 |

N Engl J Med. 2017 Sep 7;377(10):923-935.

# Early diagnosis of COPD

- **No consensus definition exists for early diagnosis of COPD**
- **However, it is generally accepted that**

**“Early diagnosis happens when an individual undergoes targeted assessment for COPD and the disease is identified before a conventional diagnosis is made by the individual’s healthcare professionals”**

Am J Respir Crit Care Med. 2024 Apr 15;209(8):928-937.

# Early diagnosis and treatment

P: ≥18 YO, Symptoms (Cough, Sputum, Dyspnea, Wheezing) within 6m
**- Asthma Screening Questionnaire ≥6**
**- COPD Diagnostic Questionnaire ≥20**

I: Pulmonologist / Educator following guideline-based care
- **Pharmacologic** and **nonpharmacologic treatment** from GINA 2017 and GOLD 2017

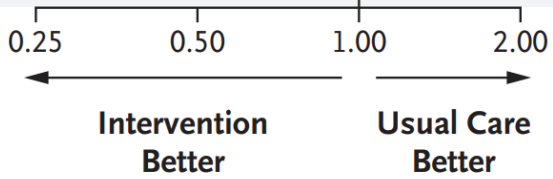
C: Primary care
O: Health care utilization events
Duration: 1yr

ORIGINAL ARTICLE

Early Diagnosis and Treatment of COPD and Asthma — A Randomized, Controlled Trial

Patient-initiated **health care utilization events** for respiratory illness over 1 year

| Group | Intervention | Usual Care | Incidence Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of participants/events per person-yr* | | | |
| Overall | 253/0.53 | 255/1.12 | 0.48 (0.36–0.63) | <0.001 |
| Asthma subgroup | 123/0.61 | 127/1.23 | 0.49 (0.33–0.73) | |
| COPD subgroup | 130/0.46 | 128/1.01 | 0.46 (0.31–0.67) | |




N Engl J Med. 2024 May 19. Online ahead of print.

# Early diagnosis and treatment

## Case-Finding Questionnaire

| Question Items | Score* |
|---|---|
| Age group, yr | |
| 40–49 (reference) | 0 |
| 50–59 | 4 |
| 60–69 | 8 |
| 70+ | 10 |
| Body mass index, kg/m$^2$ | |
| < 24 (reference) | 5 |
| 25.4–29.7 | 1 |
| > 29.7 | 0 |
| Smoking intensity, pack-yr | |
| 0–14 (reference) | 0 |
| 15–24 | 2 |
| 25–49 | 3 |
| 50+ | 7 |
| Symptoms/history | |
| Weather affects cough | 3 |
| Phlegm without a cold | 3 |
| Phlegm in the morning | 3 (no) |
| Wheeze frequency (any) | 4 |
| Have or had any allergies | 3 (no) |

Chest. 2006 Jun;129(6):1531-9.

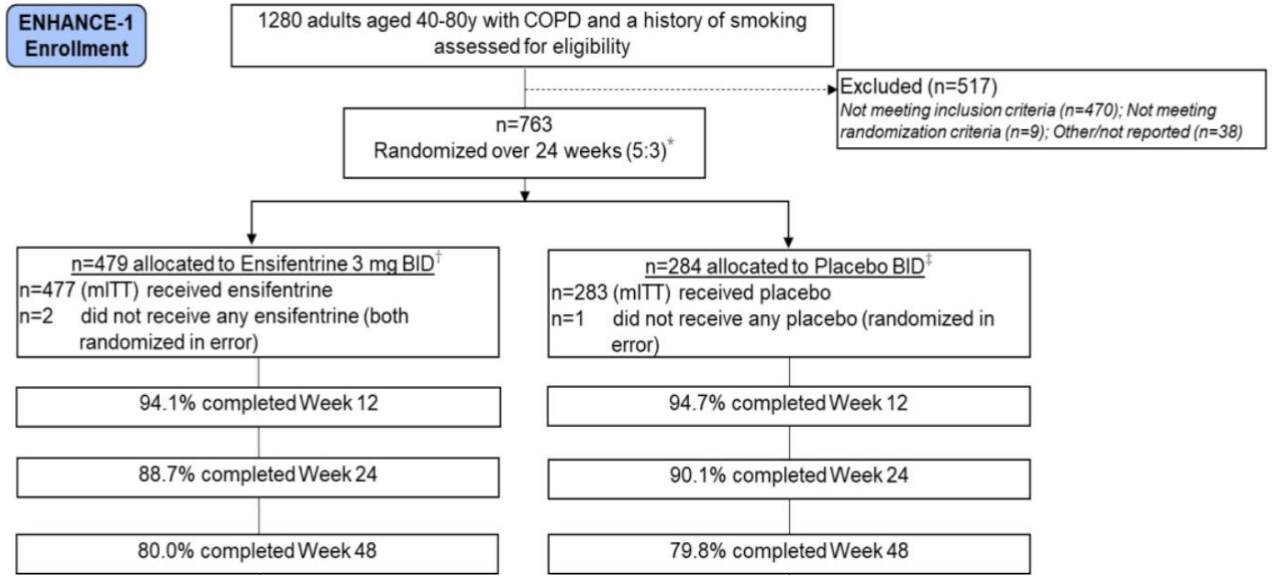
| COPD Subgroup | | Intervention Arm N=130 | Control Arm N=128 |
|---|---|---|---|
| Age (Years) * | | 66.8 (10.0) | 65.9 (10.8) |
| Male | | 65% | 64% |
| **Pre-bronchodilator spirometry** | | | |
| | FEV1 L | 2.00 (0.65) | 2.01 (0.69) |
| | FEV1 % pred | 70.0 (16.6) | 69.8 (16.4) |
| | FEV1/FVC | 0.57 (0.09) | 0.58 (0.08) |
| **Post-bronchodilator spirometry** | | | |
| | FEV1 L | 2.17 (0.67) | 2.16 (0.72) |
| | FEV1 % pred | 75.7 (16.0) | 75.2 (16.5) |
| | FEV1/FVC | 0.59 (0.09) | 0.60 (0.09) |
| **Smoking status** | | | |
| | Lifetime non-smokers | 13% | 12% |
| | Previous smokers | 49% | 51% |
| | Current smokers | 38% | 37% |

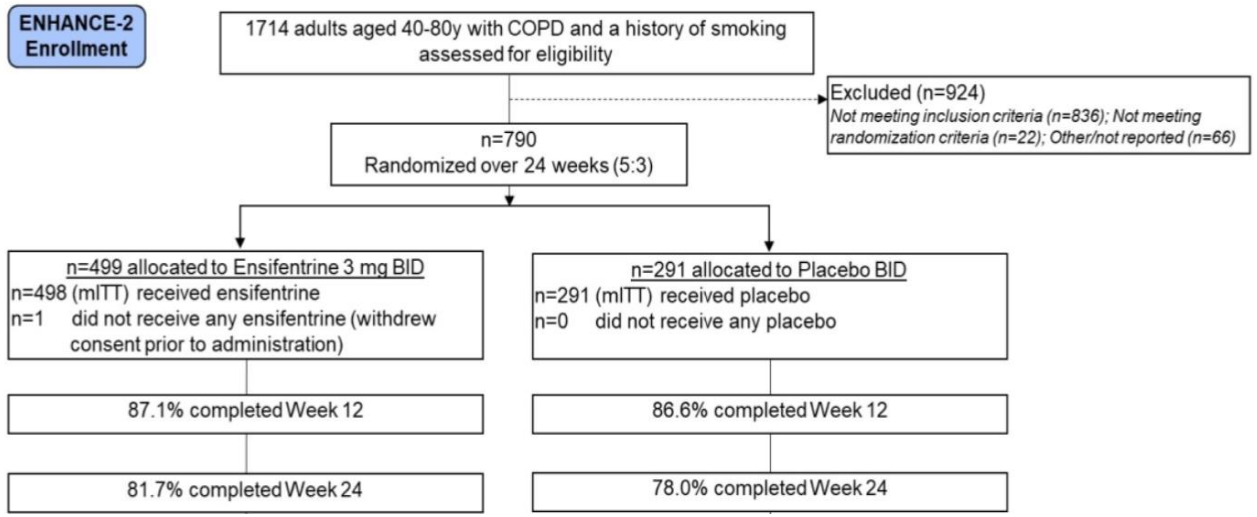
N Engl J Med. 2024 May 19. Online ahead of print.

# Ensifentrine (PDE-3/4 dual-inhibitor)

## Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease (the ENHANCE Trials)

ENHANCE-1, 2 studies, Phase 3 trials, 48wk & 24wk
P: COPD patients, 40-80 YO, ≥10 PY, $FEV_1$ 30-70%, mMRC ≥2 (**predominantly GOLD B**)
I: **Ensifentrine** 3mg bid via a **standard jet nebulizer**
C: Placebo
O: $FEV_1$ improvement at 12wk




Am J Respir Crit Care Med. 2023 Aug 15; 208(4): 406–416.

# Ensifentrine (PDE-3/4 dual-inhibitor)

**Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease (the ENHANCE Trials)**

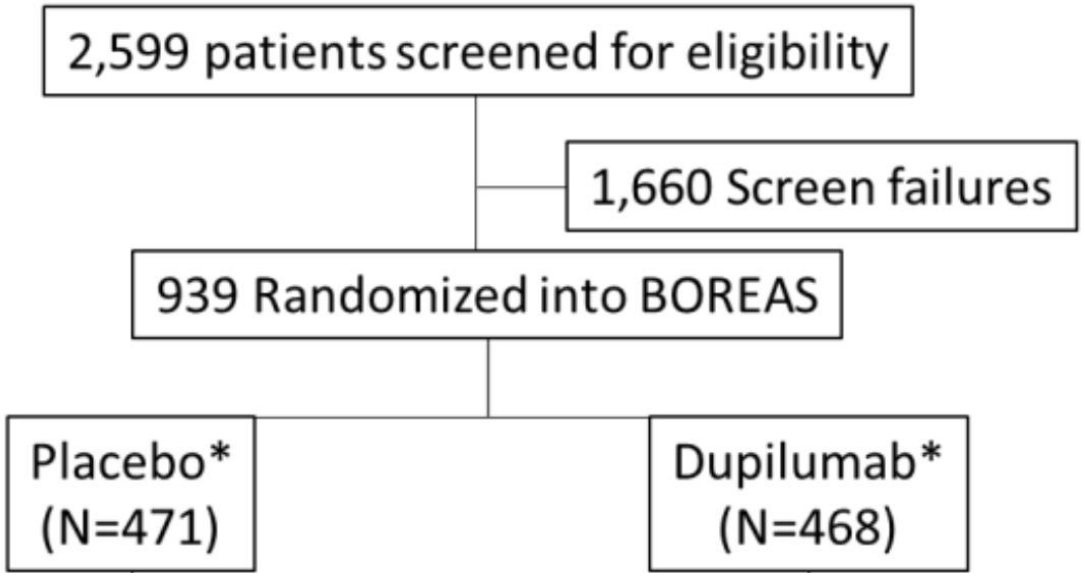
| Treatment Group | ENHANCE-1 | | ENHANCE-2 | |
|---|---|---|---|---|
| | Ensifentrine 3 mg BID (*n* = 477) | Placebo BID (*n* = 283) | Ensifentrine 3 mg BID (*n* = 498) | Placebo BID (*n* = 291) |
| Moderate or severe COPD exacerbations over 24 wk | | | | |
| Annualized exacerbation event rate, LS mean (95% CI) | 0.26 (0.17, 0.40) | 0.41 (0.27, 0.63) | 0.24 (0.18, 0.32) | 0.42 (0.30, 0.57) |
| Rate ratio (95% CI) | 0.64 (0.40, 1.00) | — | 0.57 (0.38, 0.87) | — |
| *P* value | 0.050 | — | 0.009 | — |
| Time to first event | | | | |
| Log-rank test vs. placebo | *P* = 0.041 | — | *P* = 0.011 | — |
| Hazard ratio (95% CI) | 0.62 (0.39, 0.97) | — | 0.58 (0.38, 0.87) | — |
| *P* value | 0.038 | — | 0.009 | — |
| Moderate or severe COPD exacerbations over 48 wk | Ensifentrine (*n* = 280) | Placebo (*n* = 89) | — | — |
| Annualized exacerbation event rate, LS mean (95% CI) | 0.25 (0.13, 0.48) | 0.44 (0.22, 0.87) | — | — |
| Rate ratio (95% CI) | 0.56 (0.32, 1.00) | — | — | — |
| *P* value | 0.052 | — | — | — |
| Time to first event | | | | |
| Log-rank test vs. placebo | *P* = 0.014 | — | — | — |
| Hazard ratio (95% CI) | 0.48 (0.28, 0.82) | — | — | — |
| *P* value | 0.007 | — | — | — |

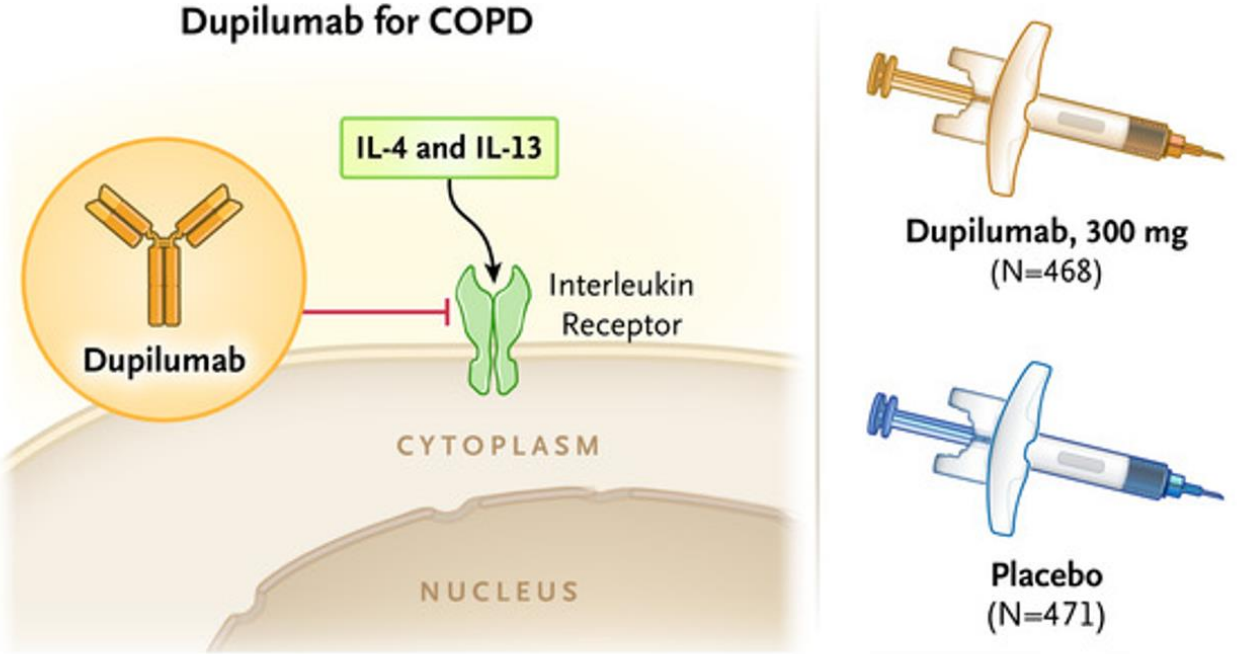
Am J Respir Crit Care Med. 2023 Aug 15; 208(4): 406–416.

# Dupilumab (Anti-IL4Rα): BOREAS study

## Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

P: COPD patients with 40-80 YO, ≥10 PY, $FEV_1$:30-70%, mMRC ≥2, on ICS/LABA/LAMA, **Chronic bronchitis, BEC ≥300/uL**, history of 2 moderate or 1 severe AE, (Asthma excluded)
I: Dupilumab 300mg SC q 2wk
C: Placebo
O: Annual rate of moderate-to-severe exacerbation
Duration: 48 weeks



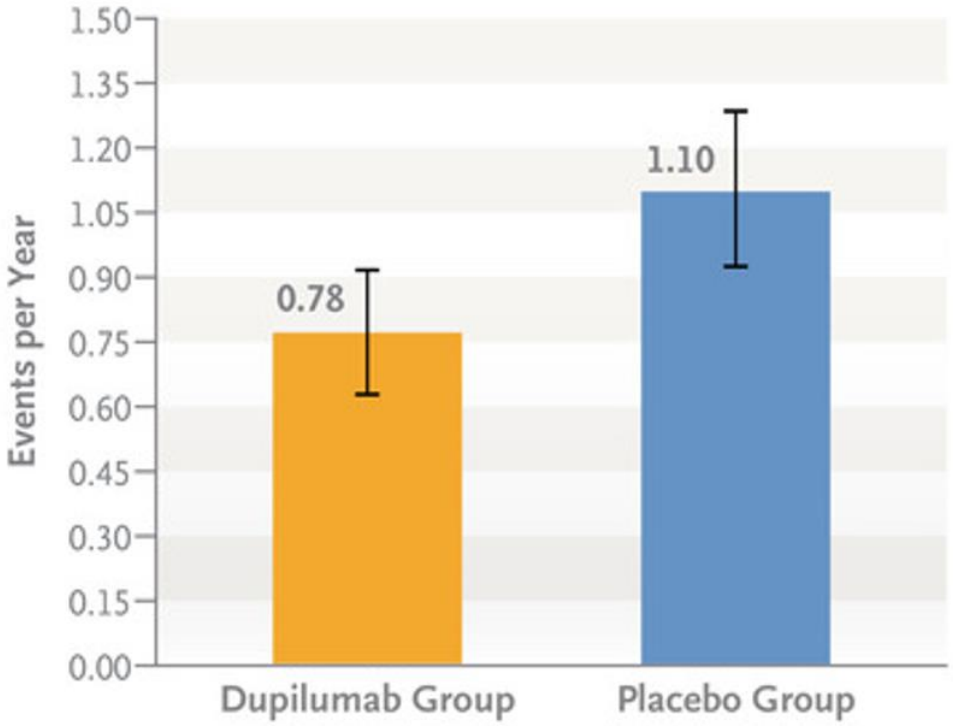

N Engl J Med. 2023 Jul 20;389(3):205-214.

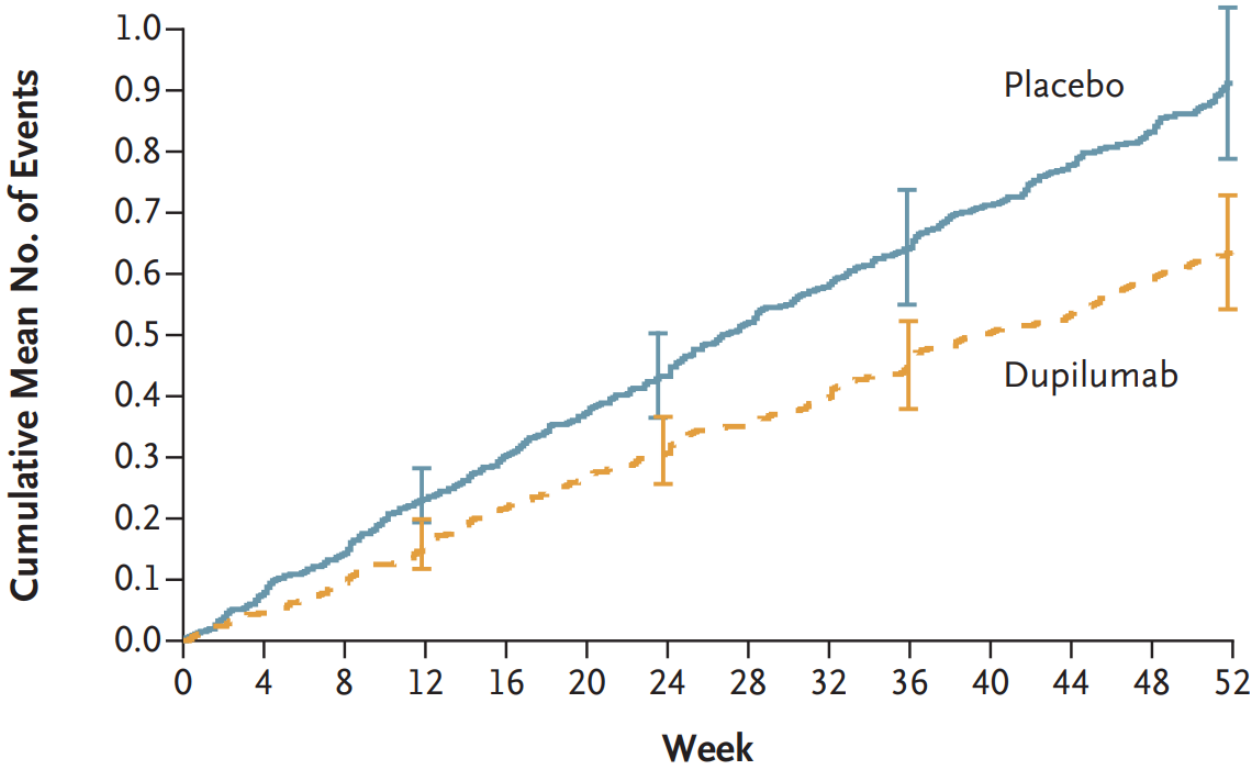
# Dupilumab (Anti-IL4Rα): BOREAS study

**Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts**

- The annualized rate of moderate to severe exacerbation was reduced in Dupilumab group

**Rate ratio, 0.70; 95% CI, 0.58-0.86; P<0.001**



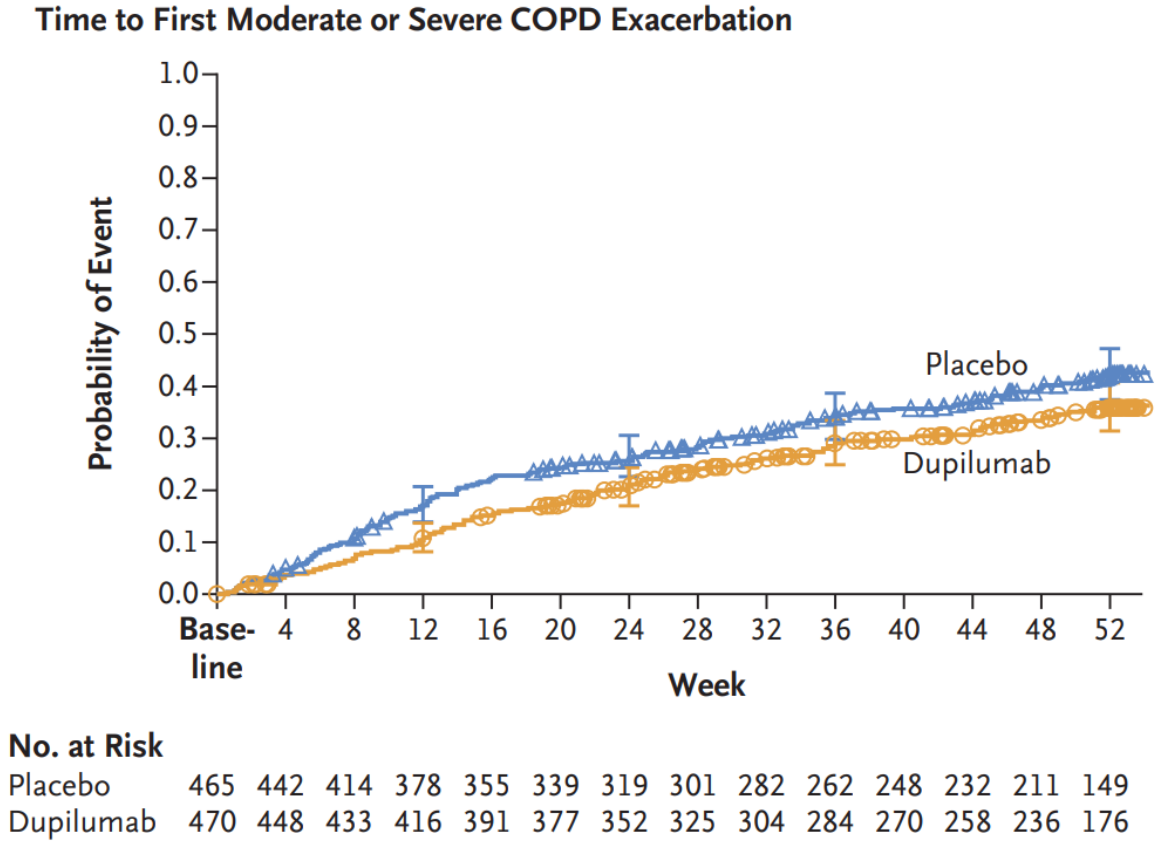

N Engl J Med. 2023 Jul 20;389(3):205-214.

# Dupilumab (Anti-IL4Rα): NOTUS study

## Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation

P: COPD patients with 40-80 YO, ≥10 PY, $FEV_1$:30-70%, mMRC ≥2, on ICS/LABA/LAMA, **Chronic bronchitis, BEC ≥300/uL**, history of 2 moderate or 1 severe AE, (Asthma excluded), **stratified by smoking status**
I: Dupilumab 300mg SC q 2wk
C: Placebo
O: Annual rate of moderate-to-severe exacerbation
Duration: 52 weeks

| | Placebo (N=465) | Dupilumab (N=470) | P Value |
|---|---|---|---|
| **MtS AE rate** | 1.30 (1.05 to 1.60) | 0.86 (0.70 to 1.06) | |
| **Rate ratio** | — | 0.66 (0.54 to 0.82) | <0.001 |

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# Tezepelumab (Anti-TSLP ab): COURSE study

COURSE study, Phase 2a trials, 52wk
P: COPD patients, 40-80 YO, ≥10 PY, $FEV_1$ 20-80%, ≥2 MtS AE, **CAT ≥15,** on ICS/LABA/LAMA, (**Asthma excluded**)
I: **Tezepelumab** 420mg SC q4W
C: Placebo
O: MtS AE rate

**COURSE Phase IIa analysis:**
**Table 1: Tezepelumab impact on COPD exacerbations versus placebo over 52 weeks[1]**

| | Reduction in exacerbations compared to placebo | Annualised rate of exacerbations |
|---|---|---|
| ***Moderate or severe exacerbations*** | | |
| **Overall population** (n=333) | 17% (90% CI: -6, 36) | 1.75 in tezepelumab group versus 2.11 in placebo group |
| **BEC less than 150 cells/µL** (n=137) | -19% (95% CI: -90, 25) | 2.04 in tezepelumab group versus 1.71 in placebo group |
| **BEC greater than or equal to 150 cells/µL** (n=196) | 37% (95% CI: 7, 57) | 1.52 in tezepelumab group versus 2.40 in placebo group |
| **BEC greater than or equal to 300 cells/µL** (n=56) | 46% (95% CI: -15, 75) | 1.20 in tezepelumab group versus 2.24 in placebo group |
| ***Severe exacerbations*** | | |
| **Overall population** (n=333) | 48% (95% CI: -11, 76) | 0.13 in tezepelumab group versus 0.25 in placebo group |

https://www.astrazeneca.com/

# Summary

- **Concept of AE-COPD**
  - AE-COPD refers to a sudden worsening of COPD symptoms that requires additional therapy or hospitalization, and is associated with increased mortality

- **A review of major clinical trials for AE-COPD**
  - Major clinical trials for AE-COPD explore various pharmacologic interventions to reduce exacerbations and improve patient outcomes
  - Group A: Long-acting bronchodilator
  - Group B: LABA/LAMA
  - Group E: LABA/LAMA, ICS/LABA/LAMA (AE Hx. + High BEC)

- **Mechanisms of bronchodilators reducing AE-COPD**
  - Bronchodilators reduce AE-COPD by improving mucus clearance, reducing inflammation, and enhancing physical activity

# Summary

- **Current pharmacologic issues on AE-COPD**
  - Current issues include managing COPD in non-smokers, young patients, early diagnosis of COPD, and Pre-COPD

- **Upcoming treatments for AE-COPD**
  - Upcoming treatments for AE-COPD include novel agents like ensifentrine, dupilumab, and tezepelumab, which target different inflammatory pathways

# Thank you for your attention

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