Asthma-COPD Overlap

The Real-World Evidence in Taiwan

胸腔重症 蘇一峰醫師

--最佳研究論文獎--

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台灣胸腔暨重症學會、台灣重症醫學會、
台灣睡眠醫學會、台灣結核病學會
2019 ATS - 美國肺氣腫基金會

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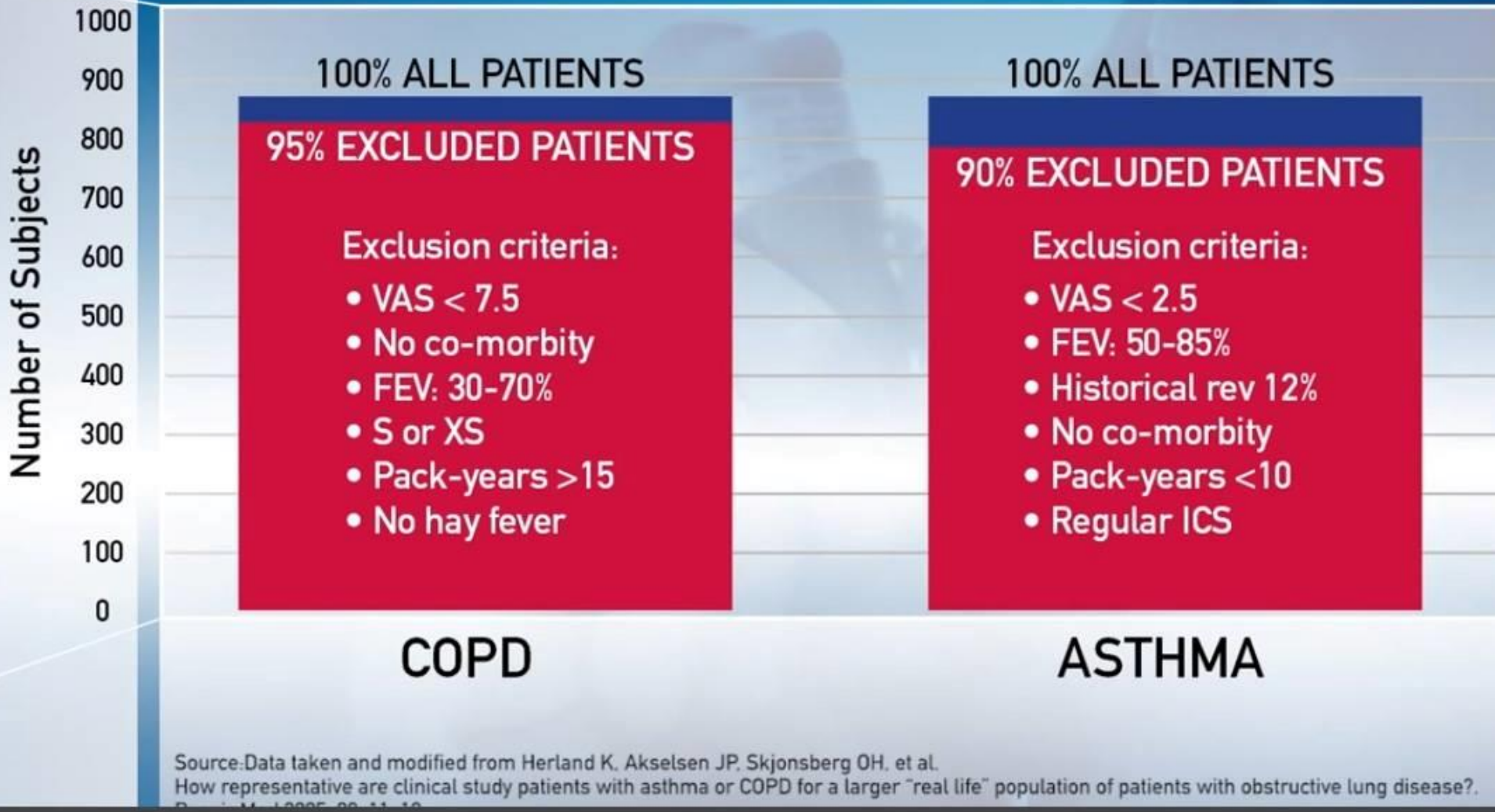
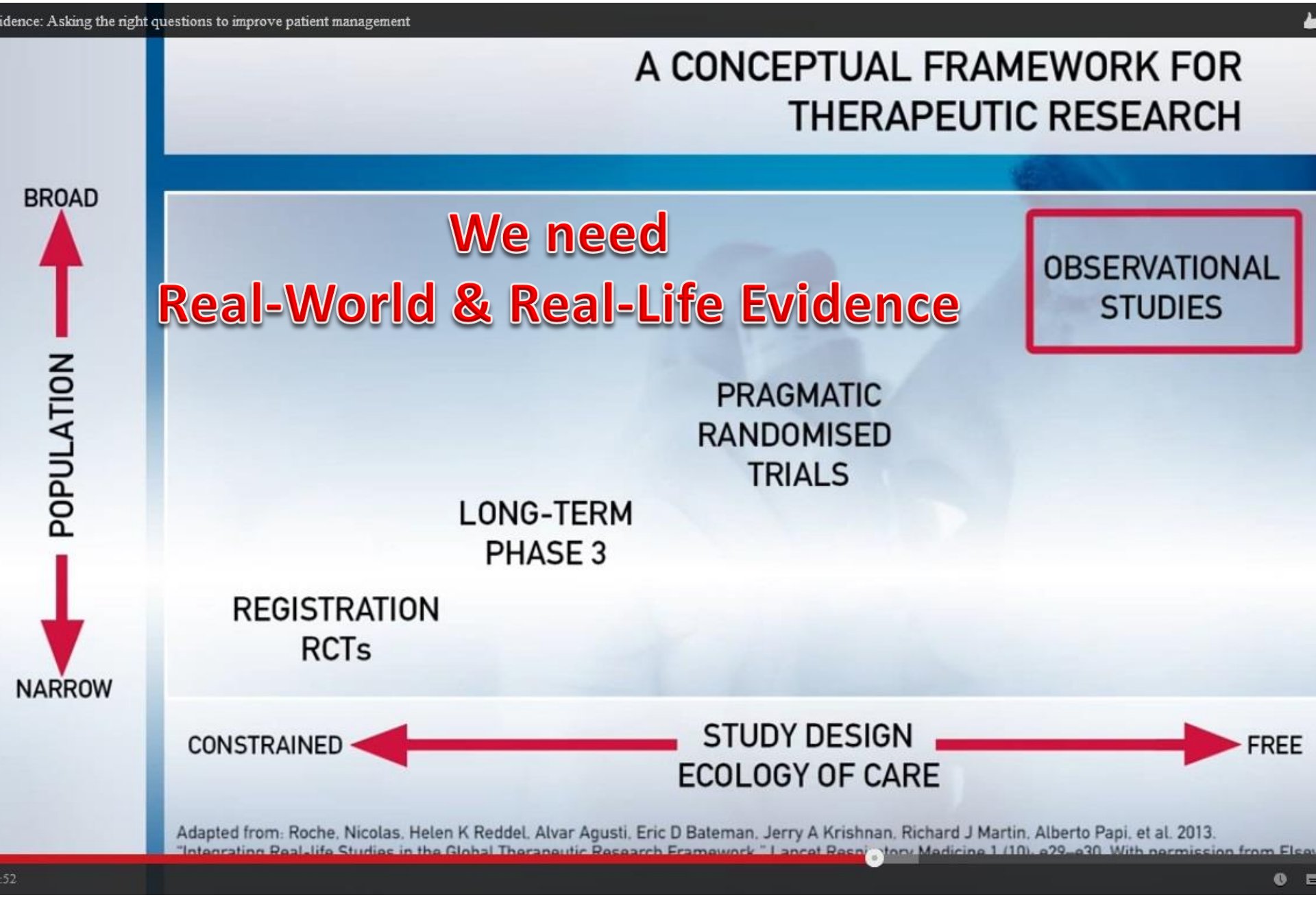
Are
Randomised Controlled Trials
achieving the results we need
for patients?

Selection of Patients for Typical Randomised Controlled Trial



Source:Data taken and modified from Herland K. Akselsen JP. Skjonsberg OH. et al.
How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease?.


A CONCEPTUAL FRAMEWORK FOR THERAPEUTIC RESEARCH
BROAD
POPULATION
NARROW
We need
Real-World & Real-Life Evidence
OBSERVATIONAL STUDIES
PRAGMATIC RANDOMISED TRIALS
LONG-TERM PHASE 3
REGISTRATION RCTs
CONSTRAINED
STUDY DESIGN ECOLOGY OF CARE
FREE
Adapted from: Roche, Nicolas, Helen K Reddel, Alvar Agusti, Eric D Bateman, Jerry A Krishnan, Richard J Martin, Alberto Papi, et al. 2013.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

N Engl J Med 2016; 374:2222-2234

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female adults aged ≥40 years.
3. Patients with stable COPD according to the current GOLD strategy (GOLD 2011).
4. Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years).
5. Patients with a **post**-bronchodilator FEV_1 ≥25 and < 60% of the predicted normal value, and **post**-bronchodilator $FEV_1/FVC < 0.70$ at Visit 101 (day -28).

   (**Post** refers to 1 h after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol).
6. A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics.
7. Patients taking stable COPD medication (at least 60 days) prior to Visit 101.
8. Patients with an mMRC grade of at least 2 at Visit 101 (day -28).

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG (human Chorionic Gonadotropin) laboratory test.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
   - Total abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
   - Female sterilization defined as surgical hysterectomy, bilateral oophorectomy, or tubal ligation at least six weeks before taking the study treatment (Single oophorectomy does not meet the definition of female sterilization).
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
   - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS).

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
3. Patients with Type I or uncontrolled Type II diabetes.
4. Patients with a history of long QT syndrome or whose QTc measured at Visit 101 (Fridericia method) is prolonged (>450 ms for males and females) and confirmed by a central assessor. These patients should not be re-screened.
5. Patients who have a clinically significant ECG abnormality at Visit 101 or Visit 201. (These patients should not be re-screened)
6. Patients who have a clinically significant laboratory abnormality at Visit 101.
7. Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.
8. Patients with paroxysmal (e.g. intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 101 and Visit 102 with a resting ventricular rate < 100/min. At Visit 101 the atrial fibrillation must be confirmed by central reading.
9. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
   - anticholinergic agents
   - long and short acting beta-2 agonists
   - sympathomimetic amines
   - lactose or any of the other excipients of trial medication
10. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
11. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered.
12. Patients who have not achieved an acceptable spirometry results at Visit 101 in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria).
13. Patients who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1.
14. Patients who develop a COPD exacerbation of any severity (mild/moderate/severe) between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
15. Patients who have had a respiratory tract infection within 4 weeks prior to screening Visit 1.
16. Patients who develop a respiratory tract infection between screening and prior to treatment will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
17. Patients requiring long term oxygen therapy prescribed for >12 hours per day.
18. Patients with any history of asthma.
19. Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years.
20. Patients with a blood eosinophil count > 600/mm^3 at Visit 101.
21. Patients with allergic rhinitis who use a H_1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen is permitted).
22. Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension).
23. Patients with clinically significant bronchiectasis.

N Engl J Med 2016; 374:2222-2234

24. Patients with a diagnosis of α-1 anti-trypsin deficiency.
25. Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active.
26. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
27. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. (Maintenance program is permitted.)
28. Patients receiving any medications in the classes listed in Table 5-1.
29. Patients receiving any COPD related medications in the classes specified in Table 5-2 must undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.
30. Patients receiving medications in the classes listed in Table 5-3 should be excluded unless the medication has been stable for the specified period and the stated conditions have been met.
31. Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
32. Patients unable to use an electronic patient diary and EXACT pro diary.
33. Patients unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication) or comply with the study regimen.

Table 5-2 Prohibited COPD-related medications during the trial

Class of Medication[1]	Minimum washout period prior to Visit 101 (Run-in)
Long-acting muscarinic antagonist(LAMA)[2]	3 days
Short acting muscarinic antagonist (SAMA)[2]	8 hours
Fixed combinations of long-acting β_2 agonists and inhaled corticosteroids (LABA/ICS) and ICS not part of a fixed dose combination	48 hours
Fixed combinations of short-acting β_2 agonists and short-acting muscarinic antagonist (SABA/SAMA)	8 hours
Long-acting β_2 agonists (LABA)	48 hours (indacaterol requires 3 days)
Short-acting β_2 agonists (SABA)[3]	6 hours
Oral Phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Parenteral or oral corticosteroids	30 days
Intra-muscular depot corticosteroids	3 months

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.
[2]LAMA and SAMA prohibited with the exception of prescribed tiotropium and ipratropium during the screening and run-in epochs only.
[3]SABA prohibited with exception of study rescue medication (see Section 5.5.4).
All of these medications are permitted for the treatment of a COPD exacerbation during the study except depot corticosteroids. If depot corticosteroid treatment is required, the patient should be withdrawn from the study treatment.

N Engl J Med 2016; 374:2222-2234

Table 5-1 Prohibited Medications

Class of Medication[1]	Minimum cessation period prior to Visit 101 (Run-in)
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Non-selective systemic beta-blocking agents[2]	7 days
Cardiac anti-arrhythmics Class Ia	7 days
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months
Other drugs with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Tricyclic antidepressants (Please note that tetracyclics, which are similar in class with regards to drug interaction are also to be excluded)	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics)	14 days
Combinations of antipsychiotic agents with antidepressants are prohibited	
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days
Other noradrenaline reuptake inhibitors	14 days
Monoamine-oxidase inhibitors	14 days
Live attenuated vaccine	30 days
Antibiotics (long term maintenance)[3]	30 days
Systematic Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	7 days
Systemic anticholinergics	7 days
IgE inhibitors (e.g., Xolair)	6 months
Leukotriene antagonists and leukotriene synthesis inhibitors	7 days

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.
[2] Selective β_1 blocking agents are permitted.
[3] Short course of antibiotics is permitted during the study.
The washout of these prohibited medications is not to be encouraged.

Table 5-3 Medication allowed under certain conditions if taken as follows

Class of Medication[1]	Condition under which medication is permitted
Selective Serotonin Reuptake Inhibitors	Stable dose for at least 30 days prior to Visit 101 (Run-in) and during the trial.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Visit 101
H_1-antagonists	(Run-in). Stable dose/regimen for at least 5 days prior to Visit 101 (Run-in). (Except mizolastin or, terfenadine)
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to a trial visit

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

RCT trials VS Real-World

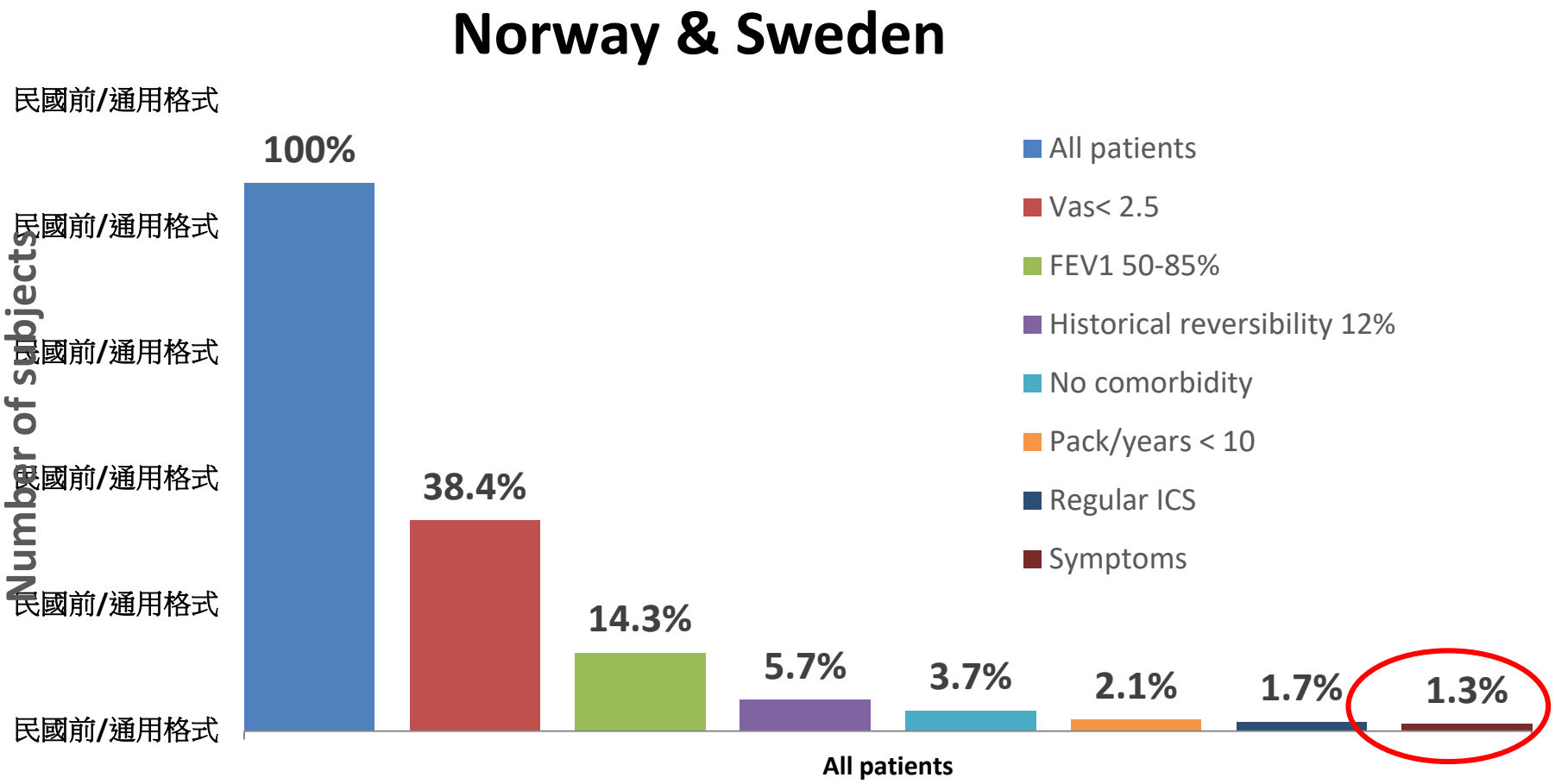


Figure 1 Number of subjects remaining as eligible asthma clinical trial patients, after applying various selection criteria.

Herland K., et al. Respir Med 2005;99(1):11-9

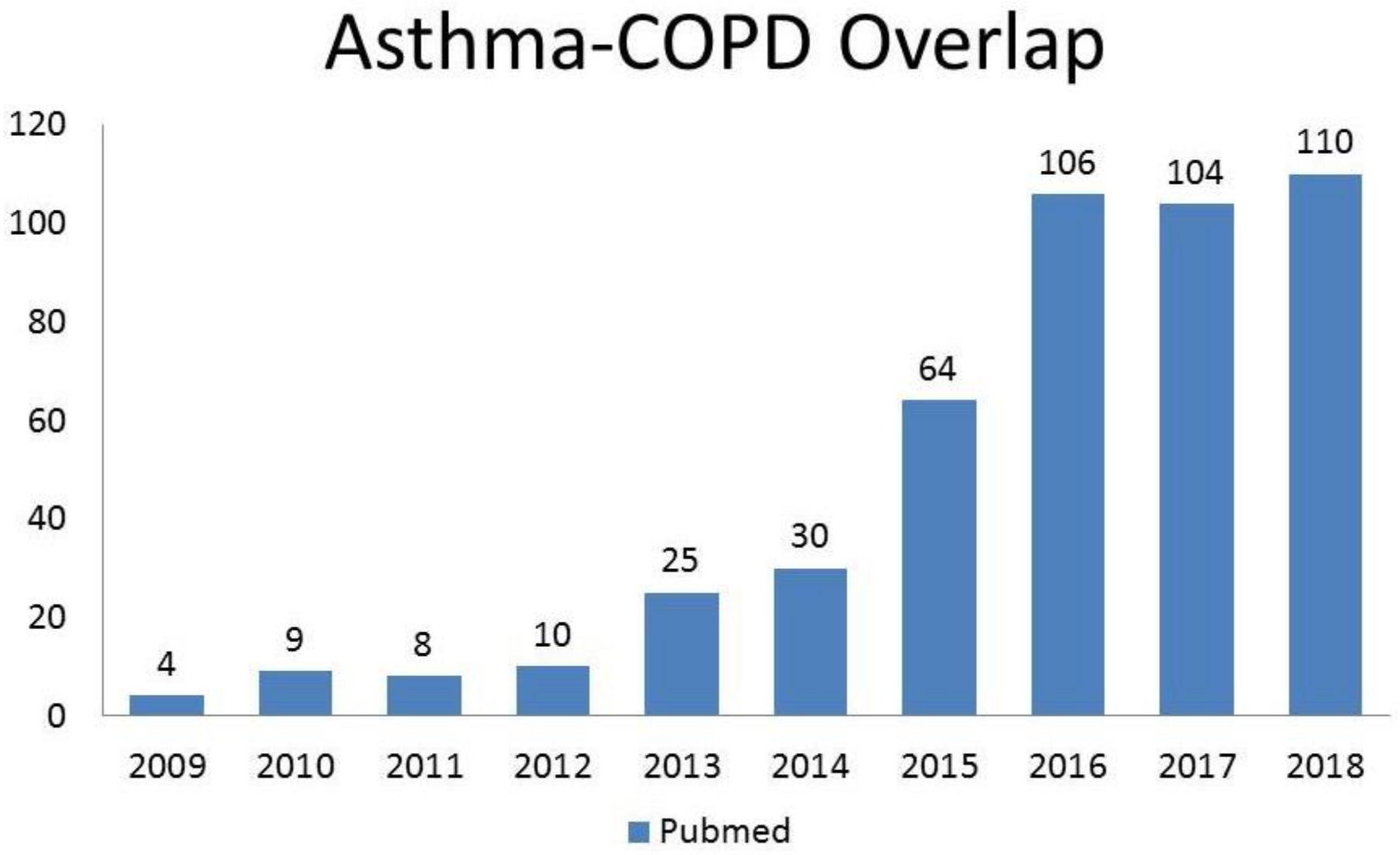
	TORCH [8]	UPLIFT [9]	VOGELMEIER [10]	VERKINDRE [11]	TONNEL [12]
Exclusion criteria					
Diagnosis of asthma, non-COPD respiratory disorders	■	■	□	□	□
History of asthma, allergic rhinitis or atopy	■	■	□	■	■
Blood eosinophil count >600 cells·μL^{-1}	□	□	□	■	□
Inclusion criteria					
Current or former smokers with ⩾10 pack-years	■	■	■	■	■
Diagnosis of COPD with pre-BD FEV_1 ⩽60% predicted	■	□	□	□	□
Post-BD (400 μg albuterol) FEV_1 increased by <10%	■	□	□	□	□
FEV_1/FVC ⩽70%	■	■	■	■	■
Post-BD FEV_1 <70% predicted	■	■	■	■	■
Residual volume >125% predicted	□	□	□	■	□

■ Included in trials ■ Not included in trials

	STEMPEL [13]	KERSTJENS [14]	PETERS [15]	AARONSON [16]	BUSSE [17]	HAAHTELA [18]	KUO [19]
Exclusion criteria							
Ever told by physician that they had chronic bronchitis, emphysema or COPD	■	■	□	■	□	□	□
Current smoker	□	□	□	□	□	■	■
Smoking >5 pack-years	□	□	□	□	□	□	■
Inclusion criteria							
Clinical diagnosis of asthma ⩾1 year prior to randomisation	■	■	□	■	■	□	■
PEF ⩾50% predicted	■	□	□	□	□	□	□
FEV_1 >40% predicted	□	□	■	□	□	□	□
Confirmed asthma diagnosis *via* either 1) 12% post-BD reversibility or 2) PC_{20} <8 mg·mL^{-1} not on ICS or <16 mg·mL^{-1} on ICS	□	□	■	□	□	□	□
Lifelong nonsmoker or smoking history of <10 pack-years and nonsmoker at enrolment	□	■	■	□	□	□	□
⩾15% FEV_1 revsersibility with inhaled β_2 agonist	□	□	□	□	■	■	■
⩾15% FEV_1 decrease following an exercise test	□	□	□	□	□	■	□
Histamine responsiveness <32 mg·mL^{-1}	□	□	□	□	□	■	□
Normal chest radiograph	□	□	□	□	□	□	■

■ Included in trials ■ Not included in trials

Eur Respir J 2016; 48: 664–673

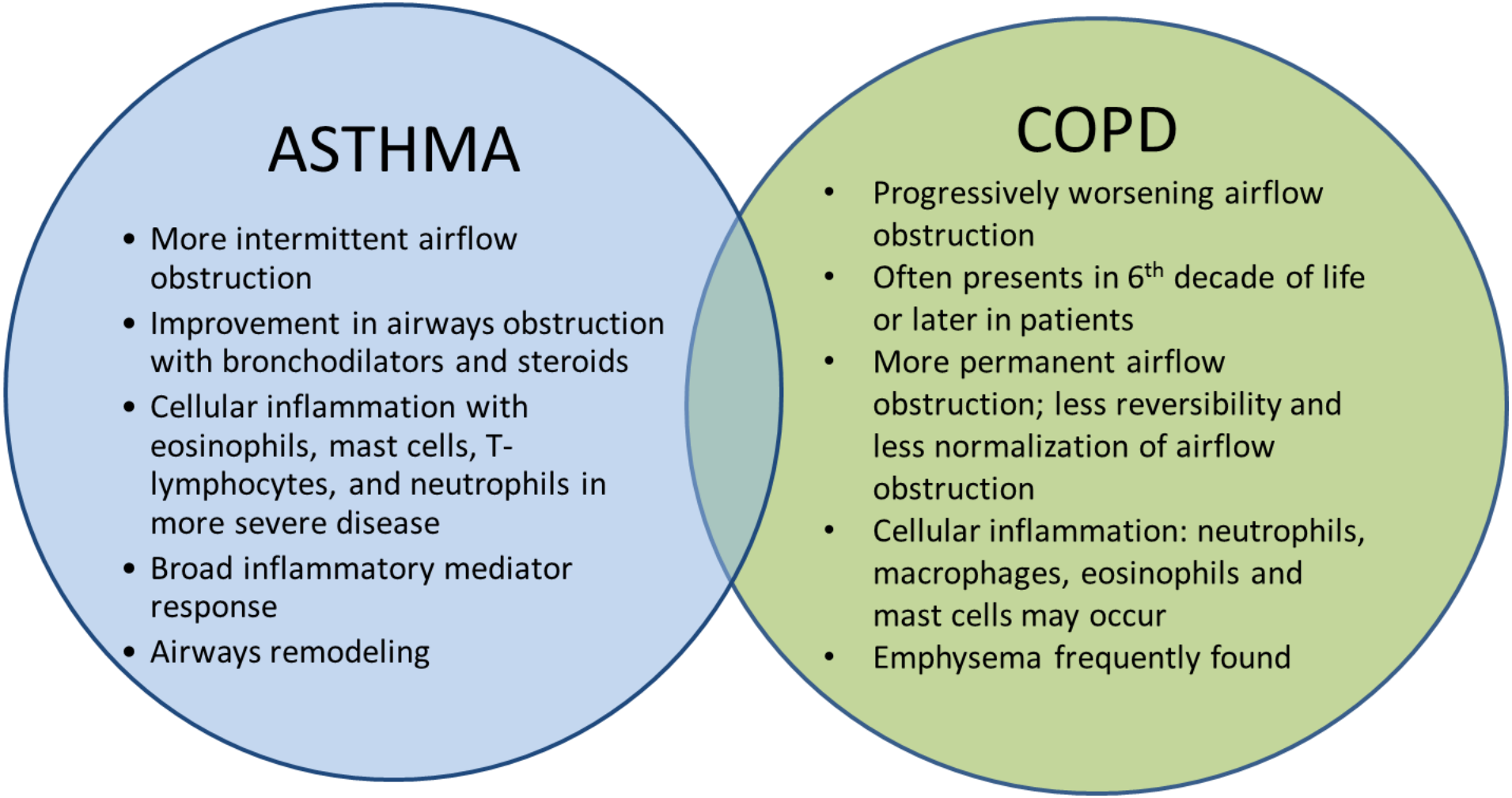

Asthma-COPD Overlap
120
100
80
60
40
20
0
4
9
8
10
25
30
64
106
104
110
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Pubmed

Background

Real World

Treatment

Background Real World Treatment

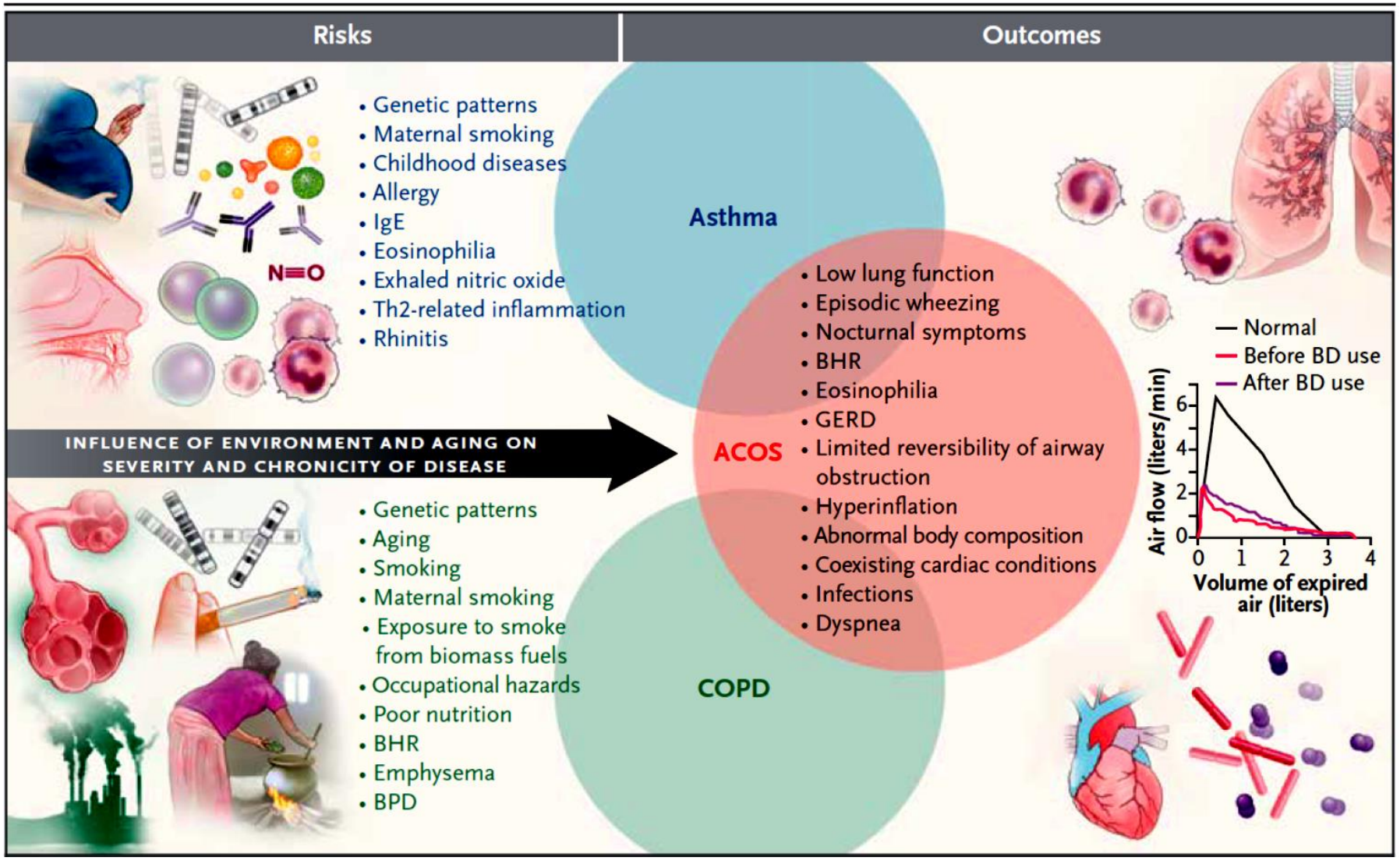


Chest. 2004;126(2 Suppl):93S-5S; discussion 159S-61S.

Background

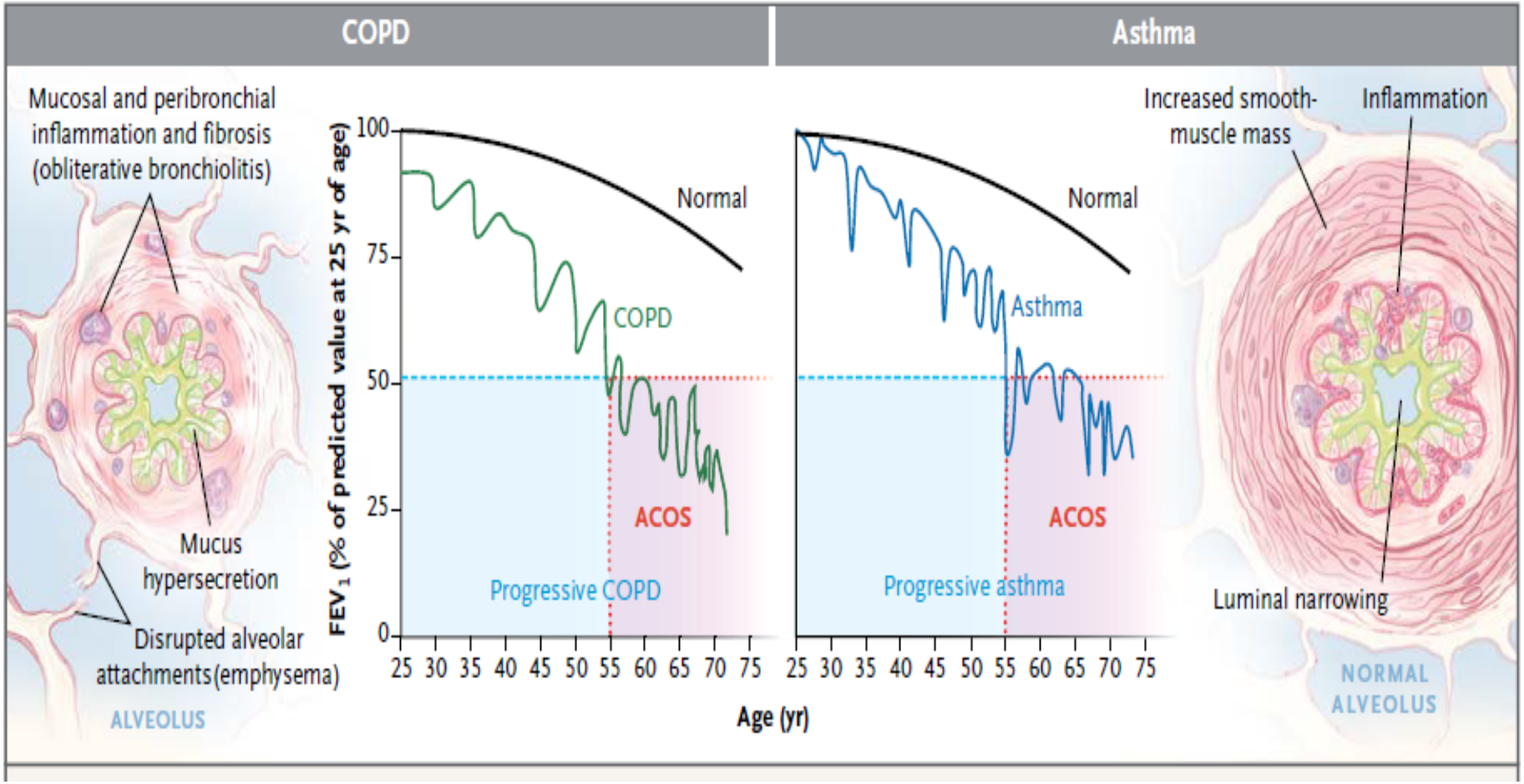
Real World

Treatment

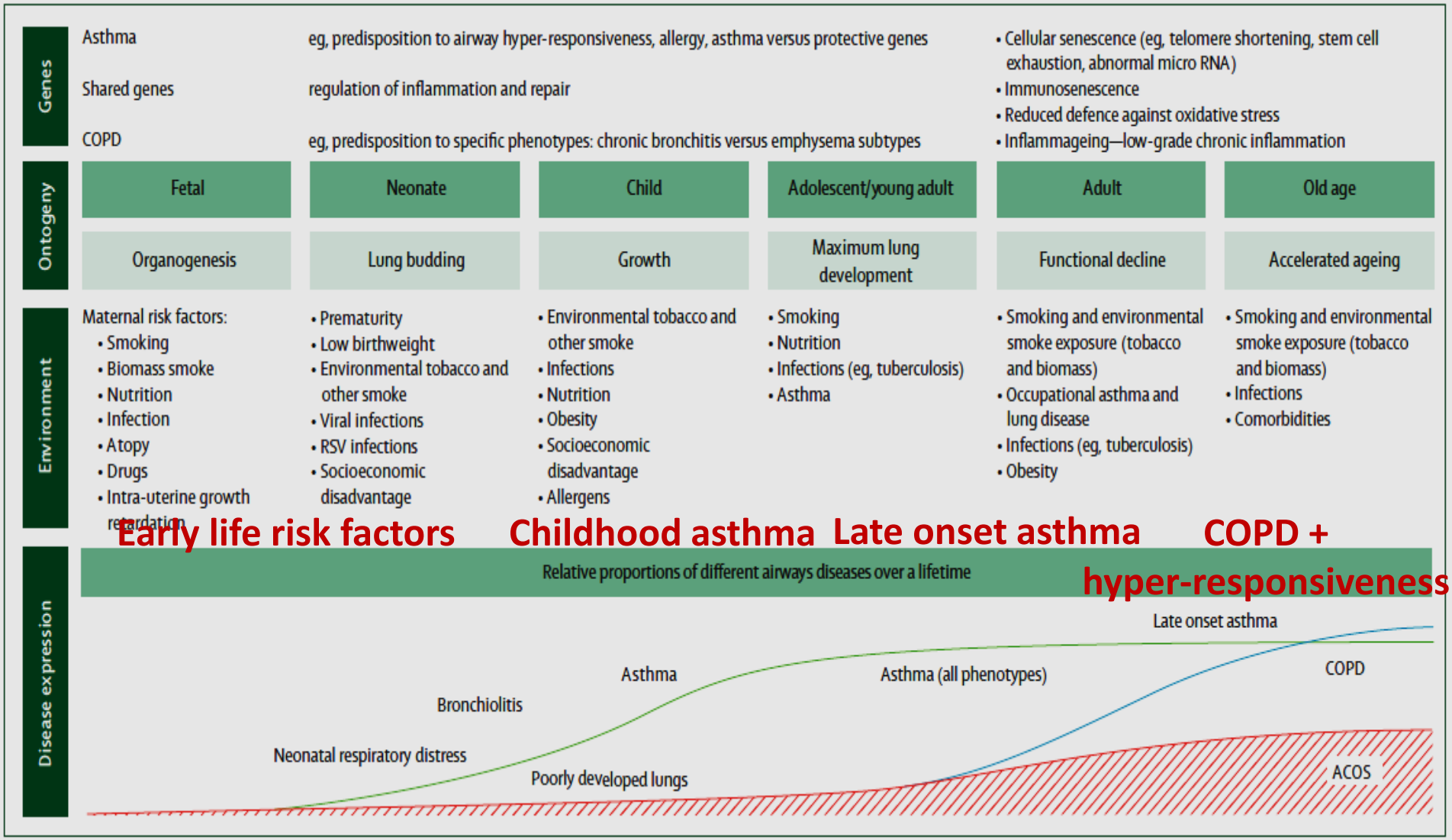


N Eng J Med 2015;373:1241

Background


COPD
Asthma
Mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis)
Mucus hypersecretion
Disrupted alveolar attachments (emphysema)
ALVEOLUS
FEV1 (% of predicted value at 25 yr of age)
100
75
50
25
0
Normal
COPD
ACOS
Progressive COPD
Normal
Asthma
ACOS
Progressive asthma
25 30 35 40 45 50 55 60 65 70 75
Age (yr)
Increased smooth-muscle mass
Inflammation
Luminal narrowing
NORMAL ALVEOLUS

Background Real World Treatment



Lancet Respir Med 2015

Background

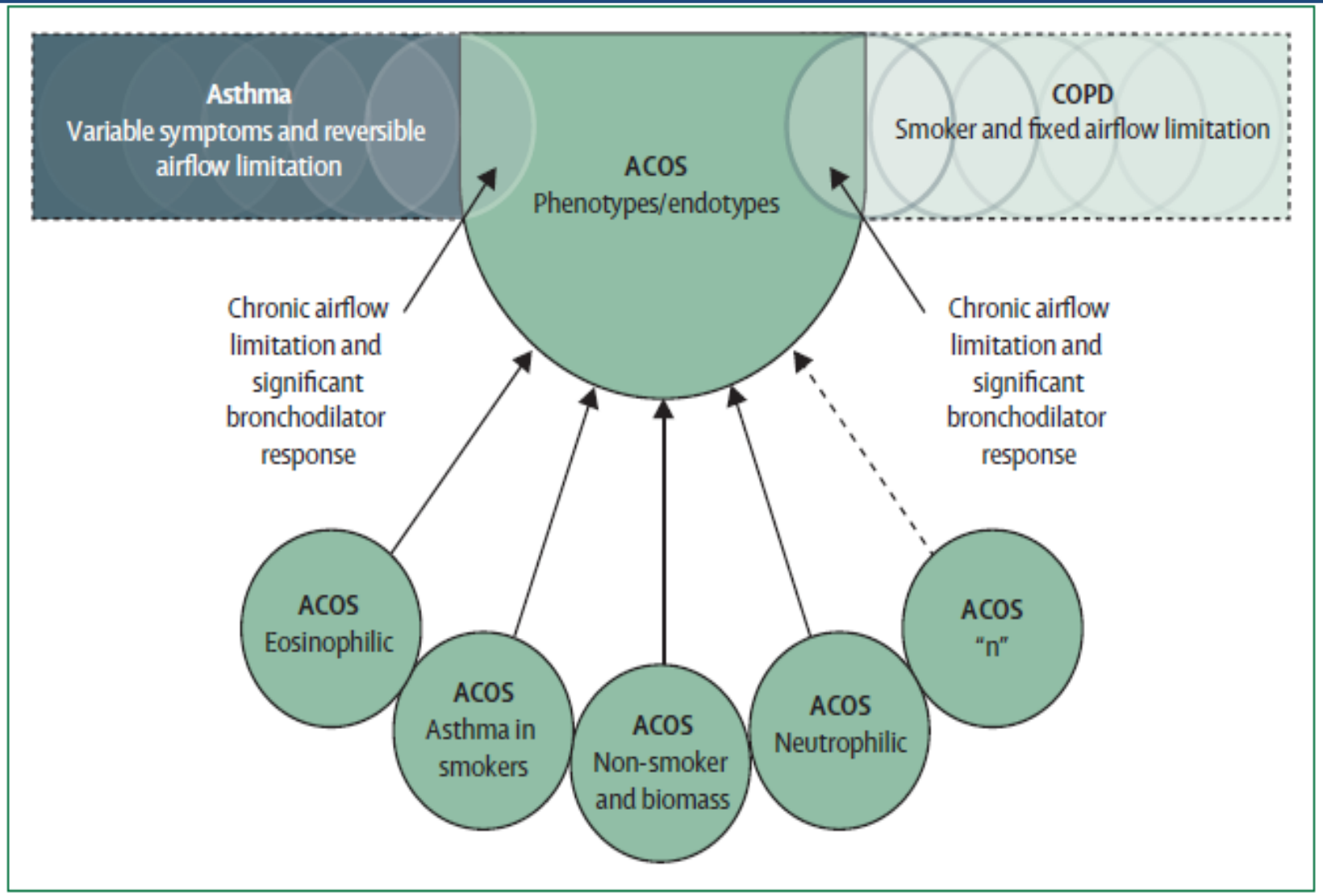
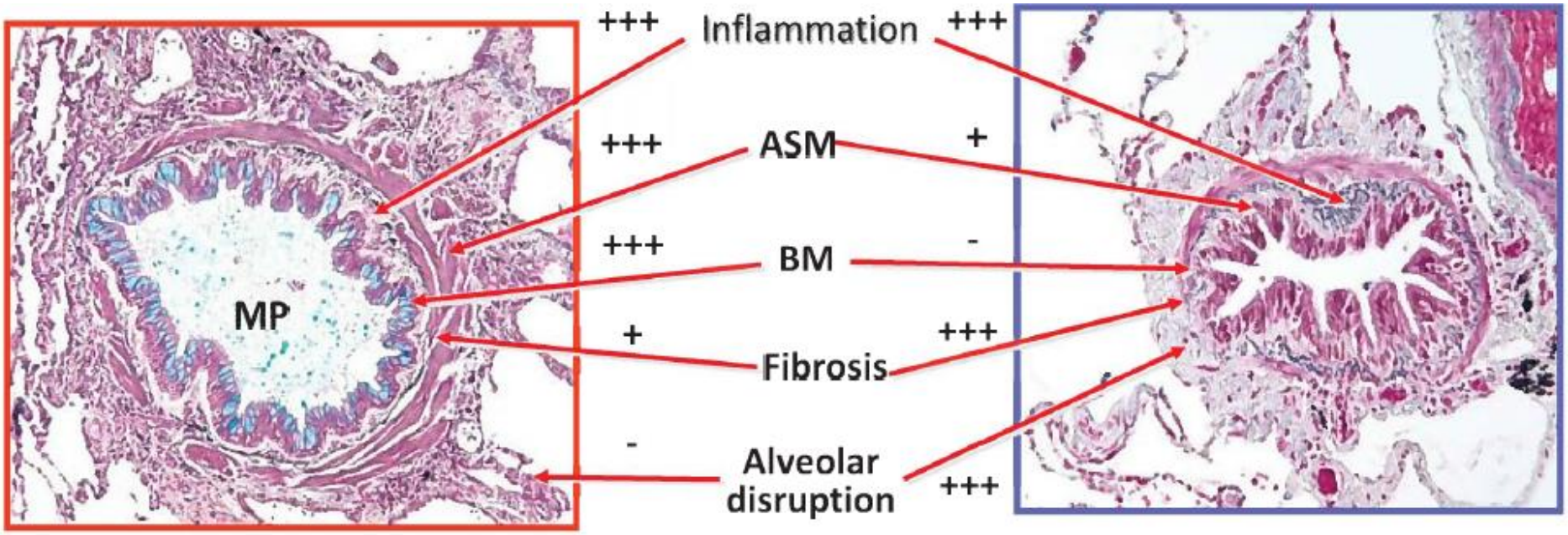


Figure 1: Phenotypes of asthma, COPD, and ACOS

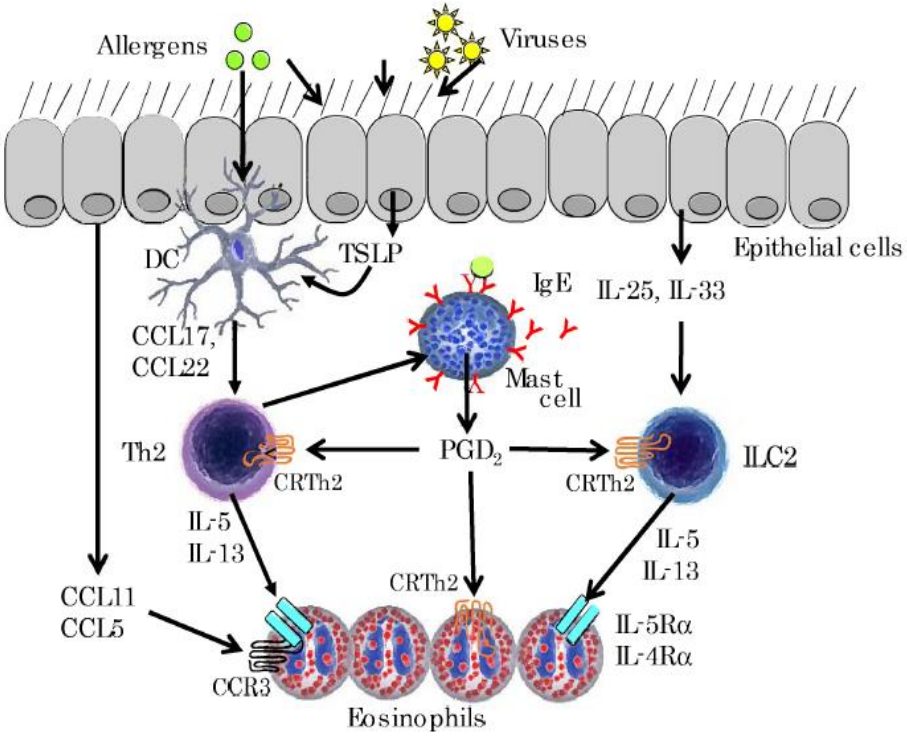
Lancet Respir Med 2015

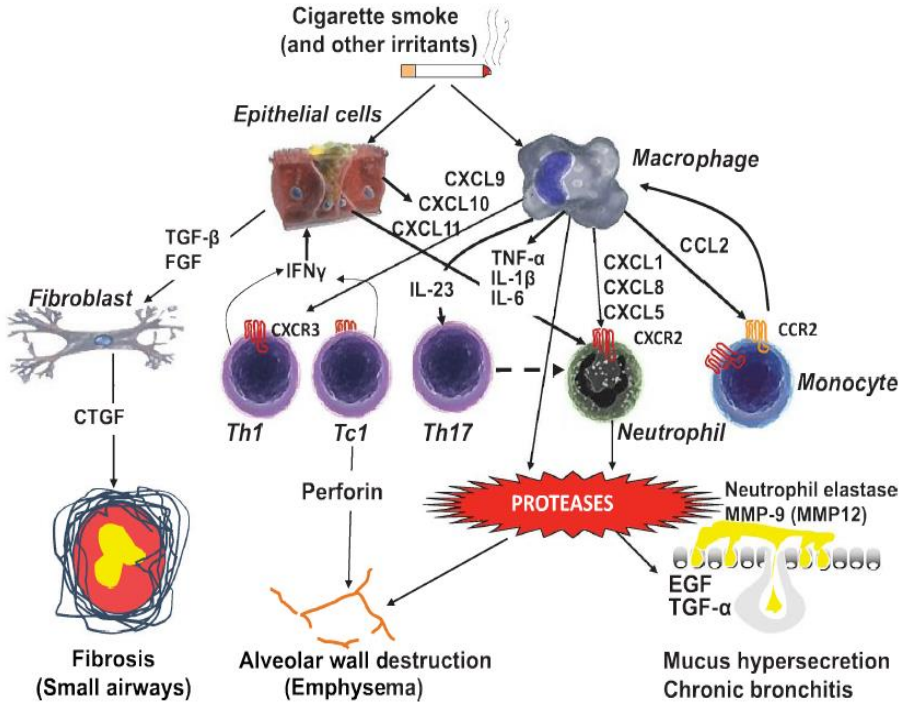
Pathophysiology of Asthma and COPD



Clin Sci (Lond). 2017 Jul 1;131(13):1541-1558.

Pathophysiology of Asthma and COPD





Clin Sci (Lond). 2017 Jul 1;131(13):1541-1558.

A nation-wide consensus of experts in COPD in Spain

Major and Minor Criteria for the Identification of the Mixed COPD/Asthma Phenotype.

Diagnostic Criteria of the Mixed COPD/Asthma Phenotype That Were Agreed Upon[a]	% of Agreement in Order to Be Considered a Major Criterion[b]	Type of Criterion
Very positive bronchodilator test (increase of FEV_1 ≥15% and ≥400 ml over baseline)	83	Major
Eosinophilia in sputum	78	Major
Personal history of asthma (history before the age of 40)	78	Major
High total IgE	50	Minor
Personal history of atopy	50	Minor
Positive bronchodilator test (increase in FEV_1 ≥12% and ≥200 ml over baseline) on 2 or more occasions	39	Minor

2 majors + 2 minors

Arch Bronconeumol. 2012 Sep;48(9):331-7.

Diagnosis of Diseases of Chronic Airflow Limitation:

Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)

STEP 2

SYNDROMIC DIAGNOSIS IN ADULTS

(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Features: if present suggest -	ASTHMA	COPD
Age of onset	❑ Before age 20 years	❑ After age 40 years
Pattern of symptoms	❑ Variation over minutes, hours or days ❑ Worse during the night or early morning ❑ Triggered by exercise, emotions including laughter, dust or exposure to allergens	❑ Persistent despite treatment ❑ Good and bad days but always daily symptoms and exertional dyspnea ❑ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	❑ Record of variable airflow limitation (spirometry or peak flow)	❑ Record of persistent airflow limitation (FEV_1/FVC < 0.7 post-BD)
Lung function between symptoms	❑ Normal	❑ Abnormal
Past history or family history	❑ Previous doctor diagnosis of asthma ❑ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	❑ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ❑ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	❑ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ❑ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	❑ Symptoms slowly worsening over time (progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	❑ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

ACOS 2015

Background

Real World

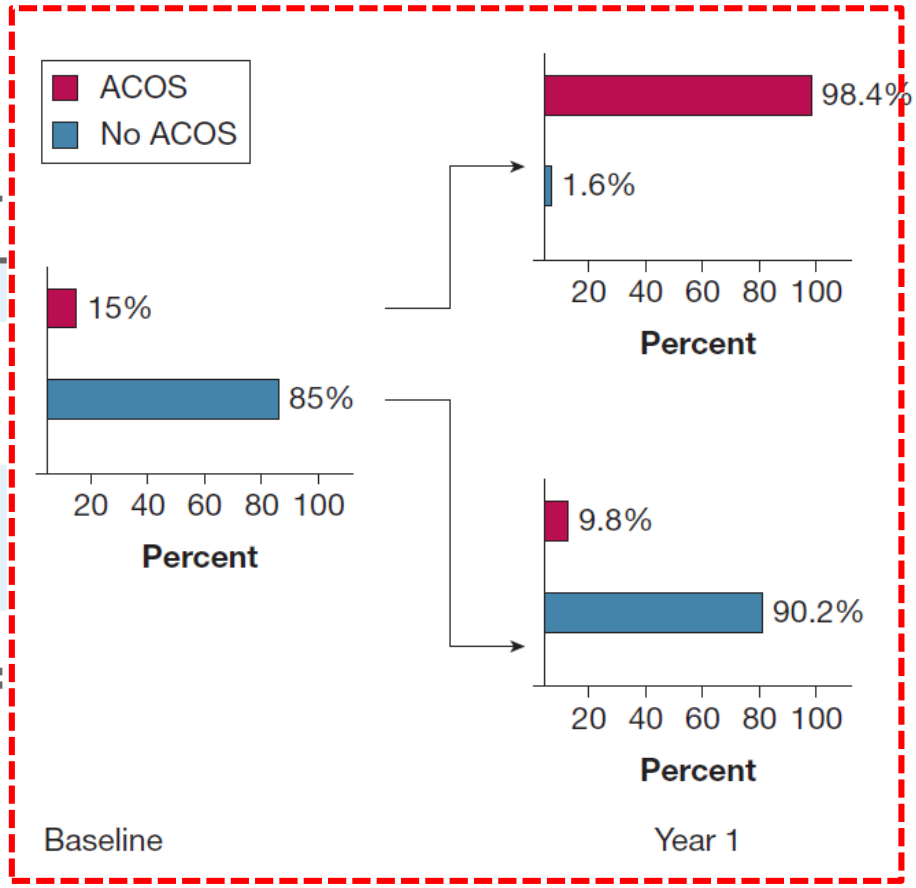
Treatment

TABLE 1] Major and Minor Criteria Used to Define ACOS

Major Criteria	Minor Criteria
Previous history of asthma	IgE > 100 IU, or
Bronchodilator response to salbutamol > 15% and 400 mL	History of atopy,
	2 separated bronchodilator responses to salbutamol > 12% and 200 mL
	Blood eosinophils > 5%

ACOS = asthma-COPD overlap syndrome.

1 major or 2 minors



Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort. Chest. 2016 Jan;149(1):45-52.

Spain

2012 Spanish Guidelines for COPD and ACO

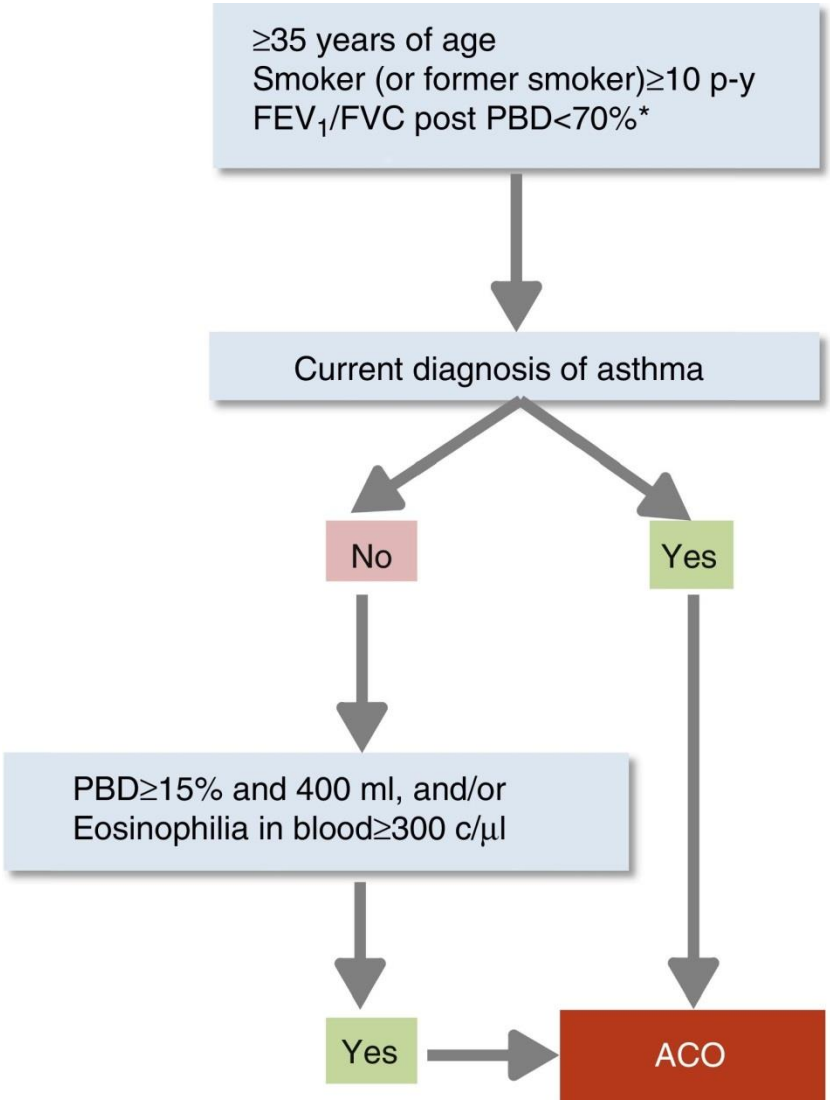
Major criteria
Very positive bronchodilator test (increase in FEV_1 >15% and >400 mL)
Eosinophilia in sputum
Personal history of asthma
Minor criteria
High levels of total IgE
Personal history of atopy
Positive bronchodilator test on at least two occasions (increase of FEV_1 >12% and >200 mL)

two major or one major and two minor

The criteria were very restrictive and identified <10% of COPD patients with ACO.

Arch Bronconeumol. 2017;53(8):443–449 Arch Bronconeumol. 2017;53(6):324–335

2017 Spanish Guidelines for COPD and ACO



The Spanish guidelines for COPD (GesEPOC) in 2012

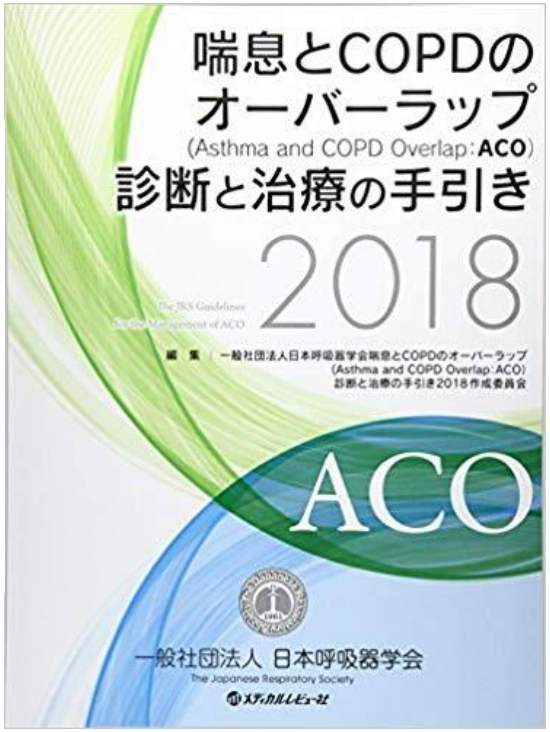
Arch Bronconeumol. 2017;53(8):443–449 Arch Bronconeumol. 2017;53(6):324–335

Therefore, the Japanese Respiratory Society defined ACO as follows: “Asthma and COPD overlap is defined as “**the coexistence of asthma and COPD in patients with chronic airway obstruction**”.

Table 1. Criteria for the diagnosis of ACO[13]

Features of COPD The presence of at least one of the following features (1, 2, or 3)	Features of BA The presence of at least two of features 1, 2, or 3 ; or at least one of features 1, 2, or 3 plus two of features 4-1 to 4-4
1. Smoking history (10 pack-years or more) or equivalent exposure to air pollution	1. Variable or paroxysmal clinical symptoms
2. Emphysematous changes on high-resolution CT	2. A documented history of asthma before the age of 40 years
3. Decreased gas exchange (%DLco < 80% or %DLco/V_A < 80%)	3. FeNO > 35 ppb
	4-1. A history of perennial allergic rhinitis 4-2. Airway reversibility (FEV_1 > 12% and > 200ml) 4-3. Peripheral blood eosinophils > 5% or > 300 cells/μl 4-4. Elevated IgE level (total or allergen-specific IgE)

Abbreviations : ACO, asthma-COPD overlap ; COPD, chronic obstructive pulmonary disease ; CT, Computed Tomography ; DLco, diffusing capacity of carbon monoxide ; V_A, alveolar volume ; BA, bronchial asthma ; FeNO, fraction of exhaled nitric oxide ; FEV_1, forced expiratory volume in 1 second ; IgE, Immunoglobulin E



Japanese Respiratory Society. The JRS Guidelines for the Management of ACO 2018. Tokyo: Medical Review; 2018

PLATINO study population

The Latin American Project for the Investigation of Obstructive Lung Disease

ACOS vs. COPD alone*

- Exacerbations (prevalence ratio 2.11; 95% CI 1.08-4.12)
- Hospitalizations (PR 4.11; 95% CI 1.45-11.67)
- Worse general health status (PR 1.47; 95% CI 1.18-1.85)

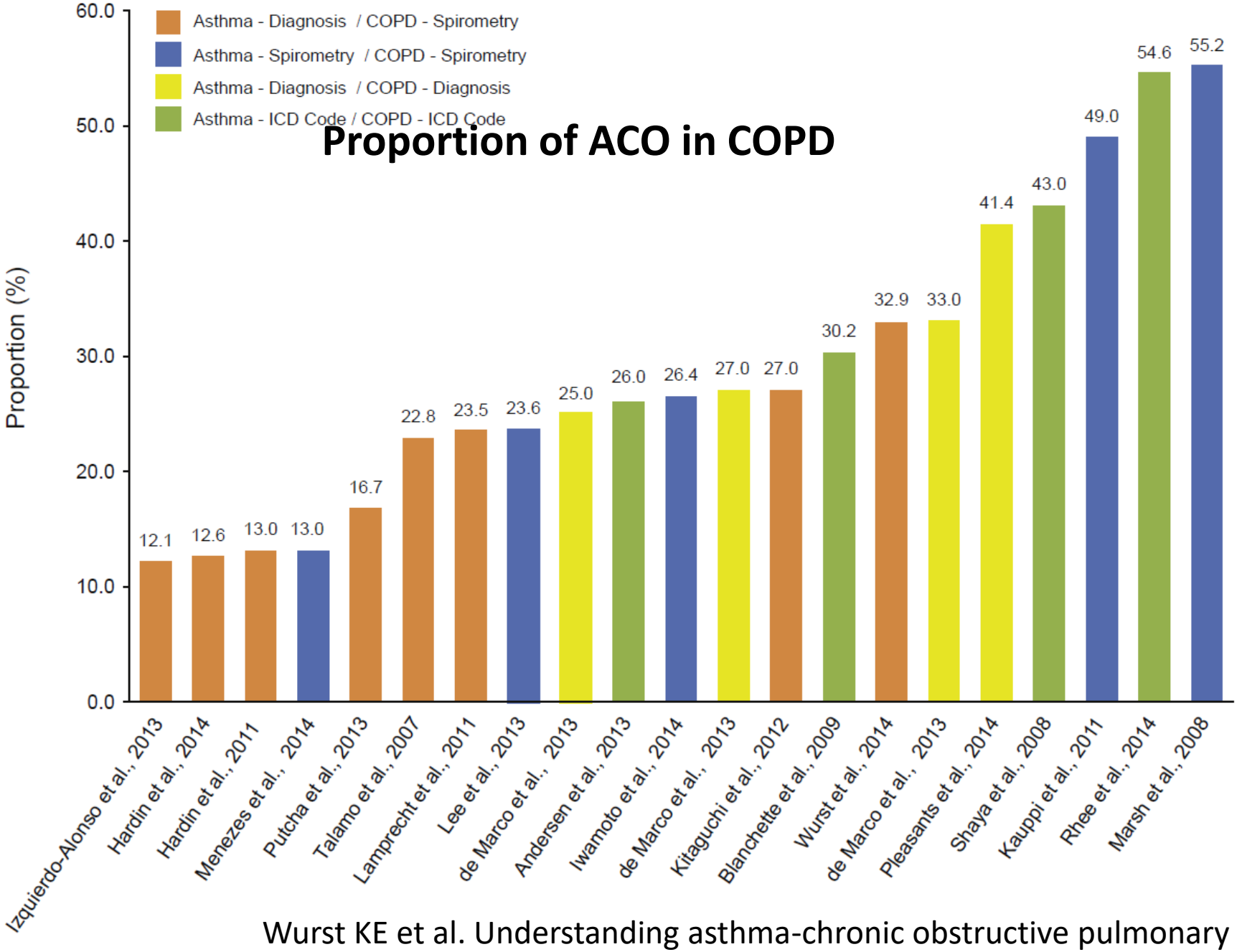
Chest. 2014 Feb;145(2):297-304.

COPD: a post-bronchodilator (post-BD) FEV_1/FVC ratio of < 0.70

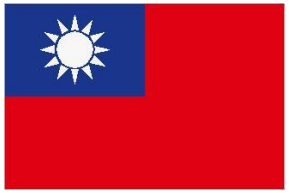
Asthma: presence of wheezing in the last year and a minimum post-BD increase in FEV_1 or FVC of 12% and 200 mL

*adjusted for age, sex, skin color, BMI, schooling , comorbidity score, pack-years, treatment (bronchodilator, corticosteroid)

Proportion of ACO in COPD



Wurst KE et al. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. Respir Med. 2016 Jan;110:1-11.



Taiwan Unmet Medical Need In ACO：Real-World Data

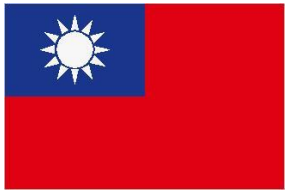
Global Unmet Medical Need In ACO：Choice of therapy

Original Article

Use of ICS/LABA Combinations or LAMA Is Associated with a Lower Risk of Acute Exacerbation in Patients with Coexistent COPD and Asthma

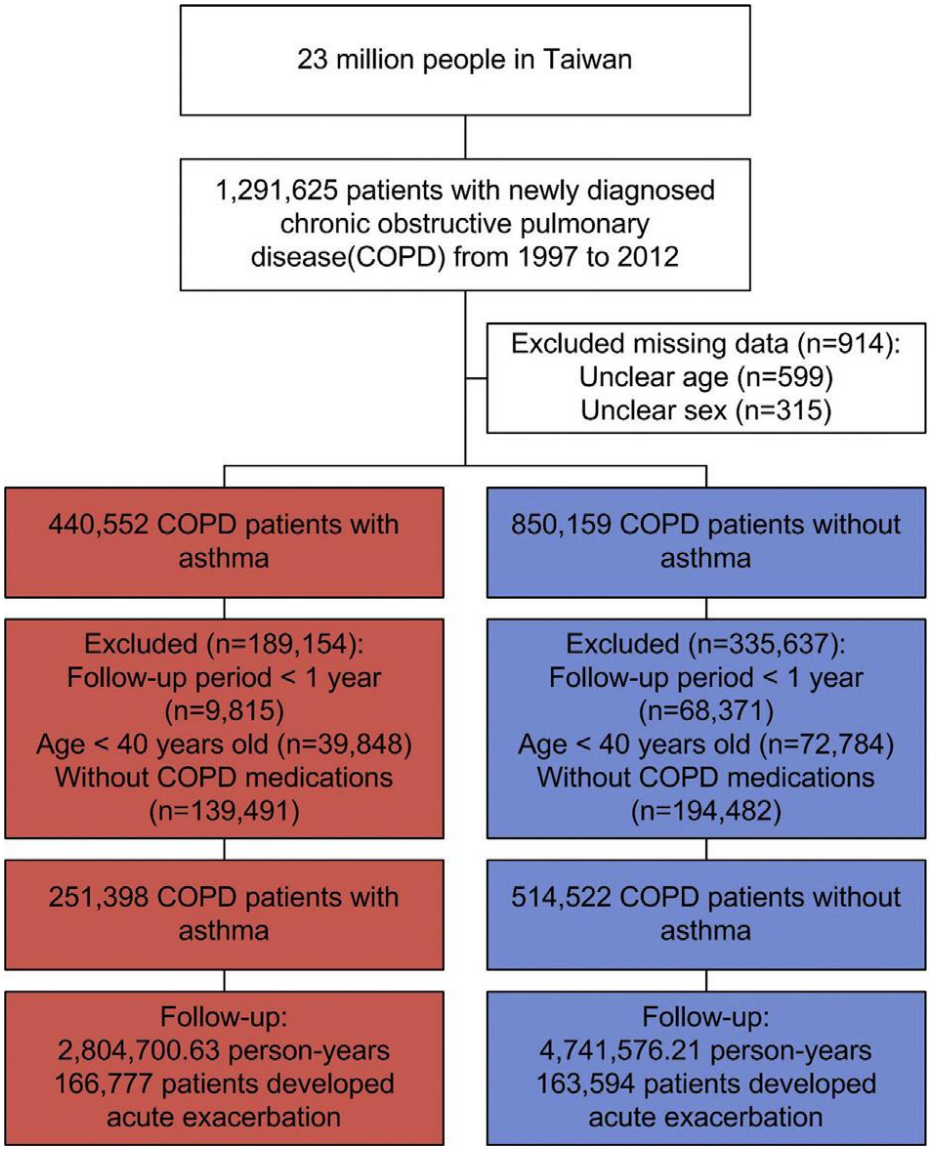
Vincent Yi-Fong Su, MD[a,b,c,*], Kuang-Yao Yang, MD, PhD[b,d,*], Yao-Hsu Yang, MD[e,f,g,h], Ying-Huang Tsai, MD, PhD[i,j], Diahn-Warng Perng, MD, PhD[b,d], Wei-Juin Su, MD, MPH[b,d], Kun-Ta Chou, MD[b,c,d], Kang-Cheng Su, MD[b,d], Yung-Feng Yen, MD, MPH, PhD[a,b], and Pau-Chung Chen, MD, PhD[h,k] *Taipei, Chiayi, Taoyuan, Taiwan*

The Journal of Allergy and Clinical Immunology: In Practice
Available online 10 February 2018

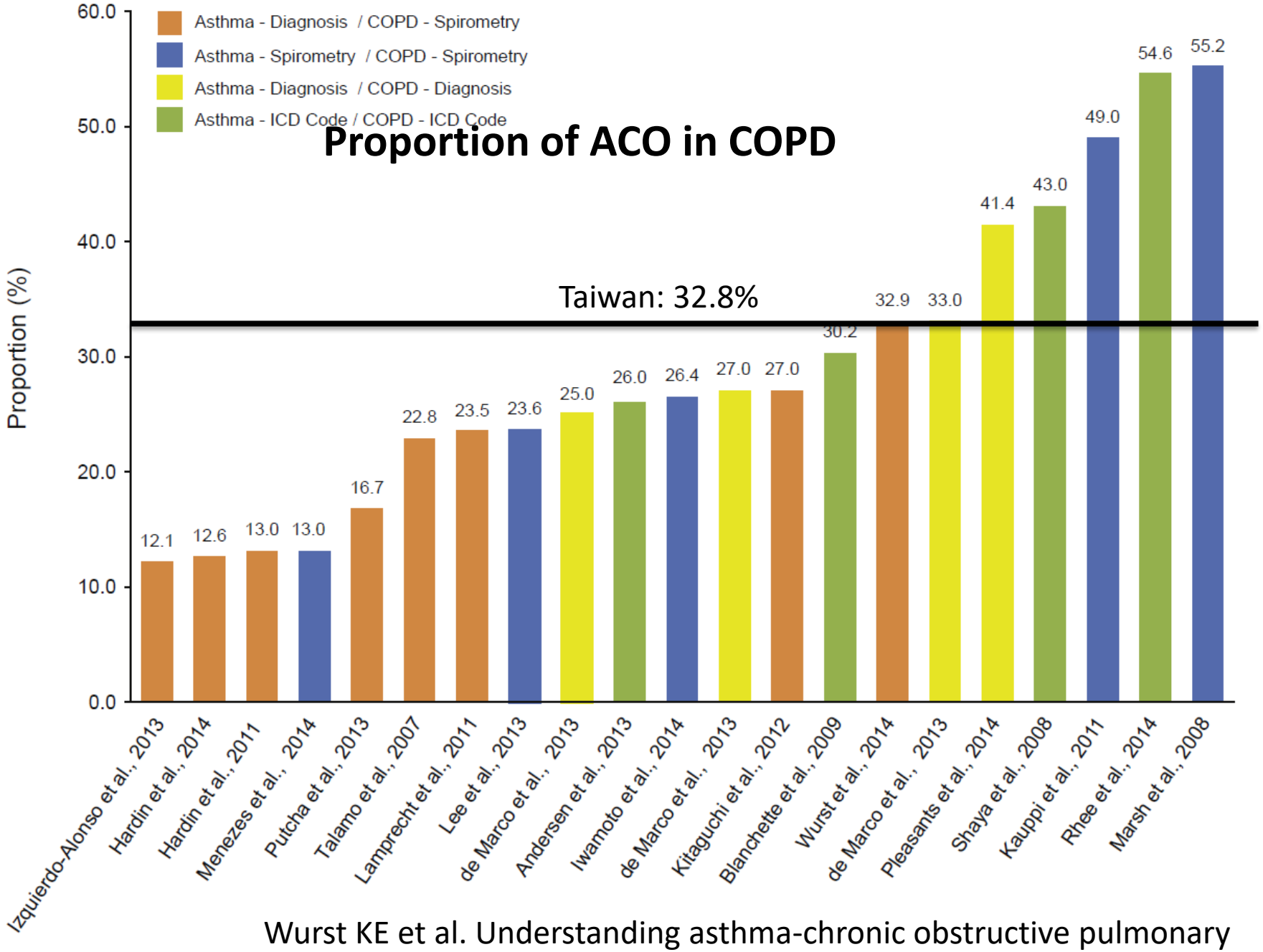


Taiwan Unmet Medical Need In ACO：Real-World Data

Global Unmet Medical Need In ACO：Choice of therapy

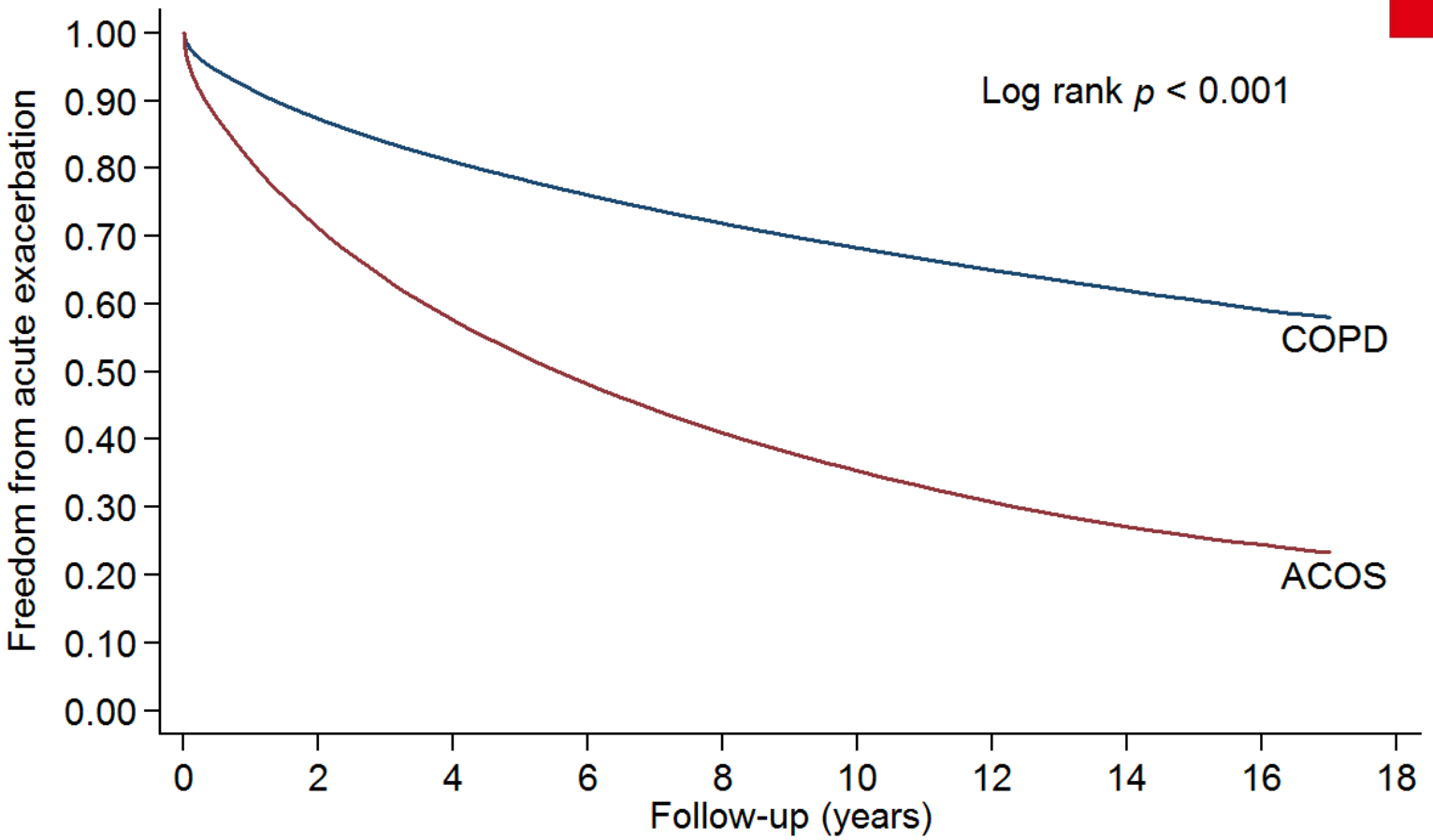


J Allergy Clin Immunol Pract. 2018 Feb 9.



Wurst KE et al. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. Respir Med. 2016 Jan;110:1-11.

Medical Burden



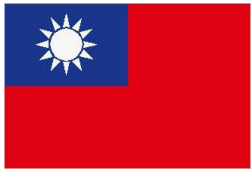
Medical Burden

TABLE I. Characteristics of the COPD + asthma cohort and COPD alone cohort

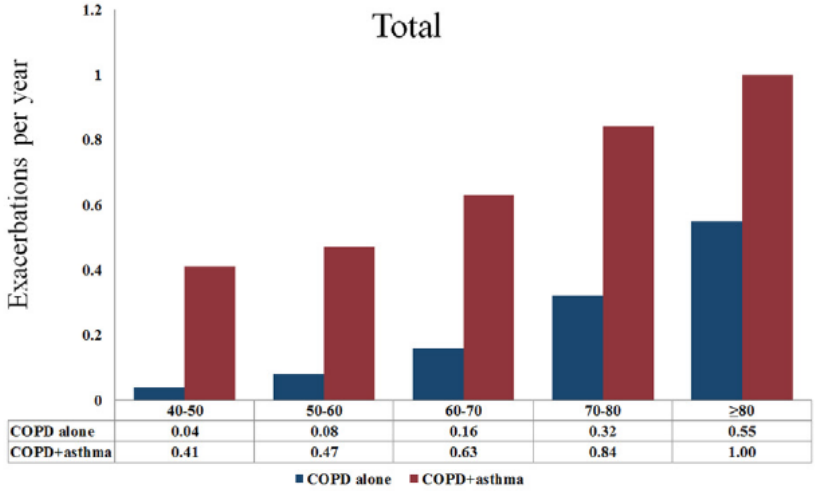
Characteristics	COPD + asthma cohort n	COPD + asthma cohort Percent	COPD alone cohort n	COPD alone cohort Percent	*P* value
N	251,398		514,522		
OPD visit/y (1st year)	1.46 ± 3.86		2.21 ± 4.06		<.0001
Time to first AE, y (mean ± SD)	4.10 ± 3.71		4.67 ± 3.92		<.0001
AE ratio (n, %)	182,482	70.3	47,243	47.8	<.0001
COPD severity (AE/y)					<.0001
Stable (0 AE/y)	84,621	33.7	350,928	68.2	
Mild (>0, <1 AE/y)	120,666	48.0	131,927	25.6	
Moderate (≥1, <2 AE/y)	24,829	9.9	18,069	3.5	
Severe (≥2, <3 AE/y)	9,652	3.8	6,433	1.3	
Very severe (≥3AE/y)	11,630	4.6	7,165	1.4	
AE/y (mean ± SD)	0.66 ± 1.51		0.24 ± 0.91		<.0001
Medications, the follow-up period*					
LABAs	158,734	63.14	69,519	13.51	<.0001
LAMA	48,465	19.28	30,508	5.93	<.0001
ICSs	134,444	53.48	39,823	7.74	<.0001
ICS/LABA combinations	147,185	58.55	52,170	10.14	<.0001
SABDs	246,588	98.09	490,909	95.41	<.0001
Medications, before first AE†					
LABAs	94,266	37.50	52,578	10.22	<.0001
LAMA	17,652	7.02	19,840	3.86	<.0001
ICSs	90,854	36.14	31,567	6.14	<.0001
ICS/LABA combinations	75,919	30.20	36,113	7.02	<.0001
SABDs	224,301	89.22	455,141	88.46	<.0001

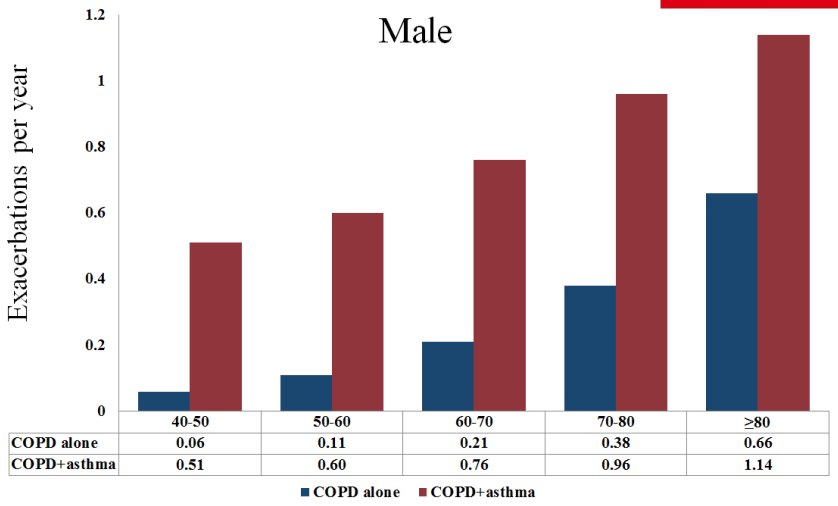
RR: 2.75

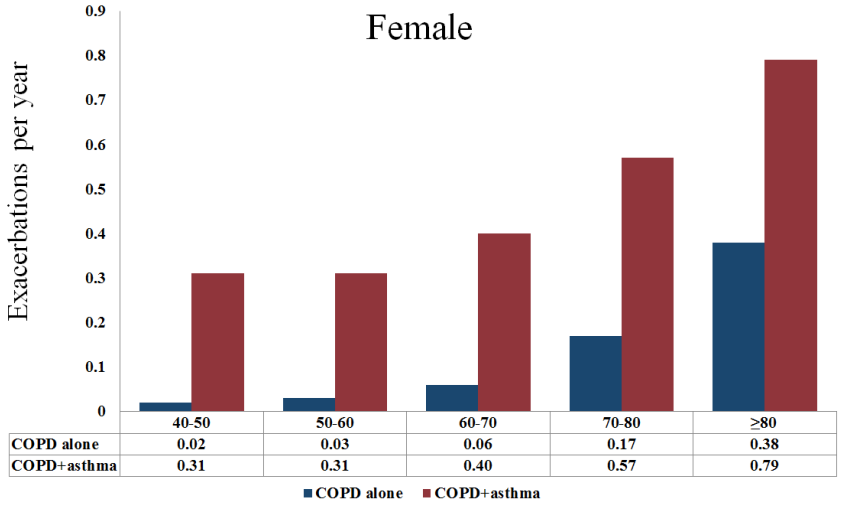
Medical Burden



A







Medical Burden

TABLE I. Characteristics of the COPD + asthma cohort and COPD alone cohort

Characteristics	COPD + asthma cohort n	COPD + asthma cohort Percent	COPD alone cohort n	COPD alone cohort Percent	*P* value
N	251,398		514,522		
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Time to first AE, y (mean ± SD)	4.10 ± 3.71		4.67 ± 3.92		<.0001
AE ratio (n, %)	182,482	70.3	47,243	47.8	<.0001
COPD severity (AE/y)					<.0001
Stable (0 AE/y)	84,621	33.7	350,928	68.2	
Mild (>0, <1 AE/y)	120,666	48.0	131,927	25.6	
Moderate (≥1, <2 AE/y)	24,829	9.9	18,069	3.5	
Severe (≥2, <3 AE/y)	9,652	3.8	6,433	1.3	RR: 2.95
Very severe (≥3AE/y)	11,630	4.6	7,165	1.4	
AE/y (mean ± SD)	0.66 ± 1.51		0.24 ± 0.91		RR: 2.75 <.0001
Medications, the follow-up period*					
LABAs	158,734	63.14	69,519	13.51	<.0001
LAMA	48,465	19.28	30,508	5.93	<.0001
ICSs	134,444	53.48	39,823	7.74	<.0001
ICS/LABA combinations	147,185	58.55	52,170	10.14	<.0001
SABDs	246,588	98.09	490,909	95.41	<.0001
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ICS/LABA combinations	75,919	30.20	36,113	7.02	<.0001
SABDs	224,301	89.22	455,141	88.46	<.0001

4.67
3.25
6.91
5.77

ACO: AE的風險因子

TABLE E1. Risk factors for acute exacerbation in patients with COPD + asthma

Variables	Unadjusted HR (95% CI)	Unadjusted *P*	Adjusted* HR (95% CI)	Adjusted* *P*	
Age ≥ 65 y	1.72 (1.70-1.74)	<.0001	1.54 (1.53-1.56)	<.0001	高齡男性
Male gender	1.35 (1.33-1.36)	<.0001	1.29 (1.28-1.31)	<.0001	
Income level					
0	Reference		Reference		
1-15,840	1.25 (1.24-1.27)	<.0001	1.08 (1.06-1.09)	<.0001	收入低
15,841-25,000	1.06 (1.04-1.07)	<.0001	0.93 (0.91-0.94)	<.0001	
≥25,000	0.63 (0.61-0.65)	<.0001	0.72 (0.69-0.74)	<.0001	
Comorbidities					
Heart failure	1.53 (1.51-1.55)	<.0001	1.39 (1.37-1.41)	<.0001	
Cerebrovascular disease	1.27 (1.25-1.29)	<.0001	1.11 (1.09-1.13)	<.0001	
Tuberculosis	1.36 (1.33-1.38)	<.0001	1.27 (1.25-1.30)	<.0001	
Pneumoconiosis	1.22 (1.19-1.25)	<.0001	1.11 (1.08-1.14)	<.0001	
Malignancy	1.09 (1.08-1.10)	<.0001	1.01 (1.00-1.02)	.1484	共病症
Chronic respiratory failure	3.89 (3.15-4.79)	<.0001	3.06 (2.48-3.79)	<.0001	
GERD	1.29 (1.23-1.35)	<.0001	1.26 (1.21-1.32)	<.0001	
ESRD	1.13 (1.09-1.17)	<.0001	1.09 (1.06-1.13)	<.0001	
Lung cancer	1.28 (1.23-1.32)	<.0001	1.10 (1.06-1.14)	<.0001	
Charlson Comorbidity Index					
0-1	Reference		Reference		
>1	1.18 (1.17-1.19)	<.0001	1.01 (1.00-1.03)	.0118	
Urbanization					
I (highest)	Reference		Reference		
II	1.15 (1.14-1.17)	<.0001	1.13 (1.12-1.15)	<.0001	住鄉下
III	1.29 (1.27-1.31)	<.0001	1.27 (1.25-1.29)	<.0001	
IV (lowest)	1.31 (1.29-1.33)	<.0001	1.32 (1.30-1.34)	<.0001	

COPD alone: AE的風險因子

TABLE E2. Risk factors for acute exacerbation in patients with COPD alone

Variables	Unadjusted HR (95% CI)	Unadjusted P	Adjusted* HR (95% CI)	Adjusted* P
Age ≥ 65 y	3.51 (3.46-3.55)	<.0001	2.83 (2.80-2.87)	<.0001
Male gender	2.02 (2.00-2.05)	<.0001	1.93 (1.91-1.96)	<.0001
Income level				
0	Reference		Reference	
1-15,840	1.30 (1.29-1.32)	<.0001	0.96 (0.95-0.97)	<.0001
15,841-25,000	0.96 (0.95-0.97)	<.0001	0.84 (0.83-0.86)	<.0001
≥25,000	0.33 (0.31-0.34)	<.0001	0.52 (0.50-0.54)	<.0001
Comorbidities				
Heart failure	2.01 (1.98-2.03)	<.0001	1.58 (1.56-1.59)	<.0001
Cerebrovascular disease	1.83 (1.81-1.85)	<.0001	1.34 (1.33-1.36)	<.0001
Tuberculosis	1.70 (1.67-1.72)	<.0001	1.50 (1.47-1.52)	<.0001
Pneumoconiosis	2.25 (2.21-2.29)	<.0001	1.71 (1.68-1.75)	<.0001
Malignancy	1.16 (1.14-1.17)	<.0001	1.00 (0.99-1.01)	.9555
Chronic respiratory failure	5.22 (4.75-5.74)	<.0001	2.94 (2.67-3.23)	<.0001
GERD	1.49 (1.45-1.53)	<.0001	1.32 (1.29-1.36)	<.0001
ESRD	1.09 (1.06-1.13)	<.0001	1.02 (0.99-1.05)	.2614
Lung cancer	1.75 (1.71-1.80)	<.0001	1.34 (1.31-1.38)	<.0001
Charlson Comorbidity Index				
0-1	Reference		Reference	
>1	1.54 (1.52-1.55)	<.0001	1.12 (1.11-1.13)	<.0001
Urbanization				
I (highest)	Reference		Reference	
II	1.18 (1.16-1.19)	<.0001	1.14 (1.13-1.16)	<.0001
III	1.37 (1.35-1.39)	<.0001	1.34 (1.32-1.36)	<.0001
IV (lowest)	1.35 (1.33-1.37)	<.0001	1.40 (1.37-1.42)	<.0001

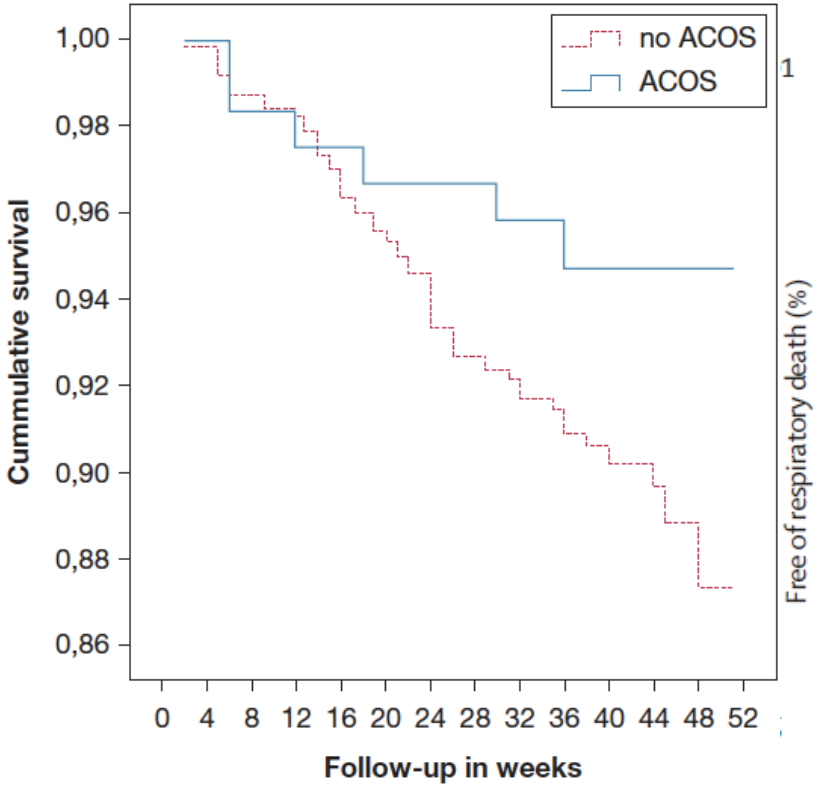
高齢男性

収入低

共病症

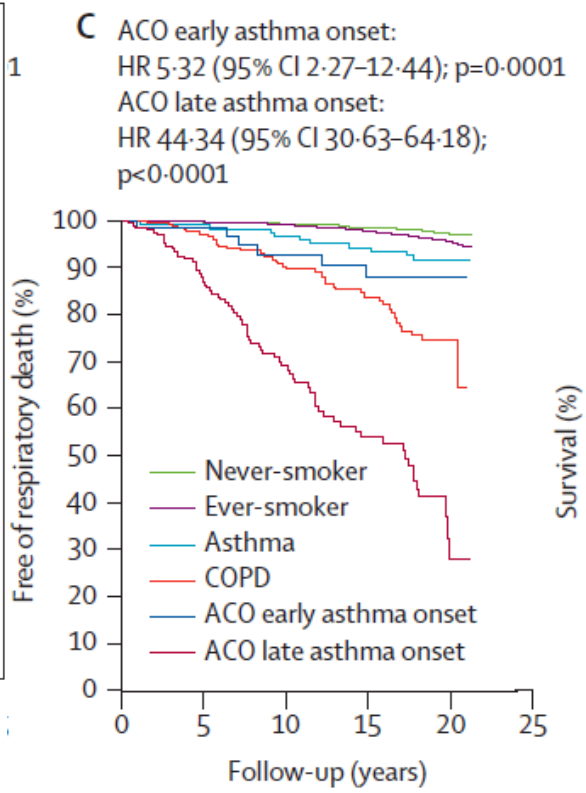
住鄉下

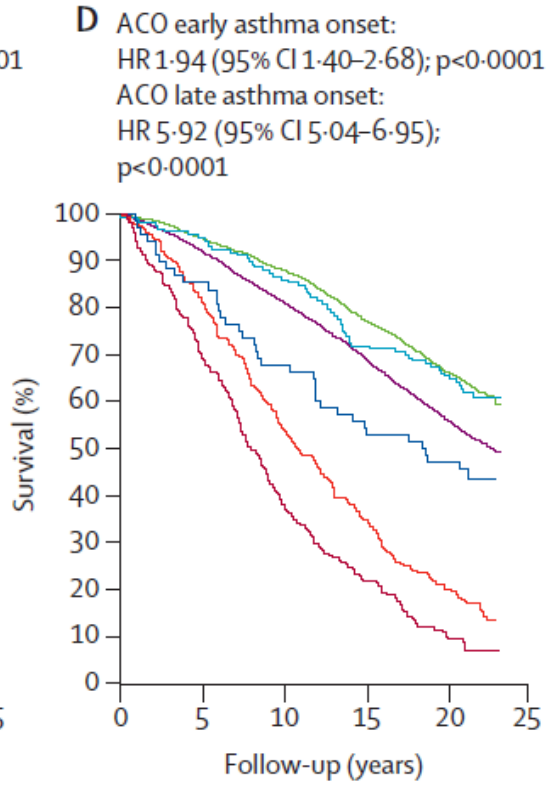
Survival in ACO vs COPD



Chest 2016;149:45-52

COPD History Assessment in Spain (CHAIN) cohort





Lancet Respir Med 2016; 4: 454–62

Copenhagen City Heart Study

Survival in ACO vs COPD

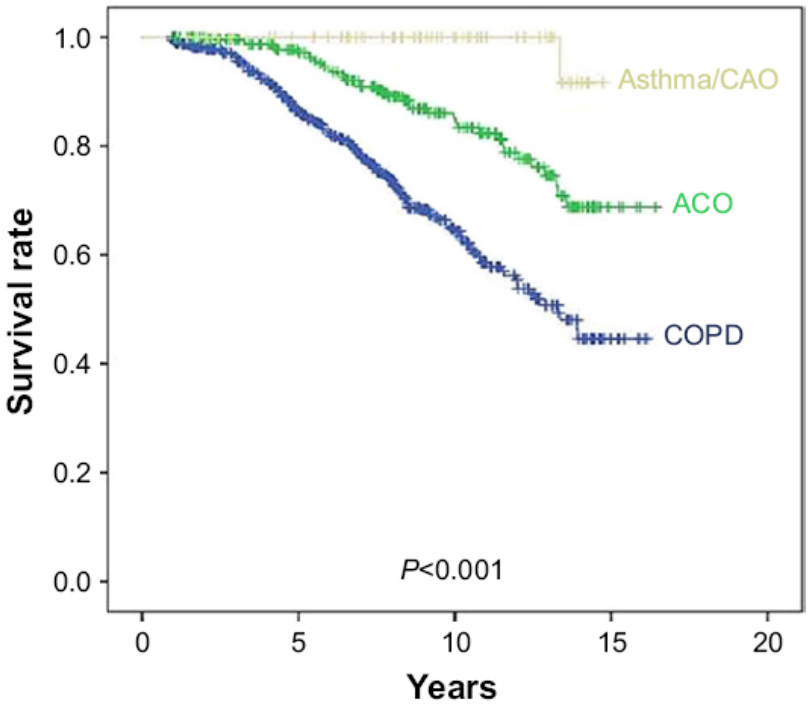


Figure 1 Kaplan–Meier survival curves for COPD, ACO, and asthma/CAO.
Abbreviations: ACO, asthma–COPD overlap; asthma/CAO, asthma with CAO; CAO, chronic airflow obstruction.

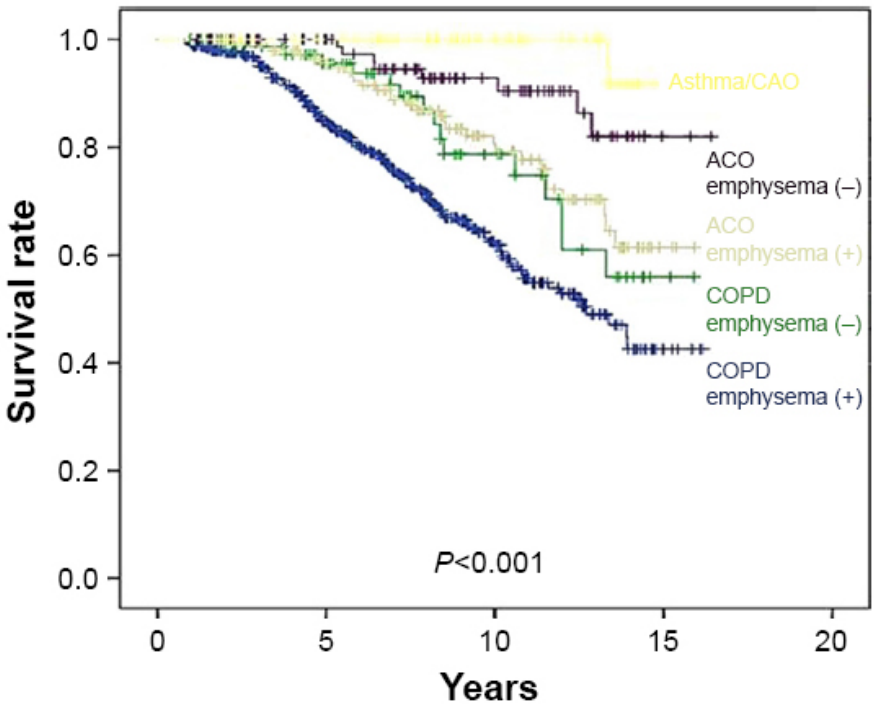
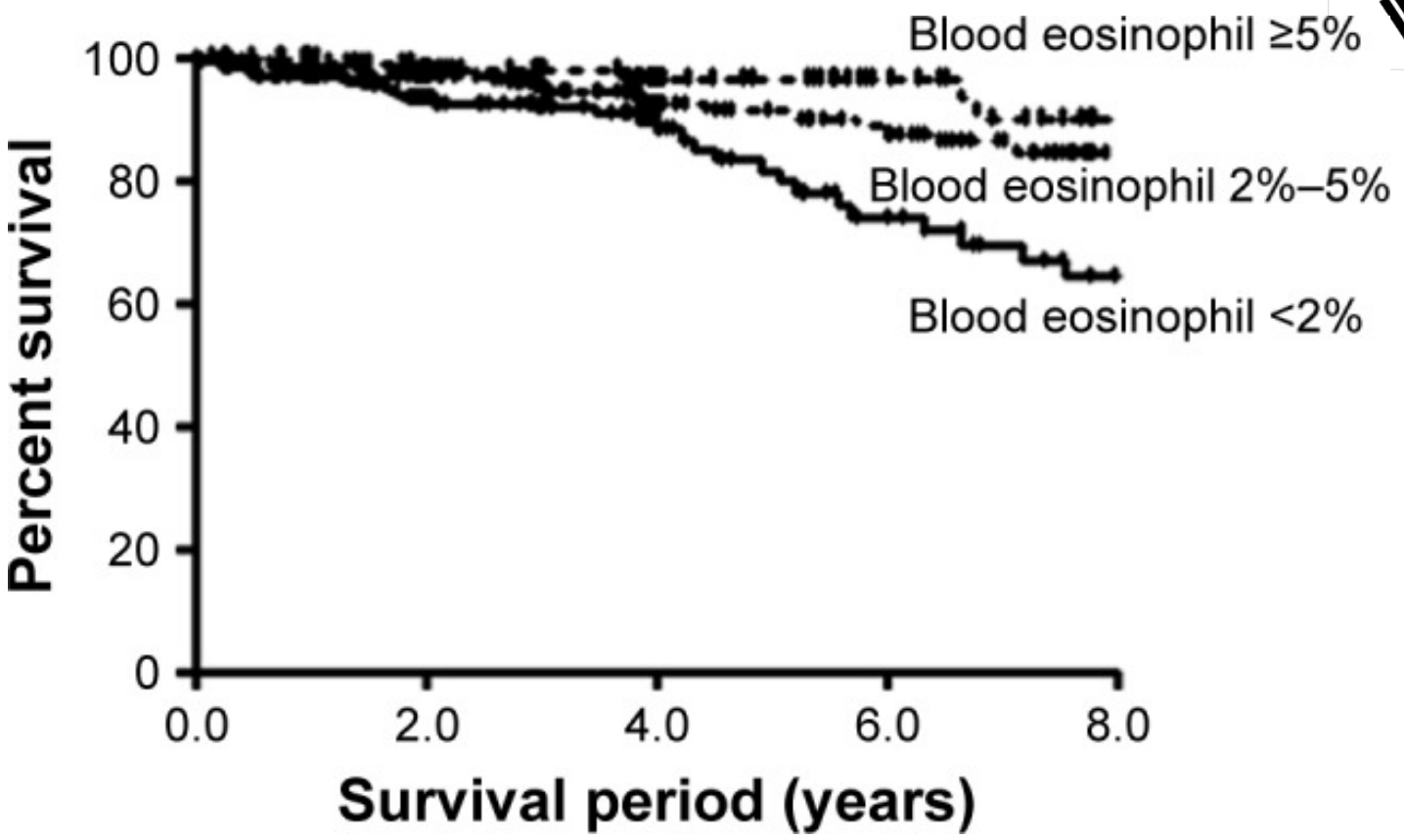


Figure 2 Kaplan–Meier survival curves for COPD, ACO, and asthma/CAO subclassified by the emphysema.
Abbreviations: ACO, asthma–COPD overlap; asthma/CAO, asthma with CAO; CAO, chronic airflow obstruction.

The Saitama Cardiovascular and Respiratory Center in Saitama, Japan

Int J Chron Obstruct Pulmon Dis. 2017 Dec 7;12:3523-3532.

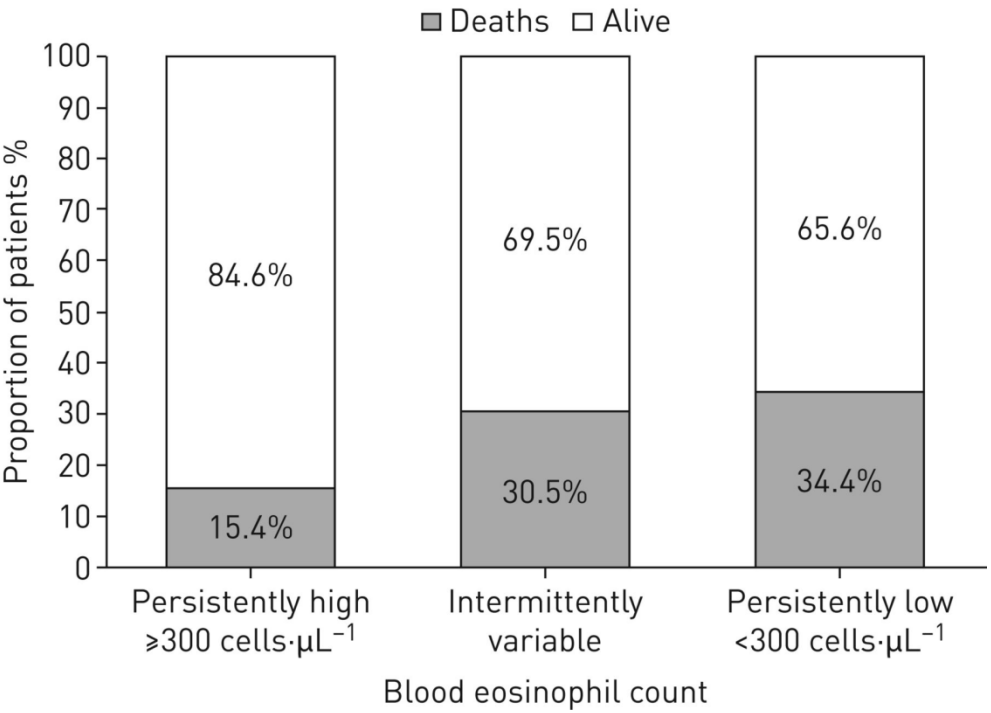
Survival in ACO vs COPD

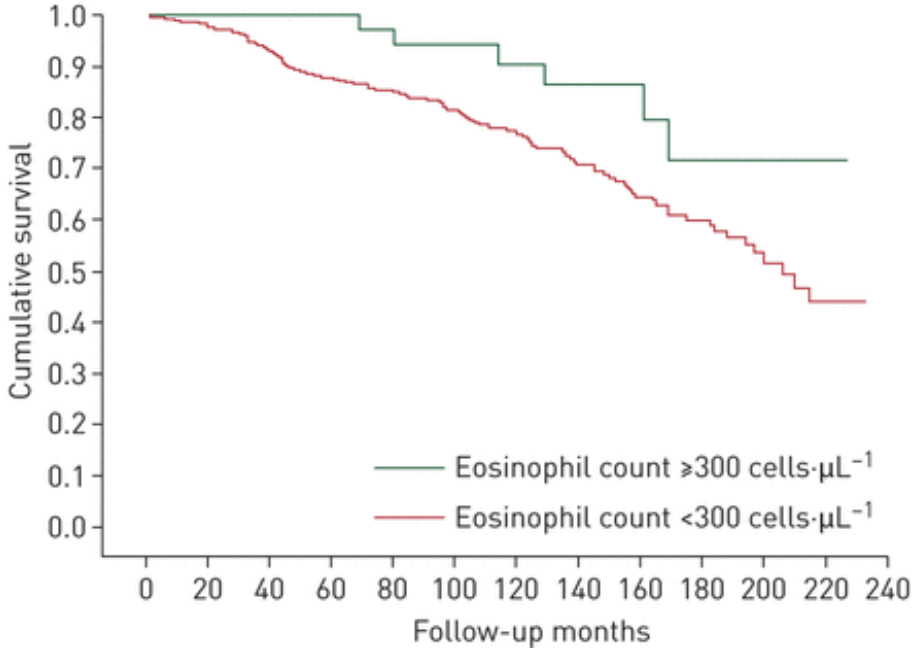


Korean Obstructive Lung Disease (KOLD) cohort

Int J Chron Obstruct Pulmon Dis. 2018; 13: 3589–3596.

Survival in ACO vs COPD





COPD from the CHAIN cohort

Eur Respir J. 2017 Nov 22;50(5).

Survival in ACO vs COPD

TABLE I. Characteristics of the COPD + asthma cohort and COPD alone cohort

Characteristics	COPD + asthma cohort n	COPD + asthma cohort Percent	COPD alone cohort n	COPD alone cohort Percent	*P* value
N	251,398		514,522		
Age, y (mean ± SD)	64.50 ± 10.82		66.63 ± 12.01		<.0001
Age, y					<.0001
<65	115,181	45.82	201,219	39.11	
≥65	136,217	54.18	313,303	60.89	
Follow-up, y (mean ± SD)	11.16 ± 3.94		9.22 ± 4.40		<.0001
Sex					<.0001
Female	96,894	38.54	180,794	35.14	
Male	154,504	61.46	333,728	64.86	
Comorbidities					
Heart failure	36,945	14.7	89,701	17.43	<.0001
Cerebrovascular disease	36,554	14.54	126,513	24.59	<.0001
Tuberculosis	16,417	6.53	43,225	8.40	<.0001
Pneumoconiosis	9,204	3.66	21,971	4.27	<.0001
Malignancy	39,080	15.55	89,606	17.42	<.0001
Chronic respiratory failure	101	0.04	704	0.14	<.0001
GERD	3,207	1.28	16,009	3.11	<.0001
ESRD	4,882	1.94	14,962	2.91	<.0001
Lung cancer	4,454	1.77	15,887	3.09	<.0001
Charlson Comorbidity Index					<.0001
0-1	132,460	52.69	207,644	40.36	
>1	118,938	47.31	306,878	59.64	

J Allergy Clin Immunol Pract. 2018 Feb 9.

Comorbidities in ACO vs COPD

TABLE 2] Sociodemographic and Clinical Characteristics of the CHAIN Cohort Population, According to the Fulfillment of ACOS Criteria

Characteristics	ACOS (n = 125)	No ACOS (n = 706)	*P* Value
Female sex	23 (18.4)	118 (16.7)	.608
Age, y	66.5 ± 8.7	67.8 ± 8.9	.133
Pack-y	53.2 ± 26.2	56.6 ± 28.7	.218
Active smoker	44 (35.2)	196 (27.8)	.058
BMI, kg/m^2	29.1 ± 5.5	27.8 ± 5.5	.052
Symptoms			
Sputum production	75 (60)	414 (58.6)	.42
Dyspnea (mMRC scale > 2)	56 (44.8)	326 (46.2)	.41
Charlson index	1.22 ± 1.5	1.29 ± 1.6	.612

Chest 2016;149:45-52

COPD History Assessment in Spain (CHAIN) cohort

Comorbidities in ACO vs COPD

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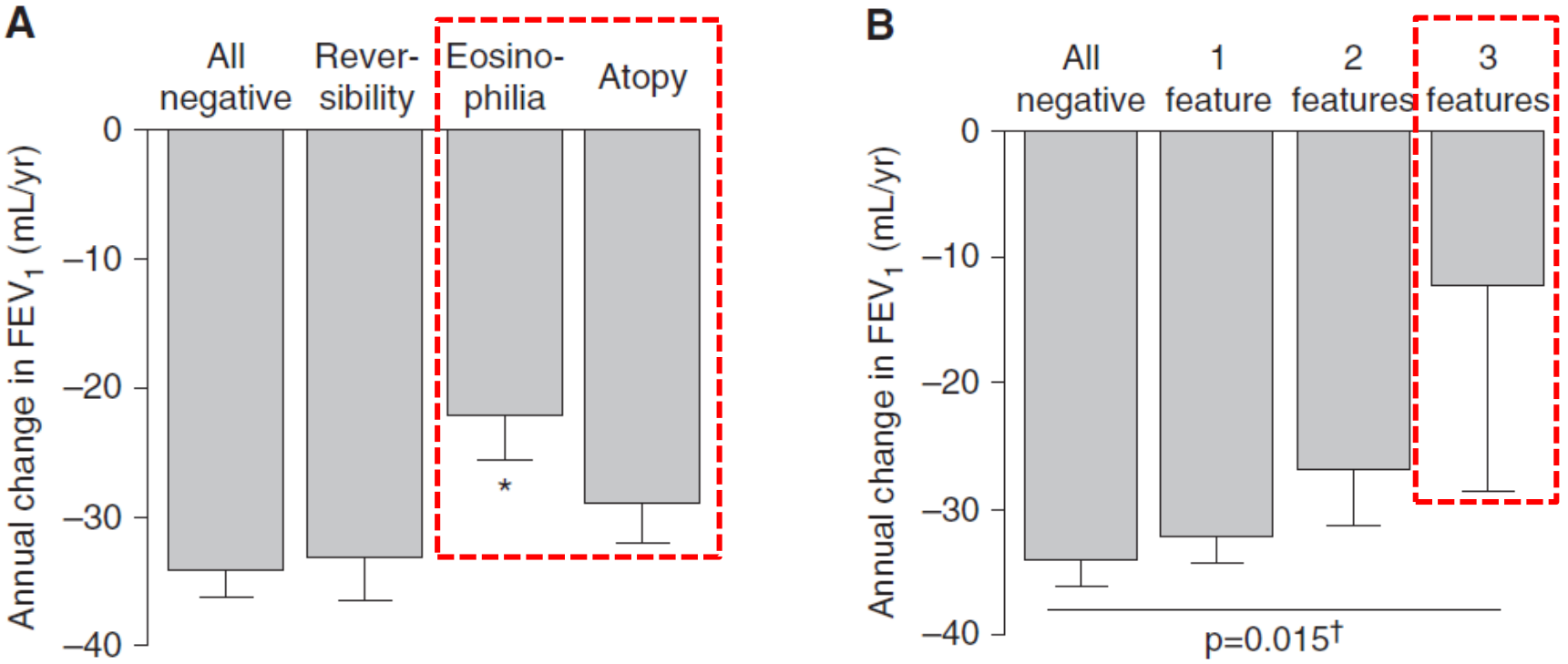
>1	118,938	47.31	306,878	59.64	

J Allergy Clin Immunol Pract. 2018 Feb 9.

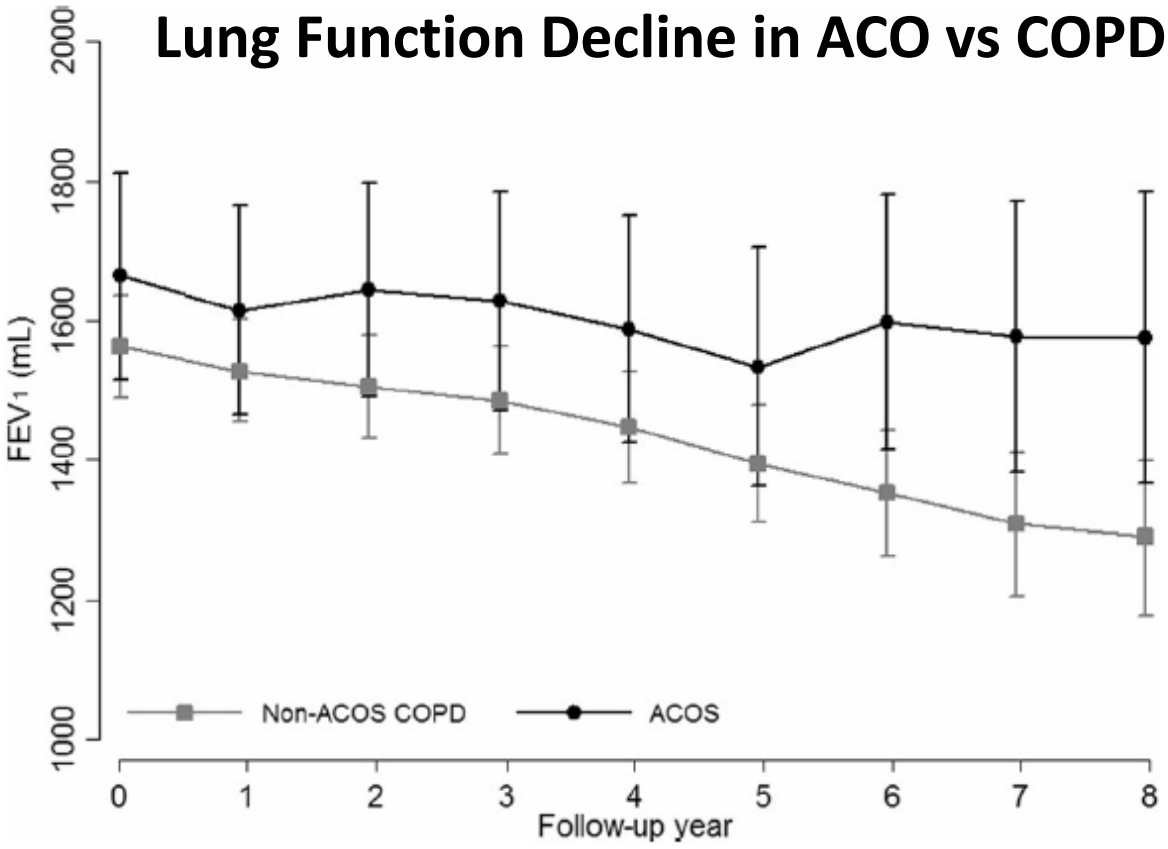
Lung Function Decline in ACO vs COPD



Hokkaido COPD cohort study

Am J Respir Crit Care Med Vol 194, Iss 11, pp 1358–1365, Dec 1, 2016

Lung Function Decline in ACO vs COPD



ACO -13.9 ml/year

COPD – 29.3 ml/year

Fig. 1 Longitudinal Changes in pre-bronchodilator forced expiratory volume in 1 s (mL) during the follow-up period in non-ACO COPD ($n = 192$) and ACO ($n = 47$). Error bar represents 95% confidence interval. ACO, asthma-chronic obstructive pulmonary disease overlap syndrome; COPD, chronic obstructive lung disease

the Korean Obstructive Lung Disease (KOLD) cohort

Park et al. Respiratory Research (2018) 19:36

Lung Function Decline in ACO vs COPD

TABLE 4] Disease Progression in ACO

Variable	ACO N = 242	COPD N = 1,359	Impact of ACO[a]		
			OR	95% CI	*P* Value
Development of oxygen requirement, No. (%)[b,e,f]	33 (14)	207 (15)	0.97	0.64-1.45	.90
Development of chronic bronchitis, No. (%)[b,e,f,h]	24 (10)	155 (11)	0.90	0.55-1.42	.67
Had a severe COPD exacerbation in prior y, No. (%)[b,e,f,g,h]	60 (25)	237 (17)	1.42	1.00-2.00	.05
			β	SE	*P* Value
No. of COPD exacerbations in prior y, mean (SD)[c,e,f,g,h]	0.81 (1.23)	0.56 (1.03)	0.20	0.07	.006
FEV_1 postbronchodilator, % predicted, mean Δ (SD)[d,e]	−2.53 (11)	−2.64 (11)	0.10	0.76	.89
FEV_1 postbronchodilator, mL, mean Δ (SD)[d,e,f,i]	−160 (313)	−188 (306)	22.70	21.73	.30
FVC postbronchodilator, % predicted, mean Δ (SD)[d,e]	−2.81 (14)	−3.69 (14)	0.84	0.97	.39
FVC postbronchodilator, mL, mean Δ (SD)[d,e,f,i]	−239 (466)	−314 (506)	65.68	35.85	.07

Five-Year Follow-up in Adult Smokers From the COPDGene Study

CHEST 2018; 153(2):368-377

多國多中心

Lung Function Decline in ACO vs COPD

TABLE 1 Baseline cross-sectional characteristics and longitudinal changes in patients defined by peripheral blood eosinophil counts during follow-up

	Persistently ⩾2%	Intermittent	Persistently <2%	ANOVA p-value
Subjects n	554	728	201	
Age years	64±7	62±7	62±7	0.025
Male sex	68	64	56	0.007
Smoking history pack-years	47±26	47±26	48±30	0.810
Current smokers	30	36	42	0.004
Post-bronchodilator FEV1 L	1.45±0.51	1.37±0.52	1.33±0.51	0.003
Post-bronchodilator FVC L	3.20±0.84	3.05±0.91	3.01±0.96	0.005
Longitudinal Changes				
FEV1 decline mL·year^{-1}	31±48	35±44	30±42	0.209
COPD exacerbations PPPY[+]	1.06±1.18	1.15±1.27	1.07±1.31	0.277
COPD hospitalisations PPPY[+]	0.16±0.38	0.22±0.49	0.23±0.45	0.283
6MWD change over 3 years m	-15±90	-20±103	-20±87	0.626
Emphysema by CT (LAA%) change[§]	1.3±4.5	1.8±4.9	2.7±5.0	0.010
SGRQ total score change[+]	0.2±12.5	1.6±12.8	-1.6±14.3	0.007

Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)

Eur Respir J. 2014 Dec;44(6):1697-700.

Medication effect ?

Lung Function Decline in ACO vs COPD

	All-Negative	Reversibility	Eosinophilia	Atopy
Number of subjects	135	57	52	67
Anticholinergics, n (%)	64 (47)	39 (68)*	26 (50)	34 (51)
β_2-Receptor agonists, n (%)	49 (36)	29 (51)	18 (35)	24 (36)
Theophylline, n (%)	63 (47)	33 (58)	20 (38)	27 (40)
Inhaled corticosteroids, n (%)	14 (10)	15 (26)*	8 (15)	9 (13)

Drug use was considered to be positive when it was used for more than half of the follow-up period during the first 5 years.
*$P < 0.05$ vs. all-negative group by chi-square test.

	All-Negative	One Feature	Two Features	Three Features
Number of subjects	135	96	31	6
Anticholinergics, n (%)	64 (47)	58 (60)	16 (52)	3 (50)
β_2-Receptor agonists, n (%)	49 (36)	37 (39)	11 (35)	4 (67)
Theophylline, n (%)	63 (47)	39 (41)	13 (42)	5 (83)
Inhaled corticosteroids, n (%)	14 (10)	15 (16)	7 (23)	1 (17)

Drug use was considered to be positive when it was used for more than half of the follow-up period during the first 5 years.

Hokkaido COPD cohort study

Am J Respir Crit Care Med Vol 194, Iss 11, pp 1358–1365, Dec 1, 2016

Lung Function Decline in ACO vs COPD

Table 2 Baseline characteristics of lung function, emphysema and use of inhalers of the study population

	Overall ($N = 239$)	Non-ACO COPD ($n = 192$)	ACO ($n = 47$)	*P*-value
Pulmonary Function Test				
FEV_1 (mL)	1486.2 (517.5)	1471.7 (532.4)	1545.5 (451.9)	0.38
FEV_1, % predicted	48.6 (15.0)	48.3 (15.2)	49.7 (14.0)	0.56
FVC (mL)	3279.2 (811.1)	3255.6 (809.1)	3375.7 (820.8)	0.36
FVC, % predicted	77.9 (17.0)	77.5 (16.9)	79.4 (17.5)	0.51
FEV1/FVC (%)	45.1 (10.2)	44.9 (10.7)	45.8 (7.8)	0.59
Post-bronchodilator FEV_1 (mL)	1657.4 (539.9)	1618.5 (540.4)	1816.2 (513.2)	0.024
Post bronchodilator FEV_1, % predicted	54.1 (15.4)	53.1 (15.3)	58.3 (15.4)	0.039
Post bronchodilator $FEV_1 < 50\%$ predicted, n (%)	102 (42.7)	86 (44.8)	16 (34.0)	0.18
Reversibility, n (%)	85 (35.6)	57 (29.7)	28 (59.6)	< 0.01
Emphysema, (%)	21.1 (14.9)	22.1 (14.9)	17.1 (14.7)	0.044
> 5%	193 (80.8)	161 (83.9)	32 (68.1)	0.014
> 10%	163 (68.2)	137 (71.4)	26 (55.3)	0.034
> 15%	133 (55.7)	110 (57.3)	23 (48.9)	0.30
Inhalers				
LAMA, n (%)	79 (33.1)	62 (32.3)	17 (36.2)	0.61
ICS/LABA or ICS, n (%)	98 (40.7)	73 (38.0)	25 (53.2)	0.051

Lung Function

the Korean Obstructive Lung Disease (KOLD) cohort

Park et al. Respiratory Research (2018) 19:36

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Eur Respir J 2019; in press

Research letter

A pilot study to test the feasibility of histological characterisation of asthma-COPD overlap

Blood eosinophils ≥ 300/l, normal DLCO% pred (above 80%), FeNO ≥ 25 ppb, FEV1% pred post bronchodilator ≥ 80%, post-bronchodilator reversibility of airway obstruction ≥ 200 ml, no hyperinflation in X-Ray, personal or family history of allergy, positive prick test, previous diagnosis with asthma, symptoms triggered by exercise, emotions, laughing, allergens, worse symptoms at night or morning, onset of symptoms in age ≤ 20 years old.

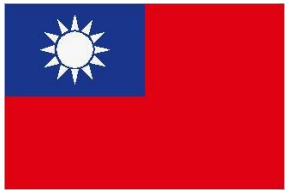
≥ 3

The histological characteristics of ACO: COPD為主

Table 1. Characteristics of patients with COPD, Asthma and COPD-Asthma overlap

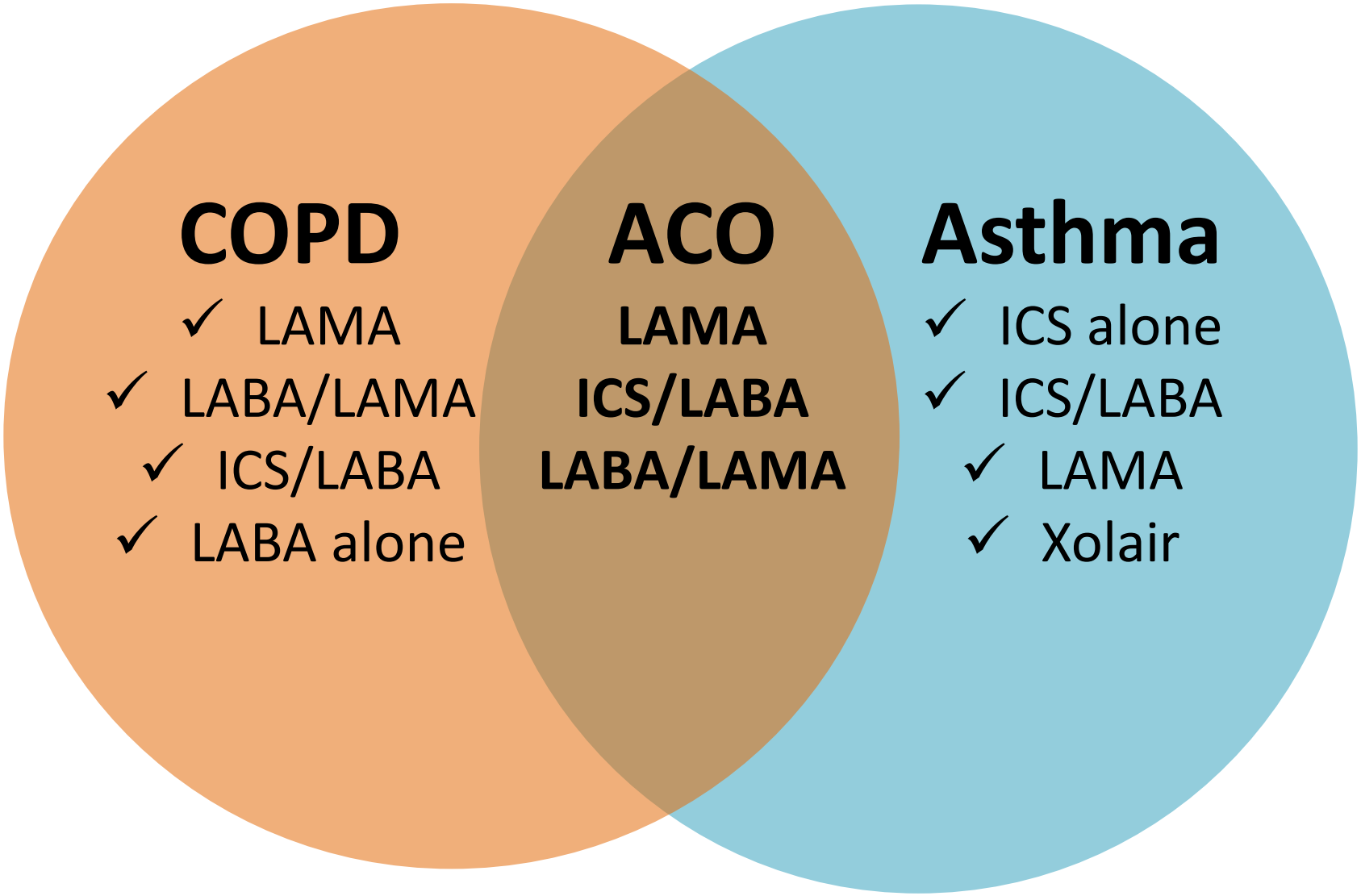
Parameter	All COPD Patients N=147	All Asthma Patients N=19	COPD patients w/o asthma features N=129 (87.8%)	Asthma patients (<10 PY) N=12 (61.1%)	Asthma patients (>10 PY) N=7 (38.8%)	COPD patients with asthma features N=18 (12.2%)
Blood eosinophils (nx1059/l, mean ± SD)*	0.21 ± 0.2	0.21 ± 0.12	0.20 ± 0.2	0.25 ± 0.1	0.17 ± 0.1	0.34 ± 0.3
Blood leucocytes (nx1059/l, mean ± SD)*	8.5 ± 3.2	9.4 ± 3.9	8.7 ± 3.2	8.3 ± 4.0	11.3 ± 3.1	7.9 ± 3.1
Blood neutrophils (n, mean ± SD)**	6.1 ± 3.0	7.2 ± 3.3	6.2 ± 3.1	6.5 ± 3.4	8.2 ± 3.0	5.3 ± 1.8
Granulocytes in the stroma**						
Absence, n (%)	102 (69.4)	18 (94.7)	90 (69.8)	12 (100)	6 (85.7)	12 (66.7)
A few, n (%)	45 (30.6)	1 (5.3)	39 (30.2)	0	1 (14.3)	6 (33.3)
Many, n (%)	0	0	0	0	0	0
Granulocytes in the epithelium**						
Absence, n (%)	120 (81.6)	19 (100)	106 (82.2)	12 (100)	7 (100)	14 (77.8)
A few, n (%)	27 (18.4)	0	23 (17.8)	0	0	4 (22.2)
Many, n (%)	0	0	0	0	0	0
Goblet cells**						
Absence, n (%)	45 (31.3)	2 (10.5)	38 (29.5)	1 (8.3)	1 (14.3)	7 (42.4)
A few, n (%)	43 (24.5)	15 (73.7)	39 (24.8)	10 (83.3)	5 (71.4)	4 (22.2)
Many, n (%)	47 (44.2)	2 (10.5)	41 (45.7)	1 (8.3)	1 (14.3)	6 (33.3)
Not detectable***	12 (8.2)		11 (8.5)			1 (5.5)
BM thicknening**						
Normal, n (%)	14 (9.3)	1 (5.3)	11 (8.5)	1 (8.3)		3 (16.7)
Mild-moderate, n (%)	59 (40.1)	14 (73.7)	57 (44.2)	9 (75.0)	5 (71.4)	2 (11.1)
Severe, n (%)	71 (48.2)	4 (21.1)	58 (45.0)	2 (16.7)	2 (28.6)	13 (72.2)
Average ASMC (%) (mean ± SD)	21.5 ± 9.4	21.5 ± 16.7	21. 0 ± 16.6	22.0 ± 7.9	20.7 ± 12.1	24.3 ± 17.7
Distance BM-ASMC (µm, mean ± SD)	80.5 ± 55.5	62.6 ± 21.1	80.4 ± 55.9	62.8 ± 23.8	62.1 ± 23.8	81.3 ± 55.2
Glands (%) (mean ± SD)	8.5 ± 13.4	4.8 ± 5.5	8.2 ± 12.9	5.1 ± 6.2	4.3 ± 4.8	10.4 ± 16.3
Eosinophils in BAL**** (mean ± SD)	0.9 ± 5.7	1.5 ± 2.8	0.9 ± 6.1	1.2 ± 2.8	2.1 ± 3.1	0.4 ± 0.9

- ✓ The proportion of ACO in COPD in Taiwan: 32.8%.
- ✓ Compared COPD alone, ACO exhibited a LOWER prevalence of comorbidities but HIGHER medical burden.
- ✓ ACO had more episodes of acute exacerbation (RR: 2.75) and better survival compared with the patients with COPD alone.

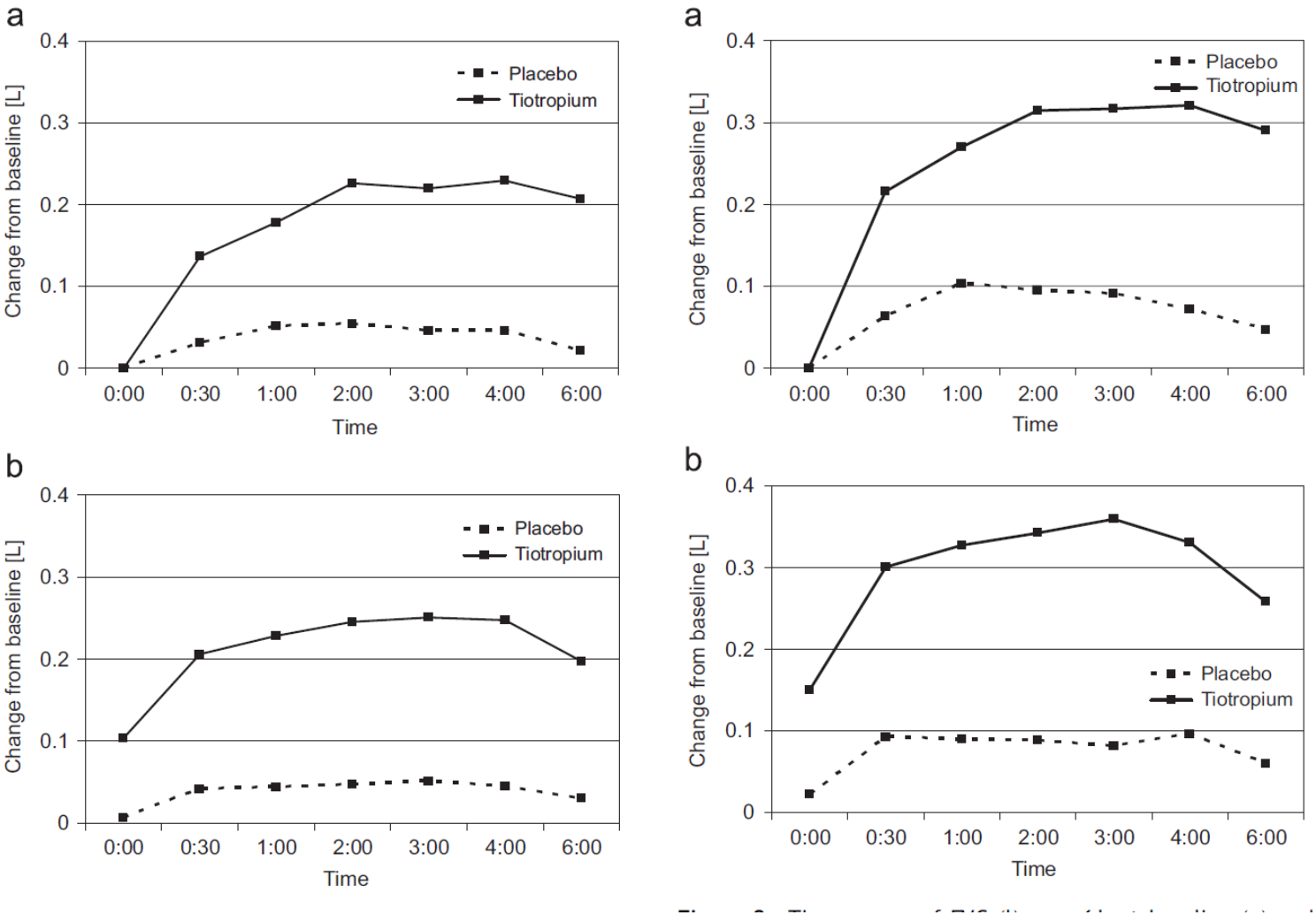


Taiwan Unmet Medical Need In ACO：Real-World Data

Global Unmet Medical Need In ACO：Choice of therapy


COPD
✓ LAMA
✓ LABA/LAMA
✓ ICS/LABA
✓ LABA alone
ACO
LAMA
ICS/LABA
LABA/LAMA
Asthma
✓ ICS alone
✓ ICS/LABA
✓ LAMA
✓ Xolair

LAMA(tiotropium) in COPD + Asthma



Respiratory Medicine (2008) 102,50–56

LAMA(tiotropium) in COPD + Asthma

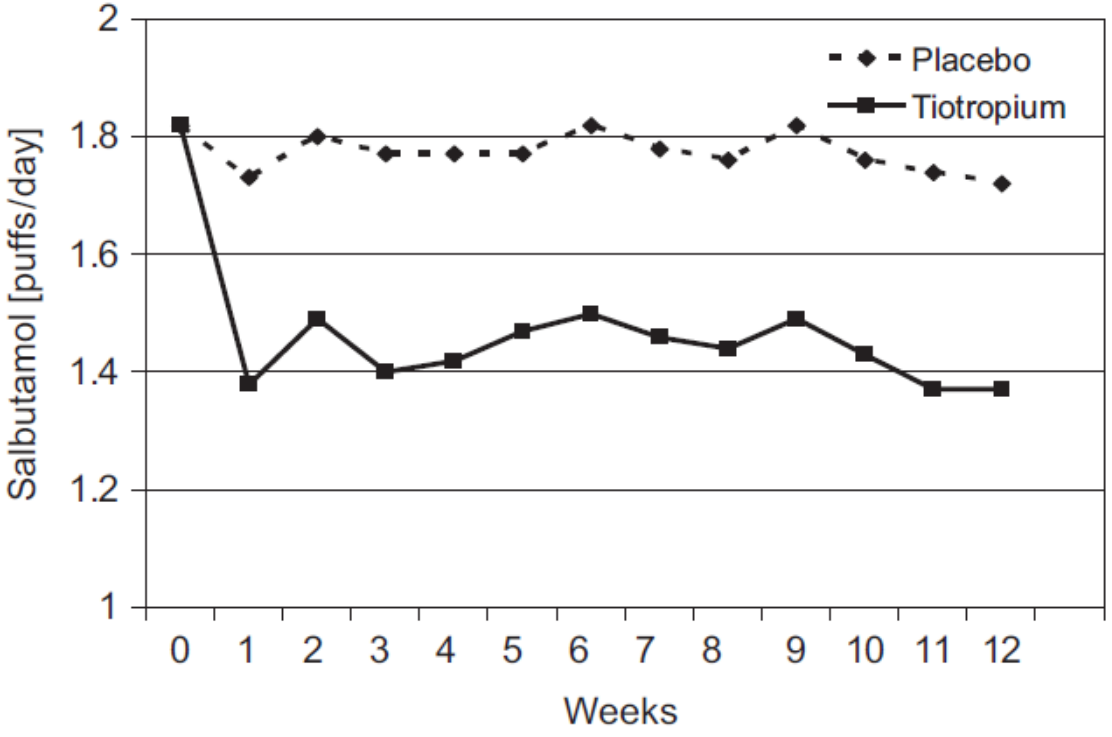


Figure 4 Weekly means for as-needed salbutamol (puffs/24 h) in the tiotropium and placebo groups ($p < 0.01$ for all weeks).

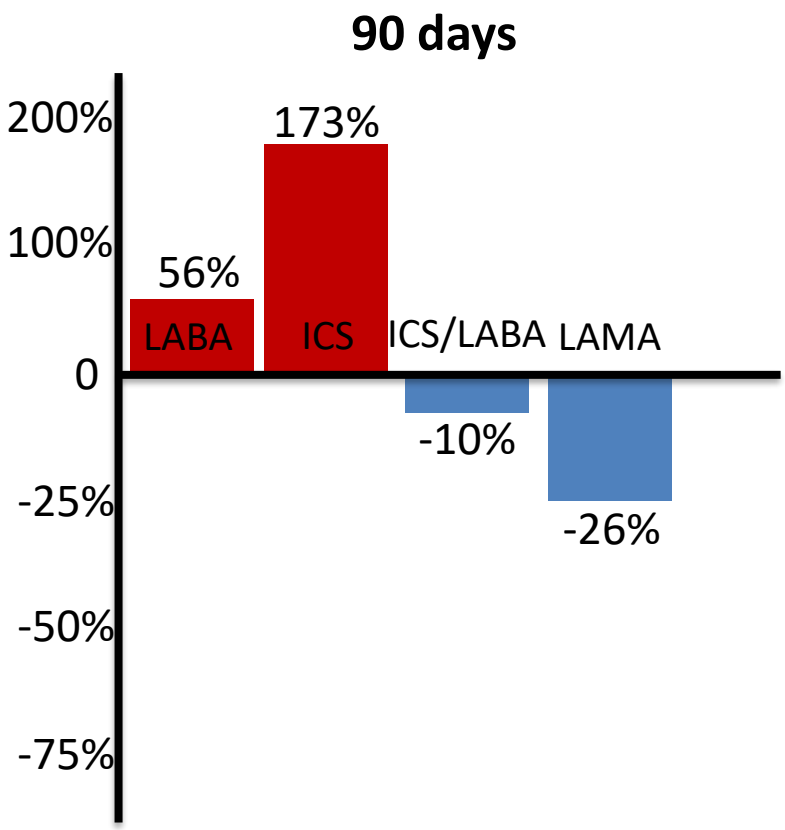
Respiratory Medicine (2008) 102,50–56

TABLE II. Medication effects on acute exacerbation in ACOS and COPD alone cohorts

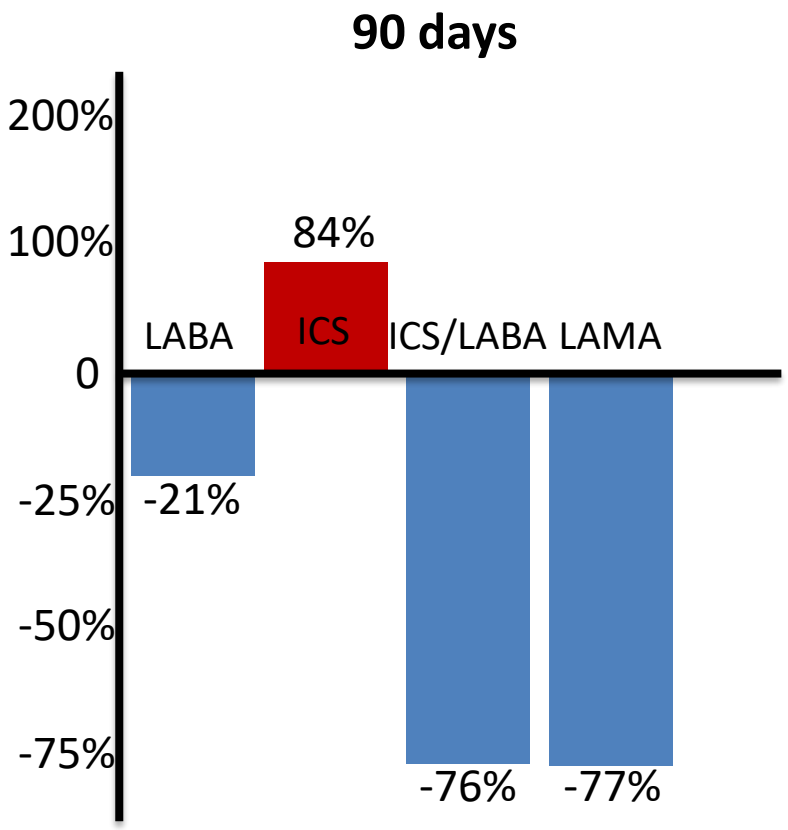
	Time-dependent model			
	1 year*		90 days†	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
COPD + asthma cohort				
Nonusers of LABAs	Reference		Reference	
LABAs	1.09 (1.07-1.12)	<.0001	0.79 (0.77-0.80)	<.0001
Nonusers of LAMA	Reference		Reference	
LAMA	0.51 (0.49-0.54)	<.0001	0.23 (0.21-0.25)	<.0001
Nonusers of ICSs	Reference		Reference	
ICSs	1.91 (1.87-1.95)	<.0001	1.84 (1.81-1.88)	<.0001
Nonusers of ICS/LABA combinations	Reference		Reference	
ICS/LABA combinations	0.61 (0.60-0.62)	<.0001	0.24 (0.23-0.25)	<.0001
COPD alone cohort				
Nonusers of LABAs	Reference		Reference	
LABAs	1.74 (1.68-1.80)	<.0001	1.56 (1.50-1.62)	<.0001
Nonusers of LAMA	Reference		Reference	
LAMA	0.91 (0.86-0.95)	.0001	0.74 (0.70-0.79)	<.0001
Nonusers of ICSs	Reference		Reference	
ICSs	2.26 (2.15-2.39)	<.0001	2.73 (2.61-2.86)	<.0001
Nonusers of ICS/LABA combinations	Reference		Reference	
ICS/LABA combinations	1.06 (1.02-1.11)	.0054	0.90 (0.85-0.95)	.0001

Acute Exacerbation

COPD alone

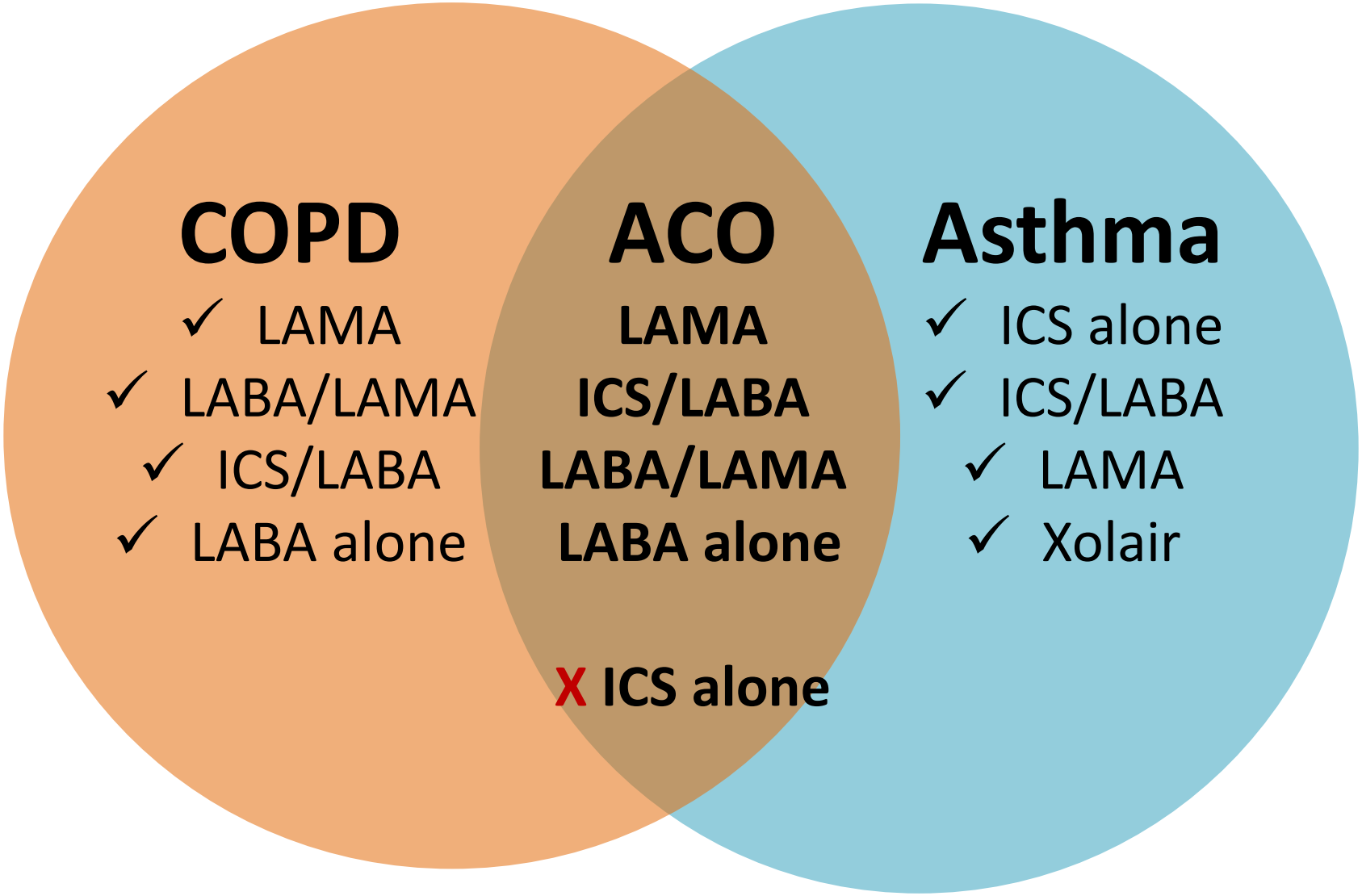


ACO



J Allergy Clin Immunol Pract. 2018 Feb 9.

ACO患者的藥物選擇


COPD
✓ LAMA
✓ LABA/LAMA
✓ ICS/LABA
✓ LABA alone
ACO
LAMA
ICS/LABA
LABA/LAMA
LABA alone
X ICS alone
Asthma
✓ ICS alone
✓ ICS/LABA
✓ LAMA
✓ Xolair

ACO患者的藥物選擇

Controversies in Allergy

Controversies in Allergy: Is Asthma Chronic Obstructive Pulmonary Disease Overlap a Distinct Syndrome That Changes Treatment and Patient Outcomes?

Donald P. Tashkin, MD, and R. Stokes Peebles, Jr., MD *Los Angeles, Calif; and Nashville, Tenn*

J Allergy Clin Immunol Pract. 2019 Apr;7(4):1142-1147.

ACO患者的藥物選擇

smoked, but who have fixed airway obstruction secondary to airway wall remodeling. Inclusion of these types of patients is critical to understand optimal therapeutic strategy for patients with ACO. It is of interest, however, that despite the lack of randomized controlled trials to assess the relative benefits and risks of different treatment options, a recent observational study from Taiwan that included more than 250,000 patients with ACO and more than 500,000 patients with COPD alone found that the same medications (ie, a long-acting muscarinic antagonist or an inhaled corticosteroid/long-acting beta-agonist combination) that were effective in lowering the risk of acute exacerbations in patients with COPD alone were also found to be effective in patients with ACO.[36]

J Allergy Clin Immunol Pract. 2019 Apr;7(4):1142-1147.

ACO患者的藥物選擇

REVIEW

Check for updates

Challenges in the management of asthma associated with smoking-induced airway diseases

Neil C Thomson

Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK

EXPERT OPINION ON PHARMACOTHERAPY 2018, VOL. 19, NO. 14, 1565-1579

Table 2. Summary of recent studies on the therapeutic response to inhaled corticosteroids and long-acting beta$_2$-agonists in current smokers and former smokers with asthma or asthma-COPD overlap (ACO).

Reference	Diagnostic label	Study design	Number of participants	Baseline patient characteristics: Age, years [Mean (SD)]	Baseline patient characteristics: Baseline FEV_1 (%, predicted) [Mean (SD)]	Baseline patient characteristics: Pack year history [Mean (SD)]	ICS/LABA daily treatment (dose) and duration	Main outcome measures
Standard-particle size ICS and LABA								
Pilcher al. 2016 [42].	Asthma	Open-label, randomized, controlled trial	59 current smokers, 97 former smokers, 147 never smokers	Current smokers, 40 (12); former smokers, 44 (13); ever smokers, 40 (15)	Current smokers, 79(18); former smokers, 79 (21); ever smokers, 84 (18)	Current smokers, median 7 (range 1–40); former smokers, median 5 (range 0.2–34); ever smokers, 0 (0–0)	Budesonide/ formoterol 200/6-µg maintenance (two actuations twice daily) and either budesonide/formoterol 200/6-µg one actuation ('single ICS/LABA maintenance and reliever therapy (SMART)' regimen) or salbutamol 100 µg 1–2 actuations for symptom relief ('Standard' regimen) for 24 weeks	Severe exacerbation (primary outcome); hospital or ED visit; FEV_1; ACQ score
Woodcock et al. 2017 [44]	Asthma	Open-label, randomized, controlled	Total, 4233, 20% current smokers	Total, 50(17)	Not recorded	Nor recorded	Fluticasone furoate, either 100 µg or 200 µg, with 25 µg vilanterol once-daily or optimized usual care for 12 months	ACT score (primary outcome); severe exacerbation; AQLQ
Ishiura et al. 2015 [45]	ACO	Open-label cross-over	16 former smokers	74(7)	Absolute values, 1.33 (0.29) L	67(39)	Fluticasone furoate with vilanterol FF/Vl 200/25 µg or fluticasone propionate with salmeterol 500/50 µg, twice-daily for 4 weeks each	FEV_1; ACT; CAT; impulse oscillometry; FeNO
Suzuki et al. 2015 [46]	ACO	Open-label observational	Subgroup of 20 with ACO	ACO, 68(11)	ACO, 57(18)	ACO, 53(36)	Budesonide/formoterol (160/4.5 µg), two inhalations; twice daily for 12 weeks	FEV_1; PEF; CAT; computed tomography images
Lee et al. 2016 [47]	ACO	Open-label observational	45 (29.6%) ACO, 107 COPD alone	ACO, median 64 (IQR 61–70), COPD, median 68 (IQR 61–71)	ACO, median 55 (IQR 44.5–65.5), COPD, median 56 (IQR 43.0–72.0)	ACO, median 44 (IQR 36.6–55.0), COPD, median 45 (IQR 30.0–55.0)	Fluticasone propionate/salmeterol (500/50 µg) or budesonide/formoterol (320/9 µg), twice daily	FEV_1; static lung volumes
Su et al. 2018 [48]	ACO	Observational retrospective matched cohort	251,398 ACO, 514,522 COPD alone	ACO, 65(11), COPD, 66(12)	Not recorded	Not recorded	Exposure to ICS/LABA (budesonide/formoterol, mometasone/formoterol, fluticasone/salmeterol) or LAMA (tiotropium) during mean follow-up period of 9.9 years	Acute exacerbation (ED and hospital admission) (Primary outcome)

Table 3. Summary of recent studies on the therapeutic response to the inhaled long-acting muscarinic antagonist tiotropium in current smokers and former smokers with asthma or asthma-COPD overlap (ACO).

Reference	Diagnostic label	Study design	Number of participants	Baseline patient characteristics: Age, years [Mean (SD)]	Baseline patient characteristics: Baseline FEV_1 (%, predicted) [Mean (SD)]	Baseline patient characteristics: Pack year history [Mean (SD)]	ICS daily treatment (dose) and duration	Main Outcome measures
Tiotropium								
Yoshida et al. 2017 [58]	Asthma	Randomized placebo controlled, cross-over	9 current smokers, 9 never smokers	Current smokers, 51 (11); never smokers, 62(12)	Current smoker, 87 (22); never smokers, 90(13)	Current smokers, 19(16)	Tiotropium 18 µg one inhalation; measurements for 24 h	FEV_1 (primary outcome); PEF; FEF_{25}; FEF_{50}
Su et al. 2018 [48]	ACO	Observational retrospective matched cohort	251,398 ACO, 514,522 with COPD alone	ACO, 65(11), COPD, 66(12)	Not recorded	Not recorded	Exposure to ICS/LABA (budesonide/formoterol, mometasone/formoterol, fluticasone/salmeterol) or LAMA (tiotropium) during mean follow-up period of 9.9 years	Acute exacerbation (ED and hospital admission) (Primary outcome)

Abbreviations: ED, emergency department; FEF_{50}, Forced Expiratory Flow at 50% of expired volume during forced vital capacity (FVC); FEF_{25}, Forced Expiratory Flow at 50% of expired volume during FVC; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; PEF, peak expiratory flow;

ACO患者的藥物選擇

Table 3. Summary of recent studies on the therapeutic response to the inhaled long-acting muscarinic antagonist tiotropium in current smokers and former smokers with asthma or asthma-COPD overlap (ACO).

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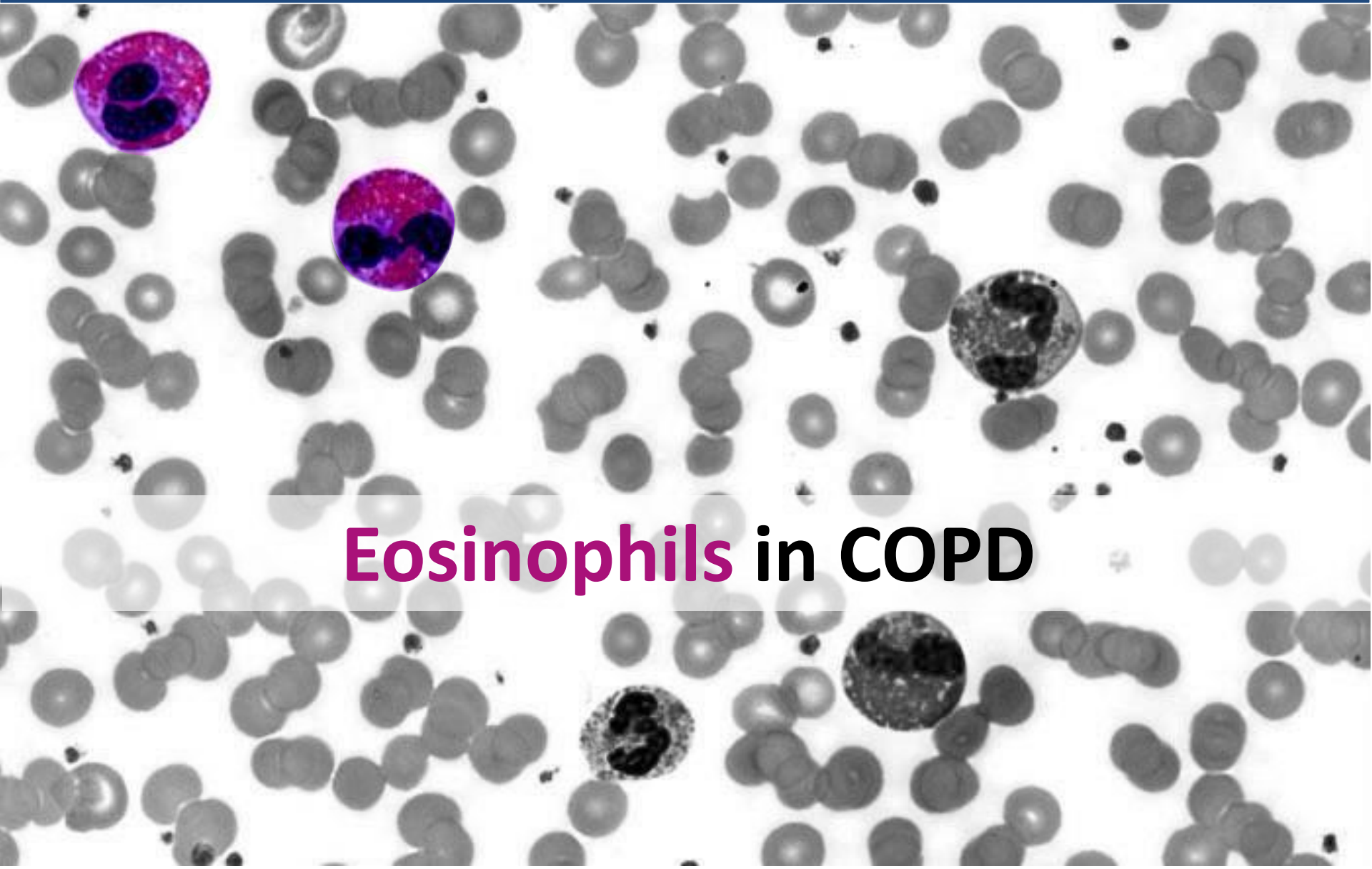
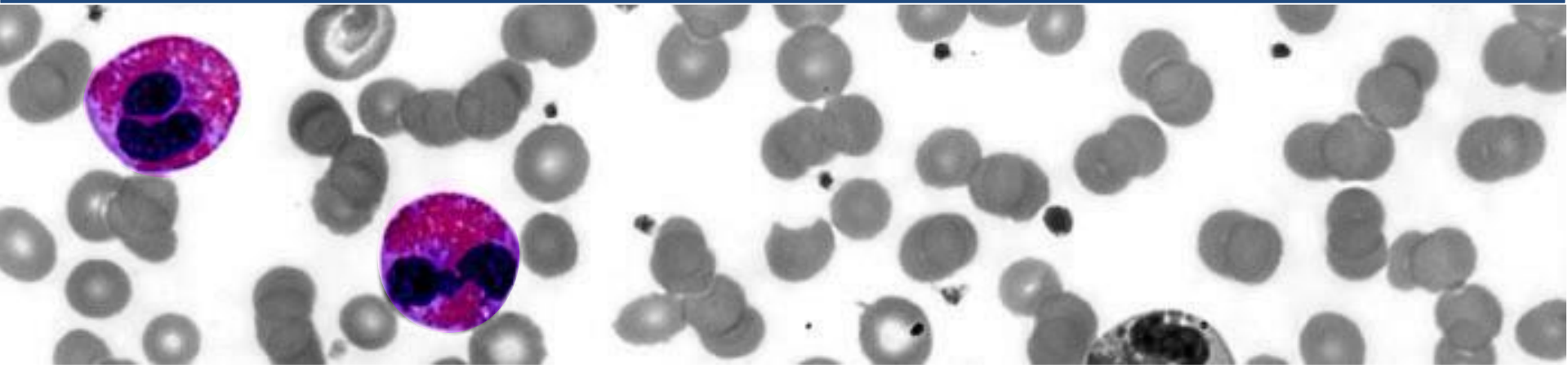
Abbreviations: ED, emergency department; FEF_{50}, Forced Expiratory Flow at 50% of expired volume during forced vital capacity (FVC); FEF_{25}, Forced Expiratory Flow at 50% of expired volume during FVC; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LAMA, long-acting muscarinic antagonist; PEF, peak expiratory flow;

EXPERT OPINION ON PHARMACOTHERAPY 2018, VOL. 19, NO. 14, 1565-1579



Eosinophils in COPD



Eosinophils in COPD = ICS/LABA ?

Seretide (Diskus, MDI)	Symbicort (Turbuhaler)	Foster (MDI)
		

Prevalence: Eosinophils in COPD

	COPD			Asthma		
	Sputum eosinophils (%)	Blood eosinophils ($\times 10^9$ cells per L)	Blood eosinophils (%)	Sputum eosinophils (%)	Blood eosinophils ($\times 10^9$ cells per L)	Blood eosinophils (%)
During stable disease						
Bafadhel et al (2011)[6]	1·2 (0·7)	0·21 (0·32)	3·21 (2·24)*	..	..	..
Bafadhel et al (2012)[7]	0·9 (0·6)	0·21 (0·28)	2·96 (1·99)*	..	..	..
Lacoste et al (1993)[27]	1·0 (1·7)†	0·26 (0·11)*	..	1·6 (2·5)†	0·50 (0·28)	..
Haldar et al (2009)[39]	..	..	..	6·2 (0·7)‡	0·34 (0·34)‡	..
Bafadhel et al (2012)[44]	1·2 (0·8–1·9)§	0·20 (0·17–0·24)§	..	2·6 (1·6–4·2)§	0·20 (0·16–0·25)§	..
Brightling et al (2014)[57]	10·4 (14·3)*‡	0·24 (0·18)*‡	..	..	..	..
Siva et al (2007)[59]	1·6 (0·6)*	0·22 (0·20)*	..	..	..	..
During exacerbations						
Bafadhel et al (2011 and 2012)[6,7]	4·4 (9·9)*	0·27 (0·22)*	3·8 (3·9)*	..	..	..
Bathoorn et al (2009)[60]	2·8 (0·8–4·8)¶	0·2 (0·1–0·4)¶	2·9 (1·9–5·8)¶	..	..	..

Data are geometric mean (log SD). *Data are mean (SD). †Bronchoalveolar lavage. ‡Only eosinophilic patients were recruited. §Data are geometric mean (95% CI). ¶Data are median (IQR). Only prospectively collected data from reviewed original research, where blood and sputum parameters were available, are shown.

Table 1: Summary of eosinophil counts in patients with asthma or COPD during stable disease and exacerbations

Lancet Respir Med. 2017 Sep;5(9):747-759.

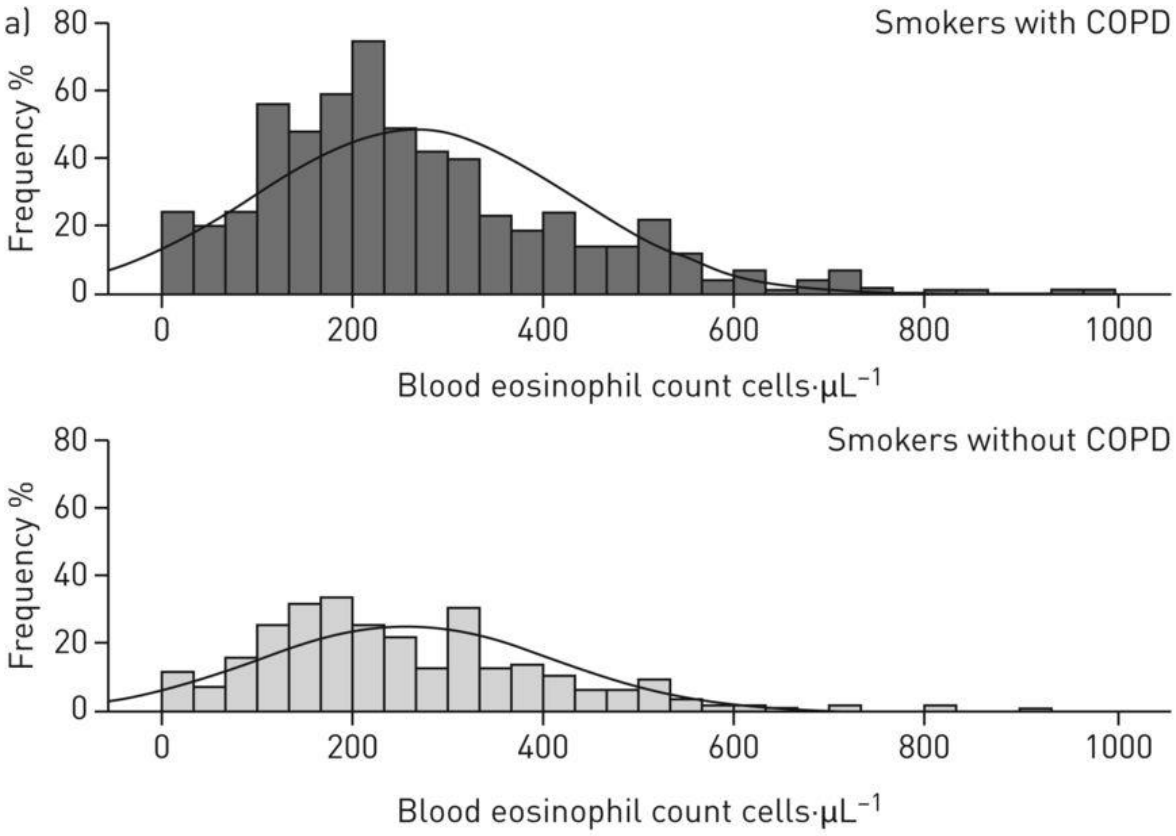
Eosinophils in COPD

（接續上頁）表 4-1-1: 病患基本特性

	第一種疾病標準：未經肺量計輔助					第二種疾病標準：經肺量計定義				
	慢性阻塞性肺病合併氣喘		慢性阻塞性肺病		*p*	慢性阻塞性肺病合併氣喘		慢性阻塞性肺病		*p*
總人數	106		183			53		68		
	人數	%	人數	%		人數	%	人數	%	
嗜伊紅性球	(n=96)		(n=137)			(n=47)		(n=47)		
佔白血球比例[Θ]，%	3.0±3.2		2.5±3.0		0.2927	3.2±3.1		2.2±2.2		0.0847
≧2%	46	47.92	59	43.07	0.4639	25	53.19	19	40.43	0.2149

Unpublished data

Eosinophils in COPD

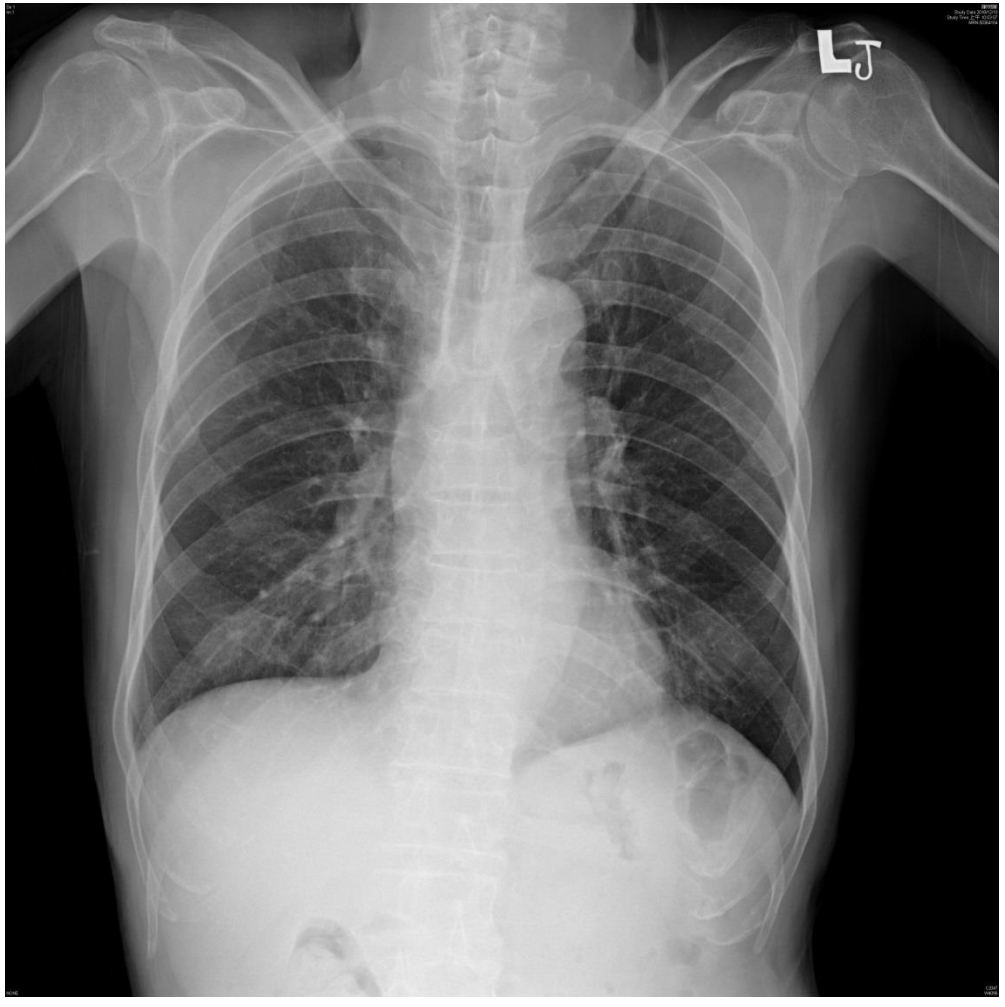


COPD from the CHAIN cohort

Eur Respir J. 2017 Nov 22;50(5).

Stability of Blood Eosinophils in COPD ?

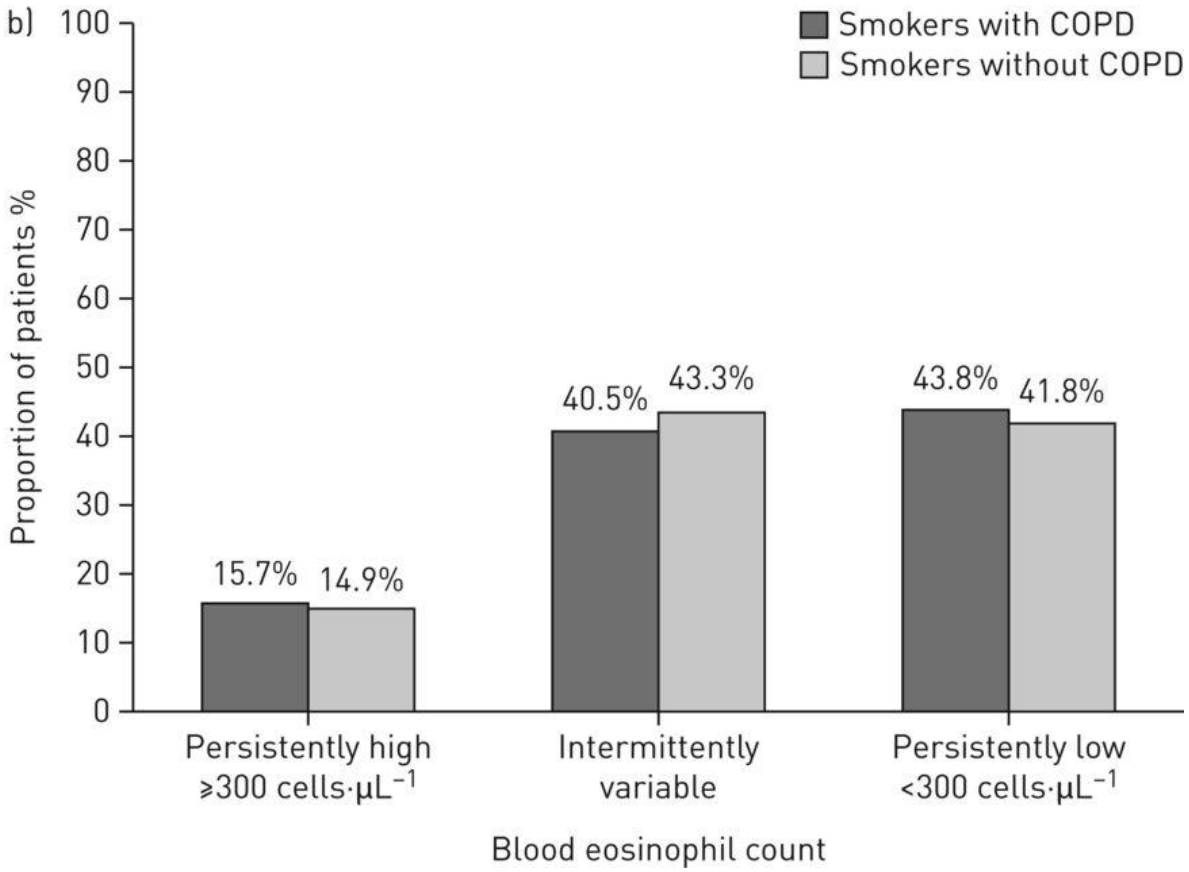
70 y/o male, COPD with AE



	12/10		
WBC		6.19	10^3/uL
RBC	L	2.23	10^6/uL
Hb	L	6.7	g/dL
Hct	L	20.7	%
MCV		92.8	fL
MCH		30.0	pg
MCHC		32.4	g/dL
RDW-CV	H	16.1	%
RDW-SD		55.7	fl
Platelet		266	10^3/uL
Neut		62.8	%
Lym		25.5	%
Mono	H	9.4	%
Eos		2.1	%
Basophil		0.2	%

	12/13		
WBC		6.25	10^3/uL
RBC	L	3.32	10^6/uL
Hb	L	9.7	g/dL
Hct	L	29.0	%
MCV		87.3	fL
MCH		29.2	pg
MCHC		33.4	g/dL
RDW-CV	H	15.8	%
RDW-SD		50.5	fl
Platelet		243	10^3/uL
Neut		50.5	%
Lym		25.3	%
Mono	H	8.2	%
Eos	H	15.7	%
Basophil		0.3	%

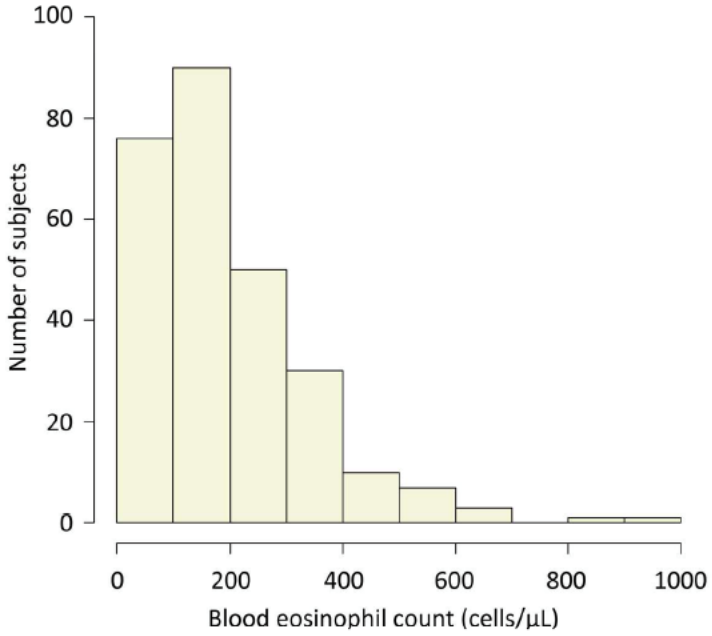
Stability of Blood Eosinophils in COPD ?

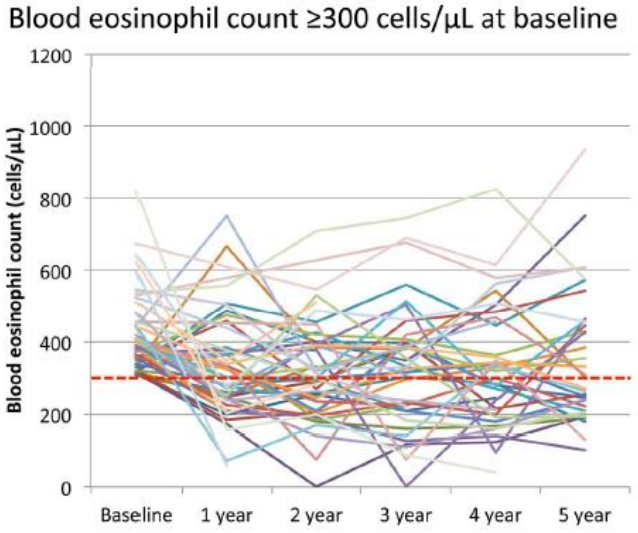


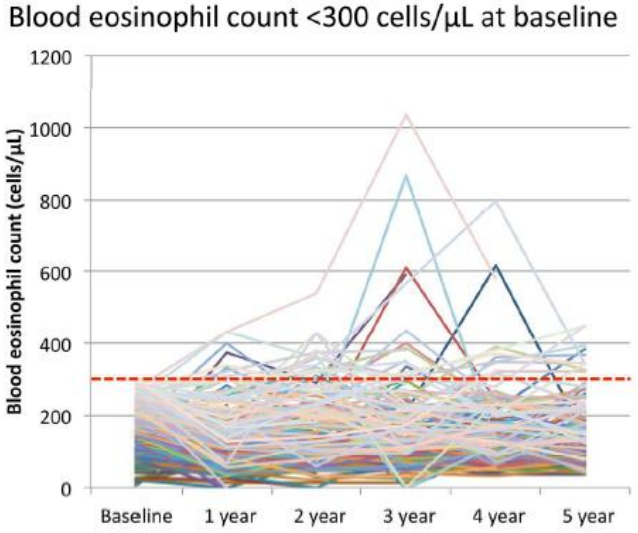
COPD from the CHAIN cohort

Eur Respir J. 2017 Nov 22;50(5).

Eosinophils in COPD







Hokkaido COPD cohort study

Am J Respir Crit Care Med Vol 194, Iss 11, pp 1358–1365, Dec 1, 2016

Eosinophils in COPD

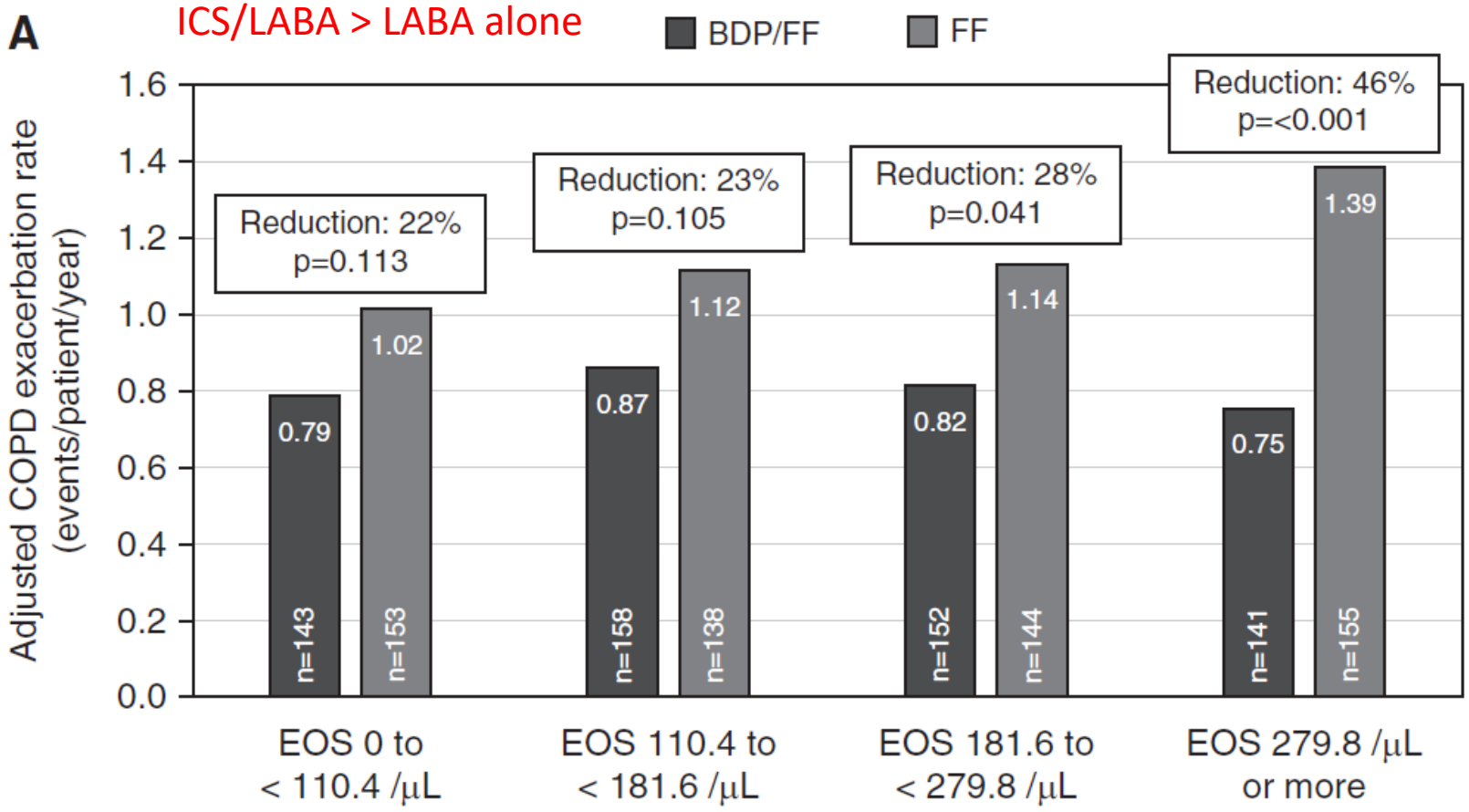
TABLE 1 Baseline cross-sectional characteristics and longitudinal changes in patients defined by peripheral blood eosinophil counts during follow-up

	Persistently ⩾2%	Intermittent	Persistently <2%	ANOVA p-value
Subjects n	554	728	201	
Age years	64±7	62±7	62±7	0.025
Male sex	68	64	56	0.007
Smoking history pack-years	47±26	47±26	48±30	0.810
Current smokers	30	36	42	0.004
Post-bronchodilator FEV_1 L	1.45±0.51	1.37±0.52	1.33±0.51	0.003
Post-bronchodilator FVC L	3.20±0.84	3.05±0.91	3.01±0.96	0.005
FEV_1 % predicted	51±15	49±16	48±15	0.009
Post-bronchodilator FEV_1/FVC %	46±12	45±11	45±11	0.445
BMI $kg \cdot m^{-2}$	27±5	27±6	26±6	0.190
Fat free mass index $kg \cdot m^{-2}$	53±12	52±13	50±13	0.009
6MWD m	395±116	385±115	377±127	0.142
Emphysema by CT (LAA%)	17±12	17±12	18±12	0.486
Oxygen saturation %	94.9±3.1	94.9±2.5	94.7±2.5	0.676
SGRQ total Score	44±18	47±18	49±19	0.002
FACIT fatigue score	37±10	36±10	36±10	0.106
mMRC score	1.4±1.0	1.6±1.0	1.7±1.1	0.006
BODE index	2.6±1.9	2.9±2.0	3.2±2.2	0.001
WBCs $\times 10^9$ L^{-1}	7.5±2.0	7.9±2.1	8.1±2.2	<0.001
Exacerbation rate#	0.75±1.18	0.86±1.23	0.85±1.09	0.232
COPD hospitalisation rate¶	0.13±0.47	0.18±0.53	0.18±0.57	0.245

ECLIPSE study 3-year follow-up period; 1st, 2nd, 3rd year

Eur Respir J 2014;44:1697–1700.

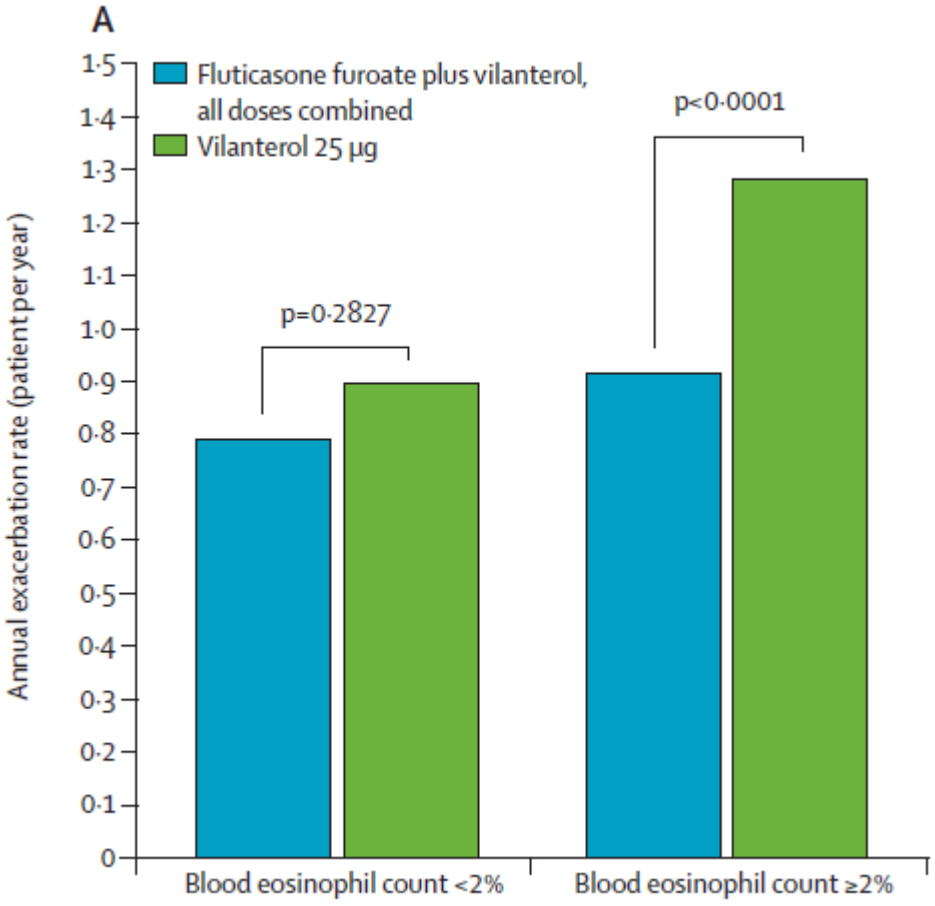
FORWARD study in Severe COPD

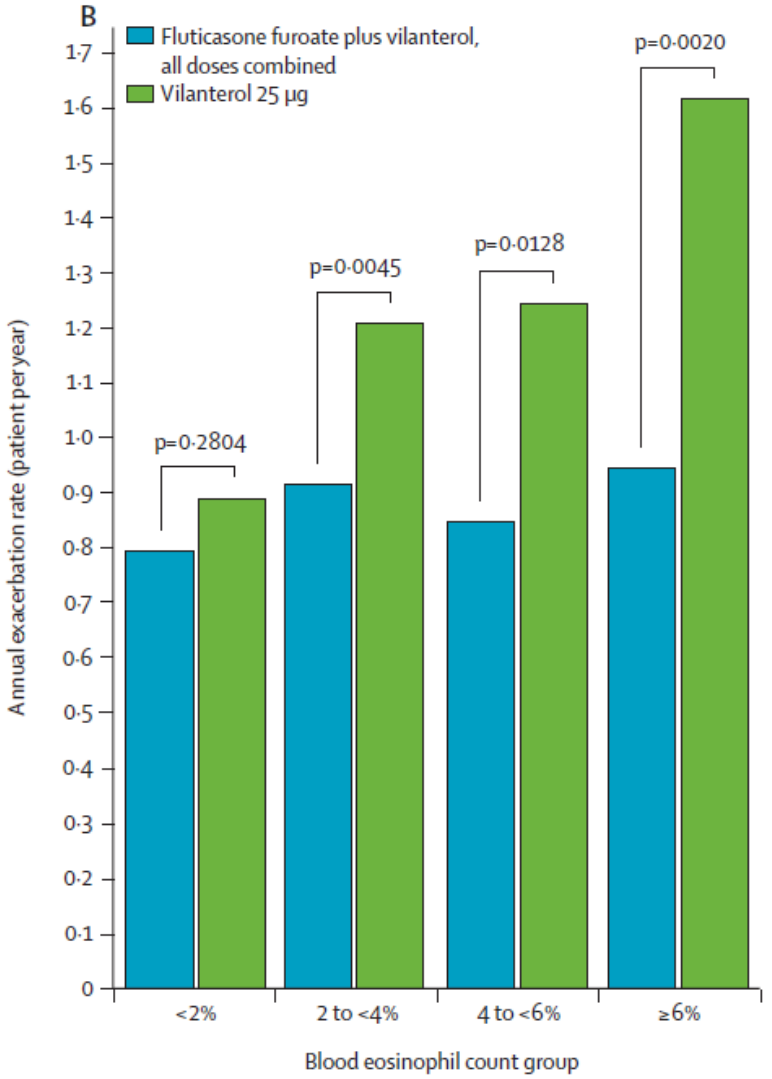


AJRCCM Volume 192 Number 4 | August 15 2015

Relvar in patients with a history of COPD exacerbations

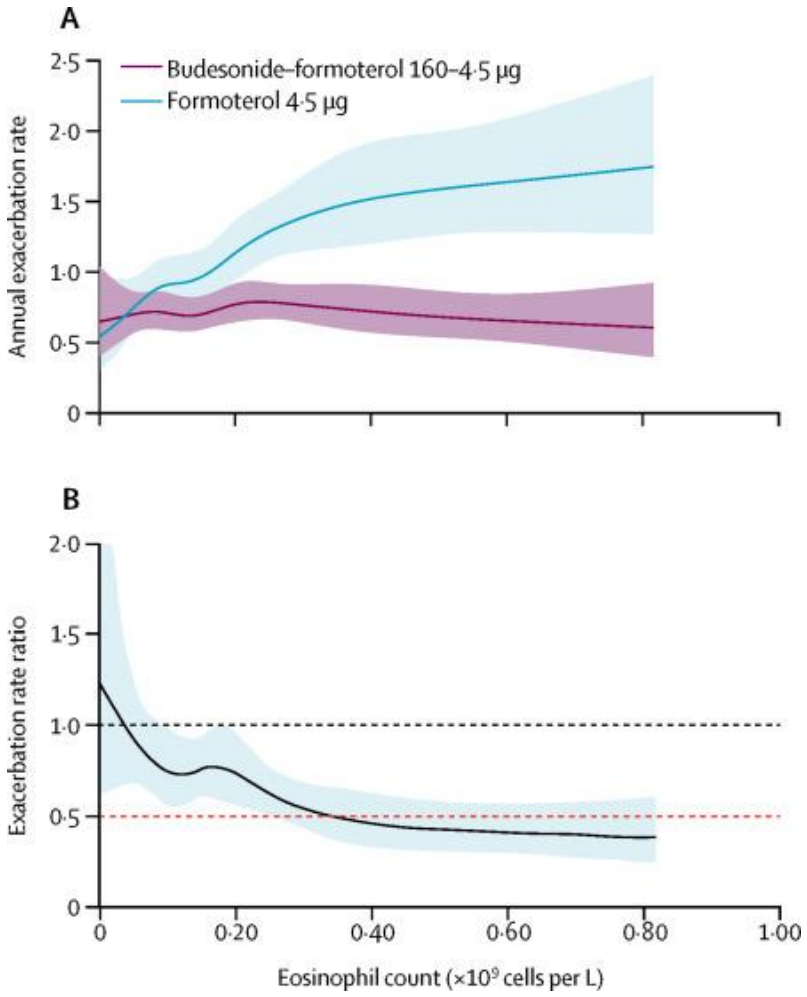
ICS/Ultra-LABA > Ultra-LABA alone

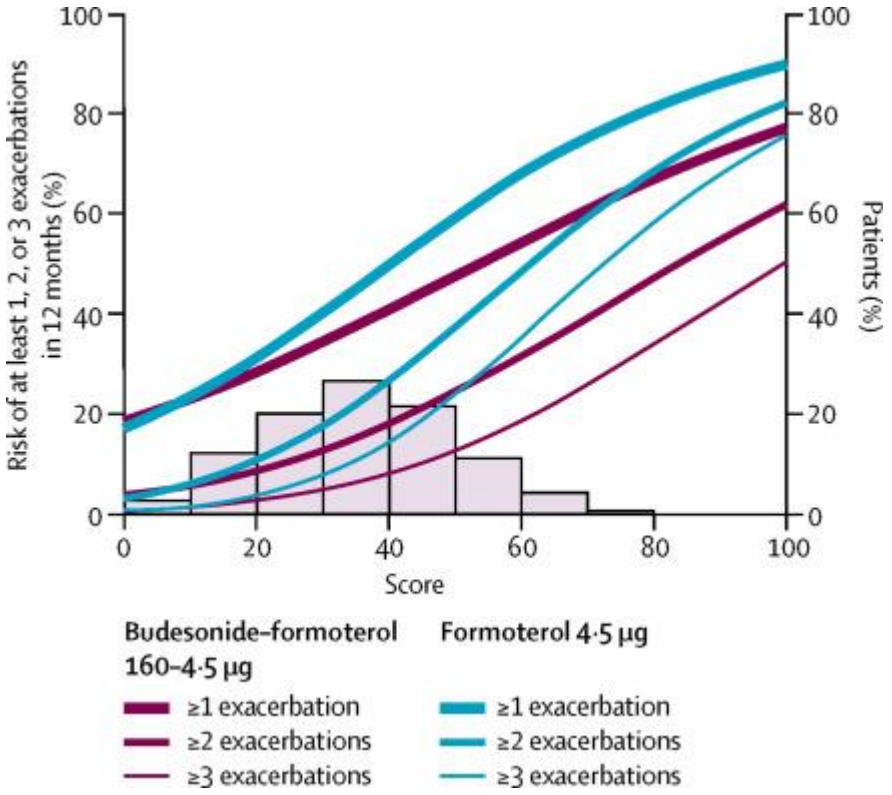




Lancet Respir Med 2015; 3: 435–42

ICS/LABA > LABA, Eso ≥ 100

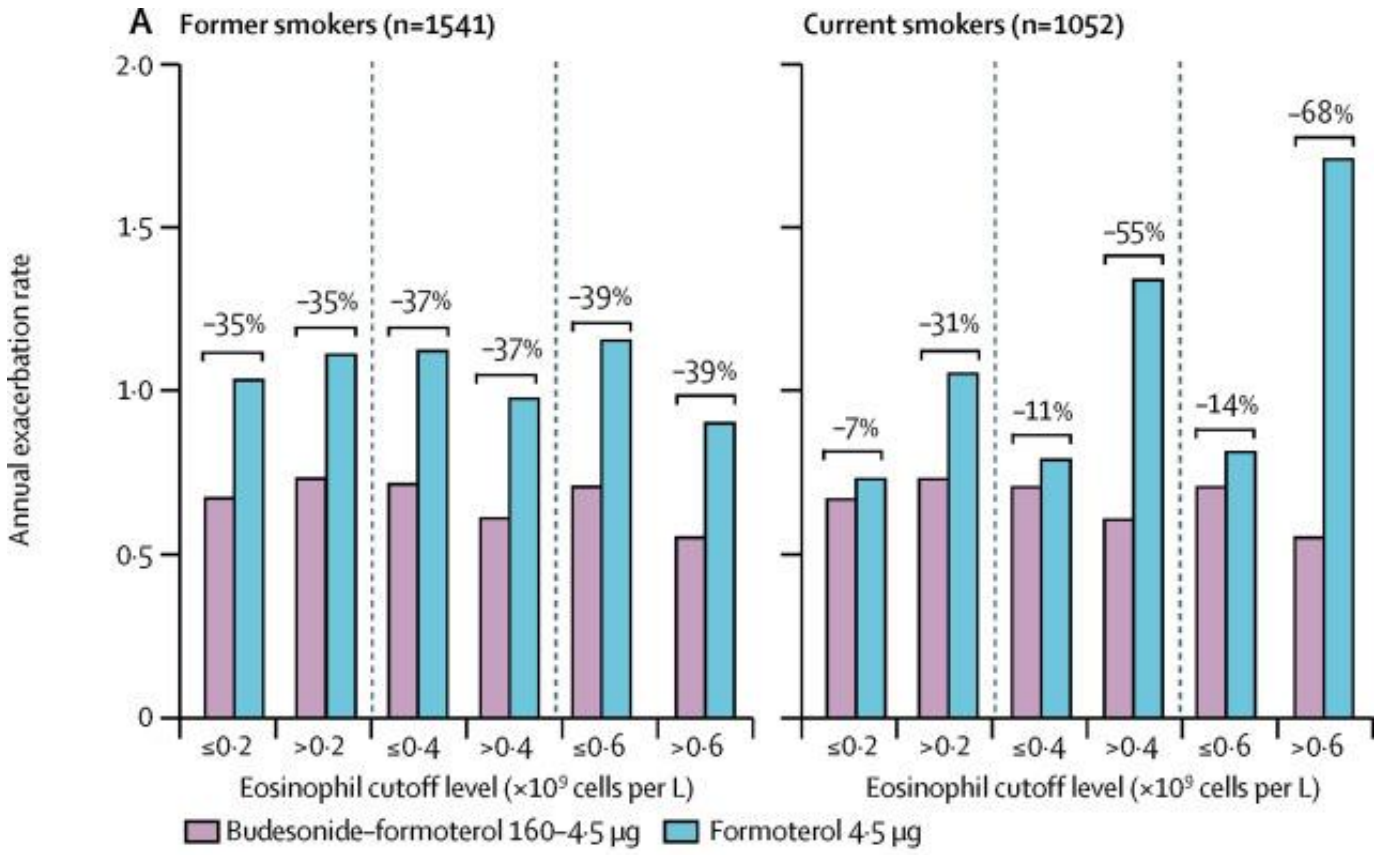




3 AstraZeneca RCTs in COPD

Lancet Respir Med. 2018 Feb;6(2):117-126.

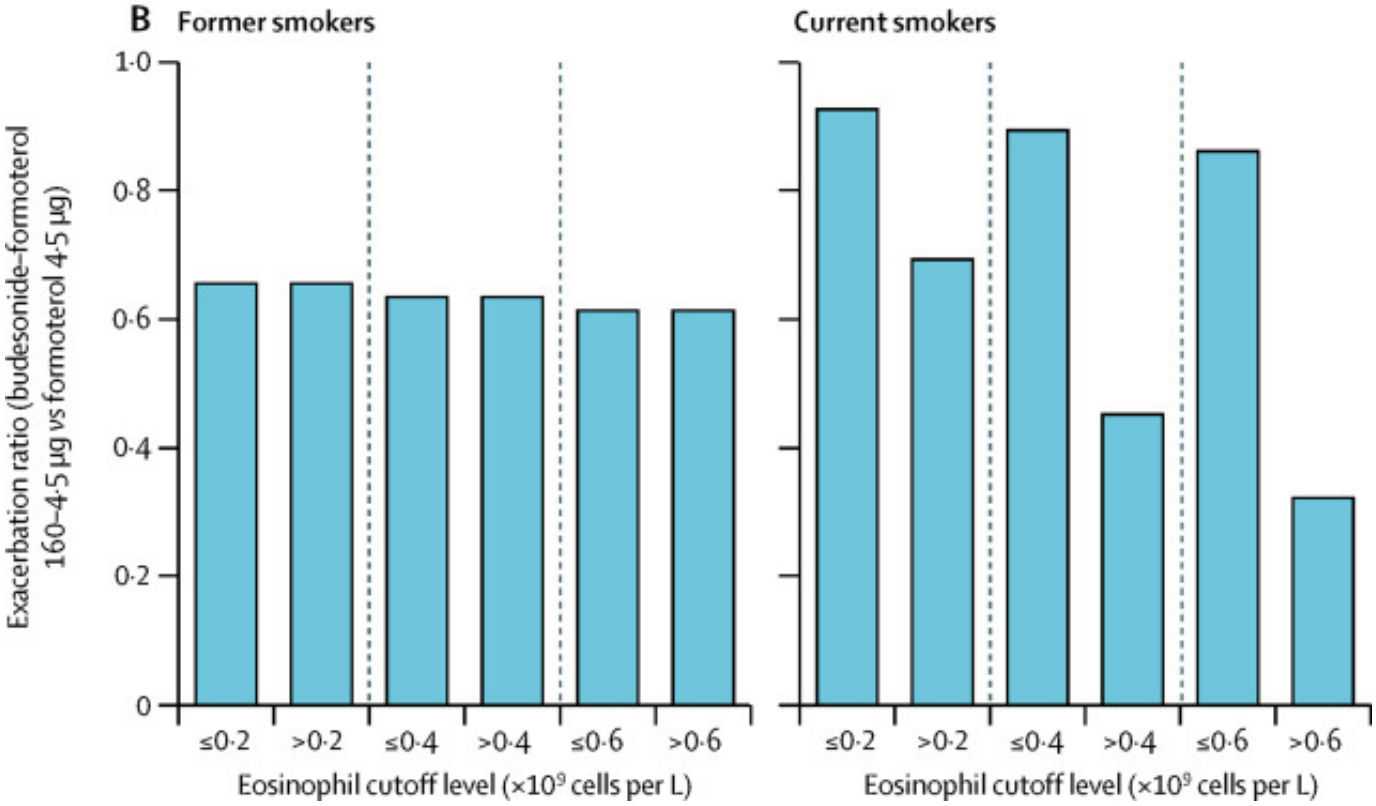
ICS/LABA > LABA, Former smokers > Current smokers



3 AstraZeneca RCTs in COPD

Lancet Respir Med. 2018 Feb;6(2):117-126.

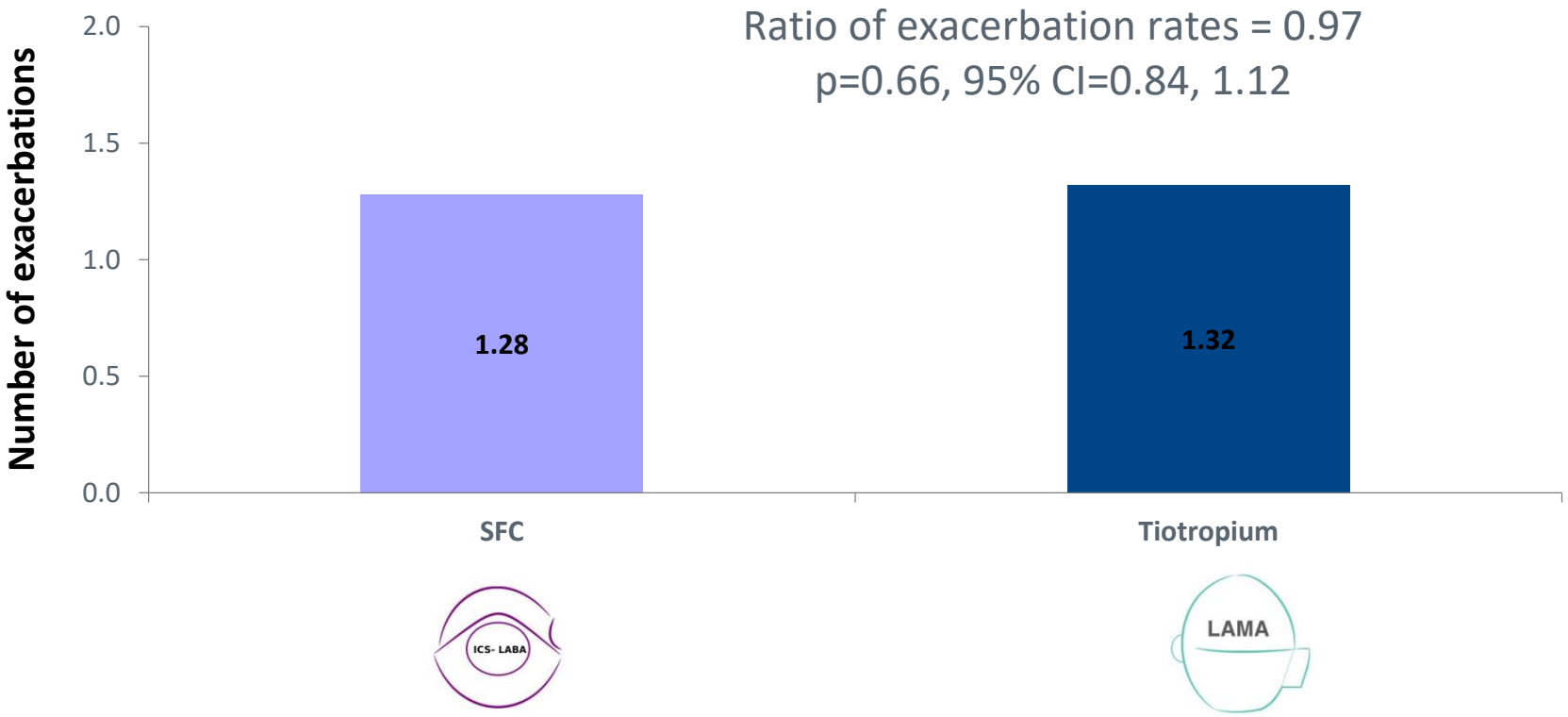
ICS/LABA > LABA,
Former smokers > Current smokers (≤200) > Current smokers (>200)
Current smokers (>600) > Current smokers (>400) > Current smokers (>200)



3 AstraZeneca RCTs in COPD

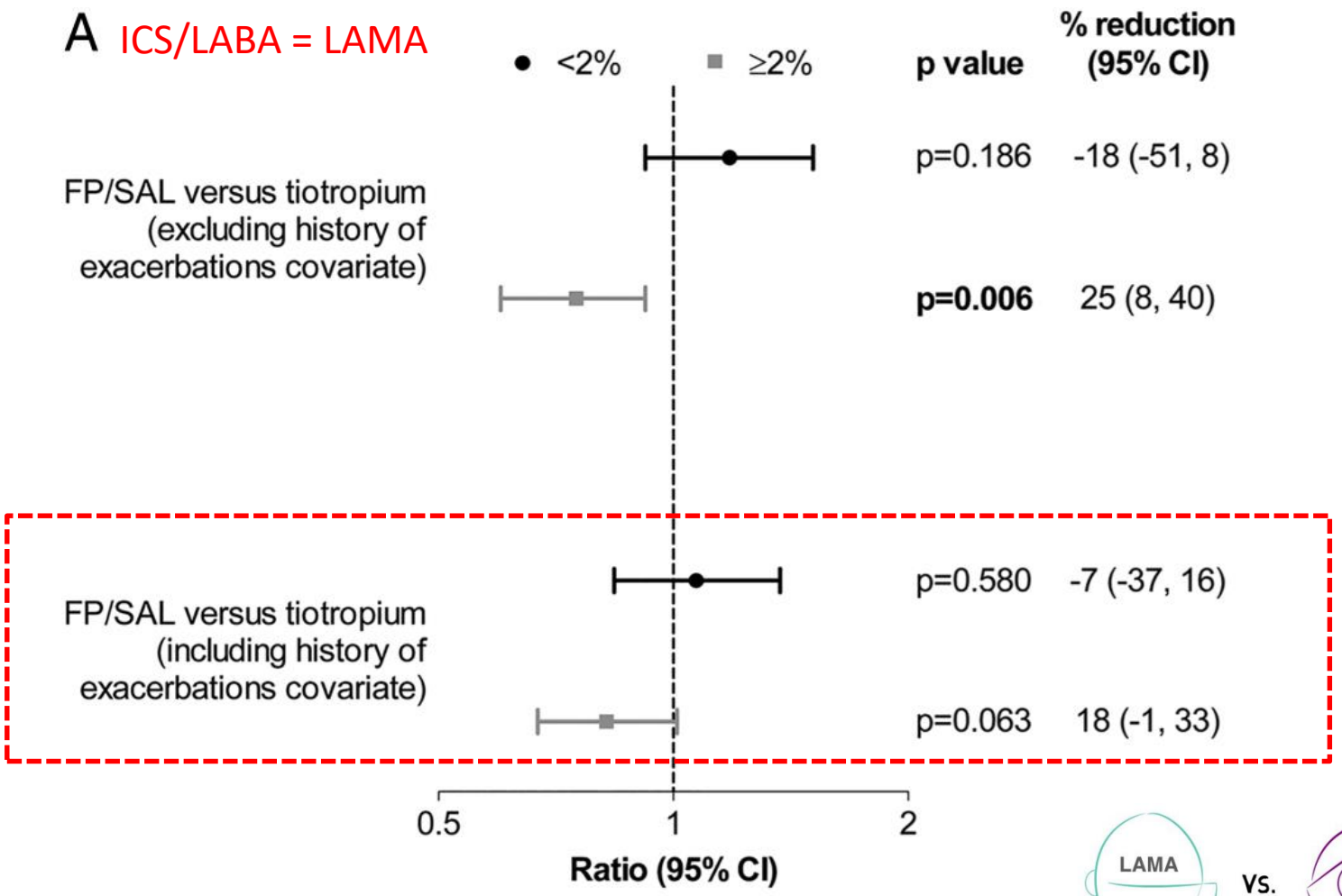
Lancet Respir Med. 2018 Feb;6(2):117-126.

INSPIRE study
LABA/ICS = tiotropium, overall exacerbation rates over 2-year trial period



Am J Respir Crit Care Med Vol 177. pp 19–26, 2008

INSPIRE study



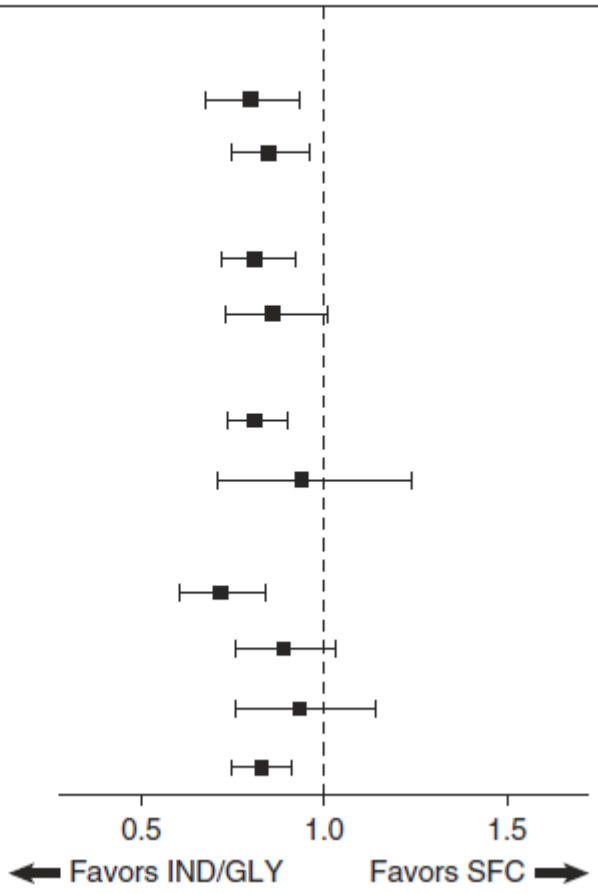
Thorax 2016;71:118–125.

FLAME: Rate ratio for all exacerbations

Ultra-LABA/LAMA > ICS/LABA

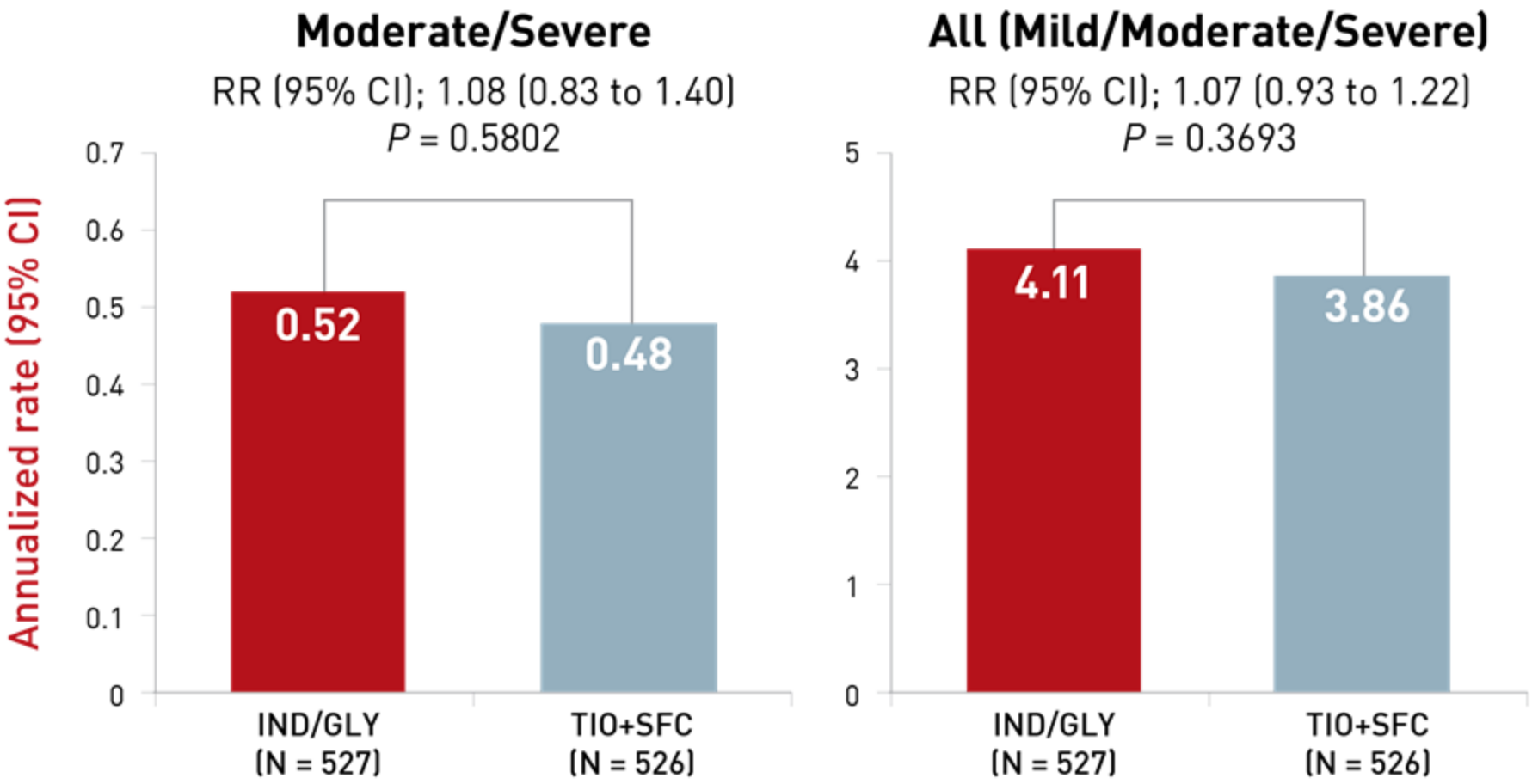
A

Subgroup	No. of patients IND/GLY	No. of patients SFC	Annualized rate IND/GLY	Annualized rate SFC	Rate ratio (95% CI)
Blood eosinophils count					
< 2 %	620	659	0.99	1.24	0.80 (0.68, 0.93)
≥ 2%	1,026	993	0.98	1.15	0.85 (0.75, 0.96)
Blood eosinophils count					
< 3 %	1,041	1,037	0.99	1.22	0.81 (0.72, 0.92)
≥ 3 %	605	615	0.98	1.14	0.86 (0.73, 1.01)
Blood eosinophils count					
< 5 %	1,442	1,444	0.98	1.20	0.81 (0.74, 0.90)
≥ 5 %	204	208	1.01	1.08	0.94 (0.71, 1.24)
Blood eosinophils count					
< 150 cells/μl	623	654	0.90	1.26	0.72 (0.61, 0.84)
150 to < 300 cells/μl	655	631	1.04	1.17	0.89 (0.76, 1.03)
≥ 300 cells/μl	368	367	1.03	1.11	0.93 (0.76, 1.14)
Overall	1,651	1,656	0.98	1.19	0.83 (0.75, 0.91)



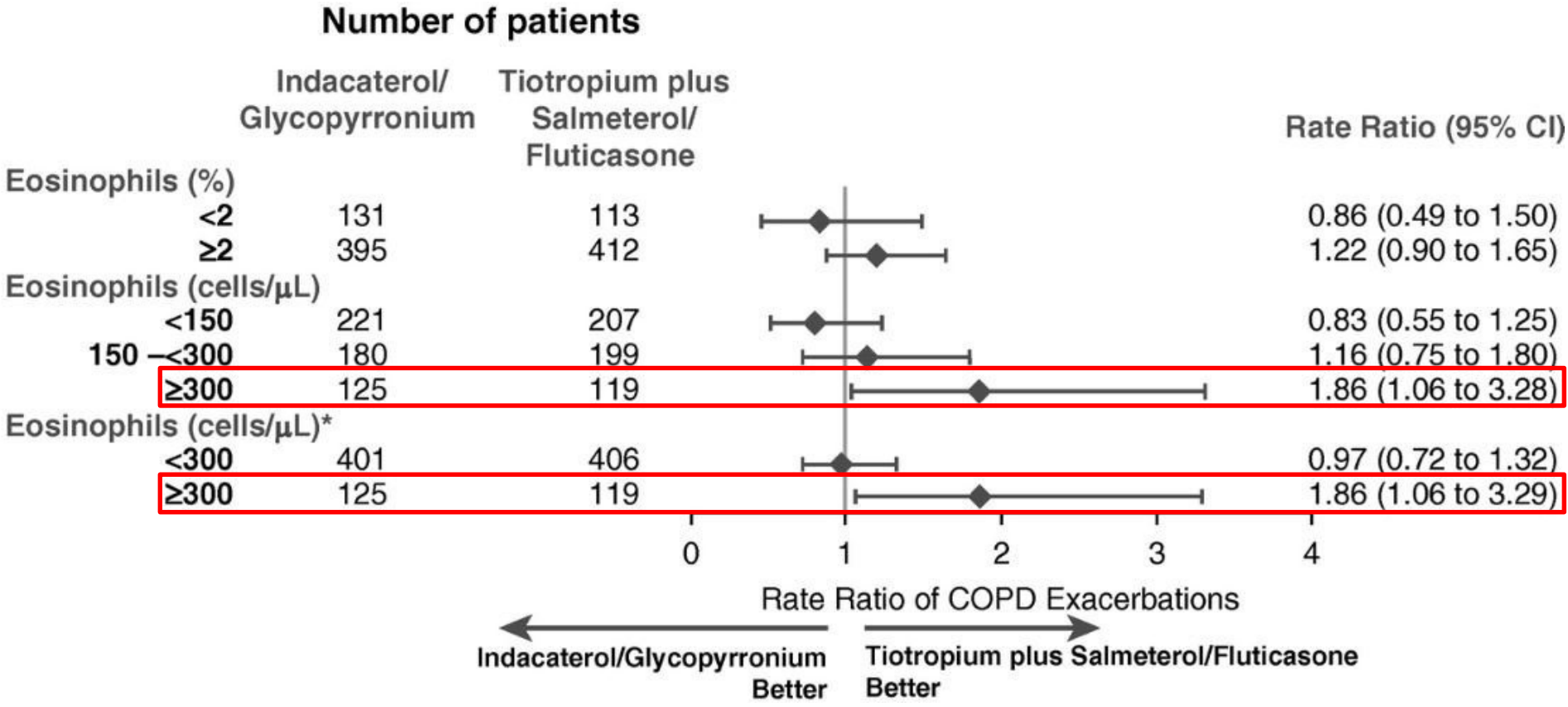
Am J Respir Crit Care Med Vol 195, Iss 9, pp 1189–1197, May 1, 2017

SUNSET: TIO+SFC->IND/GLY



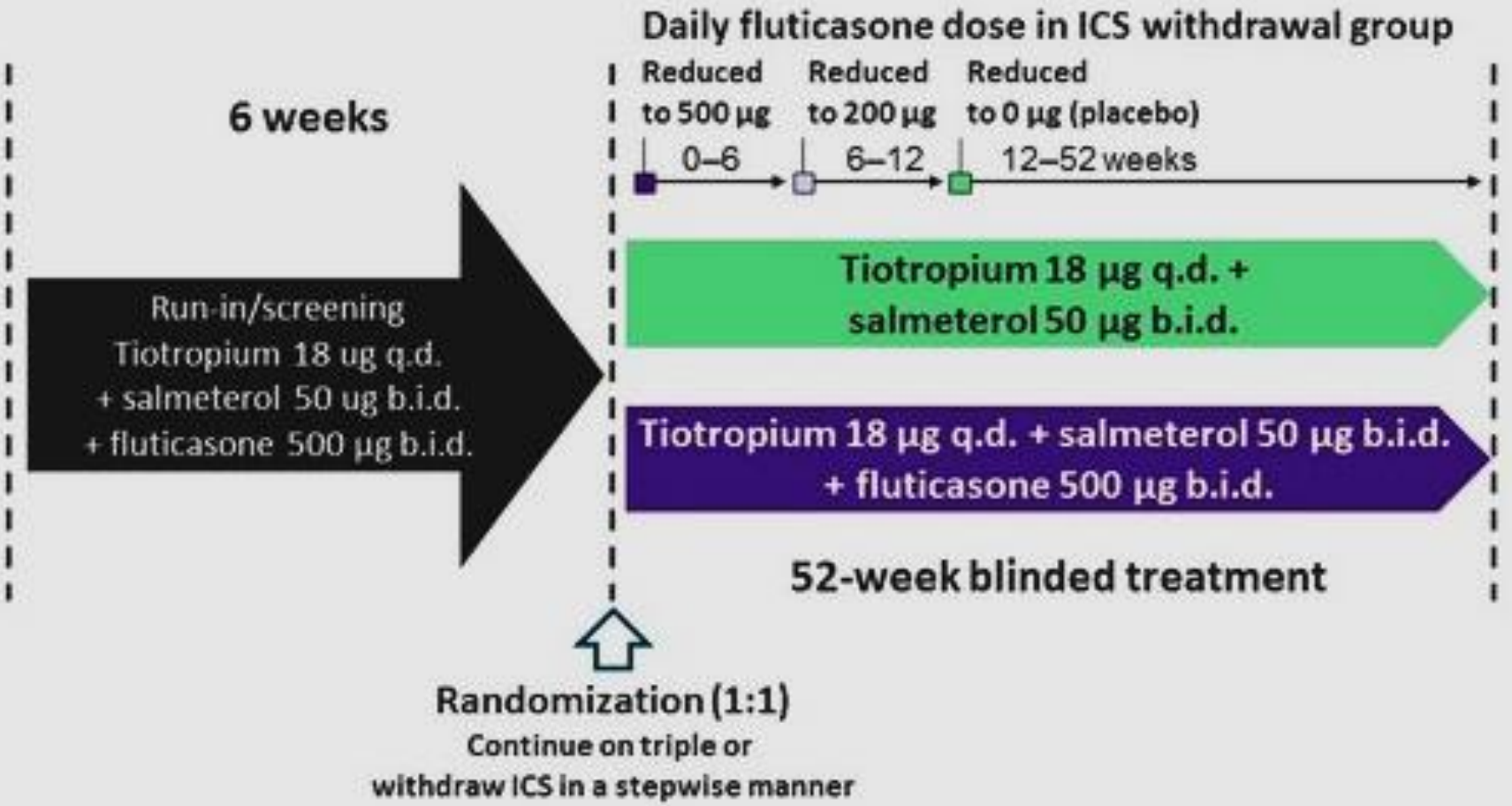
Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339.

SUNSET: Blood Eos 300 cells/uL

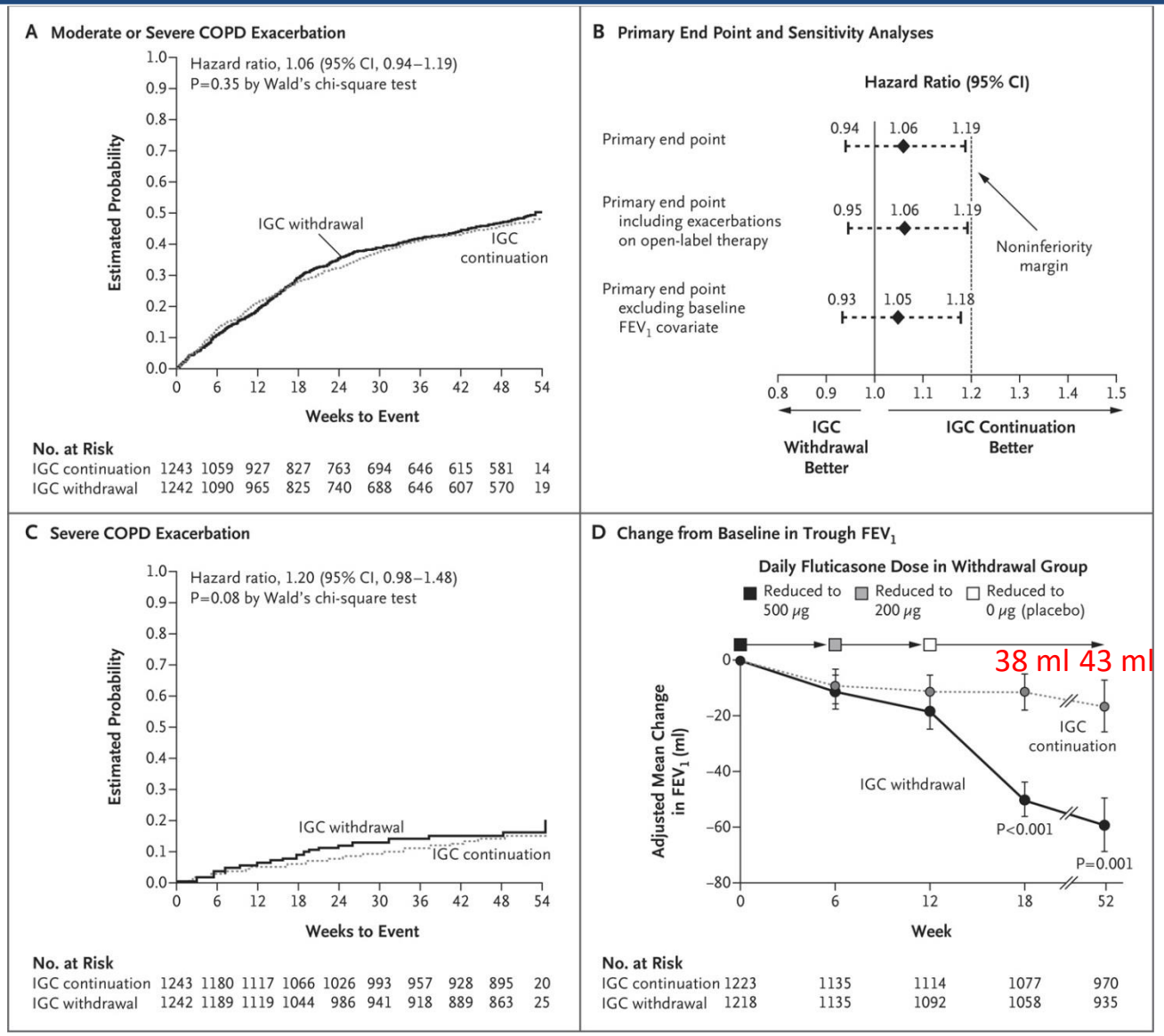


Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339.

WISDOM study



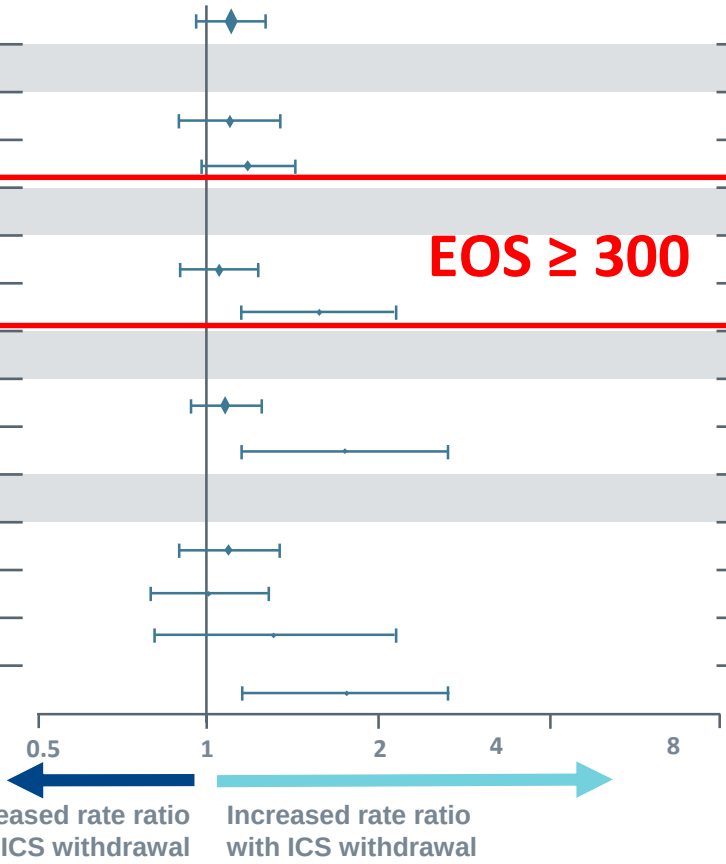
N Engl J Med 2014; 371:1285-1294



N Engl J Med 2014; 371:1285-1294

WISDOM-Rate ratios (ICS withdrawal/ICS) for moderate-to-severe exacerbations

Factors	Patients, n	Rate ratio	P-value
Total	2296	1.10	0.1655
Baseline eosinophils (<150/µL vs ≥150µL)			
<150/µL	1067	1.08	0.4449
≥150µL	1172	1.17	0.0943
Baseline eosinophils (<300/µL vs ≥300µL)			
<300/µL	1791	1.04	0.5930
≥300µL	448	1.56	0.0055
Baseline eosinophils (<400/µL vs ≥400µL)			
<400/µL	1992	1.07	0.3934
≥400µL	247	1.73	0.0090
Baseline eosinophils (mutually exclusive subgroups)			
<150/µL	1067	1.08	0.4443
150 – <300/µL	724	1.00	0.9693
300 – <400/µL	201	1.30	0.2840
≥400/µL	247	1.73	0.0089

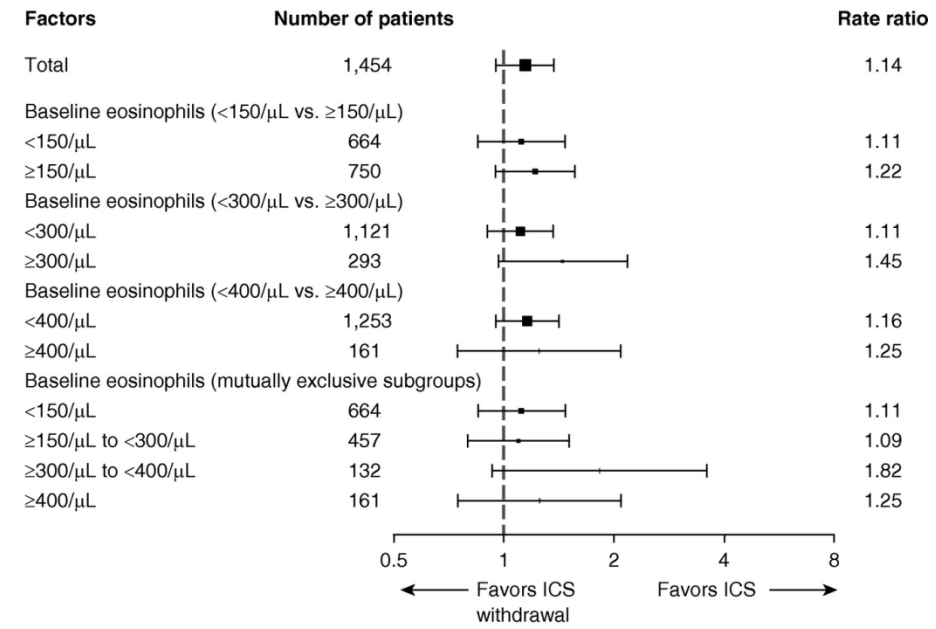


* Following complete ICS withdrawal

Watz H, et al. *Lancet Resp Med* 2016. Published Online: 7 April 2016 (doi:10.1016/S2213-2600(16)00100-4).

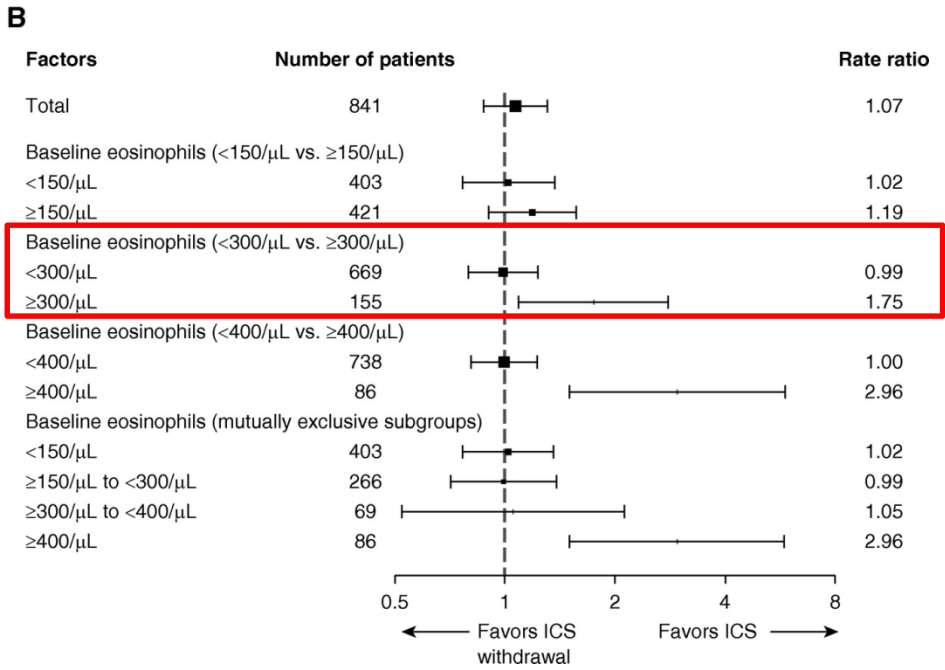
WISDOM: Blood Eos 300 cells/uL

A



One exacerbation per year

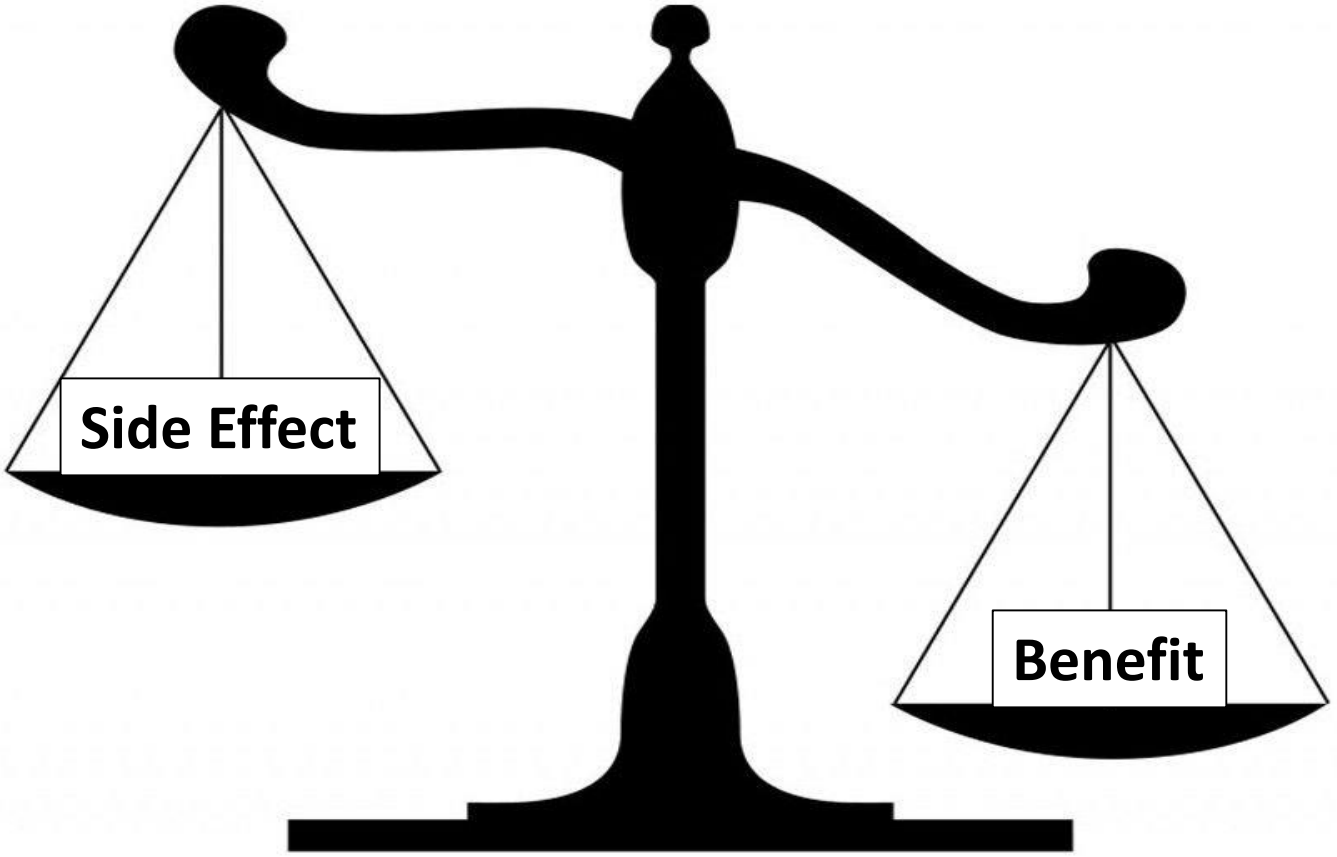
B



≥2 exacerbation per year

Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339.

ICS in COPD

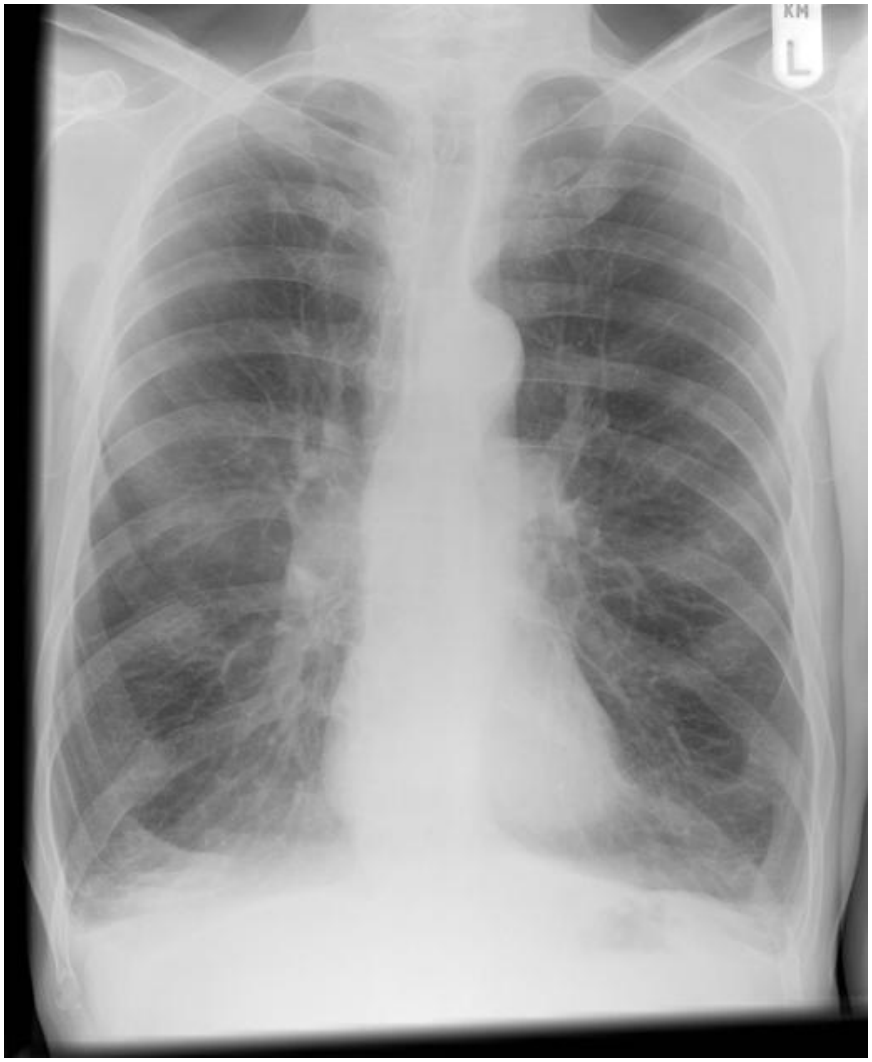


Potential side effects associated with ICSs for COPD

Side effect and evidence[1]	RCT	Observational Study	Systematic review
Pneumonia	✔	✔	✔
Fracture	(no effect)	✔	✔
Skin thinning/easy bruising	✔		
Cataract		✔	
Diabetes	✔	✔	✔
Oropharyngeal candidiasis	✔	✔	✔

Price D et al. Prim Care Respir J. 2013;22:92-100.

AE or Pneumonia ?



➢ **Clinical Problem**

Dyspnea

Much sputum

Respiratory failure

➢ **Treatment**

Antibiotics

Bronchodilators

Systemic steroid

Ventilator support

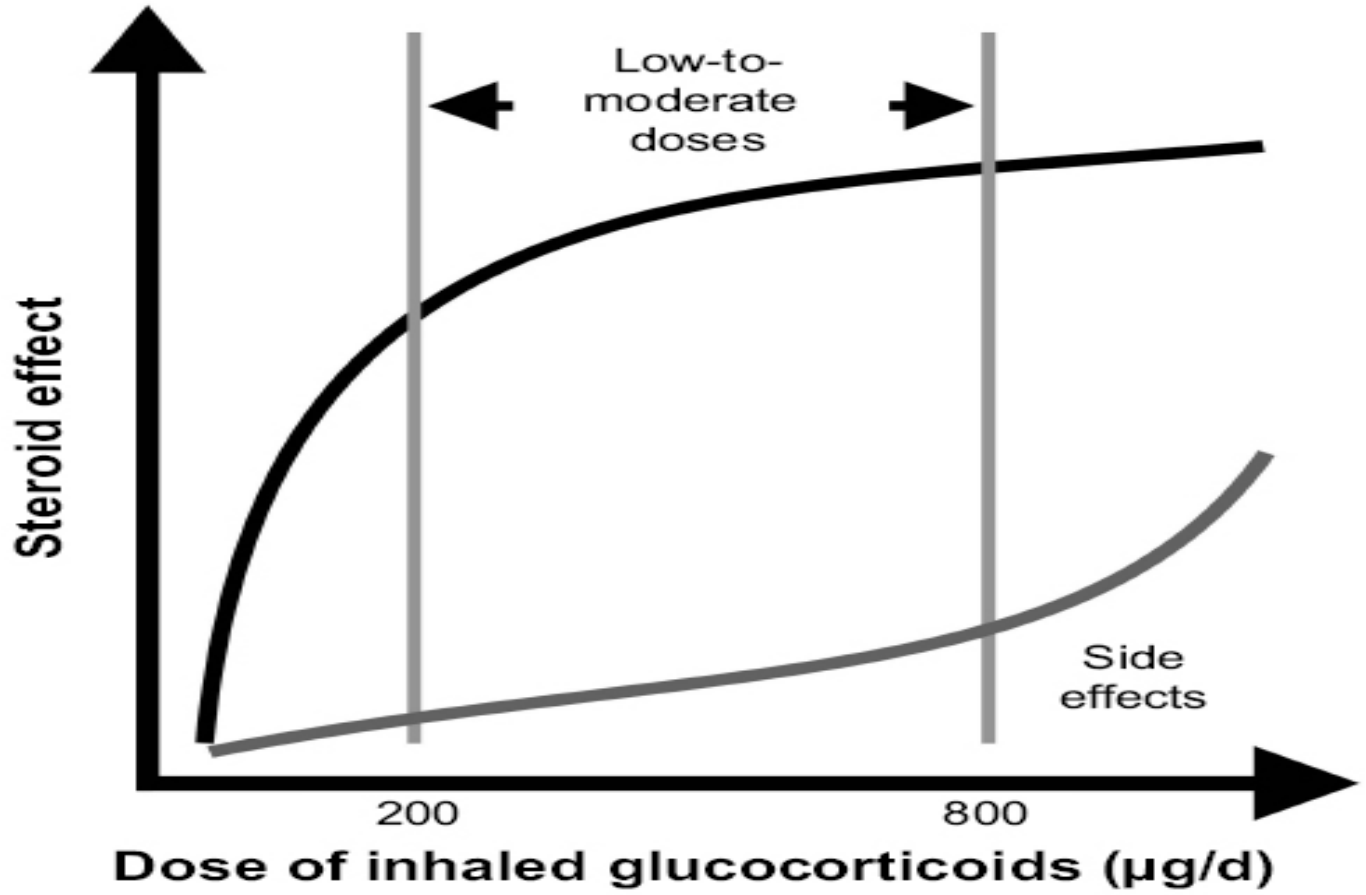


Figure 2 The dose-response curve of ICS.
Note: Reproduced from Kankaanranta et al, 2004,[56] with the permission of *Respiratory Research*.
Abbreviation: ICS, inhaled corticosteroids.

Int J Chron Obstruct Pulmon Dis. 2018 Oct 25;13:3539-3547.

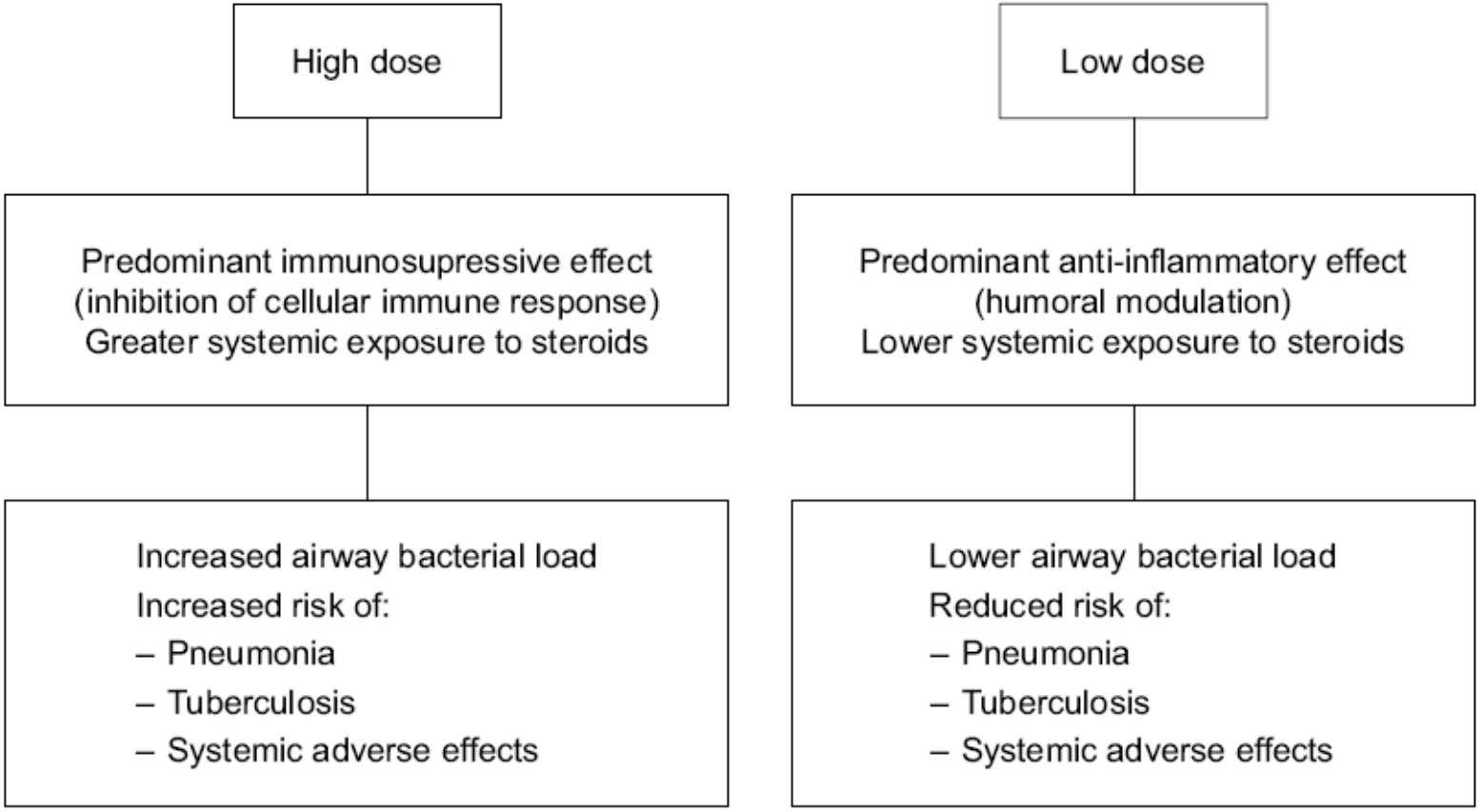
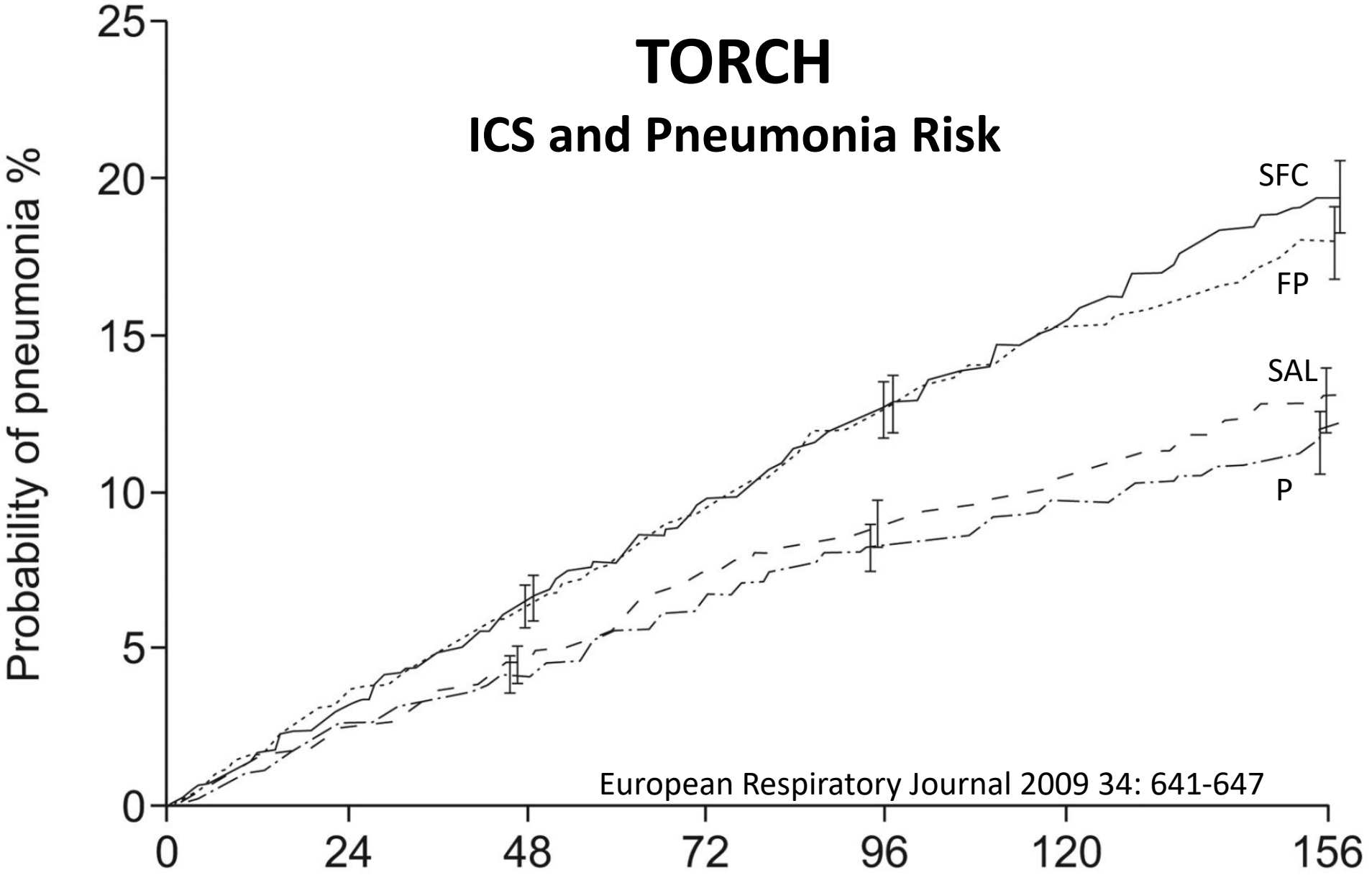


Figure 3 Pathophysiological mechanisms involved in systemic adverse effects of ICS in COPD patients.
Abbreviation: ICS, inhaled corticosteroids.

Int J Chron Obstruct Pulmon Dis. 2018 Oct 25;13:3539-3547.

TORCH

ICS and Pneumonia Risk



European Respiratory Journal 2009 34: 641-647

TORCH

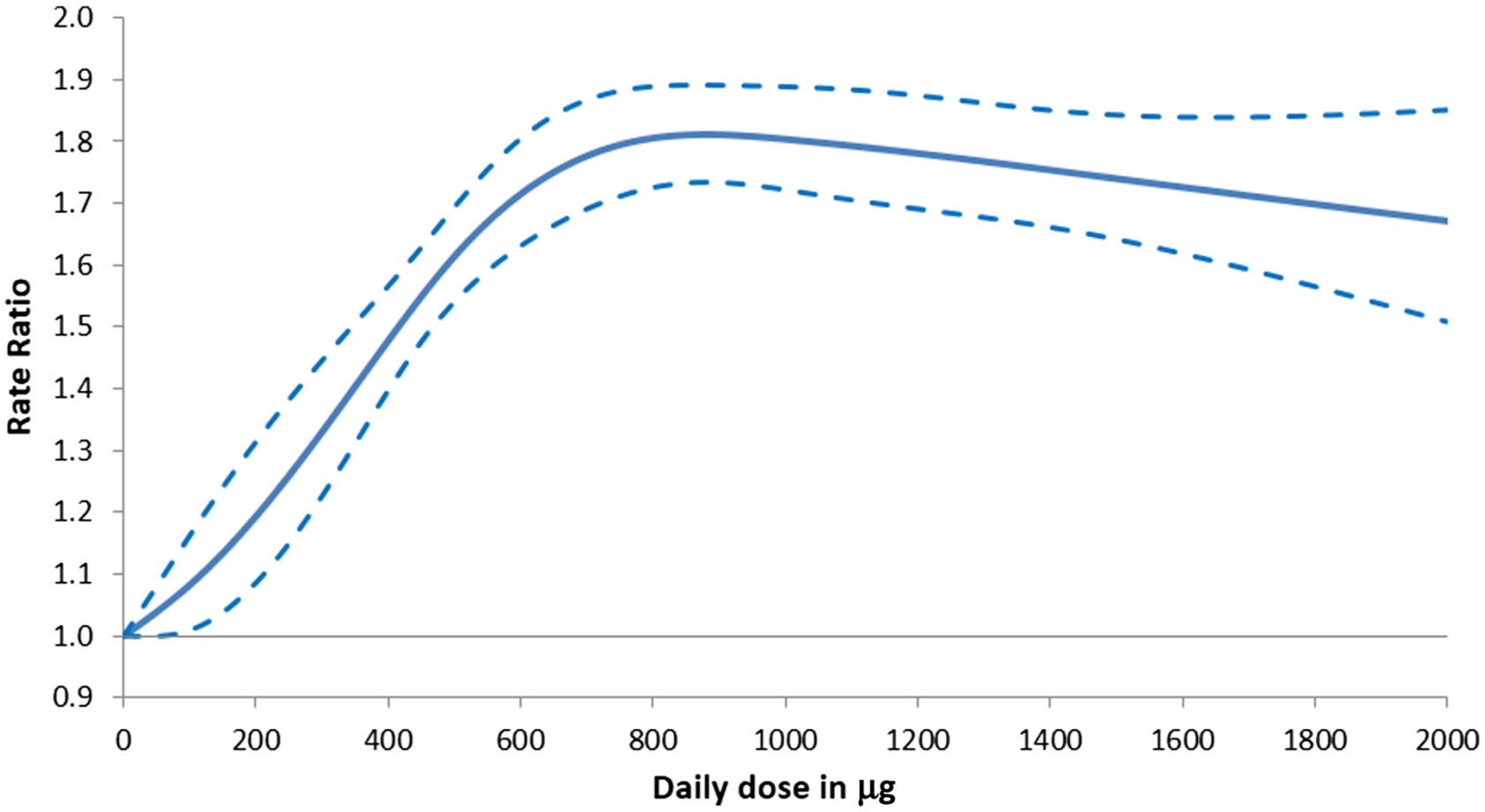
COPD Acute Exacerbation		Pneumonia	
Placebo	1.13	Placebo	0.052
LABA	0.97	LABA	0.052
ICS	0.93	ICS	0.084
ICS/LABA	0.85 ↓0.12	ICS/LABA	0.088 ↑0.036

0.12/0.036 = 3.333

N Eng J Med. 2007;356(8):775–789.

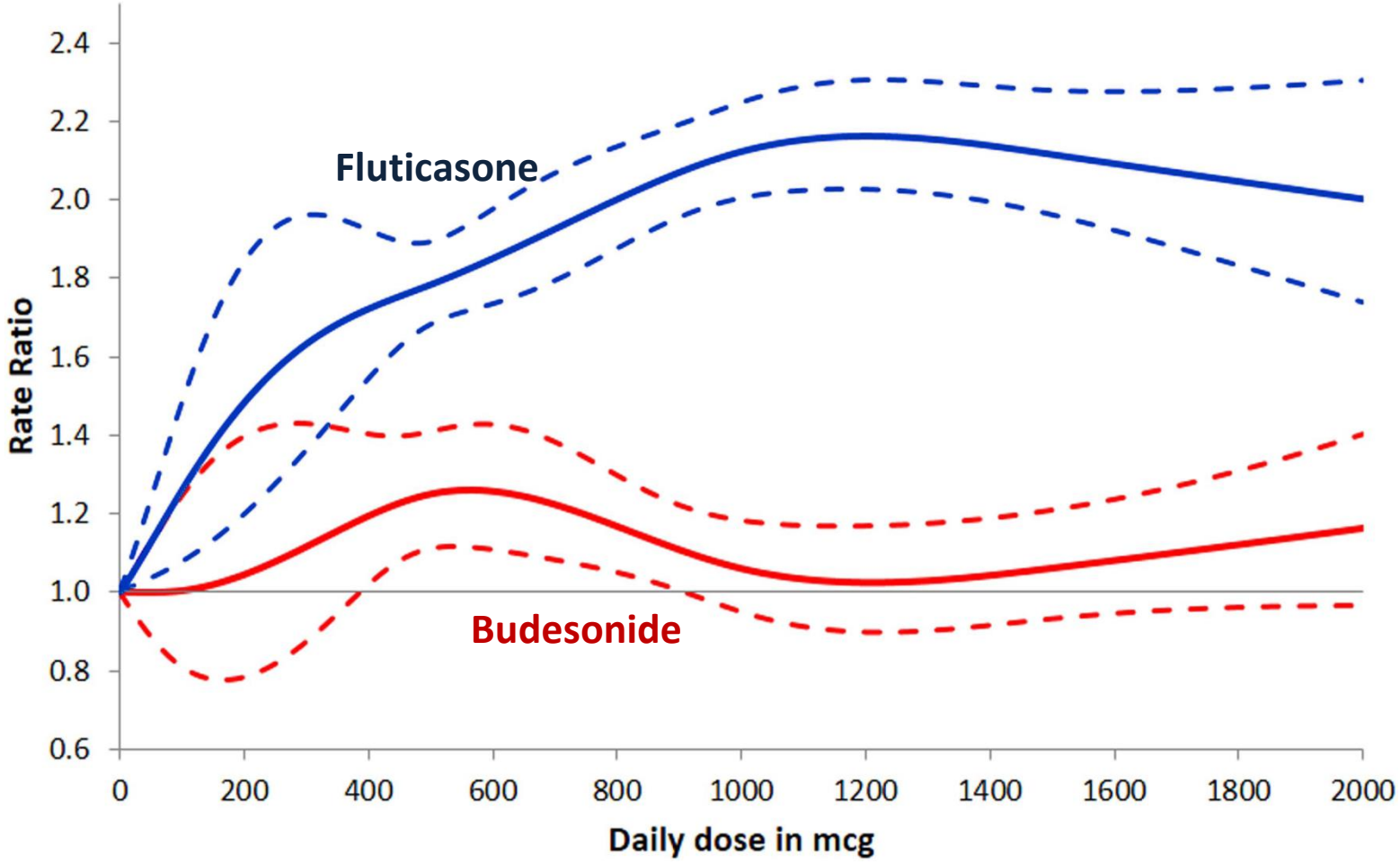
European Respiratory Journal 2009 34: 641-647

Real-world ICS and Pneumonia Risk



Thorax 2013;68:1029–1036.

Real-world ICS and Pneumonia Risk



Thorax 2013;68:1029–1036.

Real-world ICS and Pneumonia Risk

Table 3 Crude and adjusted rate ratios of serious pneumonia associated with current use, dose and past use of inhaled corticosteroids among patients with COPD

Inhaled corticosteroid exposure	Pneumonia cases	Controls	Crude rate ratio	Adjusted* rate ratio	95% CI
Number of subjects	20 344	197 705			
No use in the year prior to index date, %	46.47	61.15	1.00	1.00	Reference
Current use, %†	37.53	22.01	2.30	1.69	1.63 to 1.75
Low dose‡	3.12	2.72	1.50	1.24	1.13 to 1.36
Medium dose	16.28	10.28	2.15	1.66	1.59 to 1.74
High dose	18.14	9.01	2.73	1.86	1.77 to 1.94
Past use, %	16.00	16.84	1.28	1.15	1.10 to 1.20
Time since stopping, %					
61–180 days	9.95	9.96	1.35	1.19	1.13 to 1.26
181–270 days	3.29	3.76	1.17	1.08	0.99 to 1.17
271–365 days	2.76	3.11	1.19	1.08	0.99 to 1.18

*Adjusted for all of the factors listed in table 1.
†Current use refers to a prescription of any one of inhaled fluticasone, budesonide, beclomethasone, flunisolide or triamcinolone in the 60 days prior to the index date.
‡Current daily dose in fluticasone equivalents, in μg/day; high: 1000 or more; moderate: 500–999; low: less than 500.
COPD, chronic obstructive pulmonary disease.

Thorax 2013;68:1029–1036.

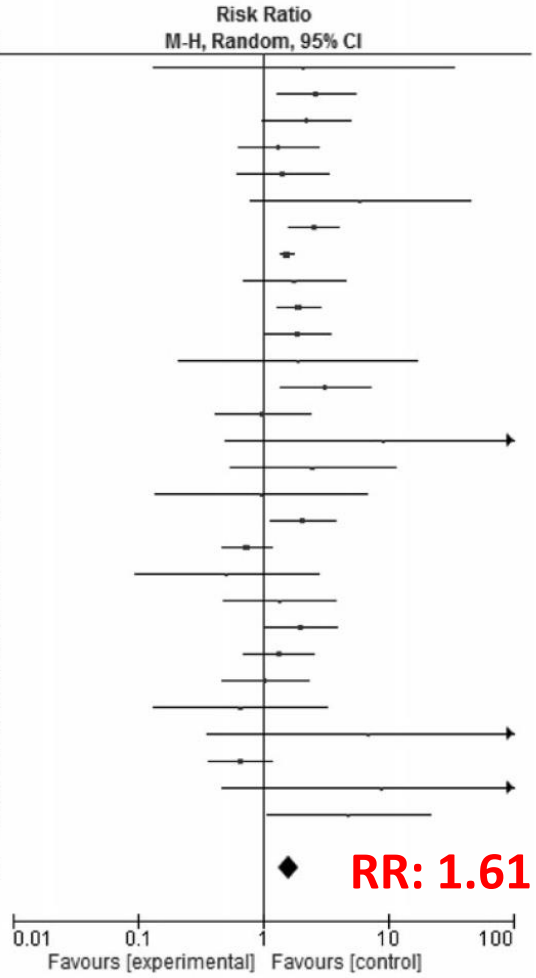
ICS and Pneumonia Risk

RCTs:

Study or Subgroup	ICS Events	ICS Total	Non-ICS Events	Non-ICS Total	Weight	Risk Ratio M-H, Random, 95% CI
Aaron 2007	1	145	1	304	0.4%	2.10 [0.13, 33.28]
Anzueto 2009	26	394	10	403	4.3%	2.66 [1.30, 5.44]
Burge 2000	18	372	8	370	3.5%	2.24 [0.99, 5.08]
Calverley 2003	16	732	12	733	4.1%	1.34 [0.64, 2.80]
Calverly 2003	13	511	9	511	3.4%	1.44 [0.62, 3.35]
Calverly 2010	12	479	1	239	0.7%	5.99 [0.78, 45.78]
Calverly 2011	58	658	23	665	7.0%	2.55 [1.59, 4.08]
Crim 2009	472	3098	301	3086	12.4%	1.56 [1.36, 1.79]
Doherty 2012	16	717	6	479	2.9%	1.78 [0.70, 4.52]
Dransfield 2013	154	2437	27	818	8.0%	1.91 [1.28, 2.86]
Ferguson 2008	29	394	15	388	5.3%	1.90 [1.04, 3.49]
FLTA 3025	4	434	1	206	0.6%	1.90 [0.21, 16.88]
Kardos 2007	23	507	7	487	3.4%	3.16 [1.37, 7.29]
Kerwin 2013	12	618	8	412	3.1%	1.00 [0.41, 2.43]
Mahler 2002	4	333	0	341	0.4%	9.22 [0.50, 170.50]
Martinez 2013	10	816	2	408	1.3%	2.50 [0.55, 11.36]
Paggiaro 1998	2	142	2	139	0.8%	0.98 [0.14, 6.85]
Pauwels 1999	33	634	16	643	5.5%	2.09 [1.16, 3.76]
Rennard 2009	30	988	40	976	7.1%	0.74 [0.47, 1.18]
SCO100470	2	518	4	532	1.0%	0.51 [0.09, 2.79]
SCO40041	8	92	6	94	2.5%	1.36 [0.49, 3.77]
Sharafkhaneh 2012	45	815	11	403	4.9%	2.02 [1.06, 3.87]
Szafranski 2003	20	406	15	406	4.8%	1.33 [0.69, 2.57]
Tashkin 2008	18	1120	9	584	3.7%	1.04 [0.47, 2.31]
Tashkin 2012	3	634	3	421	1.2%	0.66 [0.13, 3.27]
van der Valk 2002	3	123	0	121	0.4%	6.89 [0.36, 131.93]
Vestbo 1999	16	145	24	145	5.5%	0.67 [0.37, 1.20]
Vogelmeier 2013	4	264	0	259	0.4%	8.83 [0.48, 163.19]
Wouters 2005	10	189	2	184	1.3%	4.87 [1.08, 21.92]
Total (95% CI)		**18715**		**14757**	**100.0%**	**1.61 [1.35, 1.93]**
Total events	1062		563			

Heterogeneity: Tau² = 0.06; Chi² = 44.30, df = 28 (P = 0.03); I² = 37%

Test for overall effect: Z = 5.20 (P < 0.00001)



COPD. 2016 Jun;13(3):312-26.

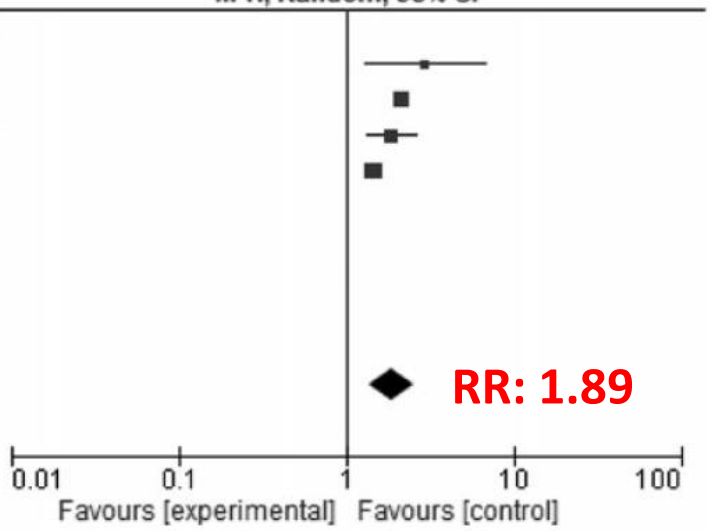
ICS and Pneumonia Risk

Observational:

Study or Subgroup	ICS Events	ICS Total	Non-ICS Events	Non-ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2011	8271	8271	7497	7497		Not estimable
Cheng 2011	20	125	9	149	9.9%	2.96 [1.30, 6.77]
Ernst 2007	11540	40366	12402	79344	33.1%	2.16 [2.10, 2.22]
Festic 2014	119	226	135	363	23.9%	1.88 [1.34, 2.63]
Joo 2010	3037	24091	10958	121495	33.0%	1.46 [1.39, 1.52]
Ko 2008	42	42	36	36		Not estimable
Malo de Molina 2010	2420	2420	3933	3933		Not estimable
Sellares 2013	340	340	394	394		Not estimable
Singayanagam 2011	376	376	114	114		Not estimable
Total (95% CI)		**76257**		**213325**	**100.0%**	**1.89 [1.39, 2.58]**
Total events	26165		35478			

Heterogeneity: Tau² = 0.08; Chi² = 226.51, df = 3 (P < 0.00001); I² = 99%

Test for overall effect: Z = 4.02 (P < 0.0001)



COPD. 2016 Jun;13(3):312-26.

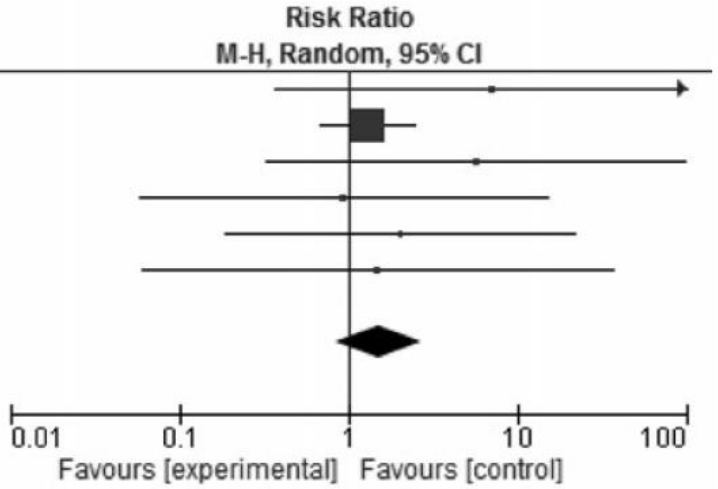
ICS and Pneumonia-associated mortality

3a. Pneumonia-associated mortality:

Study or Subgroup	ICS Events	ICS Total	Non-ICS Events	Non-ICS Total	Weight	Risk Ratio M-H, Random, 95% CI
Calverly 2011	3	658	0	665	3.8%	7.07 [0.37, 136.69]
Crim 2009	21	3098	16	3086	78.8%	1.31 [0.68, 2.50]
Dransfield 2013	8	2437	0	818	4.1%	5.71 [0.33, 98.83]
Kardos 2007	1	408	1	384	4.3%	0.94 [0.06, 14.99]
SCO40041	2	92	1	94	5.8%	2.04 [0.19, 22.15]
Sharafkhaneh 2012	1	815	0	403	3.2%	1.49 [0.06, 36.38]
Total (95% CI)		**7508**		**5450**	**100.0%**	**1.50 [0.85, 2.67]**
Total events	36		18			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.33$, $df = 5$ ($P = 0.80$); $I^2 = 0\%$

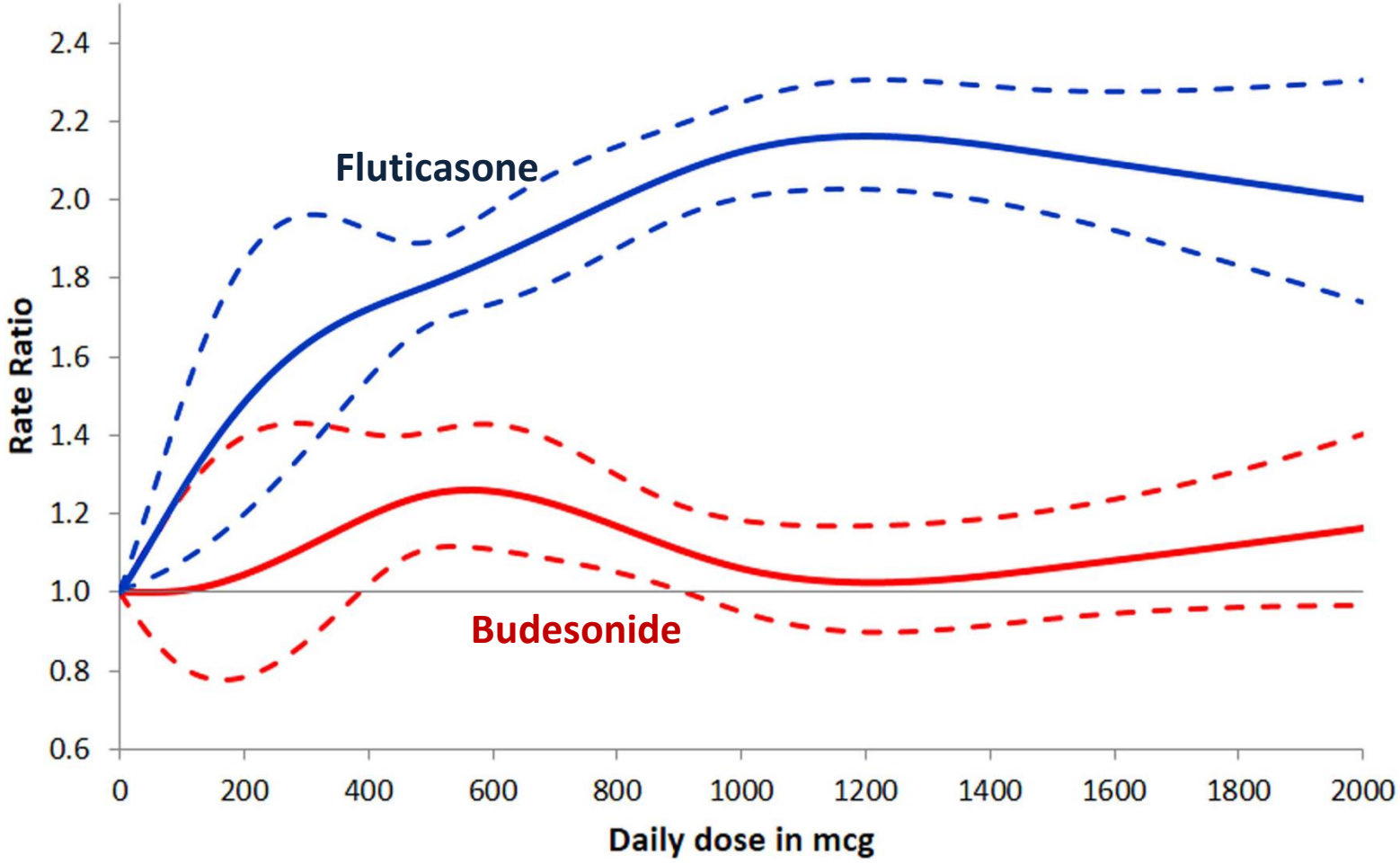
Test for overall effect: $Z = 1.39$ ($P = 0.16$)



RR: 1.50 [0.85-2.67]

COPD. 2016 Jun;13(3):312-26.

Real-world ICS and Pneumonia Risk



Thorax 2013;68:1029–1036.

Real-world ICS and Pneumonia Risk

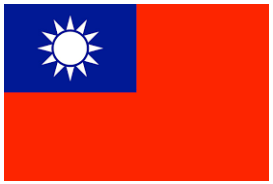


Table 4 Sensitivity analyses for risk of pneumonia and pneumonia requiring MV among COPD patients using fluticasone/salmeterol and budesonide/formoterol

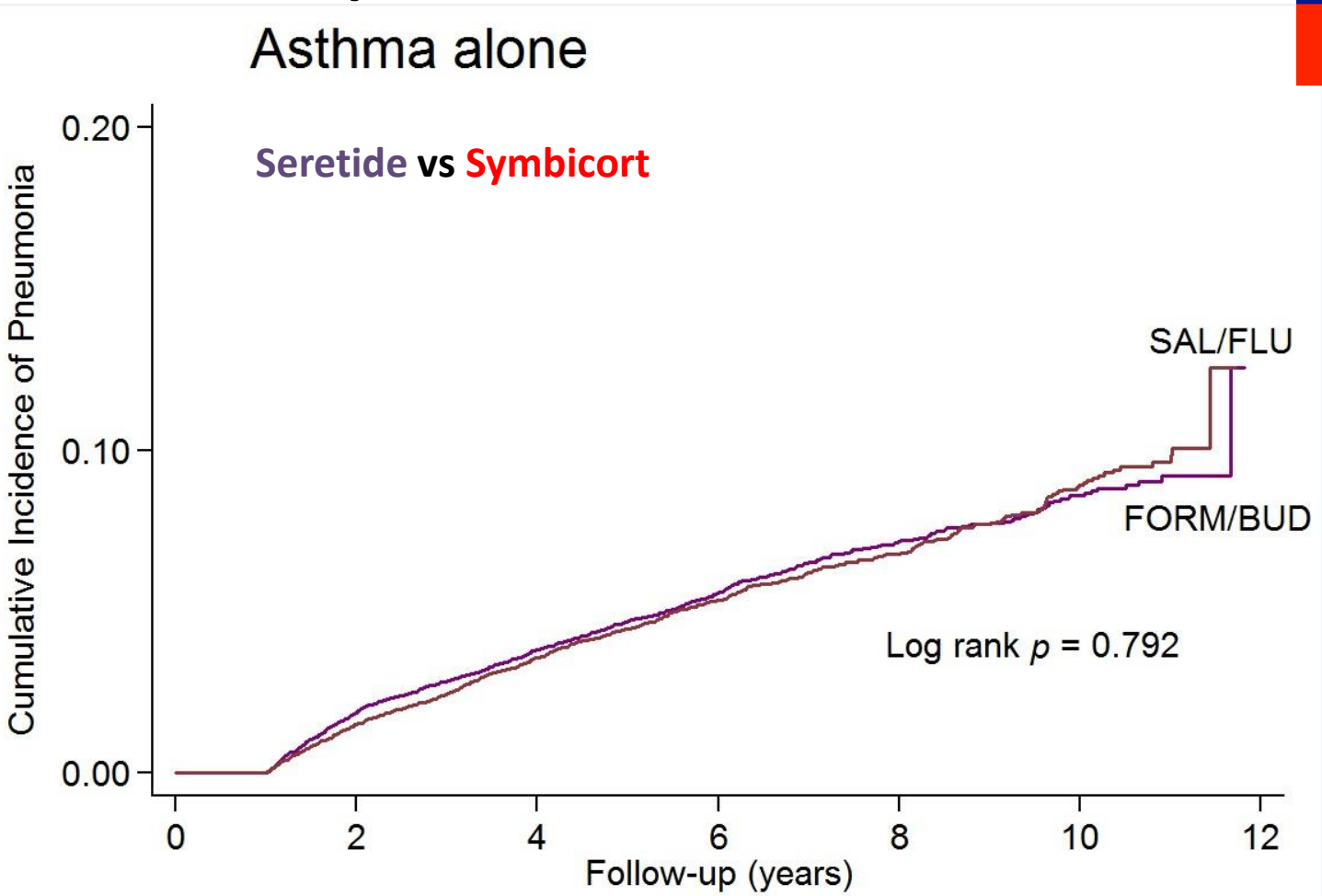
Seretide vs Symbicort

	Before propensity score matching		After propensity score matching	
	Crude	Adjusted*	Crude	Adjusted*
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary analysis				
Mortality	1.32 (1.24–1.41)	1.09 (1.01–1.17)	1.09 (1.02–1.17)	1.09 (1.01–1.17)
Pneumonia	1.31 (1.25–1.38)	1.13 (1.08–1.20)	1.12 (1.06–1.17)	1.13 (1.08–1.20)
Pneumonia requiring MV	1.39 (1.28–1.50)	1.13 (1.04–1.24)	1.16 (1.07–1.25)	1.14 (1.05–1.24)
ITT analysis + competing risk				
Mortality	–	–	–	–
Pneumonia	1.24 (1.17–1.30)	1.08 (1.03–1.14)	1.11 (1.05–1.18)	1.11 (1.05–1.18)
Pneumonia requiring MV	1.27 (1.17–1.38)	1.09 (1.01–1.18)	1.09 (1.00–1.19)	1.09 (1.00–1.19)
As-treated analysis				
Mortality	1.54 (1.39–1.70)	1.23 (1.09–1.37)	1.25 (1.12–1.38)	1.21 (1.08–1.35)
Pneumonia	1.44 (1.34–1.54)	1.17 (1.08–1.26)	1.17 (1.09–1.25)	1.17 (1.08–1.26)
Pneumonia requiring MV	1.70 (1.51–1.91)	1.32 (1.16–1.51)	1.34 (1.19–1.52)	1.32 (1.15–1.51)
As-treated analysis + competing risk				
Mortality	–	–	–	–
Pneumonia	1.32 (1.22–1.42)	1.11 (1.03–1.20)	1.12 (1.03–1.22)	1.12 (1.03–1.22)
Pneumonia requiring MV	1.48 (1.30–1.68)	1.20 (1.06–1.37)	1.21 (1.05–1.40)	1.21 (1.05–1.39)

Note: *Adjusted for propensity score.
Abbreviations: HR, hazard ratio; MV, mechanical ventilation; ITT, intention-to-treat.

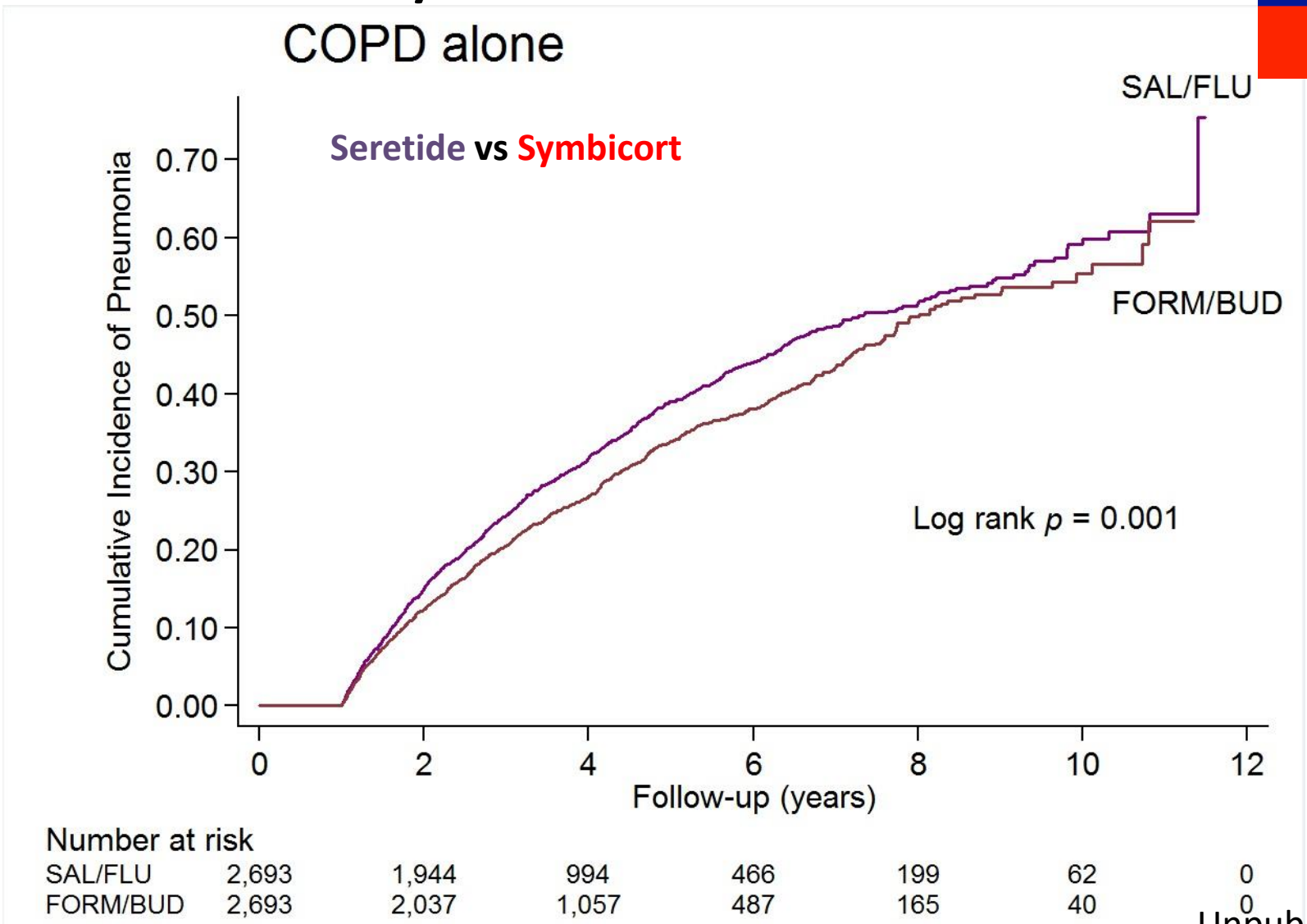
Int J Chron Obstruct Pulmon Dis. 2017; 12: 2477–2485.

ICS/LABA and Pneumonia Risk



Unpublished Data

ICS/LABA and Pneumonia Risk



Unpublished Data

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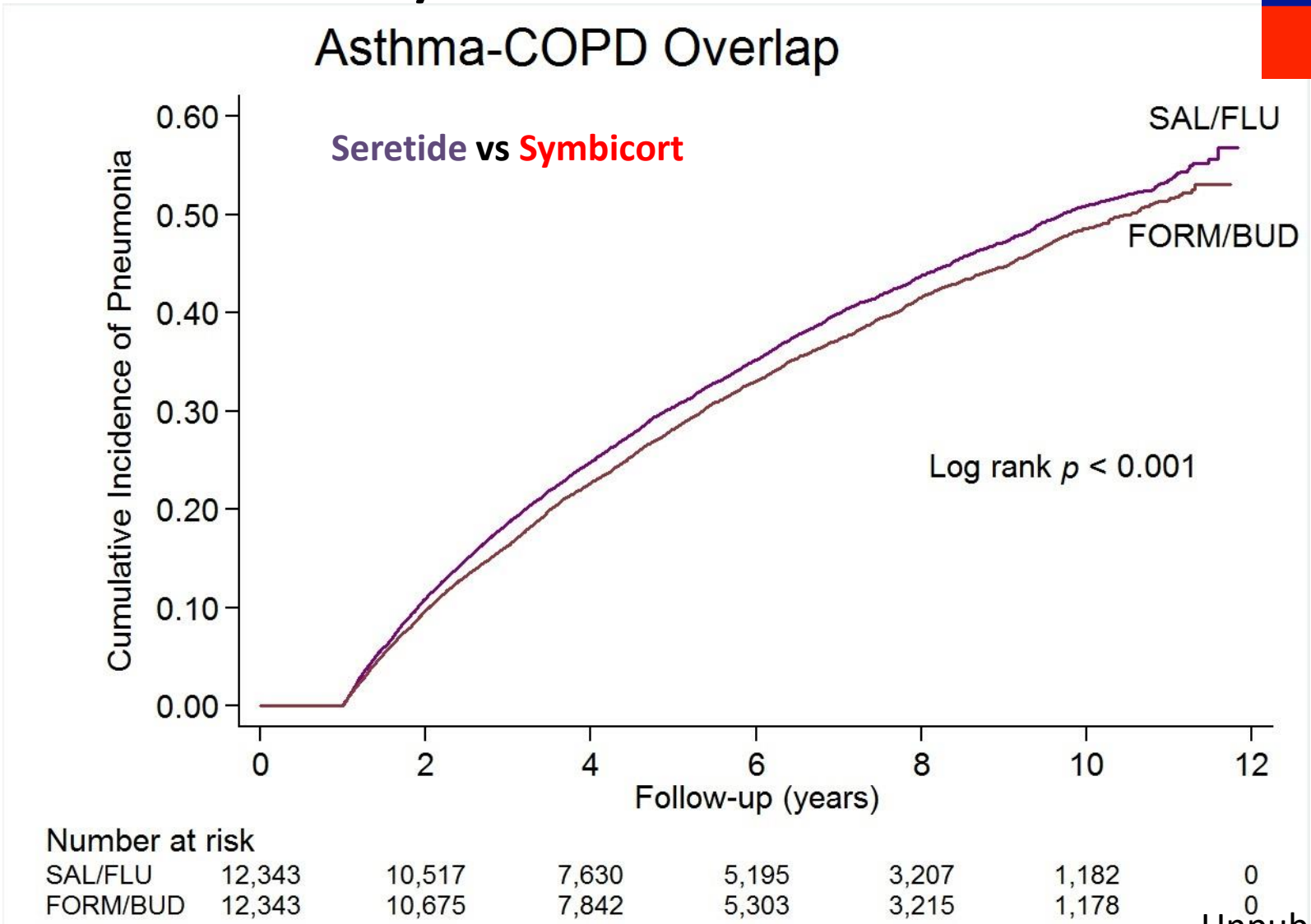
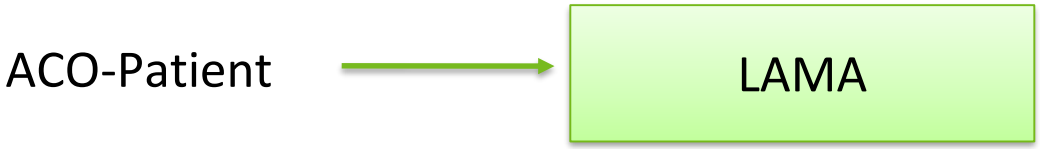


Unpublished Data

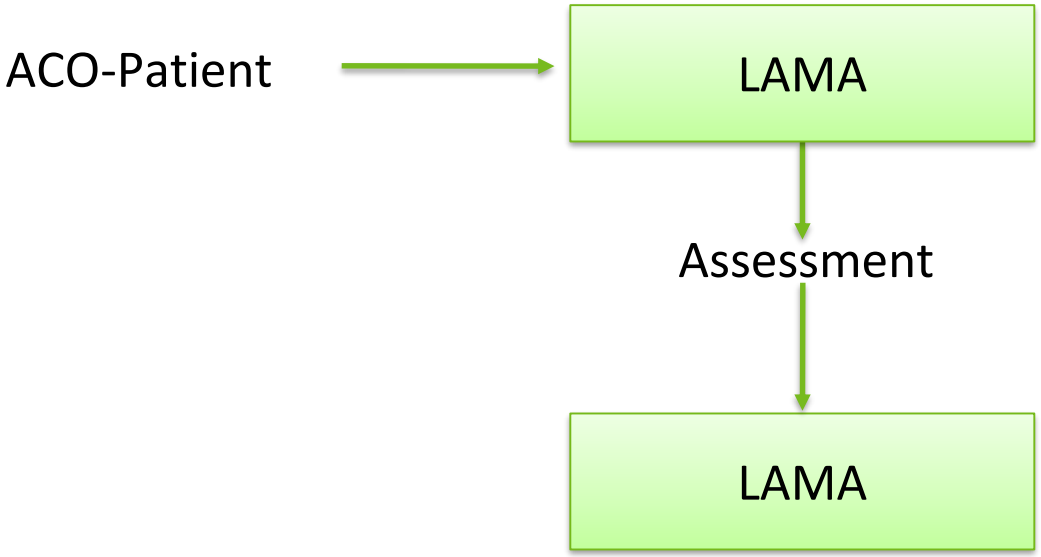
Stepwise Pharmacotherapy for **Stable** ACO



Strong Evidence

Weak Evidence

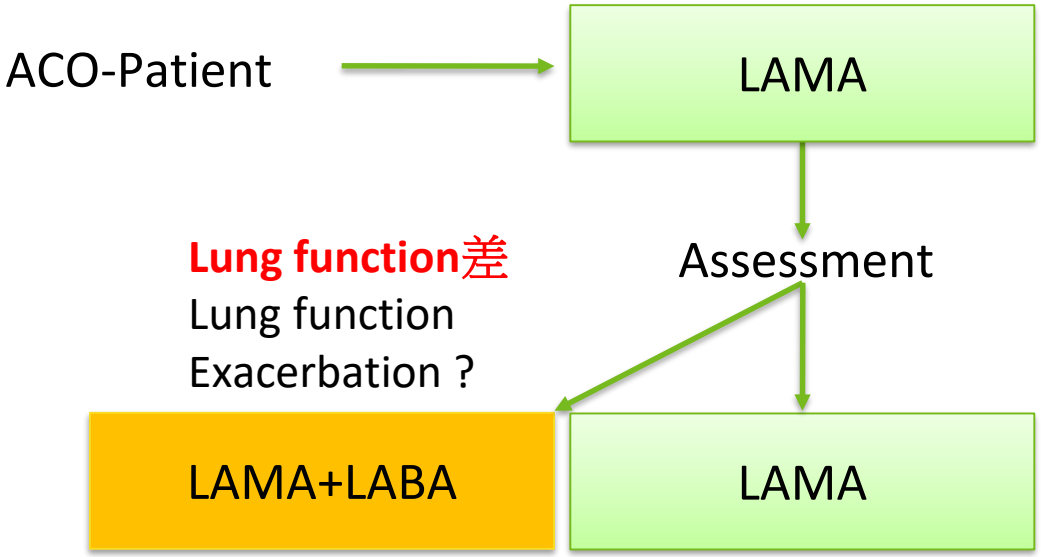
Stepwise Pharmacotherapy for **Stable** ACO



Strong Evidence

Weak Evidence

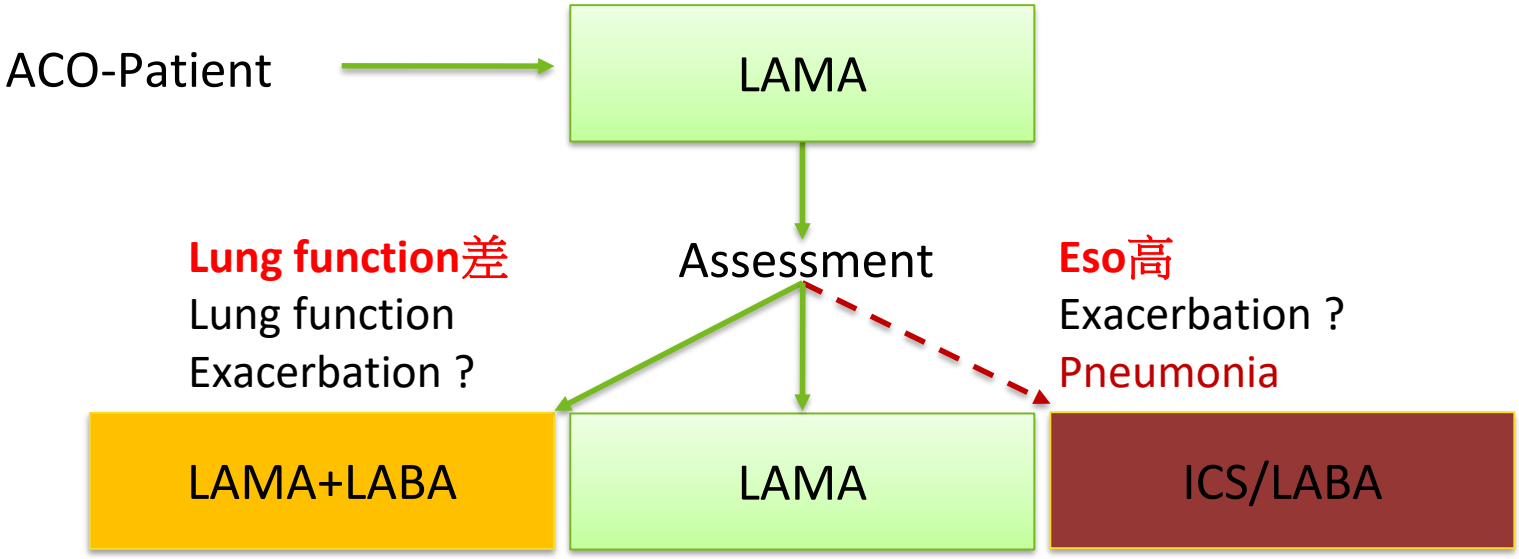
Stepwise Pharmacotherapy for **Stable** ACO



Strong Evidence

Weak Evidence

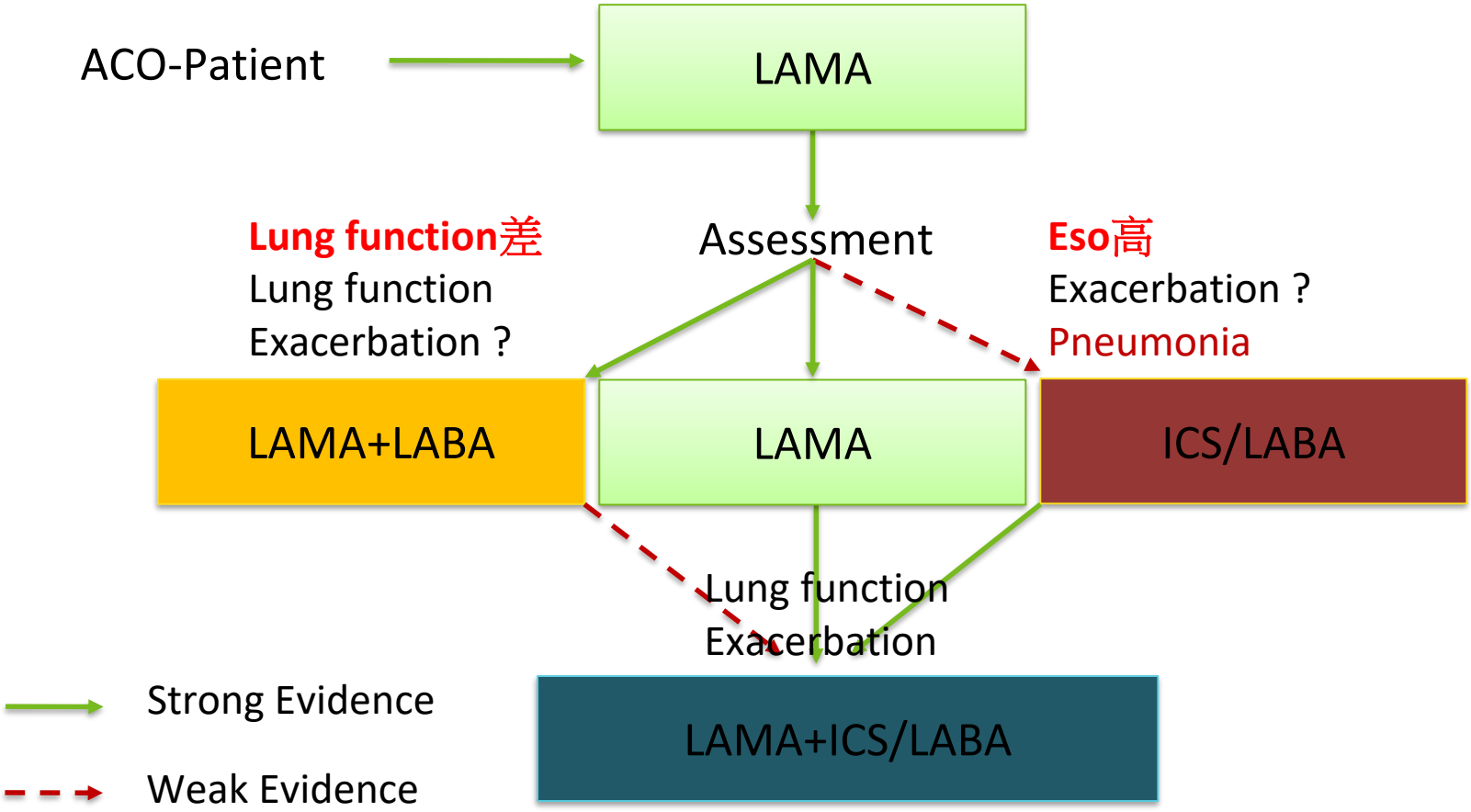
Stepwise Pharmacotherapy for **Stable** ACO



Strong Evidence

Weak Evidence

Stepwise Pharmacotherapy for **Stable** ACO



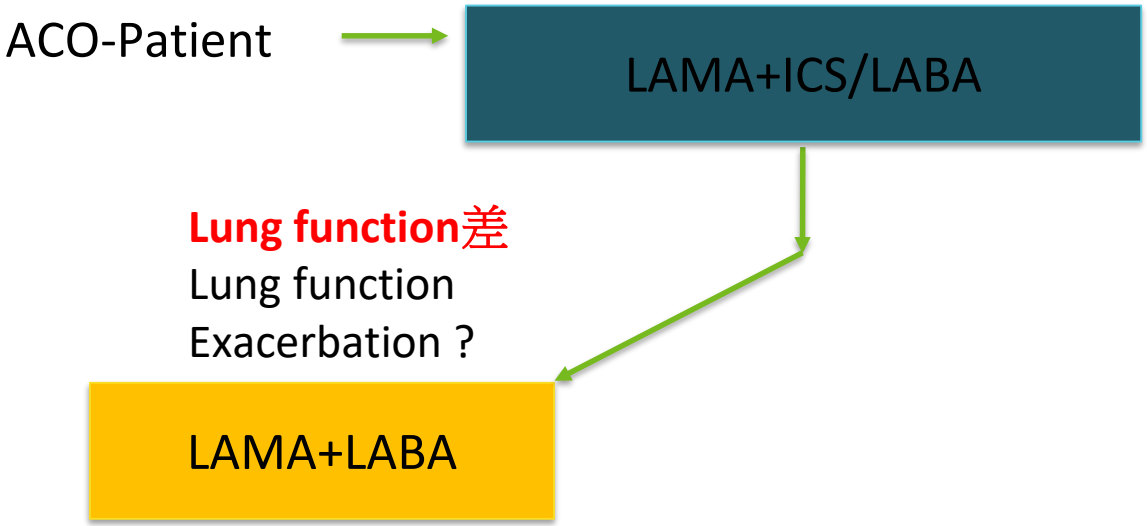
Stepwise Pharmacotherapy for **Unstable** ACO

ACO-Patient → LAMA+ICS/LABA

→ Strong Evidence

- - → Weak Evidence

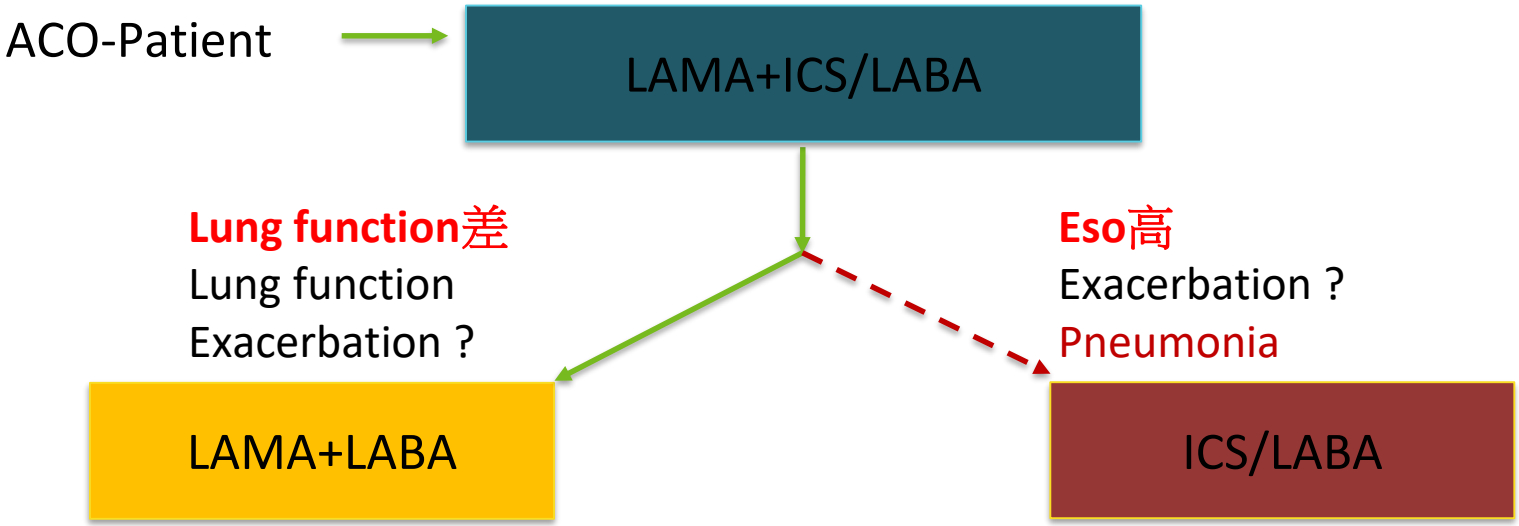
Stepwise Pharmacotherapy for **Unstable** ACO



Strong Evidence

Weak Evidence

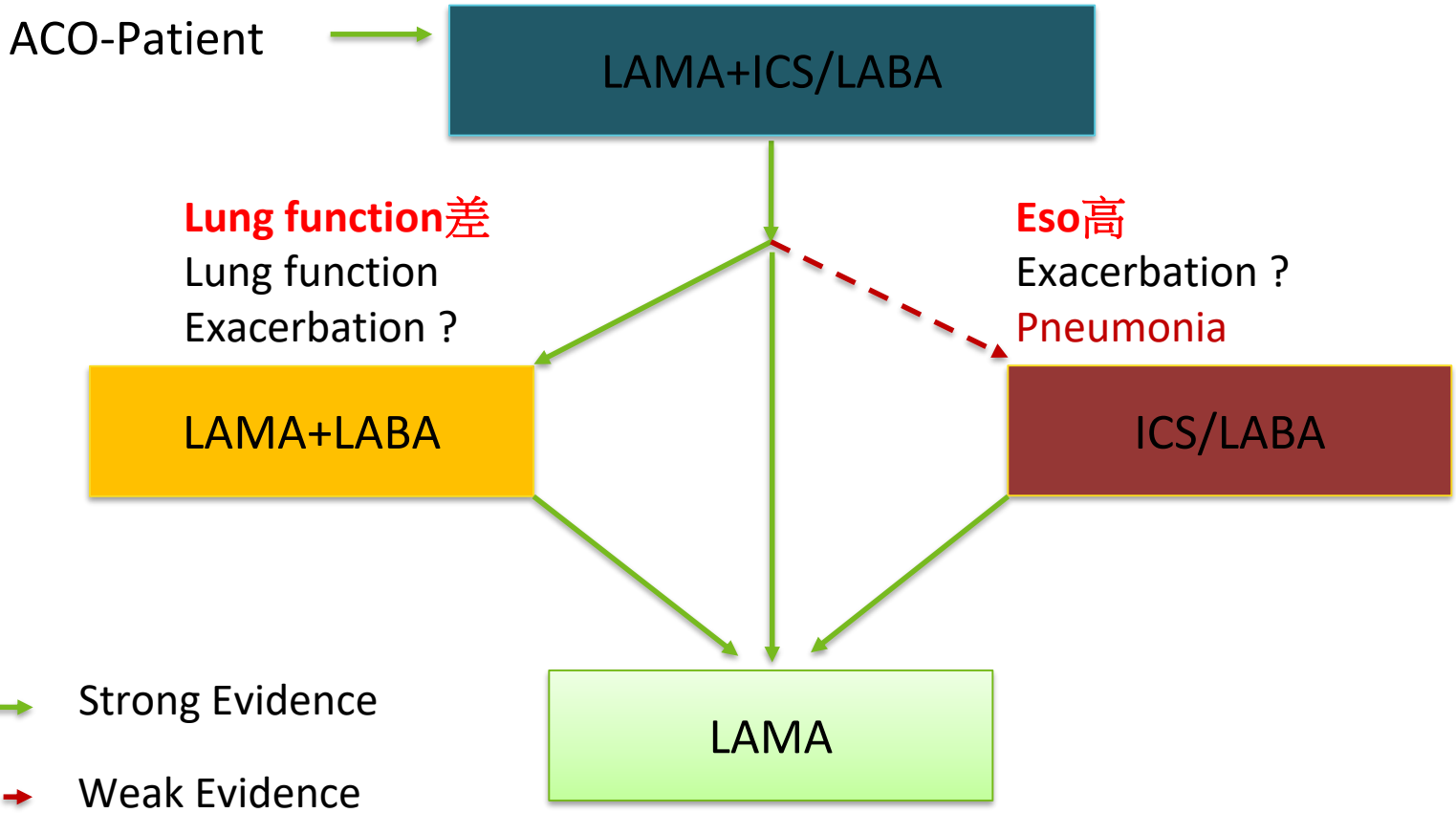
Stepwise Pharmacotherapy for **Unstable** ACO



Strong Evidence

Weak Evidence

Stepwise Pharmacotherapy for **Unstable** ACO



ACO Case 1

- 60 y/o female
- Admission due to pneumonia
- PH: MDS, childhood Asthma, COPD, Breast cancer, right, s/p operation, HTN, Hyperlipidemia, CAD
- Smoking index: 50 pack-year
- OPD medications:
  - Symbicort 1 puff BID
  - Spiriva 2 puff QD
  - Berotec PRN
  - Actein 600mg QD
  - Regrow 1# HS, Brown Mixture…etc

ACO Case 1

- 60 y/o female
- Admission due to pneumonia
- PH: MDS, childhood Asthma, COPD, Breast cancer, right, s/p operation, HTN, Hyperlipidemia, CAD
- Smoking index: 50 pack-year
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  - Symbicort 1 puff BID
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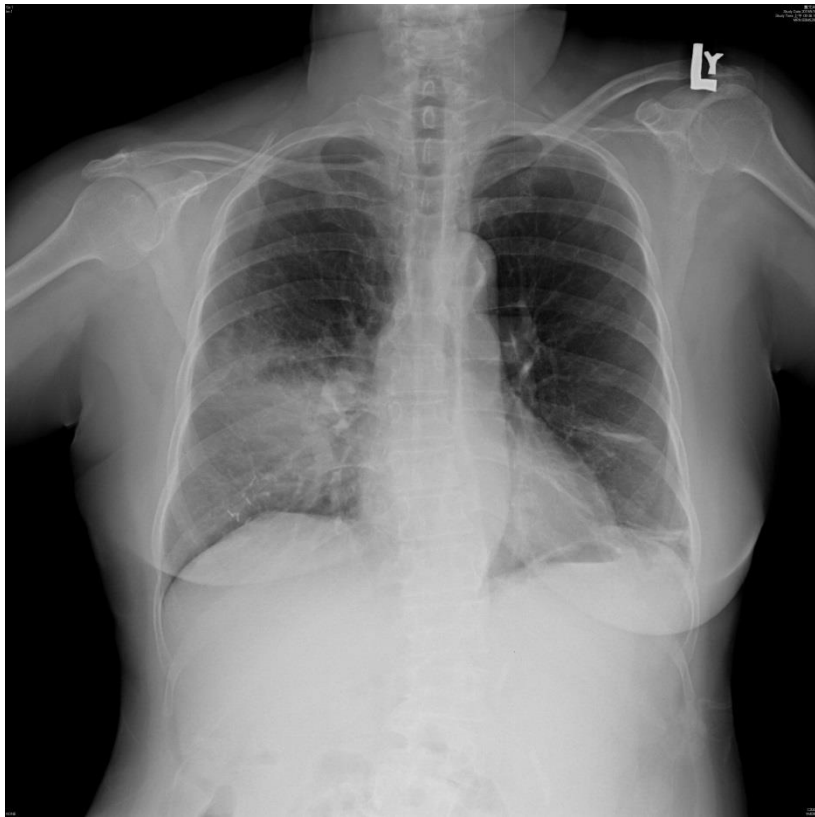
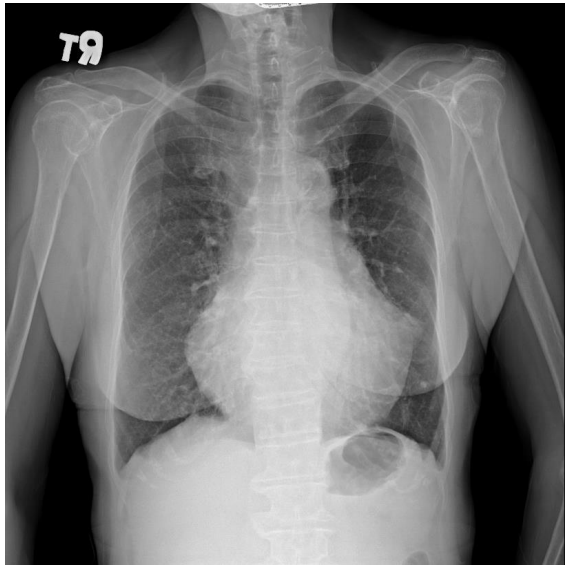
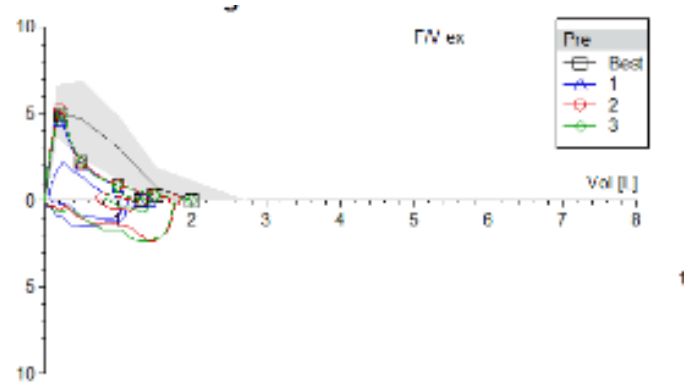
  - Actein 600mg QD
  - Regrow 1# HS, Brown Mixture…etc



ACO Case 2

- 81 y/o female
- C.C: Dry cough and dyspnea
- PH: Childhood Asthma, COPD, CAD, CHF, peptic ulcer
- OPD medications:
  - Spiriva: 2puff QD 106/12-107/04
  - ICS/LABA: 2puff BID 107/05-

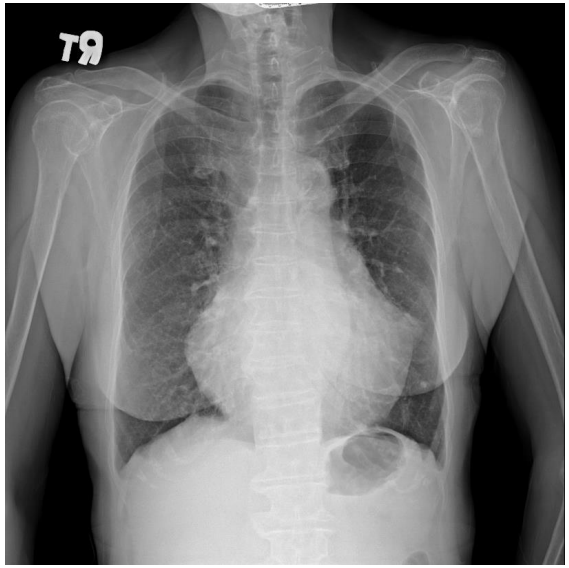


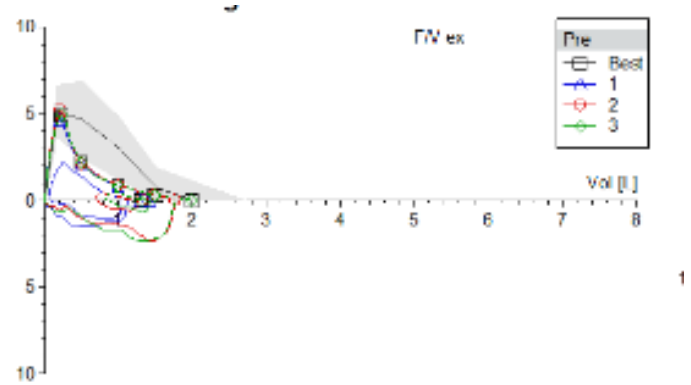


	Pred	Best	%...	1	2	3
FVC	2.00	1.99	99	1.41	1.75	1.99
FEV1	1.62	1.30	80	1.26	1.31	1.30
FEV1%F	73.71	65.31	89	90.35	74.88	65.31
MMEF	2.14	0.71	33		0.73	0.71
MEF75	4.66	2.20	47	2.15	2.07	2.20
MEF50	3.01	0.82	27	0.84	0.84	0.82
MEF25	0.74	0.28	38		0.31	0.28
PEF	5.15	4.92	96	4.61	5.23	4.92
PEF*		1.27		1.26	1.33	1.27
Level date		18-...				
Level time		14:47				
E code		24		14	14	20

ACO Case 2

- 81 y/o female
- C.C: Dry cough and dyspnea
- PH: Childhood Asthma, COPD, CAD, CHF, peptic ulcer
- OPD medications:
  - Spiriva: 2puff QD 106/12-107/04
  - ICS/LABA: 2puff BID 107/05-

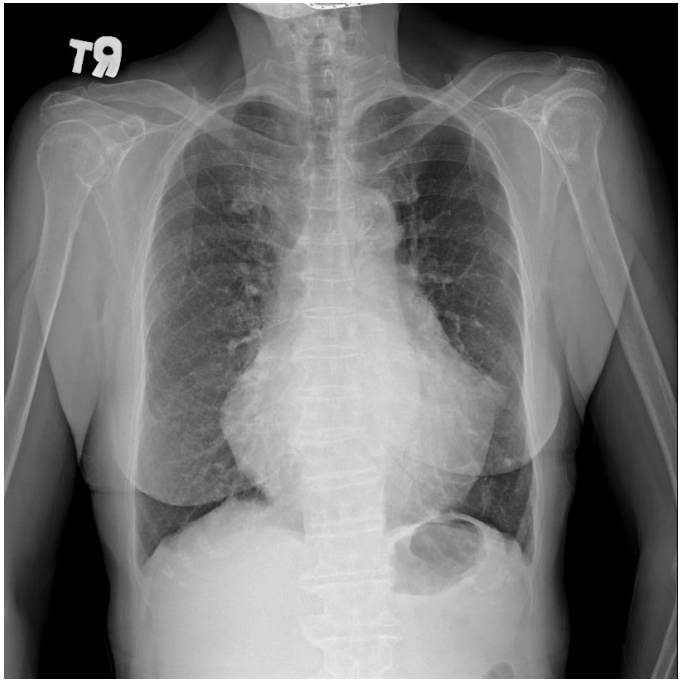


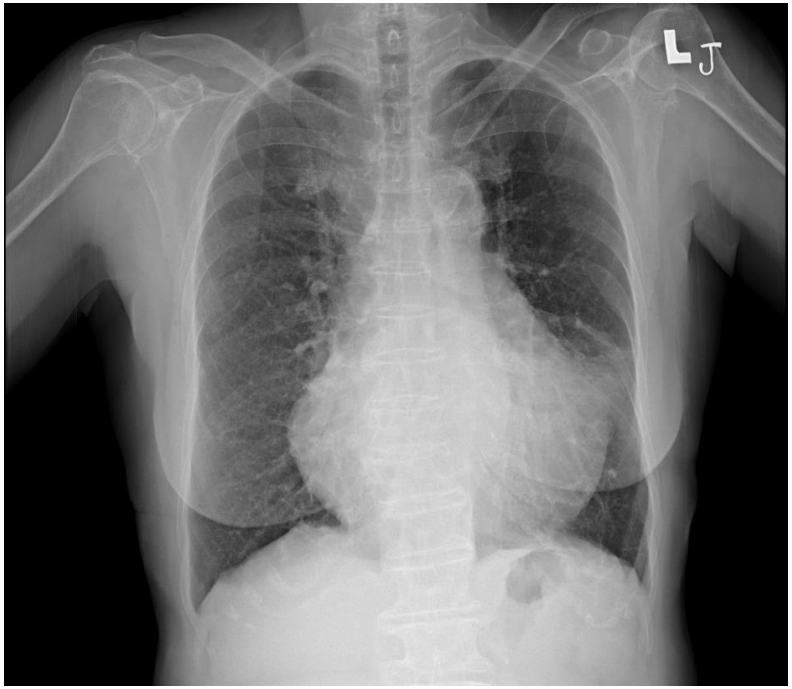


	Pred	Best	%...	1	2	3
FVC	2.00	1.99	99	1.41	1.75	1.99
FEV1	1.62	1.30	80	1.26	1.31	1.30
FEV1%F	73.71	65.31	89	90.35	74.88	65.31
MMEF	2.14	0.71	33		0.73	0.71
MEF75	4.66	2.20	47	2.15	2.07	2.20
MEF50	3.01	0.82	27	0.84	0.84	0.82
MEF25	0.74	0.28	38		0.31	0.28
PEF	5.15	4.92	96	4.61	5.23	4.92
PEF*		1.27		1.26	1.33	1.27
Level date		18-...				
Level time		14:47				
E code		24		14	14	20

ACO Case 2

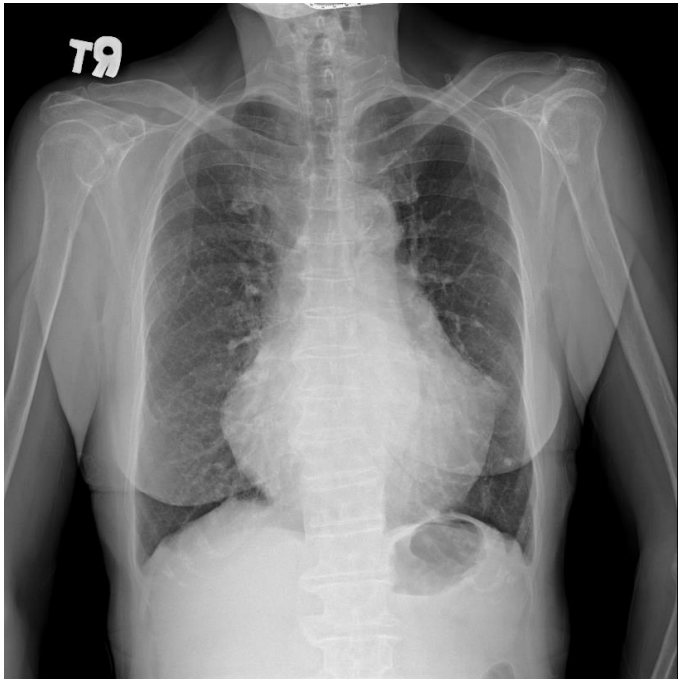
- 81 y/o female
- C.C: Productive cough with yellowish sputum
- Spiriva: 2puff QD 106/12-107/04
- ICS/LABA: 2puff BID 107/05-

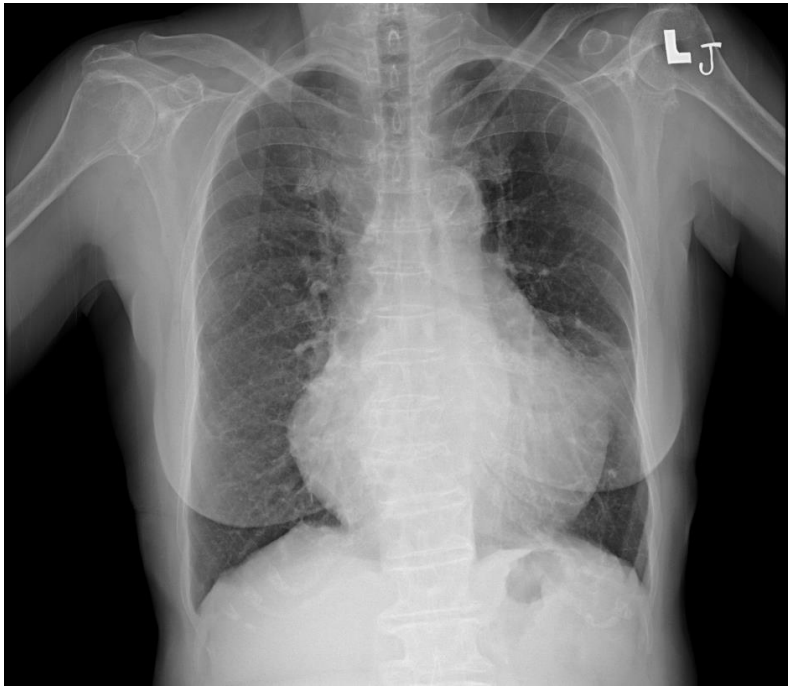




ACO Case 2

- 81 y/o female
- C.C: Productive cough with yellowish sputum
- Spiolto: 2 puff QD, 107/07-now





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BMJ 2019;365:l2141 doi: 10.1136/bmj.l2141 (Published 9 May 2019)

NEWS

COPD: spirometry does not occur in 60% of admissions, audit shows

Jacqui Wise

Validation study –
COPD (86.2% sensitivity) and asthma (92.0% sensitivity).

The Journal of Allergy and Clinical Immunology: In Practice

Use of ICS/LABA Combinations or LAMA is Associated with a Lower Risk of Acute Exacerbation in Patients with Coexistent COPD and Asthma

Vincent Yi-Fong Su, MD*, Kuang-Yao Yang, MD, PhD*, Yao-Hsu Yang, MD, Ying-Huang Tsai, MD, PhD, Diahn-Warng Perng, MD, PhD, Wei-Juin Su, MD, MPH, Kun-Ta Chou, MD, Kang-Cheng Su, MD, Yung-Feng Yen, MD, MPH, PhD, Pau-Chung Chen, MD, PhD

DOI: https://doi.org/10.1016/j.jaip.2018.01.035

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

PATIENTS

Between March 13, 2012, and October 23, 2014, we recruited patients who were 40 years of age or older, had received a documented diagnosis of COPD from a general practitioner, and had had one or more COPD exacerbations in the previous 3 years. Patients had to be taking regular maintenance inhaler therapy, defined as the use of one or more long-acting bronchodilators; inhaled glucocorticoids, alone or in combination with a long-acting bronchodilator; or a combination of inhaled glucocorticoids, a long-acting beta-agonist (LABA), and a long-acting muscarinic antagonist (LAMA). There were no restrictions regarding smoking history or spirometric values. Among the few exclusion criteria were an exacerbation within the previous 2 weeks and long-term use of oral glucocorticoids. Details of the trial design and the analysis approach have been published previously.[7,8]

2199/2799 = 78%

Patients were recruited in primary care practices by the health care professionals who provided their normal, everyday care. All the patients provided written informed consent. The trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the provisions of the 2008 Declaration of Helsinki. The trial protocol was approved by the National Research Ethics Service Committee North West, Greater Manchester South. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

N Engl J Med 2016; 375:1253-1260

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Top 5† inclusion/exclusion criteria not satisfied:

327 (12.3%)	FEV_1 outside of 25–60% of predicted normal, or FEV_1/FVC ≥0.70
69 (2.6%)	History of long QT syndrome or QTc >450 ms at start of run-in
62 (2.3%)	COPD exacerbation before randomization‡
57 (2.1%)	Eosinophil count >600/mm^3 at start of run-in
50 (1.9%)	Spirometry results not acceptable according to ATS/ERS criteria

Top 5† inclusion/exclusion criteria not satisfied:

446 (19.6%)	FEV_1 outside of 25–60% of predicted normal, or FEV_1/FVC ≥0.70
63 (2.8%)	Eosinophil count >600/mm^3 at start of run-in
56 (2.5%)	History of long QT syndrome or QTc >450 ms at start of run-in
53 (2.3%)	Spirometry results not acceptable according to ATS/ERS criteria
40 (1.8%)	COPD exacerbation before randomization‡

N Engl J Med 2016; 374:2222-2234