KYUNG HEE UNIVERSITY
MEDICAL CENTER

Asthma-COPD overlap (ACO)

ACO should be considered as a distinct phenotype ?

2018.4.14 대한 결핵 및 호흡기학회
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Chronic obstructive pulmonary diseases

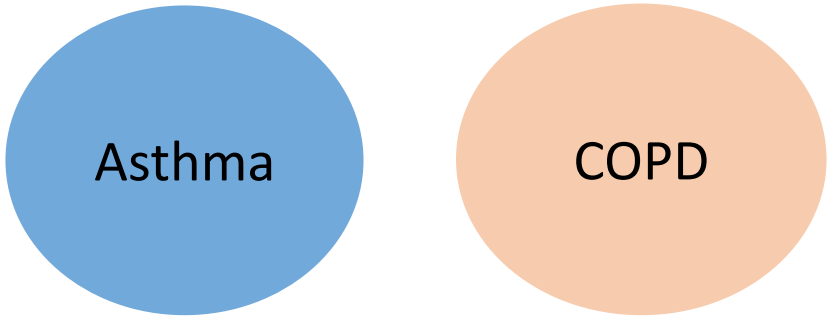
- Traditional views

Dutch Hypothesis

"Spectrum of disease"
one form can switch to another

British Hypothesis

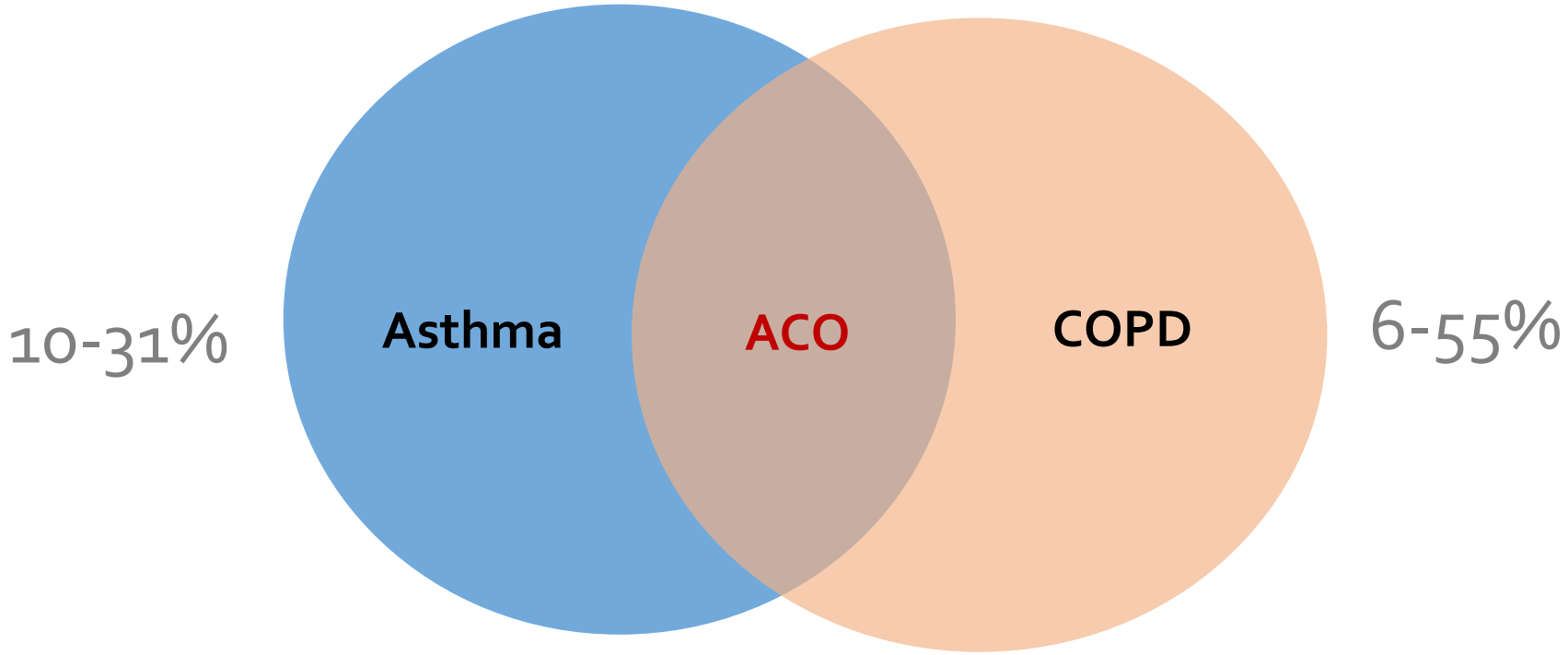
"Distinct diseases"



Orie NG et al. Charles C Thomas, 1961.
Am J Respir Crit Care Med 2006;174:240-3.

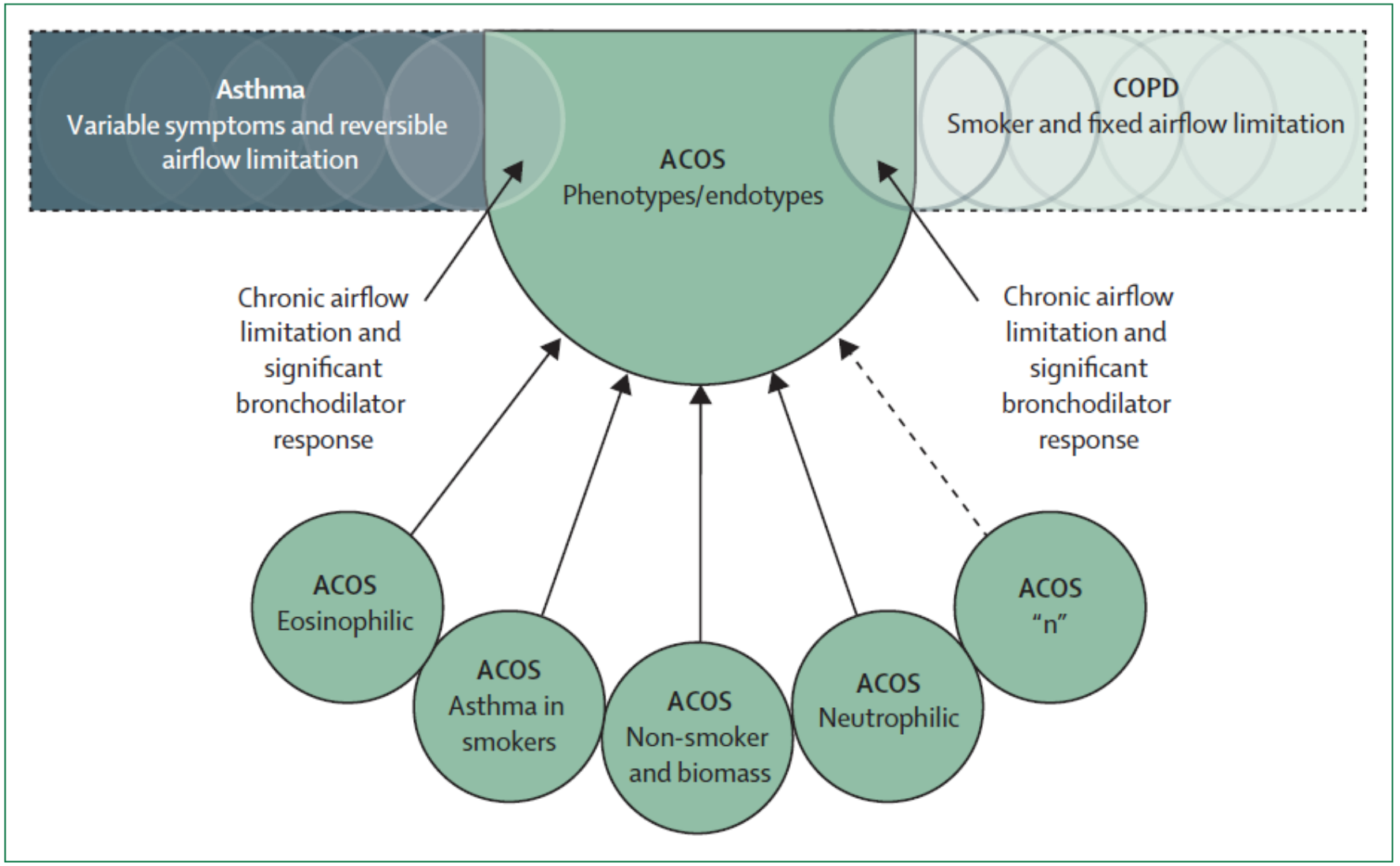
Concept of ACO

- Asthma-COPD overlap (ACO) is characterized by **persistent airflow limitation** with several features that it shares with both asthma and COPD.



Vanfleteren LE et al. Thorax 2014 Jan; 69(1): 72–9.
To T et al. Am J Respir Crit Care Med 2016;194:429-38.
Wurst KE et al. Respir Med. 2016 Jan;110:1-11.

Synonyms



Bateman ED et al. Lancet Respir Med 2015;3:719-28.

Clinical trials in selected asthma and COPD

	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	□	□	□	□	□	□	■

	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	□	□	□	■	□

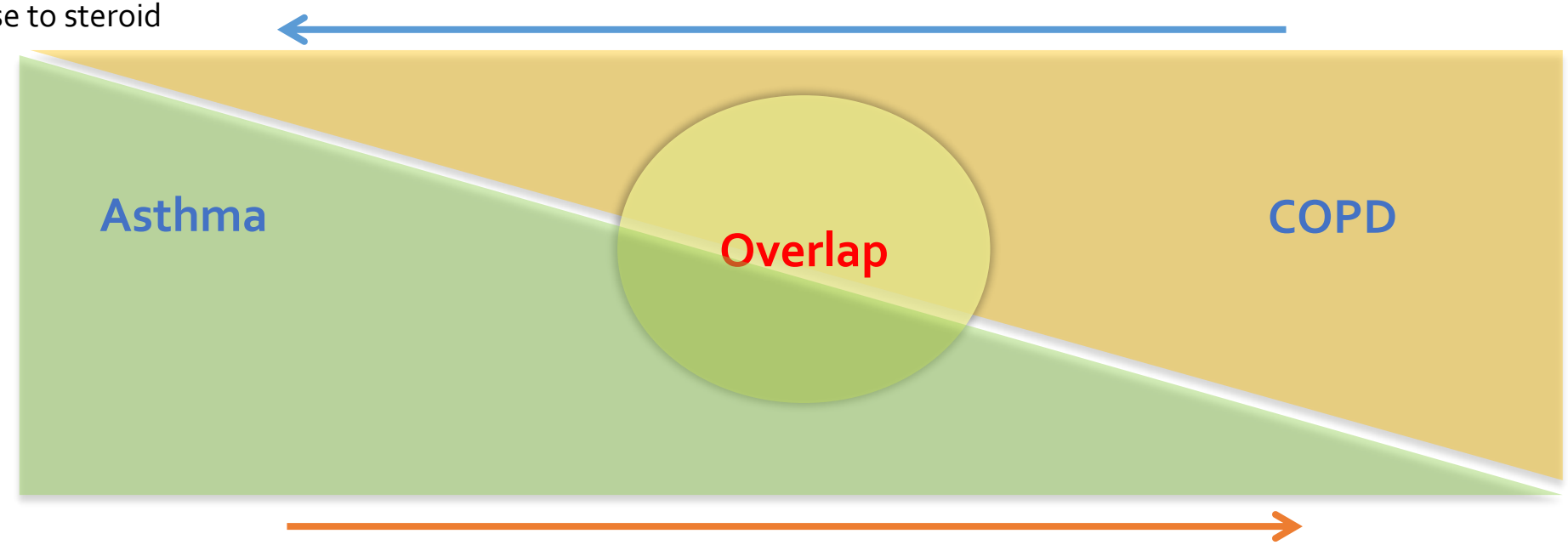
■ Included in trials □ Not included in trials

Sin DD et al. Eur Respir J. 2016 Sep;48(3):664-73.

How can we diagnose ACO?

ACO between asthma and COPD

Eosinophilic inflammation
Medium sized
CD_4+ (Th_2) cells
Hx of asthma/atopy <40yrs
AHR
Good response to steroid



≥40 yrs
Smoking
Neutrophils, macrophages
Small airway
CD_8+ (Tc_1) cells
Not fully reversible
Poor response to steroid

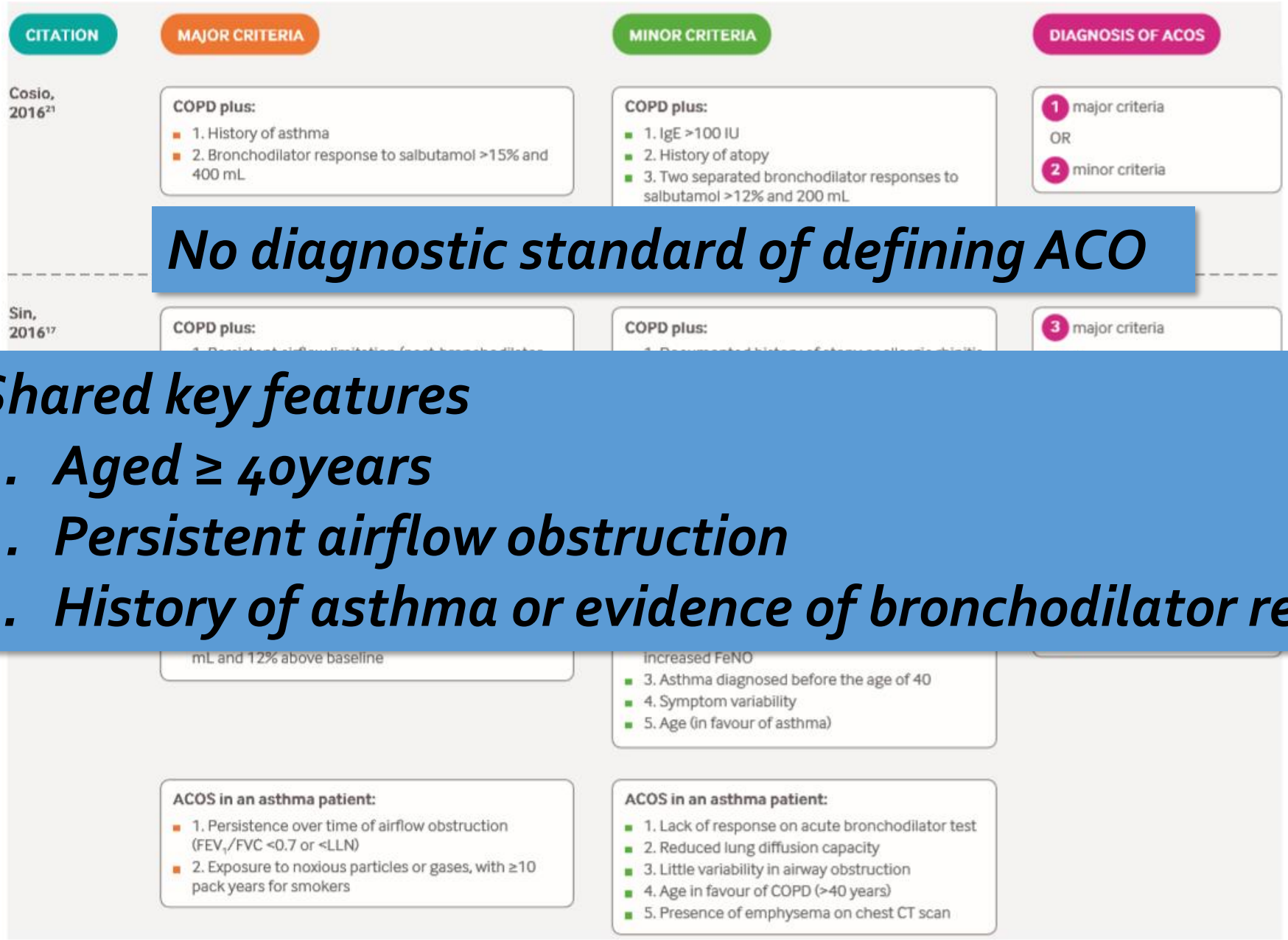
GINA & GOLD : stepwise approach

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	❑ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema …bacco
Time course		… time …ment
Chest X-ray		

Syndromic diagnosis of airways disease: how to use Box 5-2b

Shaded columns list features that, when present, best identify patients with typical asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, the patient is likely to have that disease. If there are similar numbers of checked boxes in each column, the diagnosis of ACO should be considered. See Step 2 for more details.

Diagnostic criteria for ACO



CITATION	MAJOR CRITERIA	MINOR CRITERIA	DIAGNOSIS OF ACOS
Cosio, 2016[21]	COPD plus: ■ 1. History of asthma ■ 2. Bronchodilator response to salbutamol >15% and 400 mL	COPD plus: ■ 1. IgE >100 IU ■ 2. History of atopy ■ 3. Two separated bronchodilator responses to salbutamol >12% and 200 mL	1 major criteria OR 2 minor criteria
Sin, 2016[17]	COPD plus: mL and 12% above baseline	COPD plus: increased FeNO ■ 3. Asthma diagnosed before the age of 40 ■ 4. Symptom variability ■ 5. Age (in favour of asthma)	3 major criteria
	ACOS in an asthma patient: ■ 1. Persistence over time of airflow obstruction (FEV_1/FVC <0.7 or <LLN) ■ 2. Exposure to noxious particles or gases, with ≥10 pack years for smokers	ACOS in an asthma patient: ■ 1. Lack of response on acute bronchodilator test ■ 2. Reduced lung diffusion capacity ■ 3. Little variability in airway obstruction ■ 4. Age in favour of COPD (>40 years) ■ 5. Presence of emphysema on chest CT scan	

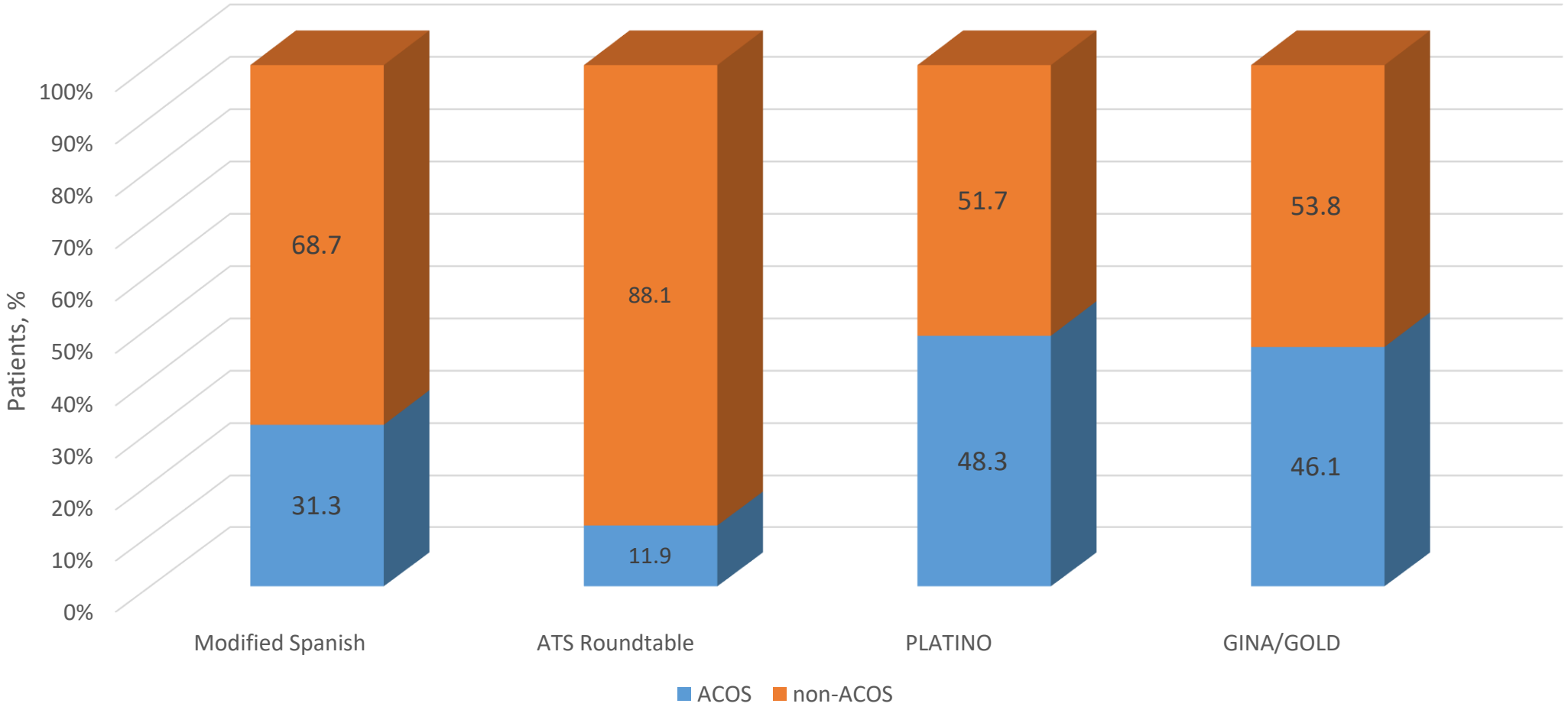
No diagnostic standard of defining ACO

Shared key features

1. ***Aged ≥ 40years***
2. ***Persistent airflow obstruction***
3. ***History of asthma or evidence of bronchodilator reversibility***

Leung JM et al. BMJ. 2017 Sep 25;358:j3772.

Different prevalence of ACO by adopted criteria



YS Jo et al., Ann Allergy Asthma Immunol 118 (2017) 696-703

Why should we focus on ACO ?

ACOS to ACO

- In 2014, GINA and GOLD published a joint document on ACOS

- **Asthma-COPD overlap syndrome (ACOS)** is characterized by
- **persistent airflow limitation** with several features usually associated with asthma and several features usually associated with COPD.
- ACOS is therefore identified in clinical practice by the features that it **shares with both asthma and COPD**. (GINA 2016)

- **Asthma-COPD overlap (ACO)** is characterized by **persistent airflow limitation** with several features usually associated with asthma and several features usually associated with COPD.
- This is not a definition, but a description for clinical use, as ACO includes several different clinical phenotypes and there are likely to be several different underlying mechanisms. (GINA 2017)

Why ACO is important ?

- Excluded from clinical trials from both asthma and COPD

  → Limited clinical data and therapeutic target
- No unified diagnostic criteria
- Controversy over distinct disease entity

- **Nevertheless**, no matter which definition is used, ACO seems to account for a considerable portion of airway disease, and ACO has distinctive features from asthma and COPD.

Demographic features

Characteristic	Control Subjects (*n* = 68,612)	ACOS (*n* = 2,594)	COPD (*n* = 4,807)	Asthma (*n* = 4,485)	*P* Value
Age, mean ± SD, yr	61.7 ± 13.6	64.0 ± 11.7	67.1 ± 11.8	59.0 ± 13.1	<0.0001
Sex, male	26,727 (39)	743 (28.6)	1,845 (38.4)	1,268 (28.3)	<0.0001
Education					
Did not g				9.2)	<0.0001
Graduate				26.4)	
Attended				29)	
Graduate				34.9)	
Marital stat					
Married				52.6)	<0.0001
Never ma				11.8)	
Divorced				35.6)	
Income, $					
<15,000				13.3)	<0.0001
15,000–2				16.6)	
25,000–3				9.5)	
35,000–5				12.1)	
>50,000				35.7)	
Employmer					
Employe				44.5)	<0.0001
Homema				7.3)	

Characteristic	Control Subjects	ACOS	COPD	Asthma
Myocardial infarction	4,384 (6.4)	520 (20.4)	929 (19.5)	274 (6.1)
Coronary heart disease	7 (6.3)	595 (23.6)	991 (21.1)	299 (6.7)
Stroke	2,968 (4.3)	366 (14.2)	527 (11.1)	262 (5.9)
Cancer	7,557 (11.0)	483 (18.7)	884 (18.5)	501 (11.2)
Arthritis	26,143 (38.3)	1,861 (72.1)	2,926 (61.2)	2,324 (52.1)
Depression	10,902 (15.9)	1,181 (45.9)	1,555 (32.5)	1,303 (29.3)
Kidney disease	2,184 (3.2)	246 (9.6)	414 (8.7)	191 (4.3)
Diabetes	9,479 (14.2)	744 (29.7)	1,024 (22.2)	817 (18.8)
Presence of at least 1 comorbidity	40,045 (58.4)	2,340 (90.2)	4,039 (84.0)*	3,204 (71.4)
Hospitalization	NA†	530 (22)	588 (13.2)*	NA†

Syndrome	Asthma (severe) [105]	ACOS	COPD [106]
Demographics	>40 years Women > men Nonsmoker or <5 pack years Obesity Atopy typical Rhinosinusitis GERD Frequent albuterol use Exercise limited in between attacks Dependence on prednisone Hallmark problem: frequent exacerbations	>40 years; 50–65 years Past or current smoker >10 pack-years Atopy present Rhinosinusitis GERD Exercise very limited Hallmark problem: very frequent exacerbations > COPD alone	≥65 years if not younger Past or current smoker >10 pack-years No atopy GERD Multiple daily albuterol Exercise very limited Oxygen dependence Hallmark problem: exacerbations and exercise intolerance

- Patients with ACO

✓Younger, more female, obese *than COPD*

✓Older *than asthma*

- Patients with ACO

✓Lower SES & education level

✓carry a higher burden of comorbidities *than asthma & COPD*

Kumbhare S et al. Ann Am Thorac Soc 2016;13:803-10.
Louie S et al. Expert Rev Clin Pharmacol. 2013 Mar;6(2):197-219.

Radiologic features: CT scan

COPDgene cohort : COPD (n=3120) vs COPD and asthma (n=450)

	COPD		COPD and asthma	Effect size	p-value
Log emphysema[#] %	1.91±1.4	>	1.44±1.6	-0.23±0.07	<0.001
Pi10 mm	3.71±0.14		3.78±0.16	0.06±0.01	<0.001
Segmental airway wall area %	62.8±3.0	<	63.6±3.3	0.61±0.16	<0.001
Subsegmental airway wall area %	65.6±2.3		66.4±2.7	0.66±0.20	0.001
Gas trapping[¶] %	39.7±20.7		35.6±21.5	0.88±1.5	0.55

Data are presented as mean±SD, unless otherwise stated. Effect size data are presented as β±SE for the COPD and asthma group. Regression models were adjusted for age, sex, pack-years, body mass index and type of computed tomography scanner. Pi10: square root of wall area of a 10-mm luminal perimeter. [#]: additionally adjusted for current smoking status; [¶]: additionally adjusted for clinical centre.

Megan Hardin et al. Eur Respir J 2014; 44: 341–350

Lung function

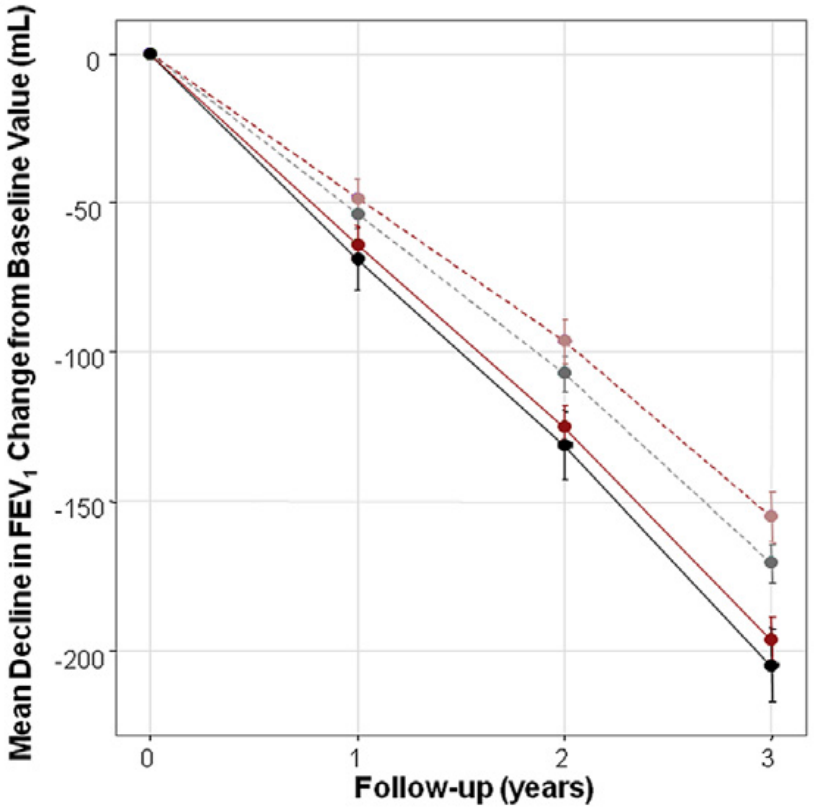
- Latin America project for the Investigation of Obstructive Lung Disease (**PLATINO**) study population
- ACO: COPD (post-BD $FEV_1/FVC < 0.7$) & asthma (wheezing in the last 12 month & positive BDR, or medical diagnosis of asthma)

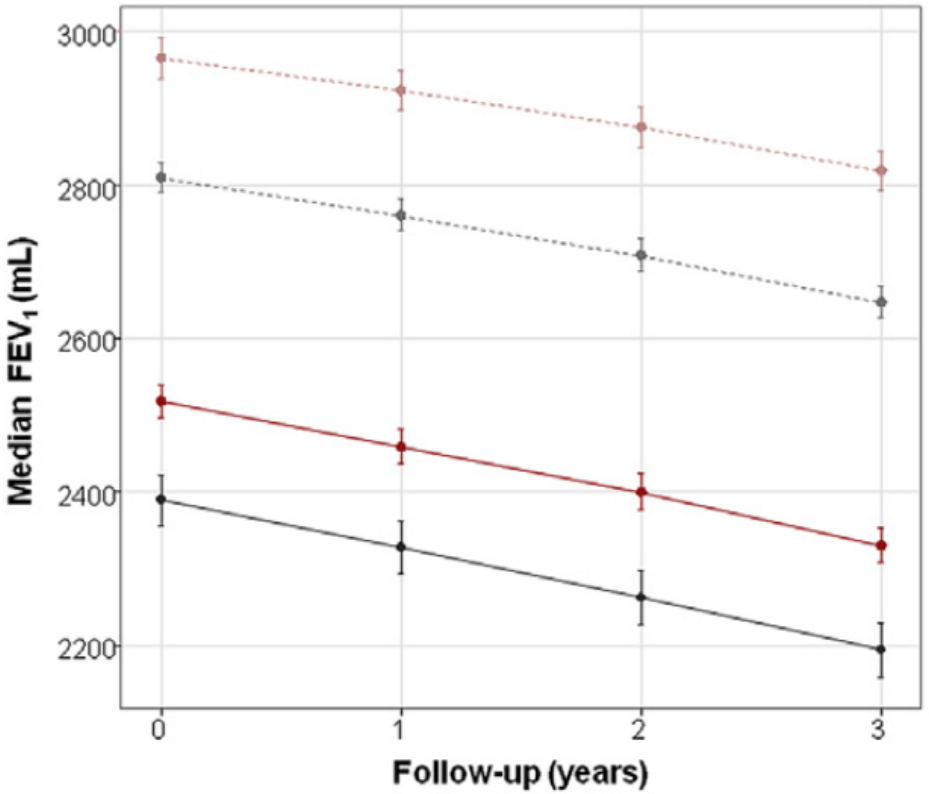
Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Prebronchodilator FEV_1, L	2.0 ± 0.6	2.1 ± 0.8	1.7 ± 0.6	< .001
Prebronchodilator FEV_1, % predicted	79.9 ± 17.2	81.4 ± 20.0	63.5 ± 18.9	< .001
Postbronchodilator FEV_1, L	2.5 ± 0.8	2.2 ± 0.8	2.0 ± 0.7	< .001
Postbronchodilator FEV_1, % predicted	94.0 ± 17.8	82.0 ± 19.2	72.1 ± 18.9	< .001
FEV_1 change, absolute, mL	448.5 ± 395.3	83.3 ± 185.5	295.7 ± 157.1	< .001
FEV_1 change, relative, %	24.1 ± 29.9	5.4 ± 12.7	19.2 ± 12.1	< .001
FEV_1 change, % predicted, %	20.5 ± 29.1	1.8 ± 12.3	15.4 ± 11.8	< .001
Prebronchodilator FVC, L	2.7 ± 0.9	3.3 ± 1.1	3.0 ± 0.9	< .001
Prebronchodilator FVC, % predicted	85.3 ± 18.4	98.0 ± 18.8	83.5 ± 17.8	< .001
Postbronchodilator FVC, L	3.2 ± 1.0	3.4 ± 1.1	3.4 ± 1.1	.099
Postbronchodilator FVC, % predicted	96.3 ± 17.5	100.6 ± 18.7	96.6 ± 21.3	.042
FVC change, absolute, mL	397.4 ± 489.9	103.5 ± 344.0	463.6 ± 348.9	< .001
FVC change, relative, %	16.1 ± 22.7	4.5 ± 13.2	17.0 ± 12.0	< .001
FVC change, % predicted, %	15.3 ± 23.0	3.5 ± 12.9	16.5 ± 11.8	< .001
Prebronchodilator FEV_1/FVC	73.7 ± 7.9	62.3 ± 9.6	57.7 ± 11.1	< .001
Postbronchodilator FEV_1/FVC	78.2 ± 4.7	62.7 ± 8.0	58.5 ± 9.5	< .001
FEV_1/FVC change	7.1 ± 11.6	1.4 ± 9.8	2.7 ± 12.4	< .001

Menezes et al. Chest 2014;145(2):297-304.

Impact of AHR on lung function change

- Lung Health Study (LHS, n=5887) and the Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) study (n=51)
- AHR by PC20 may represent a spectrum of the ACO phenotype





Difference in FEV_1 decline : 13.2 mL/y (95% CI, 7.3-19.0; p=.007)

AHR (PC20 cut-off = 4 mg/mL)
No AHR (PC20 cut-off = 4 mg/mL)
AHR (PC20 cut-off = 15 mg/mL)
No AHR (PC20 cut-off = 15 mg/mL)

Tkacova R et al. J Allergy Clin Immunol 2016;138:1571-9.

Change of lung function

- European Community Respiratory Health Survey, median 5-year lung function change
- ACO : COPD (post-BD $FEV_1/FVC < 0.7$) & asthma (positive methacholine challenge test)

	Healthy	Asthma alone	ACOS	COPD alone	Overall p-value#
Subjects	5659	941	218	166	
FEV_1 change mL·year^{-1}	−26.2 (−31.1– −21.3)	−25.3 (−30.5– −20.1)	−25.9 (−32.2– −19.6)	−37.3 (−44.0– −30.6)***	<0.001
FEV_1 change % of baseline·year^{-1}	−0.69 (−0.83– −0.55)	−0.68 (−0.83– −0.53)	−0.66 (−0.84– −0.47)	−1.17 (−1.37– −0.97)***	<0.001
FVC change mL·year^{-1}	−19.8 (−25.6– −14.1)	−21.3 (−27.4– −15.2)	−25.5 (−33.0– −18.0)*	−37.0 (−45.0– −29.0)***	<0.001
FVC change % of baseline·year^{-1}	−0.42 (−0.55– −0.29)	−0.45 (−0.59– −0.31)	−0.55 (−0.72– −0.38)*	−0.81 (−0.99– −0.63)***	<0.001
Hospital/ER admission for breathing problems¶ %	3.6 (2.7–4.5)	11.9 (8.7–15.0)***	15.8 (9.9–21.8)***	8.1 (3.5–12.7)**	<0.001

De Maro R et al. Eur Respir J. 2015 Sep;46(3):671-9.

Change of lung function

- Copenhagen City Heart Study, FEV_1 decline for 18 years
- ACO : COPD (post-BD $FEV_1/FVC < 0.7$) & asthma (self-reported asthma)

	Decline in FEV_1 in mL per year	p value	p value	p value	p value
Healthy never-smokers	20·9 (1·2)	Reference	0·15	<0·0001	0·19
Ever-smokers without asthma or COPD	20·7 (1·4)	0·88	0·13	<0·0001	0·17
Asthma	25·6 (3·3)	0·15	Reference	0·0003	0·77
COPD	39·5 (2·5)	<0·0001	0·0003	Reference	0·02
ACO with early asthma onset	27·3 (5·0)	0·19	0·77	0·02	Reference
ACO with late asthma onset	49·6 (3·0)	<0·0001	<0·0001	0·003	0·0001
Male sex (reference: female sex)	4·8 (1·2)	<0·0001	..	..	..
Age (years)	0·6 (0·1)	<0·0001	..	..	..
Height (cm)	0·4 (0·1)	<0·0001	..	..	..
Smoking (reference: non-smokers)					
Quitters	2·3 (1·8)	0·22	..	..	..
Current smokers	8·0 (1·1)	<0·0001	..	..	..

Peter Lange et al. Lancet Respir Med 2016; 4: 454–62.

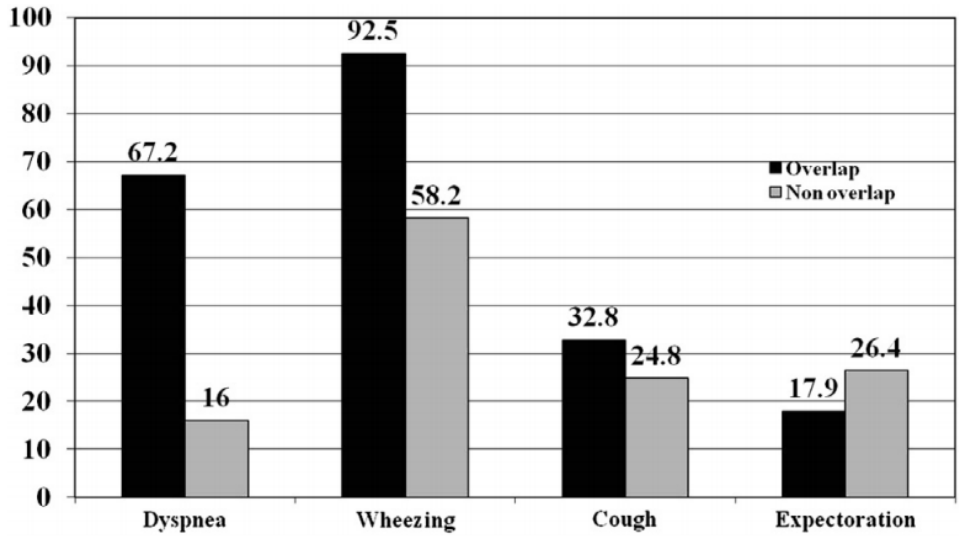
Respiratory symptoms

EPI-SCAN study

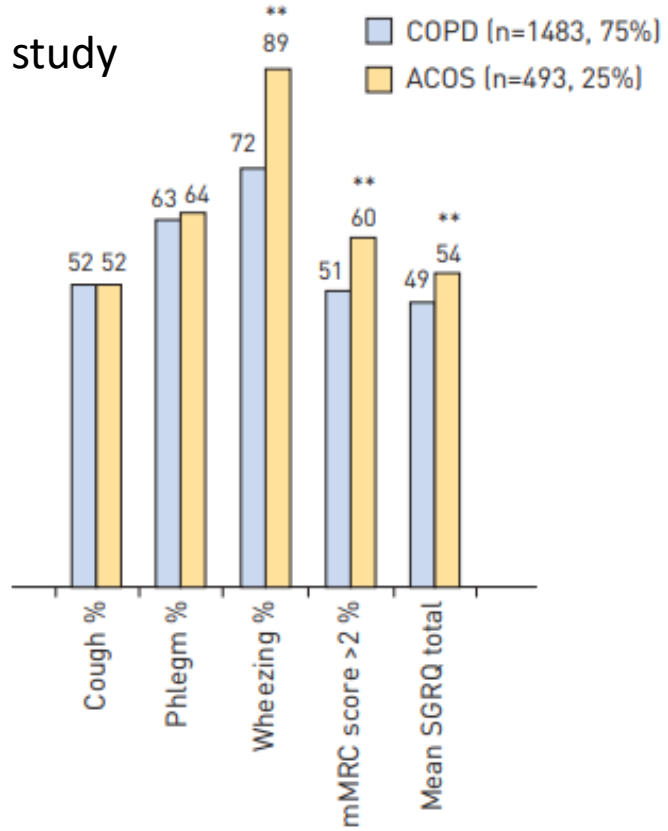
: population based cohort in Spain

COPD (n=318)

Overlap (n=67)



ECLIPSE study



PLATINO study

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Respiratory symptoms, yes				
Cough	35 (41.7)	163 (27.4)	45 (50.6)	<.001
Phlegm	33 (39.3)	151 (25.4)	38 (42.7)	<.001
Wheezing	84 (100.0)	174 (29.3)	89 (100.0)	<.001
Dyspnea	58 (69.1)	278 (47.4)	58 (65.2)	<.001

Menezes et al. Chest 2014;145(2):297-304.

Wurst KE et al. Eur Respir J. 2016 May;47(5):1559-62.

Marc Miravitlles et al. Respiratory Medicine (2013) 107, 1053-1060.

Overall health status and QoL

EPI-SCAN study

	All COPD ($n = 385$)	Overlap ($n = 67$)	Non-overlap ($n = 318$)	*P* value
EQ-5D				
Utility score	0.81 (0.19)	0.76 (0.19)	0.82 (0.19)	0.037
VAS score	70.8 (16.9)	66.9 (14.8)	71.5 (17.2)	0.067
SGRQ	21.2 (18.3)	31.1 (20.2)	19.4 (17.4)	<0.001
Global	26.8 (22.1)	37.3 (22.5)	24.9 (21.5)	<0.001
Symptoms				
Activity	29.7 (25.5)	41.3 (27.2)	27.6 (24.7)	<0.001
Impact	14.1 (16.8)	23.1 (20.2)	12.4 (15.6)	<0.001

Variable	Total (N = 301)	Modified Spanish		*P* Value	ATS Roundtable		*P* Value	PLATINO		*P* Value	GINA/GOLD		*P* Value
		ACOS (n = 91)	Non-ACOS (n = 200)		ACOS (n = 5)	Non-ACOS (n = 37)		ACOS (n = 140)	Non-ACOS (n = 150)		ACOS (n = 42)	Non-ACOS (n = 49)	
Indexes of dyspnea and quality of life, mean (SD)													
SGRQ	34.3 (17.6)	37.4 (18.6)	33.1 (17.1)	.07	34.9 (18.5)	39.0 (18.5)	.64	39.4 (17.7)	29.5 (16.3)	<.01	37.1 (16.7)	36.3 (18.0)	.82
CAT	15.4 (7.3)	17.2 (7.9)	14.7 (7.0)	.01	18 (7.2)	17.5 (7.1)	.89	17.8 (7.7)	13.1 (6.2)	<.01	17.3 (6.6)	17.2 (7.5)	.93
CCQ	18.8 (9.2)	19.0 (9.4)	18.7 (9.3)	.86	13.2 (5.6)	19.5 (9.4)	.20	20.6 (9.1)	16.5 (9.0)	<.01	19.7 (9.0)	18.5 (8.7)	.54
6MWD, m	437.6 (109.4)	461.0 (97.3)	427.9 (111.8)	.02	527.6 (50.4)	438.6 (98.0)	.06	441.6 (109.4)	436.3 (107.4)	.70	433.2 (92.6)	437.6 (113.6)	.85
mMRC	1.5 (0.9)	1.4 (0.8)	1.6 (0.9)	.03	1.0 (0.7)	1.4 (0.7)	.29	1.5 (0.8)	1.5 (0.9)	.67	1.2 (0.7)	1.4 (0.6)	.20
ACT	18.3 (4.4)	17.0 (4.6)	20.1 (3.4)	<.01	16.2 (4.8)	17.5 (4.2)	.58	17.4 (4.5)	20.1 (3.5)	<.01	17.7 (3.9)	19.2 (4.0)	.16
Mini-AQLQ	74.2 (17.0)	69.7 (18.4)	80.6 (12.9)	<.01	67.0 (17.3)	72.0 (19.4)	.63	70.4 (17.0)	82.3 (14.2)	<.01	70.9 (16.8)	80.1 (12.5)	.02
History of exacerbation during past 1 year													
Total No. (%)	87 (28.9)	46 (50.5)	39 (19.5)	<.01	2 (40)	21 (56.8)	.48	57 (40.7)	30 (20.0)	<.01	21 (50)	18 (36.7)	.20
Frequency, mean (SD) No. per years	0.7 (1.8)	1.3 (2.4)	0.4 (1.4)	<.01	1.6 (3.0)	1.6 (2.7)	.98	1.1 (2.4)	0.3 (0.8)	<.01	1.1 (2.1)	1.1 (2.6)	.92
Moderate to severe, No. (%)	71 (23.6)	42 (46.1)	28 (14.0)	<.01	2 (40)	19 (51.3)	.63	48 (34.3)	23 (15.3)	<.01	17 (40.5)	16 (32.6)	.44
Frequency, mean (SD) No. per year	0.4 (1.2)	1.0 (1.8)	0.2 (0.7)	<.01	0.8 (1.3)	1.3 (2.4)	.62	0.7 (1.5)	0.2 (0.8)	<.01	0.9 (2.1)	0.7 (1.4)	.56

Marc Miravitlles et al. Respiratory Medicine (2013) 107, 1053-1060.
YS Jo et al., Ann Allergy Asthma Immunol 118 (2017) 696-703.

Exacerbation in the past year

- **PLATINO** study

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Exacerbations past year				
Unadjusted, PR (95% CI)	2.54 (1.42-4.52)	1.00 (Ref)	3.01 (1.74-5.21)	< .001
Adjusted,[a] PR (95% CI)	1.65 (0.93-2.92)	1.00 (Ref)	2.11 (1.08-4.12)	.056
Number of exacerbations past year				
Unadjusted, RR (95% CI)	1.04 (0.40-2.69)	1.00 (Ref)	5.48 (1.74-17.22)	.010
Adjusted,[a] RR (95% CI)	0.98 (0.32-3.02)	1.00 (Ref)	4.20 (1.05-16.62)	.069
Hospitalizations past year				
Unadjusted, PR (95% CI)	[b]	1.00 (Ref)	4.76 (1.70-13.31)	< .001
Adjusted,[a] PR (95% CI)	[b]	1.00 (Ref)	4.11 (1.45-11.67)	< .001
Number of hospitalizations past year				
Unadjusted, RR (95% CI)	[b]	1.00 (Ref)	5.90 (1.74-20.01)	< .001
Adjusted,[a] RR (95% CI)	[b]	1.00 (Ref)	5.24 (1.49-18.38)	< .001
Limitations due to physical health				
Unadjusted, PR (95% CI)	1.46 (1.00-2.13)	1.00 (Ref)	1.38 (0.95-1.99)	.074
Adjusted,[a] PR (95% CI)	1.18 (0.83-1.68)	1.00 (Ref)	1.27 (0.86-1.88)	.400

Menezes et al. Chest 2014;145(2):297-304.

Exacerbation

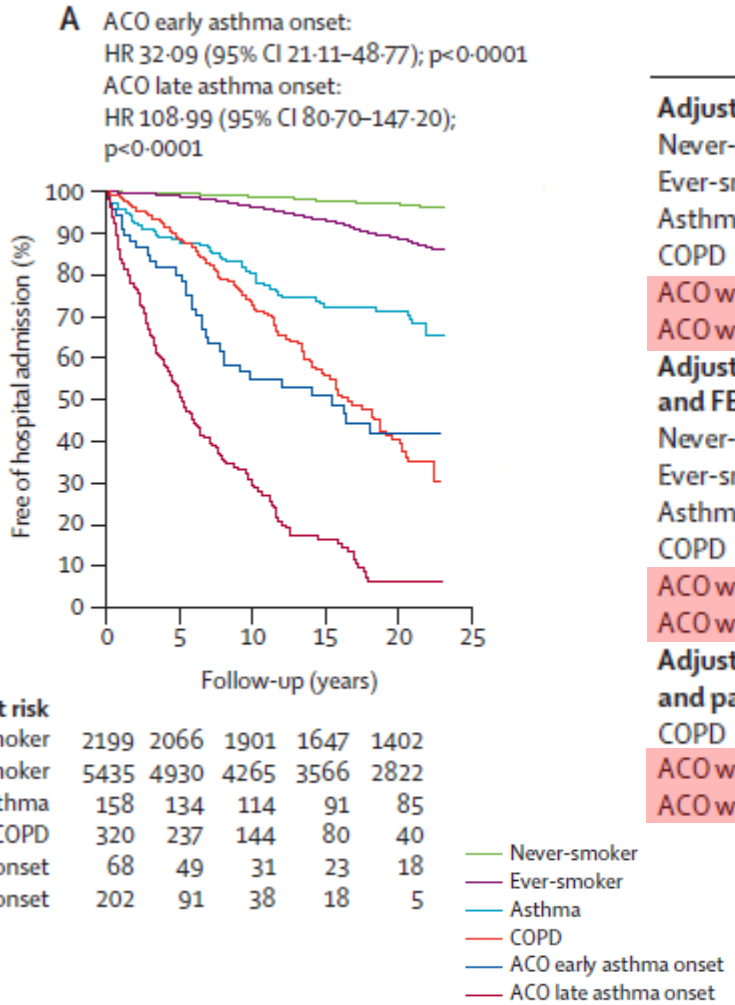
- European Community Respiratory Health Survey, median 5-year lung function change
- ACO : COPD (post-BD $FEV_1/FVC < 0.7$) & asthma (positive methacholine challenge test)

	Healthy	Asthma alone	ACOS	COPD alone	Overall p-value#
Subjects	5659	941	218	166	
FEV_1 change mL·year^{-1}	−26.2 (−31.1– −21.3)	−25.3 (−30.5– −20.1)	−25.9 (−32.2– −19.6)	−37.3 (−44.0– −30.6)***	<0.001
FEV_1 change % of baseline·year^{-1}	−0.69 (−0.83– −0.55)	−0.68 (−0.83– −0.53)	−0.66 (−0.84– −0.47)	−1.17 (−1.37– −0.97)***	<0.001
FVC change mL·year^{-1}	−19.8 (−25.6– −14.1)	−21.3 (−27.4– −15.2)	−25.5 (−33.0– −18.0)*	−37.0 (−45.0– −29.0)***	<0.001
FVC change % of baseline·year^{-1}	−0.42 (−0.55– −0.29)	−0.45 (−0.59– −0.31)	−0.55 (−0.72– −0.38)*	−0.81 (−0.99– −0.63)***	<0.001
Hospital/ER admission for breathing problems¶ %	3.6 (2.7–4.5)	11.9 (8.7–15.0)***	15.8 (9.9–21.8)***	8.1 (3.5–12.7)**	<0.001

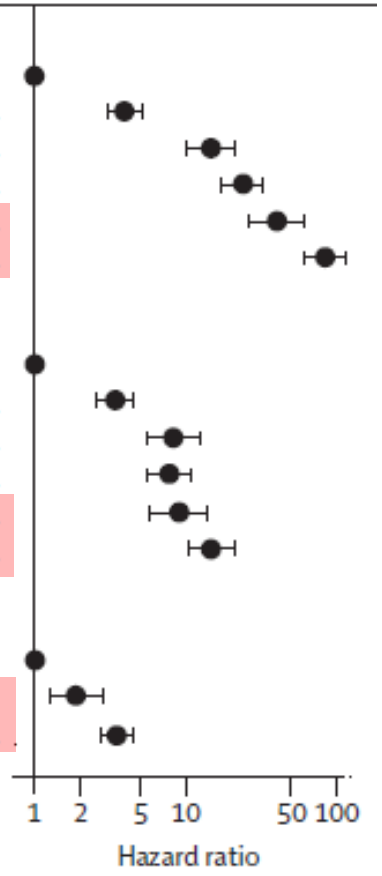
De Maro R et al. Eur Respir J. 2015 Sep;46(3):671-9.

Exacerbation : hospital admission

- Copenhagen City Heart Study, hospital admission and mortality for 22 years

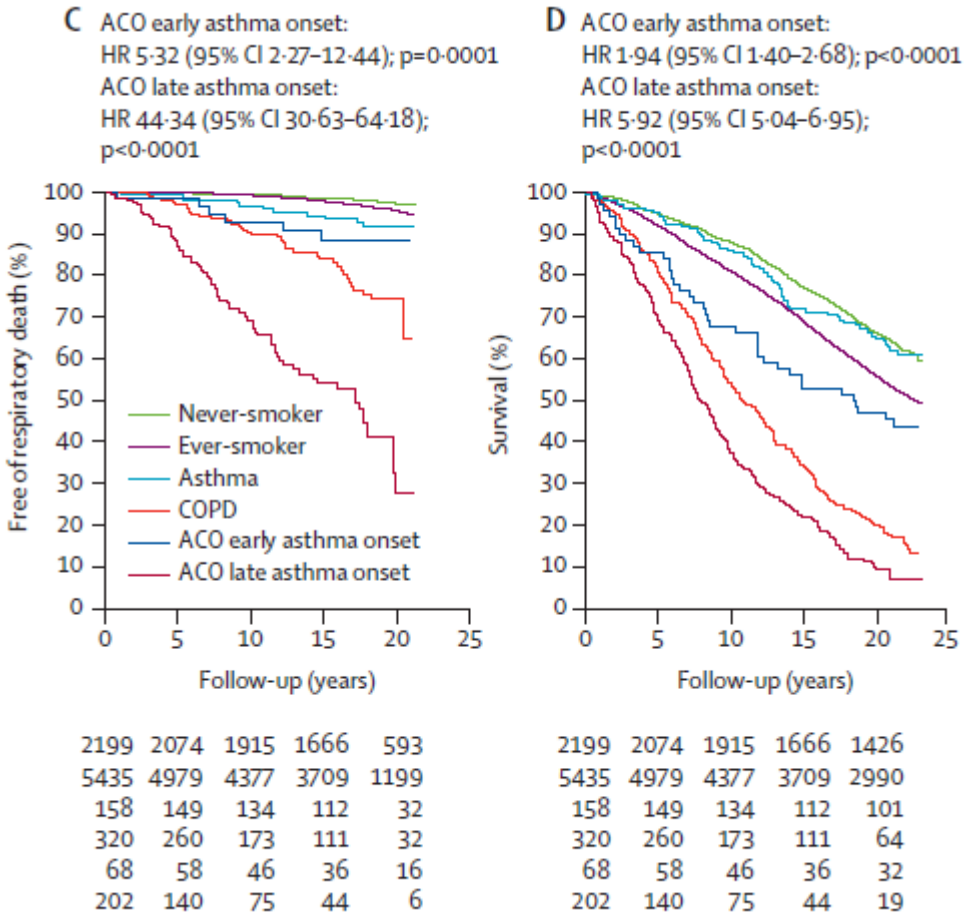


	Participants (n)	Acute hospital admission for COPD and asthma		
		Events (n [%])	Hazard ratio (95% CI)*	p value
Adjusted for age and sex	**8382**	**929 (15%)**		
Never-smokers without disease	2199	62 (4%)	1·00 (reference)	
Ever-smokers without disease	5435	511 (14%)	3·93 (3·02–5·13)	<0·0001
Asthma	158	46 (35%)	14·74 (10·06–21·59)	<0·0001
COPD	320	123 (70%)	23·80 (17·43–32·50)	<0·0001
ACO with early asthma onset	68	34 (58%)	39·48 (25·93–60·11)	<0·0001
ACO with late asthma onset	202	153 (94%)	83·47 (61·67–112·98)	<0·0001
Adjusted for age, sex, BMI, and FEV_1 % of predicted value	**8367**	**922 (15%)**		
Never-smokers without disease	2199	62 (4%)	1·00 (reference)	
Ever-smokers without disease	5435	511 (14%)	3·40 (2·61–4·43)	<0·0001
Asthma	143	39 (32%)	8·29 (5·52–12·44)	<0·0001
COPD	320	123 (70%)	7·75 (5·56–10·82)	<0·0001
ACO with early asthma onset	68	34 (58%)	9·00 (5·75–14·10)	<0·0001
ACO with late asthma onset	202	153 (94%)	14·74 (10·40–20·91)	<0·0001
Adjusted for age, sex, BMI, and pack-years	**581**	**306 (75%)**		
COPD	320	123 (70%)	1·00 (reference)	
ACO with early asthma onset	67	34 (59%)	1·90 (1·26–2·87)	0·002
ACO with late asthma onset	194	149 (94%)	3·52 (2·74–4·54)	<0·0001

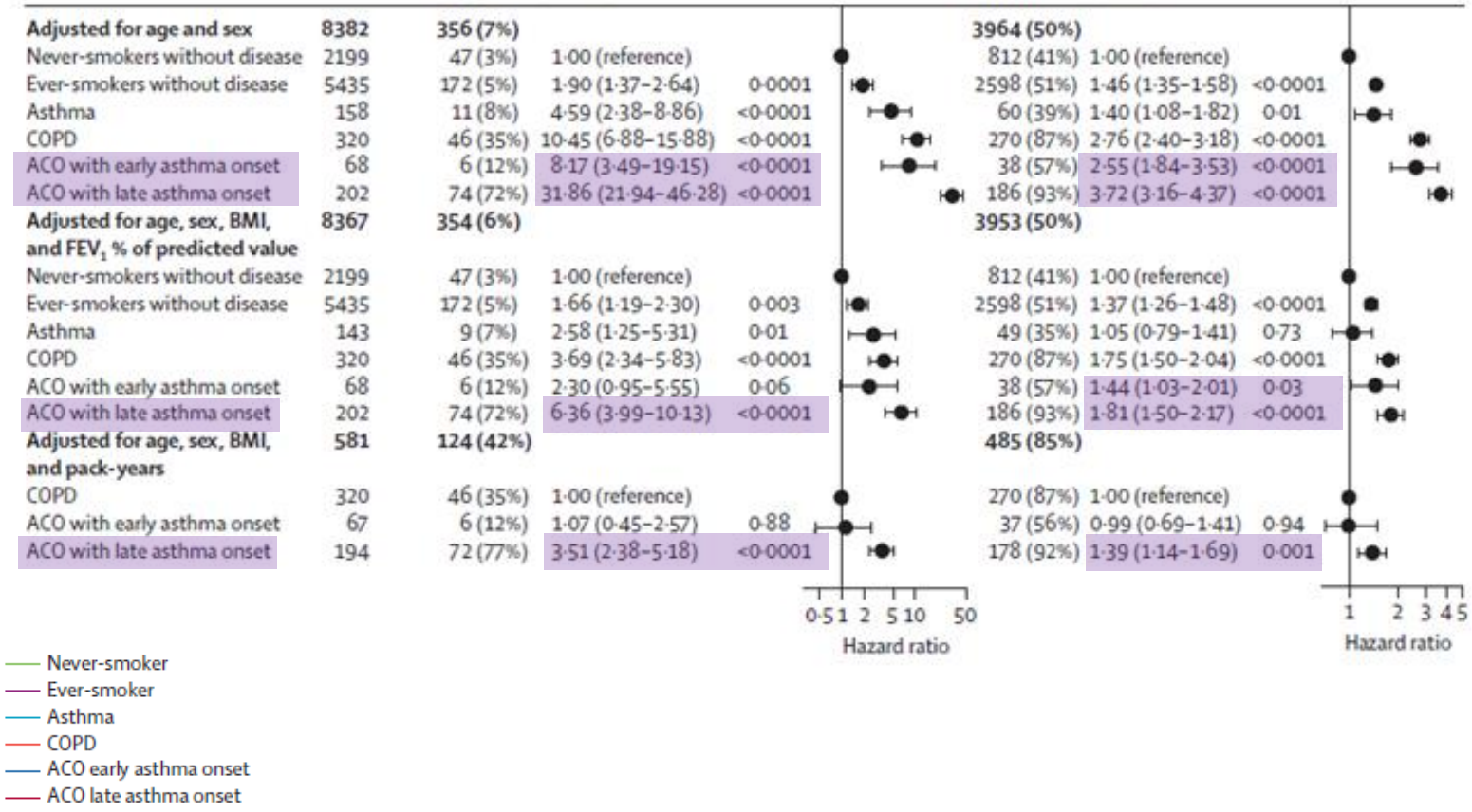


Peter Lange et al. Lancet Respir Med 2016; 4: 454–62.

Mortality



	Participants (n)	Respiratory mortality			All-cause mortality		
		Events (n [%])	Hazard ratio (95% CI)*	p value	Events (n [%])	Hazard ratio (95% CI)*	p value
Adjusted for age and sex	**8382**	**356 (7%)**			**3964 (50%)**		
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·90 (1·37–2·64)	0·0001	2598 (51%)	1·46 (1·35–1·58)	<0·0001
Asthma	158	11 (8%)	4·59 (2·38–8·86)	<0·0001	60 (39%)	1·40 (1·08–1·82)	0·01
COPD	320	46 (35%)	10·45 (6·88–15·88)	<0·0001	270 (87%)	2·76 (2·40–3·18)	<0·0001
ACO with early asthma onset	68	6 (12%)	8·17 (3·49–19·15)	<0·0001	38 (57%)	2·55 (1·84–3·53)	<0·0001
ACO with late asthma onset	202	74 (72%)	31·86 (21·94–46·28)	<0·0001	186 (93%)	3·72 (3·16–4·37)	<0·0001
Adjusted for age, sex, BMI, and FEV_1 % of predicted value	**8367**	**354 (6%)**			**3953 (50%)**		
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·66 (1·19–2·30)	0·003	2598 (51%)	1·37 (1·26–1·48)	<0·0001
Asthma	143	9 (7%)	2·58 (1·25–5·31)	0·01	49 (35%)	1·05 (0·79–1·41)	0·73
COPD	320	46 (35%)	3·69 (2·34–5·83)	<0·0001	270 (87%)	1·75 (1·50–2·04)	<0·0001
ACO with early asthma onset	68	6 (12%)	2·30 (0·95–5·55)	0·06	38 (57%)	1·44 (1·03–2·01)	0·03
ACO with late asthma onset	202	74 (72%)	6·36 (3·99–10·13)	<0·0001	186 (93%)	1·81 (1·50–2·17)	<0·0001
Adjusted for age, sex, BMI, and pack-years	**581**	**124 (42%)**			**485 (85%)**		
COPD	320	46 (35%)	1·00 (reference)		270 (87%)	1·00 (reference)	
ACO with early asthma onset	67	6 (12%)	1·07 (0·45–2·57)	0·88	37 (56%)	0·99 (0·69–1·41)	0·94
ACO with late asthma onset	194	72 (77%)	3·51 (2·38–5·18)	<0·0001	178 (92%)	1·39 (1·14–1·69)	0·001



Peter Lange et al. Lancet Respir Med 2016; 4: 454–62.

Health care utility

Healthcare utilization

	Overlap syndrome	COPD without asthma	*p*-value
Cost of all medical utilization (USD)			
Cost of outpatient services	790 ± 71	413 ± 512	<0.001
Cost of inpatient services	3,373 ± 4,628	3,010 ± 5,013	<0.001
Total cost	1,807 ± 3,096	829 ± 2,215	<0.001
Used days			
Outpatient services	9.2 ± 9.76	7.4 ± 8.11	<0.001
Inpatient services	25.44 ± 34.74	23.19 ± 36.41	<0.001
Total used days	16.81 ± 24.56	10.5 ± 17.46	<0.001

2009 NHI database of Korea.
Among 185,147 COPD patients,
101,004 were classified with overlap and
84,143 were COPD without asthma

Factors affecting medical cost

	Unadjusted			Adjusted		
Variable	β	exp (β)	*p*-value	β	exp (β)	*p*-value
Age (year)	0.015	1.015	<0.001	0.012	1.012	<0.001
Male gender	0.530	1.699	<0.001	0.276	1.317	<0.001
Overlap syndrome	1.082	2.951	<0.001	0.645	1.907	<0.001
Hospitalization in the last year	1.319	3.740	<0.001	0.753	2.122	<0.001
Medical aid[#]	0.613	1.845	<0.001	0.474	1.605	<0.001
Type of hospital use	0.790	2.204	<0.001	0.568	1.764	<0.001

Rhee CK et al. COPD. 11:163–170, 2014.

Recommendation of ICS

GINA Global Strategy for Asthma Management and Prevention 2017

Favors asthma as a single diagnosis

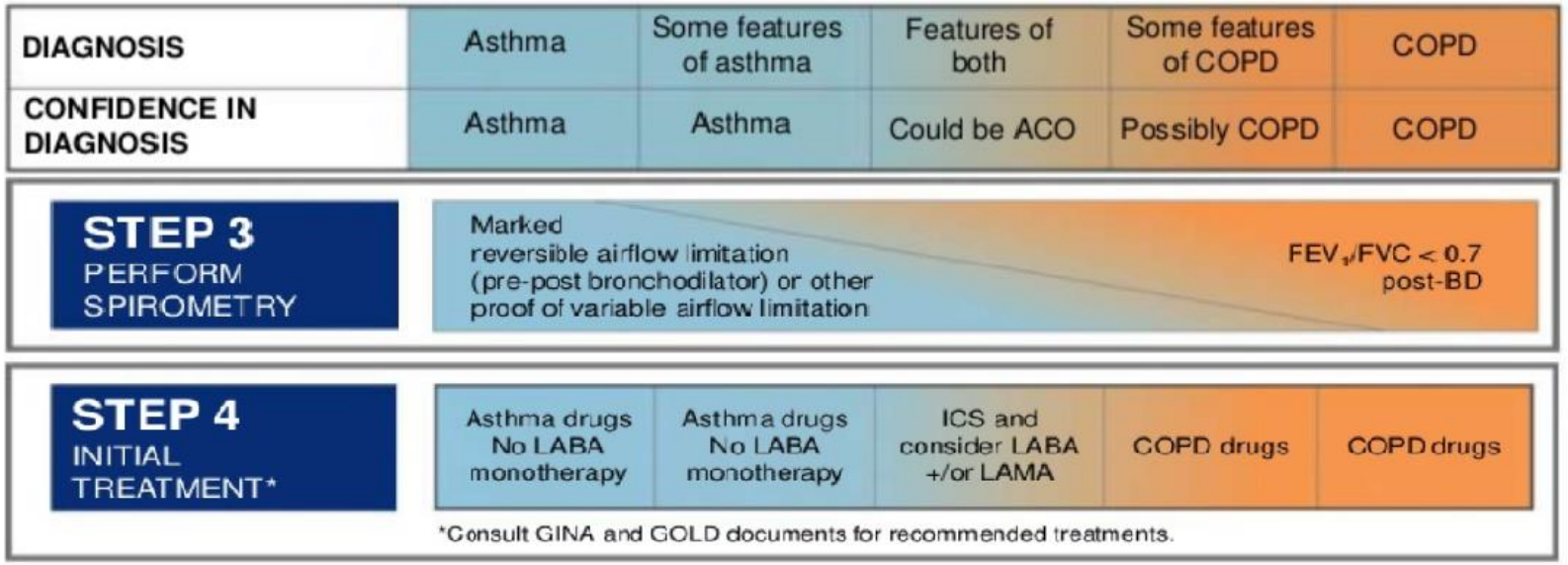
Based on ICS, with add-on treatment if needed

Favors COPD as a single disease

Bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS alone as monotherapy

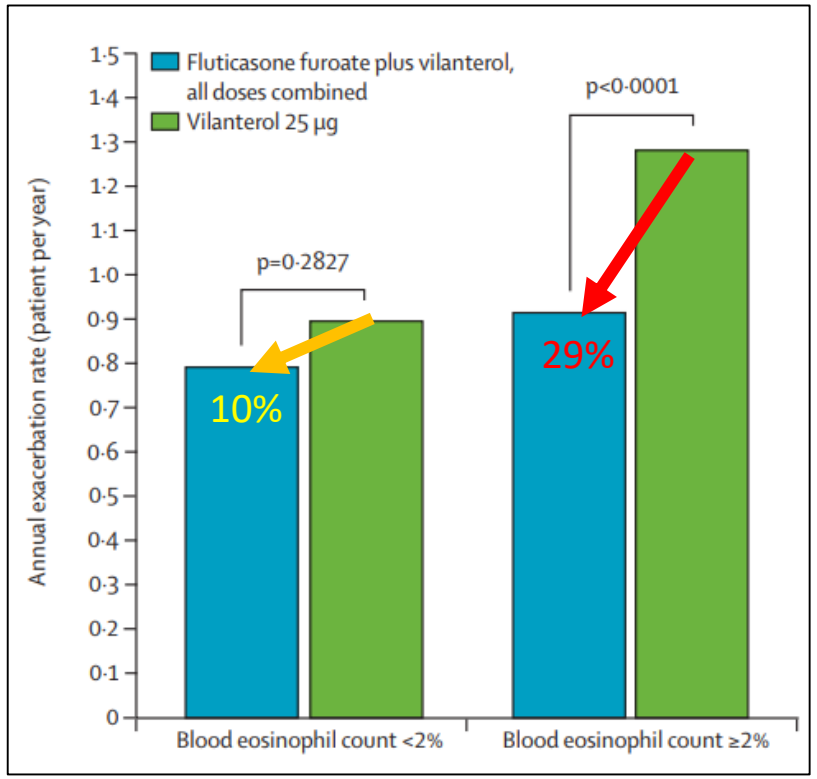
Asthma and COPD overlap

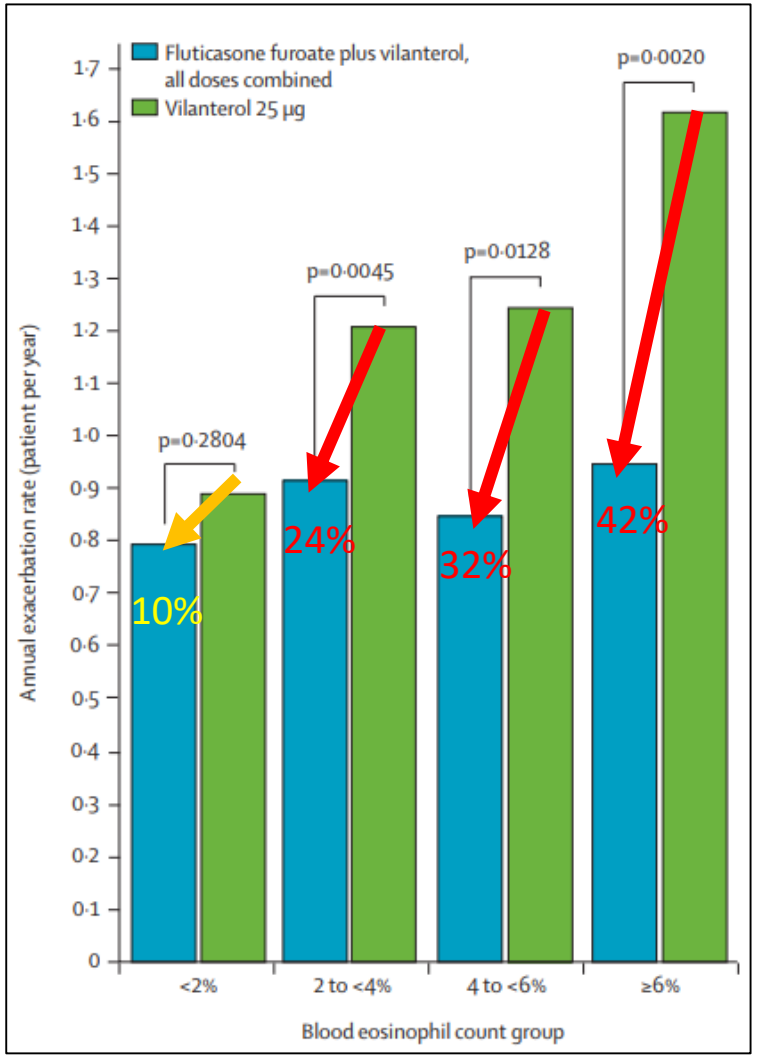
Recommendation : start treatment for asthma
Includes an ICS in a low or moderate dose depending on level of symptoms and risk of adverse effects
Usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed
If there are features of asthma, do not treat with a LABA without ICS



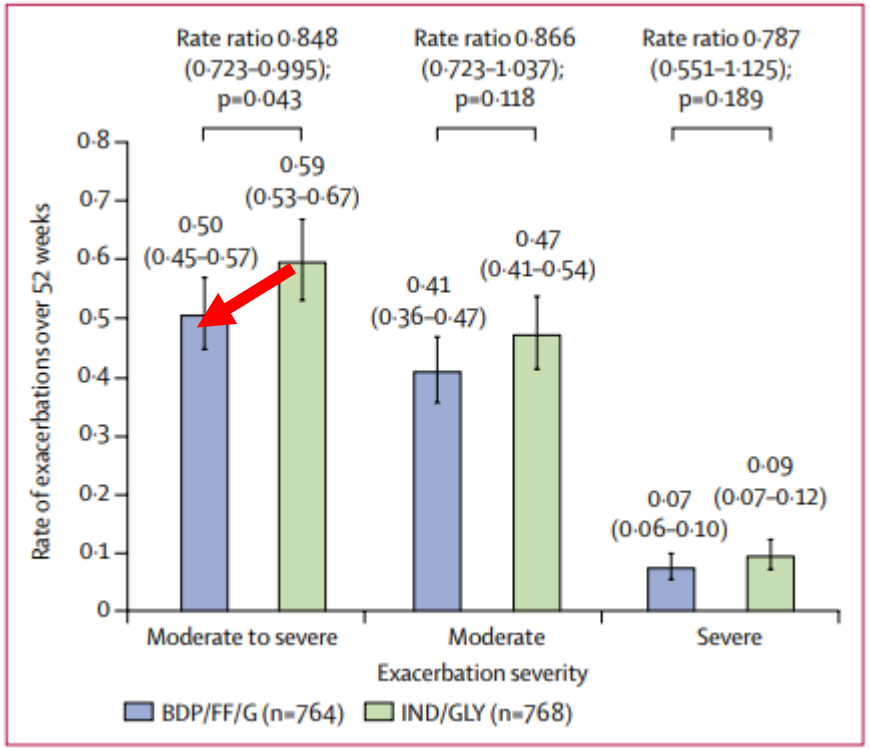
ICS in COPD

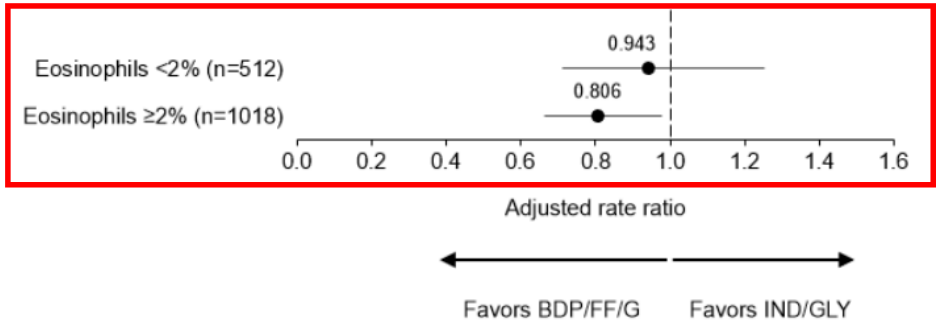
3177 COPD patients
ICS/LABA vs LABA on exacerbation





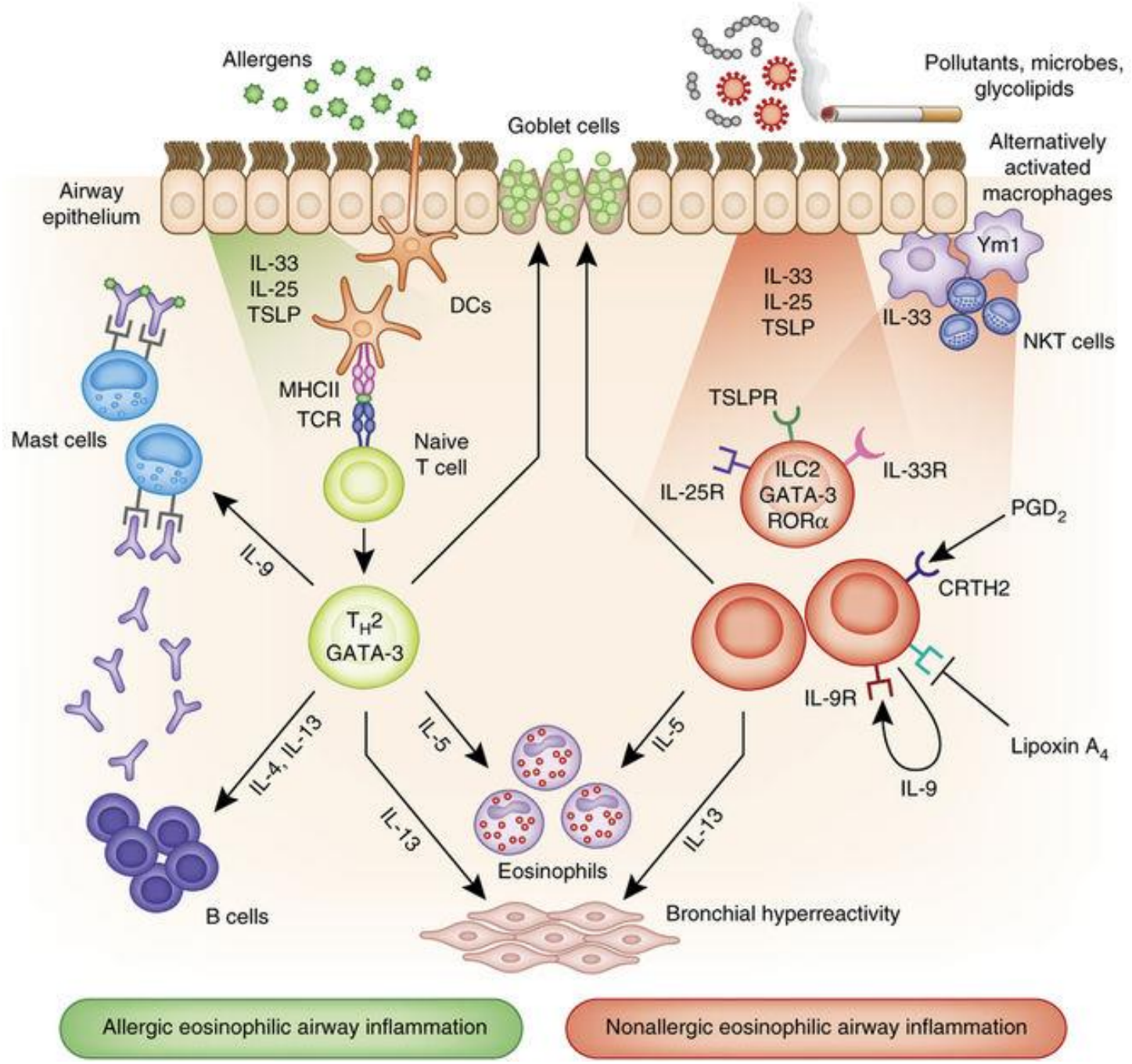
Triple vs LABA/LAMA on exacerbation
TRIBUTE trial





Pascoe S et al. Lancet Respir Med 2015; 3: 435–42.
Papi A et al. Lancet 2018:391:1076-84.

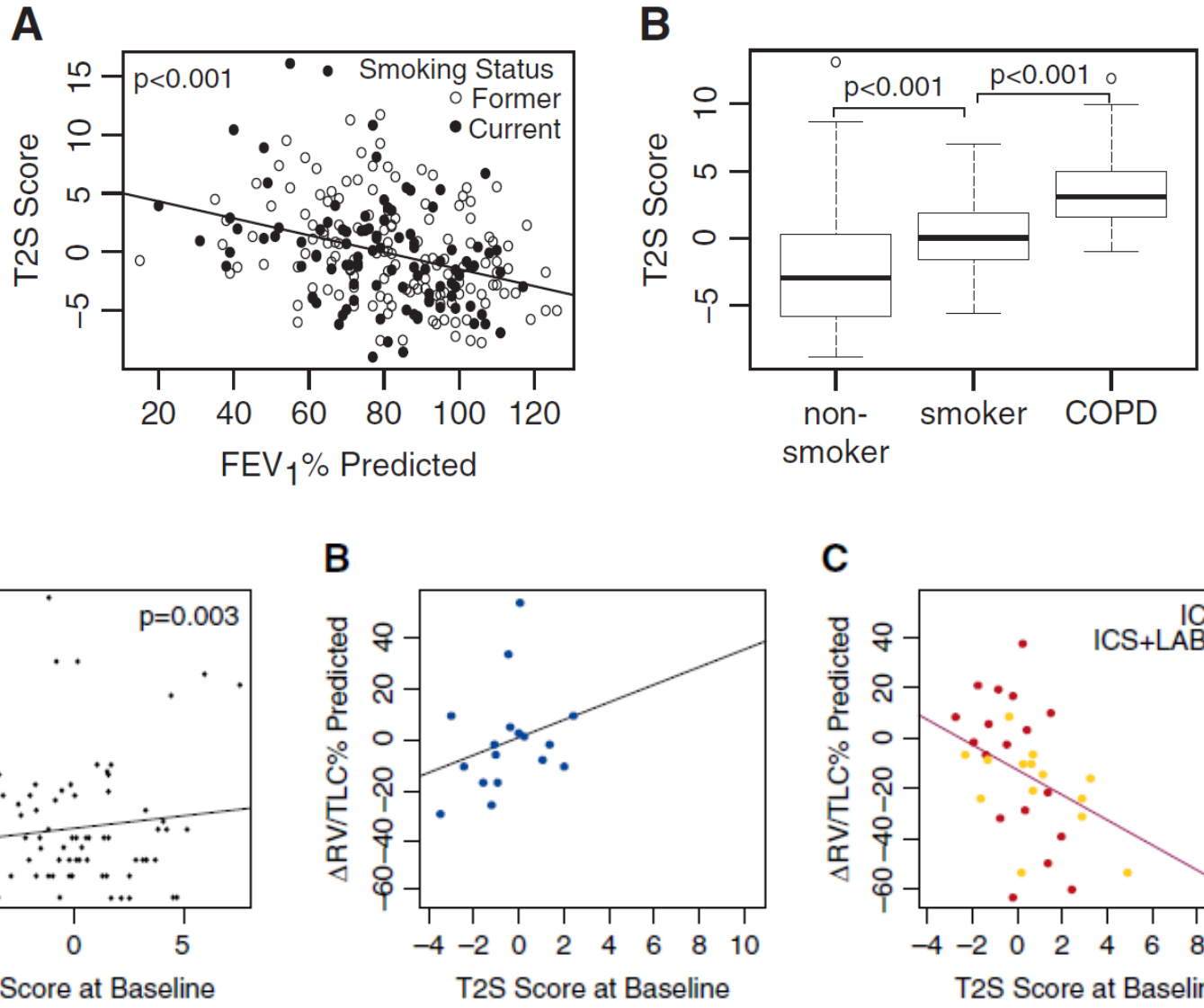
Airway inflammation



Nat Immunol. 2015 Jan;16(1):45-56.

Th-2/eosinophilic/allergic pathways in COPD

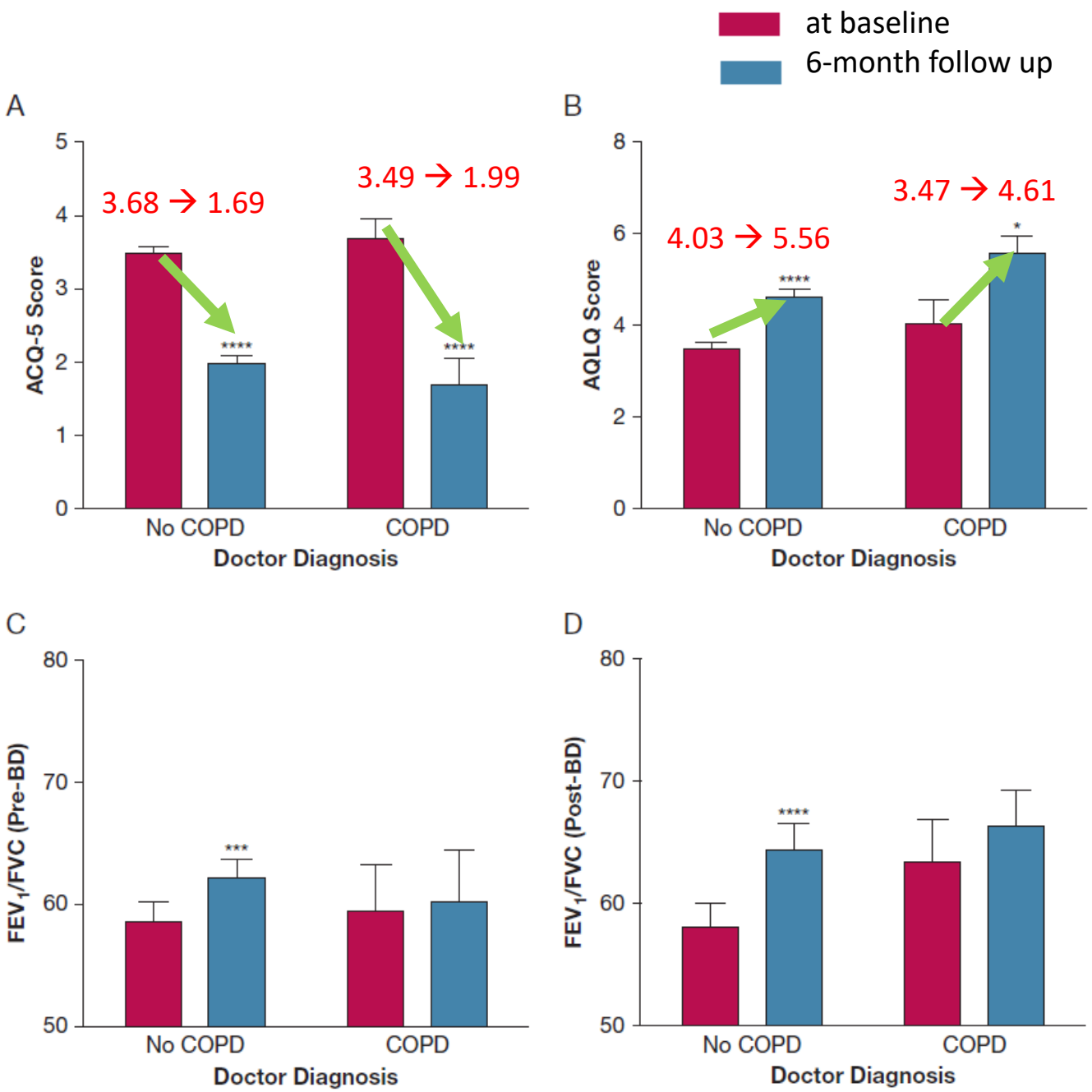
- COPD dataset
- Epithelial brushing & Endobronchial biopsy
- Th2 signature (T2S) score



Christenson SA et al. Am J Respir Crit Care Med. 2015 Apr 1;191(7):758-66.

Anti-eosinophil drugs
Omalizumab (anti-IgE)

- Australian Xolair Registry (AXR)
- ACO (n=17) vs severe asthma (n=160)
- 6 months of omalizumab treatment



Maltby S et al. CHEST 2017; 151(1):78-89.

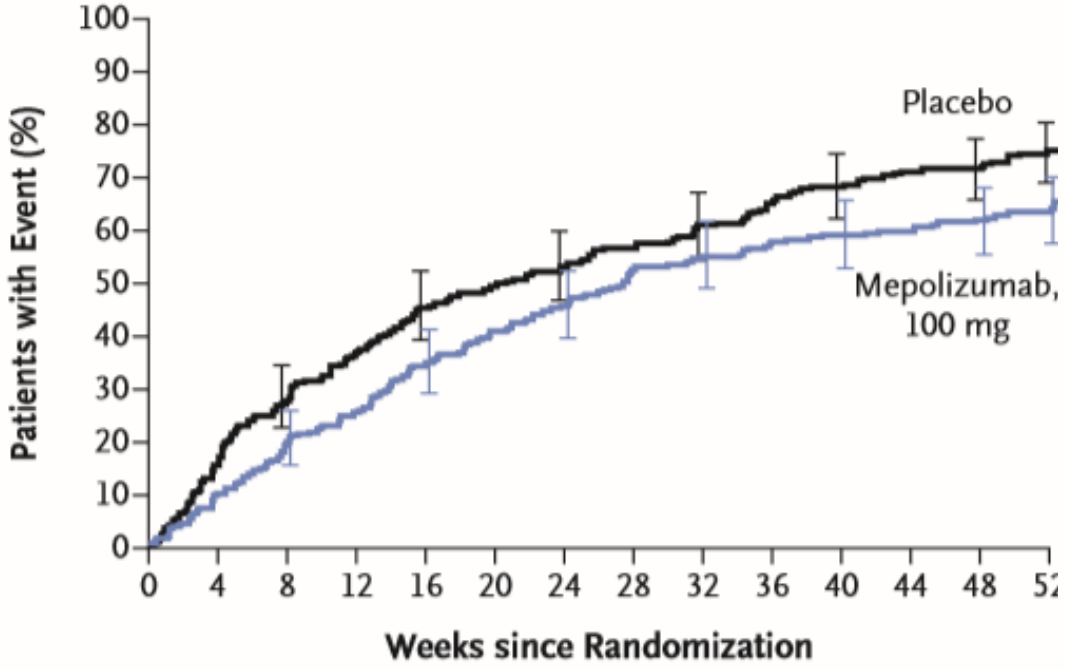
Anti IL-5 therapy : Mepolizumab

Time to the 1st moderate to severe exacerbation
192 vs 141 days; HR, 0.75; 95% CI, 0.60-0.94;
adjusted p=0.04

derate to severe e
fluticasone propio

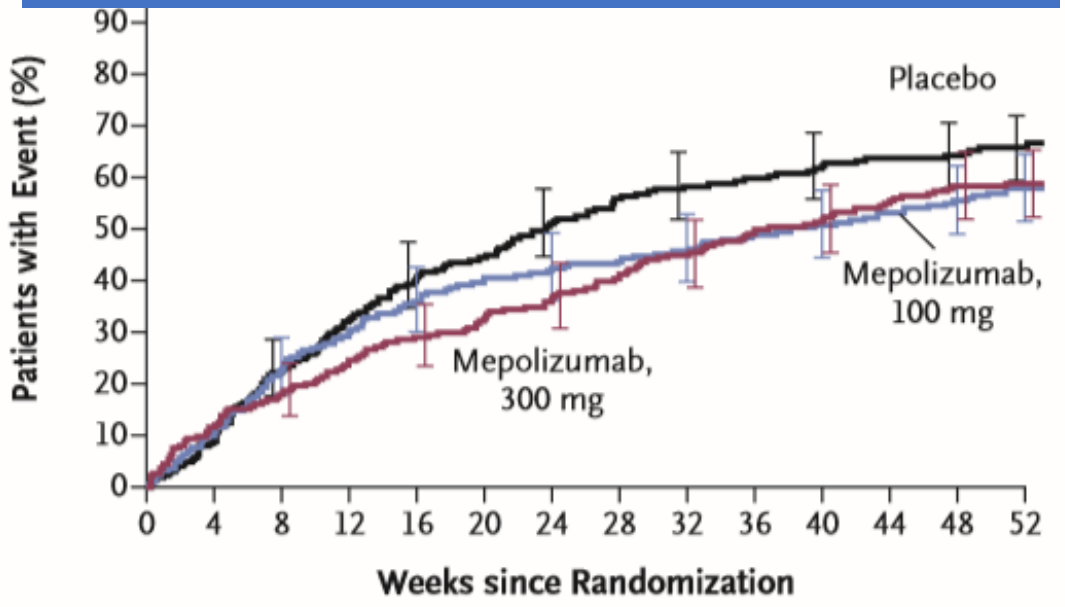
Time to the 1st moderate to severe exacerbation
267 vs 257 vs 166 days
HR, 0.85 for 100mg & 0.77 for 300mg
Adjusted p=0.14, in both

A METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype



No. at Risk														
Placebo	229	193	164	142	120	109	99	92	83	74	67	60	59	44
Mepolizumab, 100 mg	233	209	187	173	151	136	125	111	104	96	91	87	83	62

C METREC



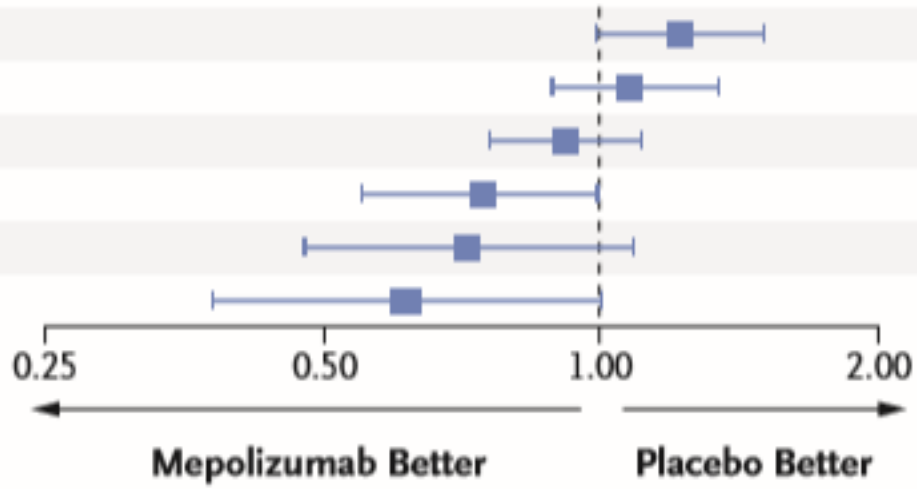
No. at Risk														
Placebo	226	207	174	151	131	120	102	91	85	82	77	73	72	49
Mepolizumab, 100 mg	223	201	173	157	141	131	126	121	116	109	105	99	94	71
Mepolizumab, 300 mg	225	198	184	171	157	150	140	130	120	111	106	98	88	76

Pavord ID et al. N Engl J Med. 2017 Oct 26;377(17):1613-1629.

Mepolizumab. Cont’

Moderate or severe exacerbations according to eosinophil count

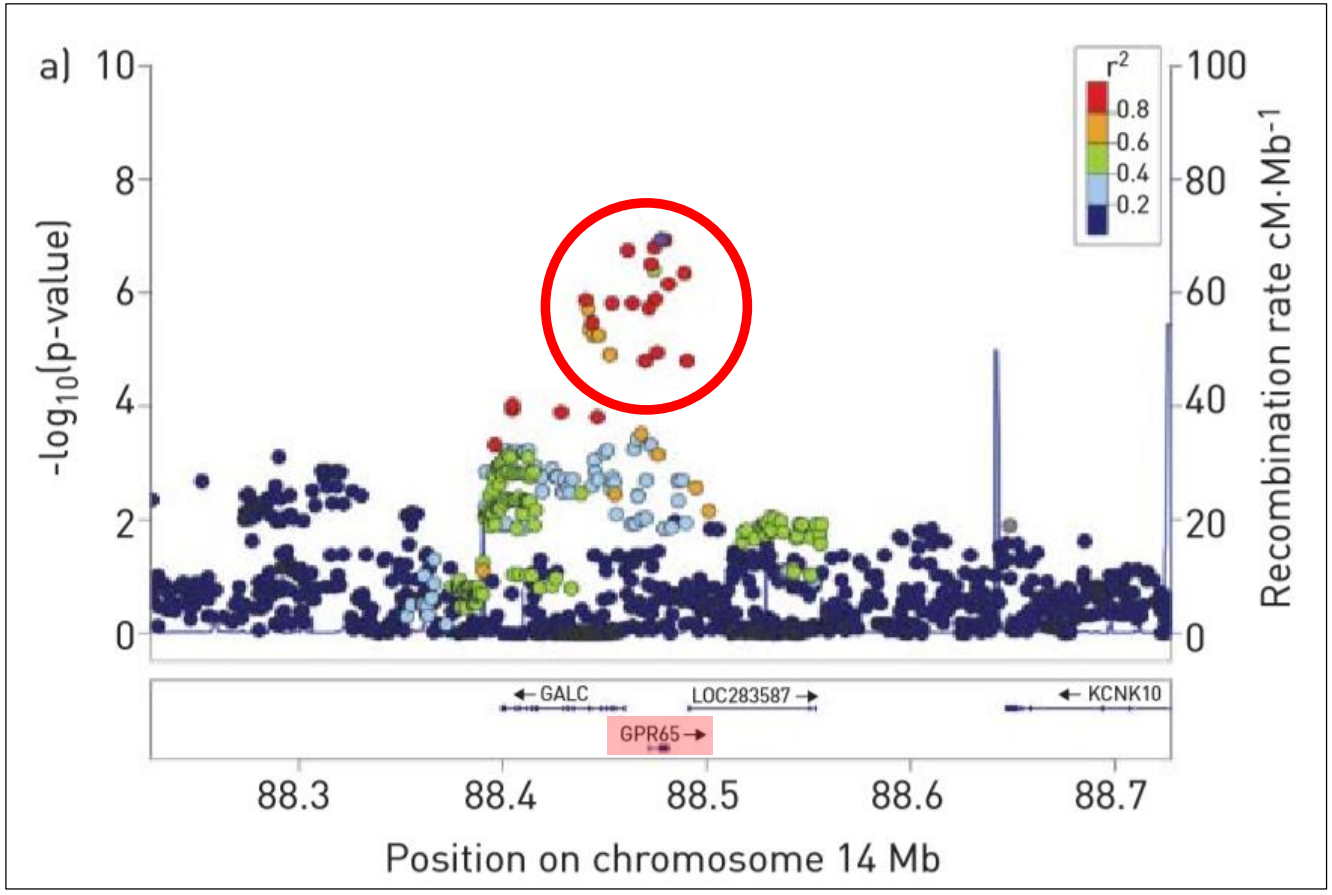
Blood Eosinophil Count	Mepolizumab Group	Placebo Group	Rate Ratio (95% CI)
cells/mm³	*no. of patients meeting criterion/total no. of patients*		
<150 with no historical count ≥300	184/184	190/190	1.23 (0.99–1.51)
<150 regardless of historical count	236/640	230/645	1.10 (0.91–1.34)
≥150 to <300	237/456	235/455	0.92 (0.76–1.11)
≥300 to <500	112/456	110/455	0.75 (0.55–1.00)
≥500	53/456	67/455	0.72 (0.48–1.09)
<150 with historical count ≥300	53/456	42/455	0.64 (0.40–1.03)



Pavord ID et al. N Engl J Med. 2017 Oct 26;377(17):1613-1629.

Genetic variants

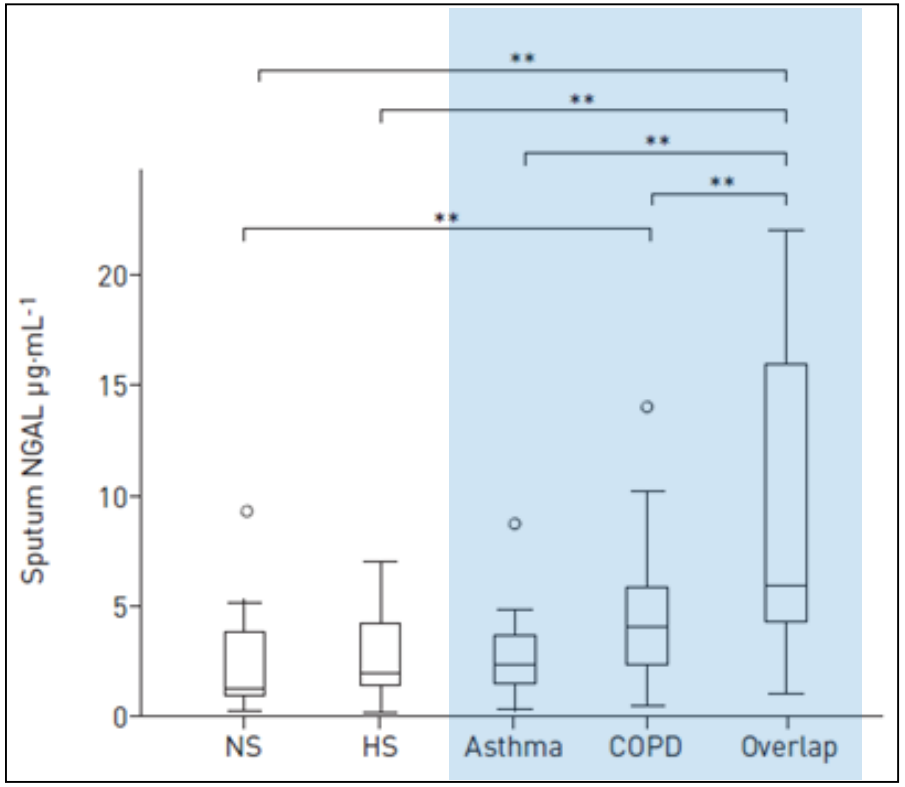
- Genome-wide association studies (GWAS) in COPDgene cohort
  : Single nucleotide polymorphisms (SNPs) in the genes CSMD1 & SOX5
  & Gene GPR65 (rs6574978, $p=1.18 \times 10^{-7}$) in meta-analysis associated with COPD and overlap.



Megan Hardin et al. Eur Respir J 2014; 44: 341–350.

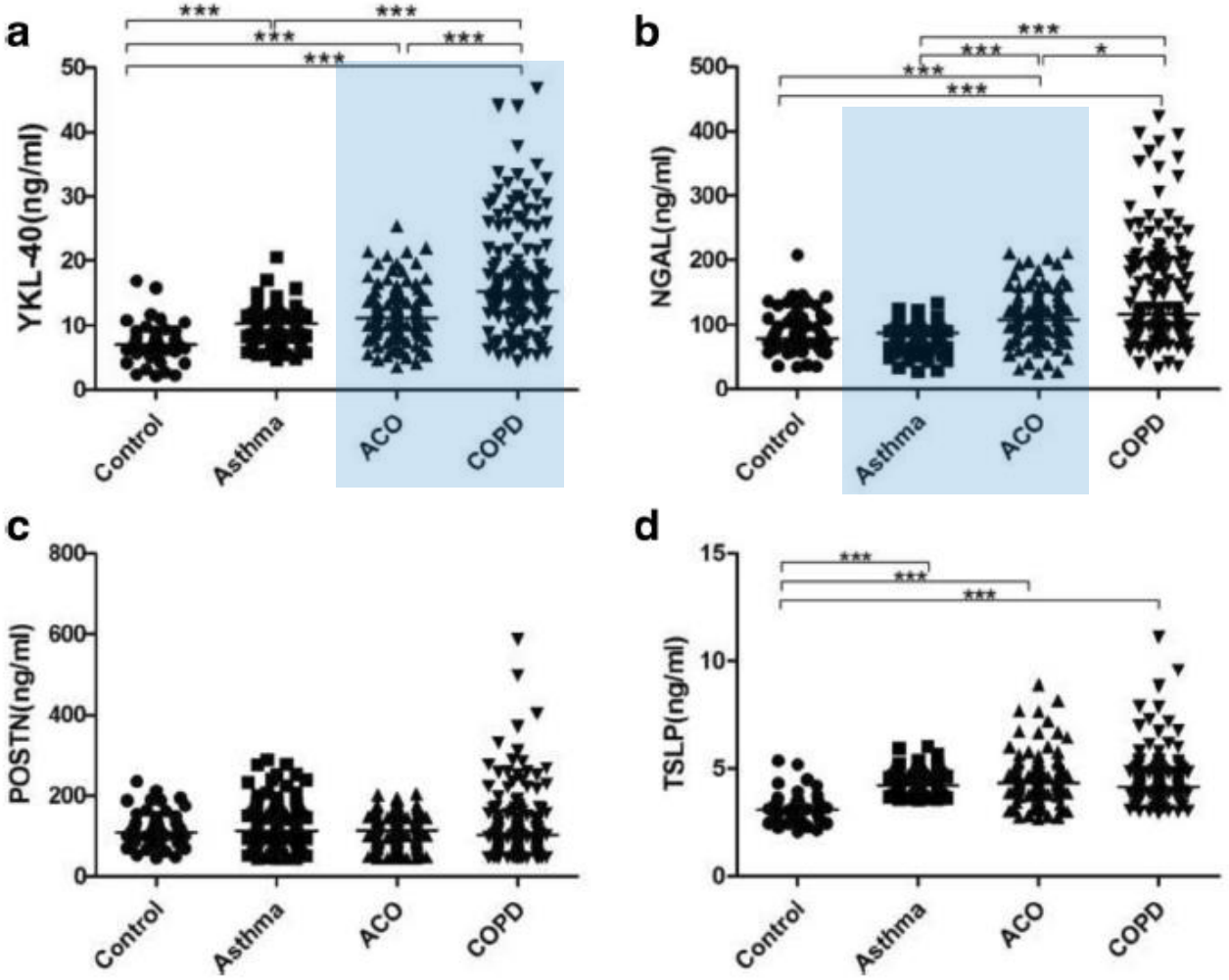
Biomarkers

Asthma (n=32), COPD (n=39), ACO (n=14)



↑Neutrophilic airway inflammation in ACO

Asthma (n=124), COPD (n=147), ACO (n=102)



Iwamoto H et al. Eur Respir J. 2014 Feb;43(2):421-9.
Wang et al. Respiratory Research (2018) 19:47.

ACO should be considered as a **distinct phenotype** ?

Summary

ACO was defined as the presence of persistent airflow limitation that shares the features of asthma and COPD.

Main characteristics of ACO

- ✓ Enhanced bronchial and systemic eosinophilic inflammation
- ✓ Increased reversibility of airflow
- ✓ Increased response to ICS

] Compared with COPD

Patients with **ACO** is more likely to

- ✓ **Frequent exacerbation**
- ✓ **Poor quality of life**
- ✓ **Increased use of health care resources**
- ✓ **Rapid decline of lung function**
- ✓ **High mortality**

Compared with either **Asthma or COPD**

Limitation & future research

- Pathogenesis, natural history and treatment effect of ACO has still many questions to be answered, because these patients are often excluded from large clinical trials of asthma and COPD.

- For identifying ACO and treat appropriately, more research is needed to establish a consistent diagnostic criteria for ACO.

Opinion: from Pro's point of view

- Are there ACO endotypes?
- I think this is not as straightforward as with asthma or COPD. More evidence of underlying mechanisms are needed.

- Nevertheless, ACO has distinctive features from asthma and COPD from demographics to prognosis. This suggests ACO is enough to be recognized as a separate phenotype rather than a subtype of asthma or COPD.

Thank you
for your attention !