# ACO Should Not be Considered as a Distinct Phenotype


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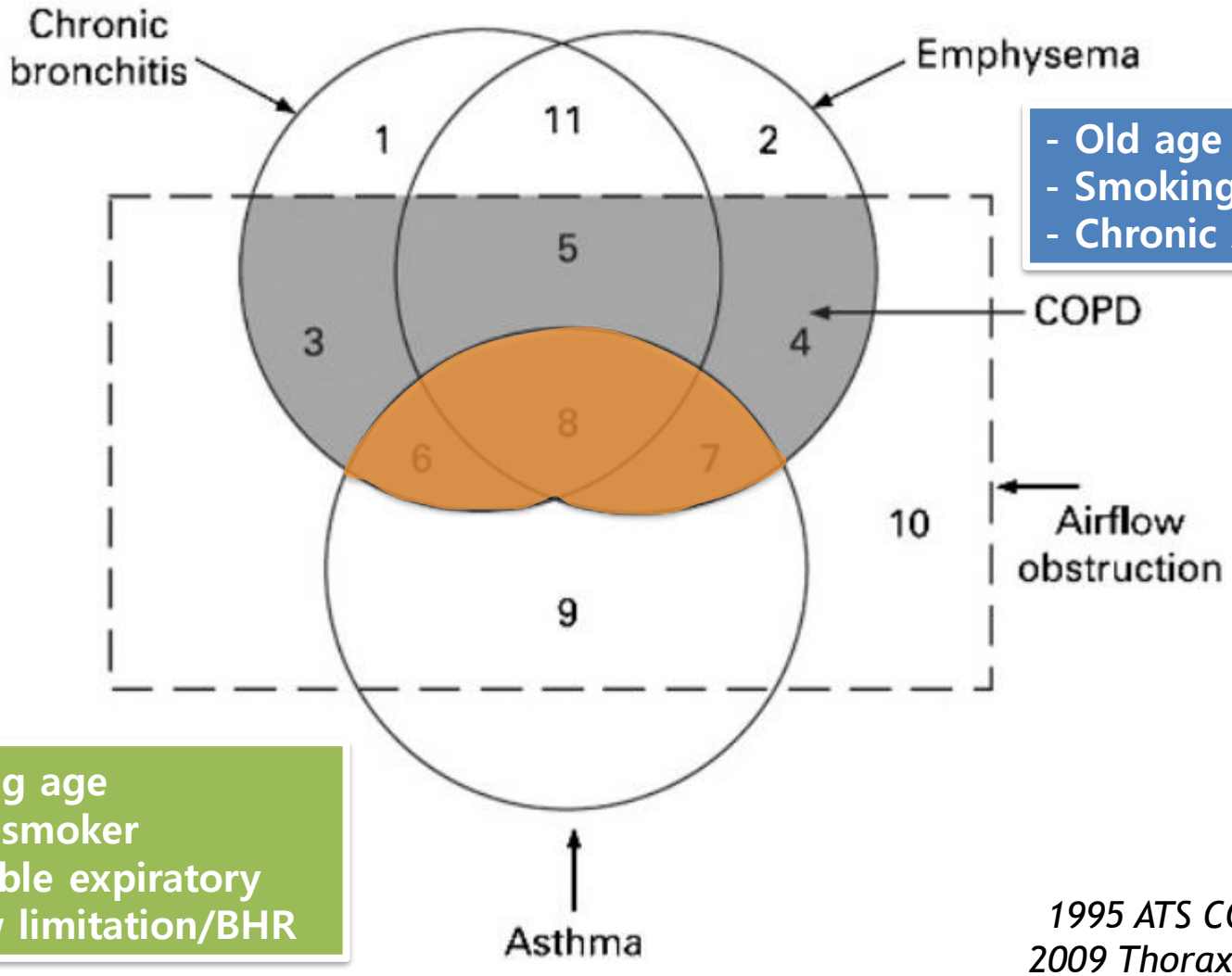
박 혜 윤

# ACO:
# Not a single discrete disease

# Why ACO is not a single discrete disease?

- New debate?
- No single and universal definition/diagnosis
- Inconsistent outcomes
- Treatment remains uncertain

# The overlap syndrome of asthma and COPD (ACOS)




- Old age
- Smoking history
- Chronic AL

- Young age
- Non-smoker
- Variable expiratory airflow limitation/BHR

*1995 ATS COPD guideline*
*2009 Thorax Gibson et al.*

# Why ACO is not a single discrete disease

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# COS, is it new?

TABLE I

CORRELATION OF PROPOSED TERMINOLOGY WITH CURRENT USAGE

| Combinations of Defined Groups of Chronic Non-specific Lung Disease | | | Current Terminology | Proposed Terminology |
|---|---|---|---|---|
| Chronic Bronchitis | Asthma | Irreversible Obstructive Lung Disease | | |
| + | 0 | 0 | Normal subject<br>Mild or subclinical bronchitis<br>Chronic bronchitis<br>Smoker's cough | Chronic bronchitis |
| 0 | + | 0 | Asthma<br>Extrinsic asthma | Asthma |
| 0 | 0 | + | "Pure" emphysema<br>Asthma | Irreversible obstructive lung disease (with or without emphysema) |
| + | + | 0 | Asthma<br>Intrinsic asthma<br>Asthmatic bronchitis | Chronic bronchitis with asthma |
| + | 0 | + | Chronic bronchitis<br>Asthma<br>Emphysema | Chronic bronchitis with obstructive lung disease (with or without emphysema) |
| 0 | + | + | Asthma<br>Emphysema | Partially reversible obstructive lung disease (with or without emphysema) |
| + | + | + | Chronic bronchitis<br>Asthma<br>Emphysema | Chronic bronchitis with partially reversible obstructive lung disease (with or without emphysema) |

## RECOMMENDATIONS FOR CLINICAL DEFINITIONS, CLASSIFICATION, AND CODING

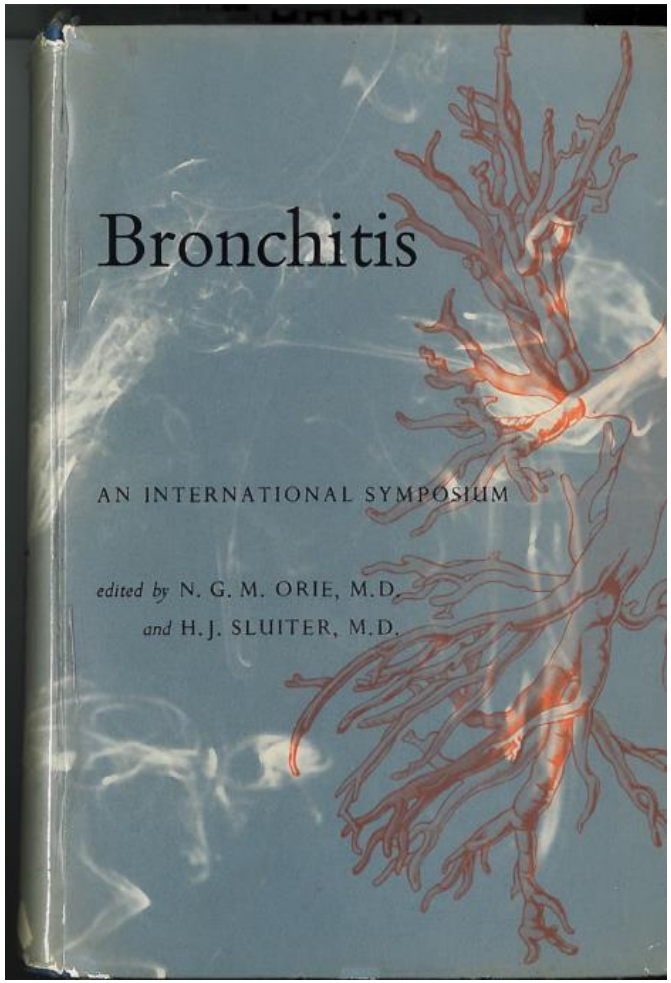
At present the diagnoses "chronic bronchitis," "asthma," and "emphysema" are used without any general agreement about the clinical conditions to which they refer. Any one (or more) of these words may be used by different clinicians to describe the condition of the same patient. It appears that chronic bronchitis is often used in Great Britain to describe cases that would be called asthma or emphysema in the United States.

These conditions together constitute a group of chronic non-specific lung diseases (accepting the bronchial tree as part of the lung) with whose definition and classification we are here concerned.

The name "chronic non-specific lung disease" is suggested for the whole group. This cumbersome phrase will seldom be used in clinical practice, for patients will usually be allocated to one of the classes designated and defined below.

*Thorax 1959, 14, 286*

# Dutch hypothesis




## THE HISTORY OF THE DUTCH HYPOTHESIS

*"…one must be impressed by the very long road medicine must travel before an understanding of disease is reached, even when its clinical symptomatology is relatively simple"* (*Bronchitis 1*, 1961, page 1).[1]

1961, Professor Orie

*"Asthma and COPD had common origins and clinical expressions were determined both by endogenous (heredity, age, and sex) and exogenous (environment: allergens, smoking, viruses, and air pollution) factors."*

**DUTCH hypothesis in 1969 by Fletcher and Pride**

# Dutch hypothesis

**TABLE** …notypes necessary to define a patient with respir… …ms according to Orie and Sluiter in *Bro…*

…ked to asthmatic constitution (infantile …chitis)

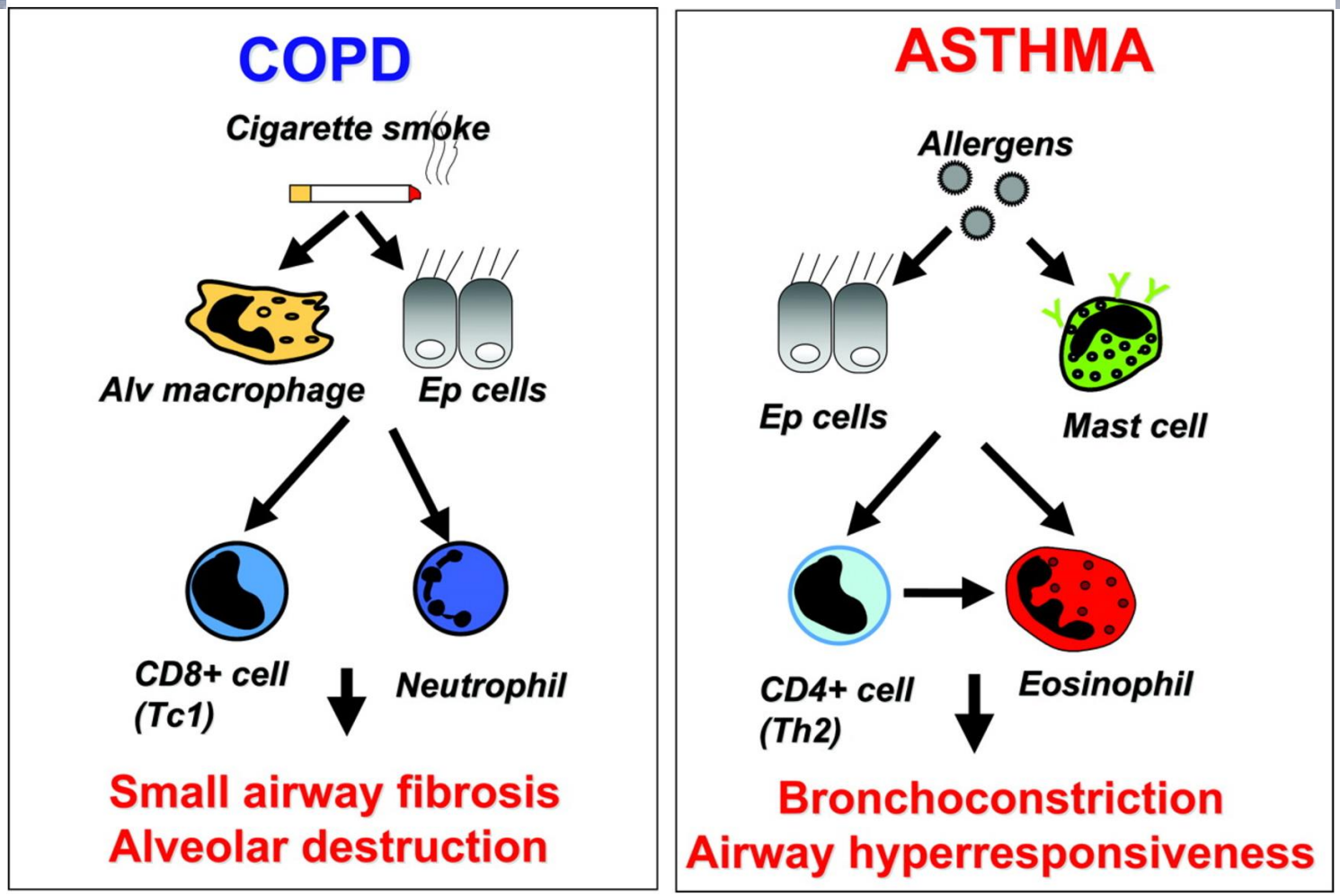
…riability in cough,

4. Ch…
5. Basic el…
   - Hyperreacti…
   - Allergy
6. Infections* (bacterial an…
7. Air pollution* (indoors and ou…
8. Lung function
   - Spontaneous and induced changes
   - Level of $FEV_1$
   - $FEV_1$ reaction to bronchodilating drugs
   - $FEV_1$ reaction to bronchoconstricting drugs
9. Blood and sputum eosinophilia

*These annotations are from another publication, also published in 1961.[5]

British hypothesis

# COPD and Asthma



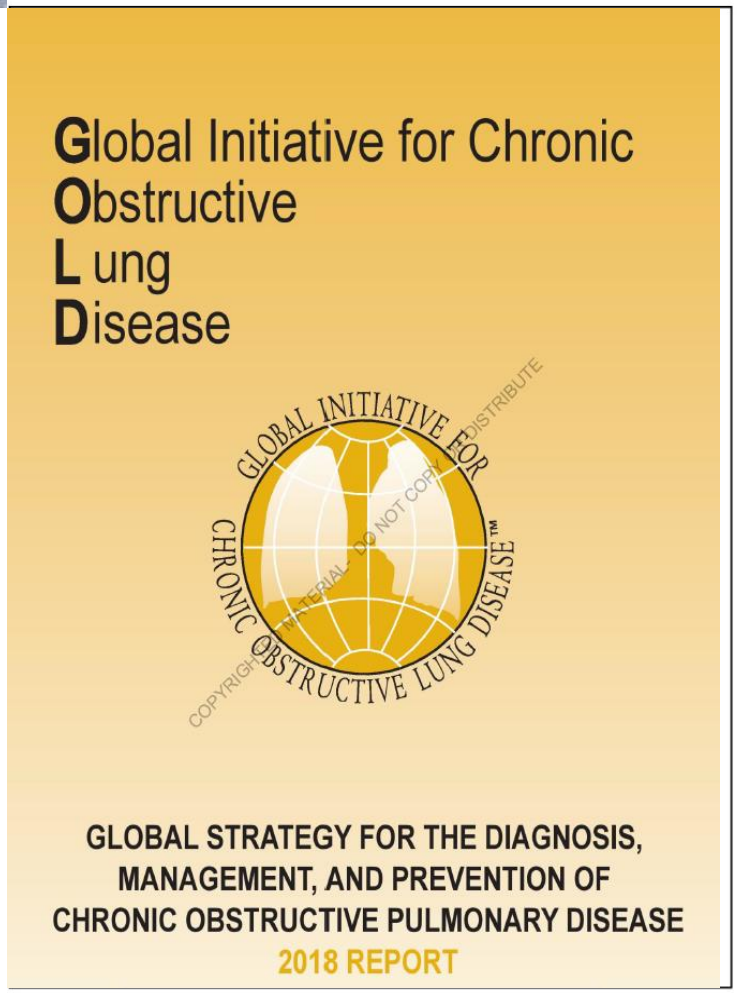

Irreversible

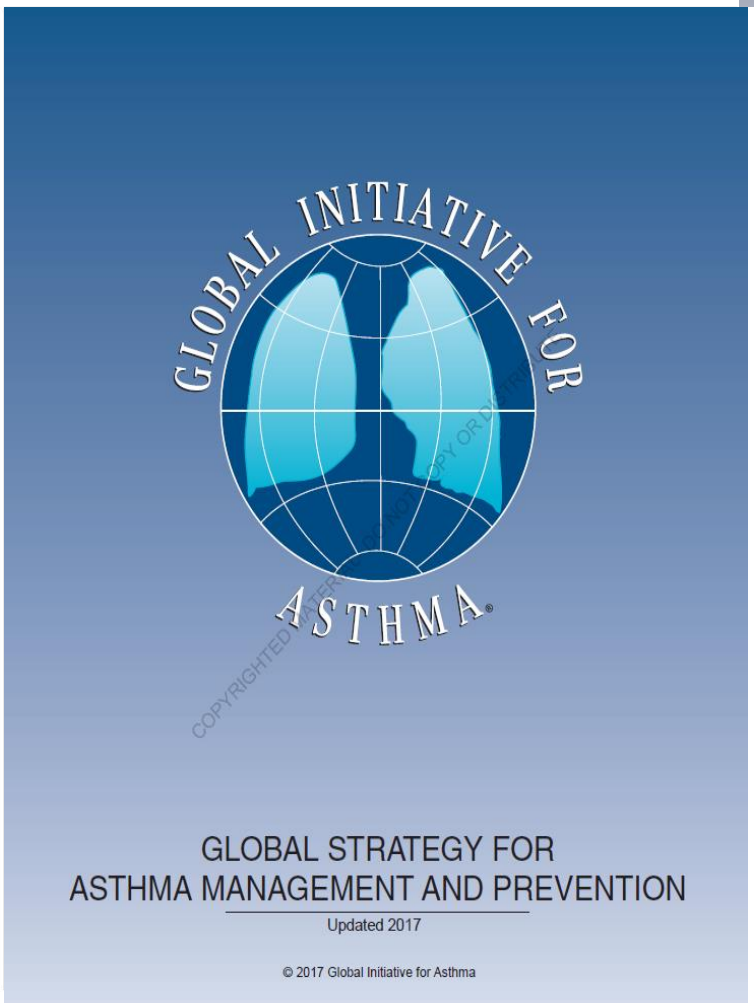
Reversible

**Airflow Limitation**

*Barns et al.2004*

# COPD and Asthma

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# COPD and Asthma


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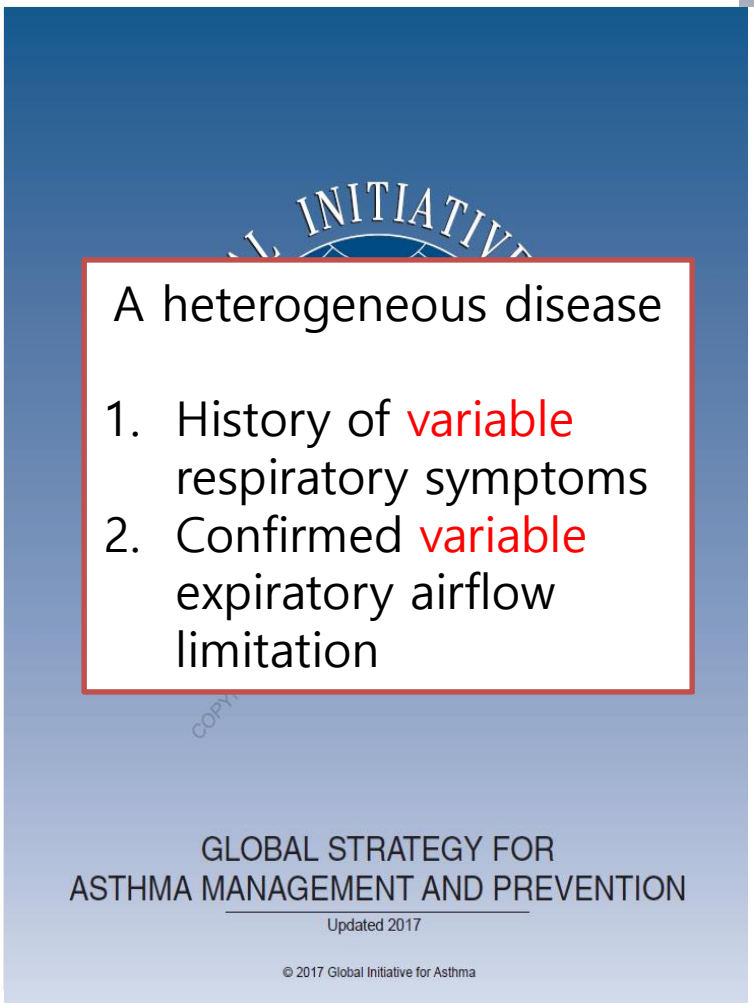


Reversible

**Airflow Limitation**

*Barns et al.2004*

# RCT in COPD *vs.* BA

**TORCH study**

- **Exclusion**
  - Diagnosis of asthma, non-COPD respiratory disorders
  - Hx of asthma, allergic rhinitis or atopy
- Inclusion
  - Smoker ≥ 10 pack-yr, pre BD FEV1 ≤ 60% or predicted with FEV1/FVC < 70%, and post BD FEV1 increased by < 10%

Patients with ACO(S)?

**Primo Tin A study**

-**Exclusion**

- Ever told by physician that hey had chronic bronchitis, emphysema or COPD

-Inclusion

- Diagnosed before 40 years, with ≥ 5 year history of asthma
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)

# Overlap syndrome

**Table 1** Definition of obstructive airway syndromes

| Syndrome | Definition |
|---|---|
| Asthma | …irring<br>…r after |
| COPD | Incompletely reversible airflow obstruction |
| Overlap syndrome | Asthma and COPD—that is, symptoms of increased variability of airflow and incompletely reversible airflow obstruction |
| Chronic bronchitis | Symptomatic mucus hypersecretion with cough and sputum daily for at least 3 months over 2 years |
| Emphysema | Abnormal airspace enlargement |

**Revisit to Dutch Hypothesis**

*Gibson et al. 2009, Thorax*

# Asthma-COPD Overlap

*Peter J. Barnes, Master FCCP*
*London, England*

PODCAST

Most clinicians can easily distinguish asthma and COPD. Asthma usually has an early onset with intermittent symptoms, a good response to inhaled therapy, and is often associated with other allergic diseases, whereas COPD is of late onset, slowly progressive symptoms, poor respon
therapy, and is usually associated w
smoking. However, patients can sor
features of both diseases, and this c
termed asthma-COPD overlap sync

Some overlap may be predicted because asthma and COPD are both common, and there is no evidence that one disease protects against the other. To call this overlap a syndrome is misleading, however; it includes different phenotypes, such as patients with COPD and eosinophilic inflammation, patients with asthma and severe disease or who smoke in whom there is predominantly neutrophilic inflammation, and patients with asthma who have largely irreversible airway obstruction due to structural changes. Thus, it may be better to refer to asthma-COPD overlap (ACO), rather than ACOS.[2] Indeed, the patients who receive a primary

# Asthma-COPD Overlap

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**Again,**
**British Hypothesis**

**Asthma-COPD**

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# Why ACO is not a single discrete disease?

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# Asthma-COPD overlap syndrome (ACOS)

**Major and Minor Criteria for Establishing the diagnosis of Mixed COPD asthma Phenotype in COPD**

| | | |
|---|---|---|
| **MAJOR** | - Personal history of asthma | 78% |
| | - Positive BDR ($FEV_1$ increase > 15% and 400mL) | 83% |
| | - Eosinophilia in sputum | 78% |
| **MINOR** | - Personal history of atopy | 50% |
| | - 2 positive BDR ($FEV_1$ increase > 12% and 200mL) | 39% |
| | - High levels of total IgE | 50% |

*Spanish guidline (2012, Arch Bronchoneumol)*

# Asthma-COPD overlap syndrome (ACOS)

**Major and Minor Criteria for Establishing the diagnosis of Mixed COPD asthma Phenotype in COPD**

**MAJOR**

- At least 10 pack-years of tobacco smoking/air pollution exposure
- Documented history of asthma before 40 years of age

  or BDR ($FEV_1$ increase > 400mL)

**MINOR**

- Documented history of atopy or allergic rhinitis
- 2 positive BDR ($FEV_1$ increase > 12% and 200mL)
- Blood Eosinophils >300clles/µL

*ATS Round table (2016 ERJ)*

# Asthma-COPD Overlap (ACO)

**Major and Minor Criteria for Establishing the diagnosis of Mixed COPD asthma Phenotype in COPD**

- ≥ 35 years
- Smoker ≥ 10 pk-yr
- Persistent post BD $FEV_1/FVC < 70\%$

- Current diagnosis of asthma or
- Positive BDR ($FEV_1$ increase > 15% and 400mL) or
- Blood Eosinophils ≥ 300cells/uL

*Modified Spanish guideline (2017)*

# Definition of ACOS

- **COPD component**
  - Persistent post-bronchodilator $FEV_1/FVC < 70\%$
- **Asthma Components**
  - Asthma before the age of 40 yr
  - A personal history of atopy
  - Episodic respiratory symptoms
  - Wheezing in the last 12 mo
  - Post-bronchodilator increase in $FEV_1$ 15% & 400mL (12% & 200ml)
  - Diurnal variation of > 20% in PEF
  - High total IgE level
  - Eosinophilia in sputum

**History**

**Symptoms**

**BD response /Th2 response**

# Definition of ACOS

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**BD response /Th2 response**

천식진료지침 AND GINA

# 천식/COPD중복 증후군(ACO(S))

| | 천식에 가까움 | COPD에 가까움 |
|---|---|---|
| 발생 시기 | □ 20세 이전 발생 | □ 40세 이후 발생 |
| 호흡기 증상의 양상 | □ 분, 시, 날에 따라 증상이 달라짐 | □ 치료에도 불구하고 지속 |
| | □ 밤이나 이른 아침에 증상이 악화됨 | □ 좋거나 나쁜 날이 있지만 항상 매일의 증상과 운동시 호흡곤란이 있음 |
| | □ 운동, 감정변화, 알레르기항원에 대한 노출에 의해 증상 유발 | □ 유발인자에 관계 없이 호흡곤란 발생에 앞서 만성적 기침, 가래 있음 |
| 폐기능 | □ 가변적 기류제한(폐활량, 최대호기유량) | □ 지속적 기류제한 (기관지확장제 투여 후 FEV1/FVC < 0.7) |
| 증상 사이의 폐기능 | □ 정상 | □ 비정상 |
| 과거력/가족력 | □ 과거에 의사에 의사에 의한 천식 진단 | □ 과거에 의사에 의한 COPD, 만성 기관지염, 혹은 폐기종 진단 |
| | □ 천식이나 다른 알레르기 질환 가족력 | □ 위험인자에 심한 노출: 흡연, 생체연료 |
| 경과 | □ 시간 경과에 따른 증상 악화 없음. 증상은 계절 혹은 해에 따라 가변적임 | □ 증상은 시간 경과에 따라 서서히 악화됨 (수 년에 걸쳐 진행) |
| | □ 저절로 호전되거나 기관지확장제 혹은 흡입스테로이드 치료 시 수 주에 걸쳐 호전 | □ 속효성기관지확장제에 의한 호전은 제한적임 |
| 흉부 X선 사진 | □ 정상 | □ 심한 과팽창 |

기도질환의 증후군적 진단

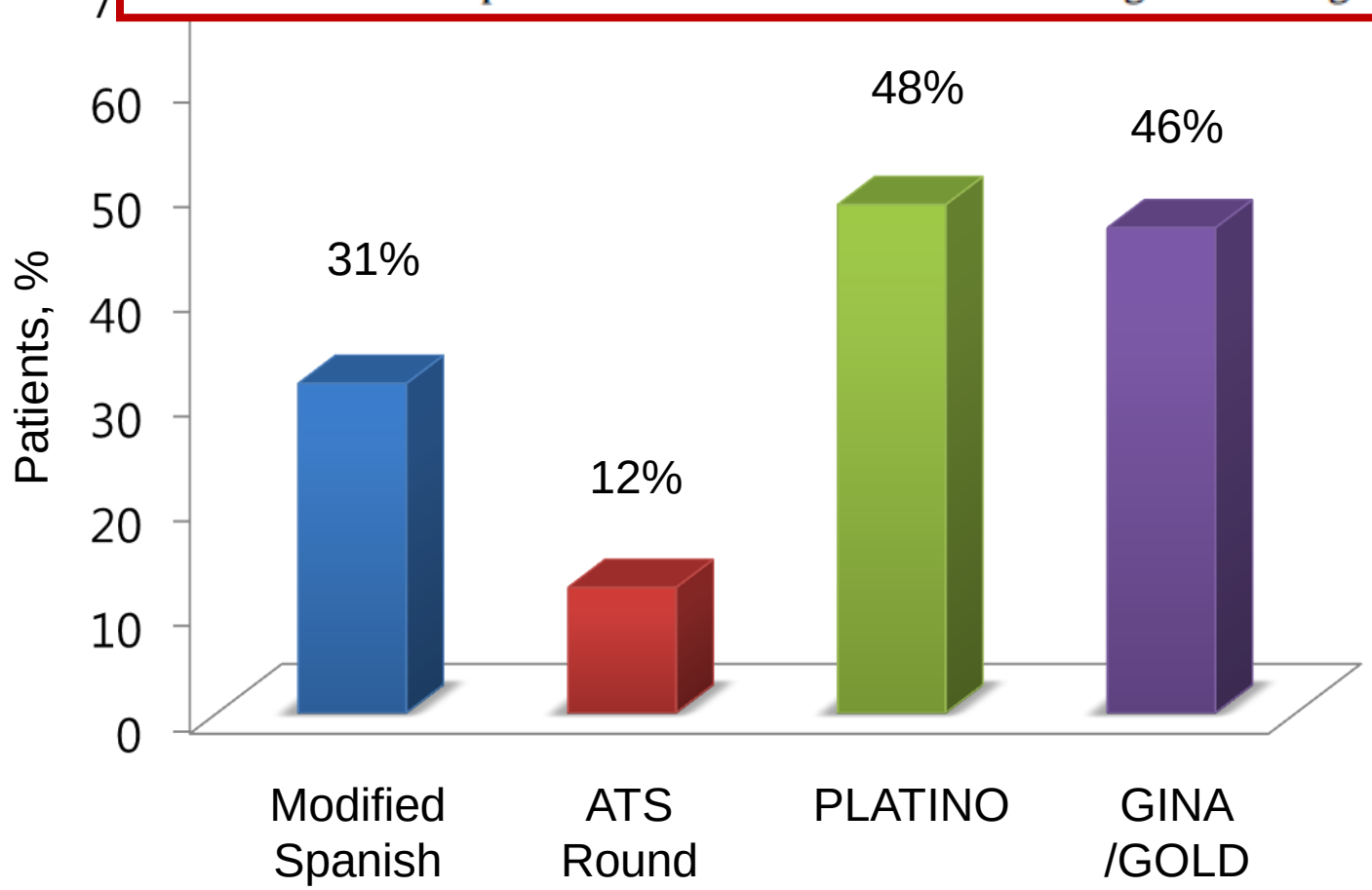
한 환자에 대해 해당사항에 대해 박스에 체크했을 때 천식이나 COPD에 대해 3가지 이상 해당하면, 그 진단을 시사함.
양쪽 수가 비슷하다면, ACOS를 고려해야 함

# Different prevalence and clinical characteristics of asthma–chronic obstructive pulmonary disease overlap syndrome according to accepted criteria

Yong Suk Jo, MD*; Jinwoo Lee, MD*,†; Ho Il Yoon, MD‡; Deog Kyeom Kim, MD§; Chul-Gyu Yoo, MD*,†; Chang-Hoon Lee, MD*

Seoul National University Airway Registry

**Conclusion:** The prevalence of ACOS varied according to the diagnostic criteria.



# Why ACO is not a single discrete disease?

- New debate?
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# ACO Clinical features

**ACO**

- **Younger/Female**
- **Less Smoking Hx**
- **Worse HRQoL**
- **More exacerbations**

COPDGene Study/ECLIPSE Study
Italian Population Study
HIRA/SMC

# ACO Clinical features

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**ACO**

- ~~**Younger/Female**~~
- ~~**Less Smoking Hx**~~

17 Meta-analysis
CHAIN Study

# ACO Clinical features

**ACO**

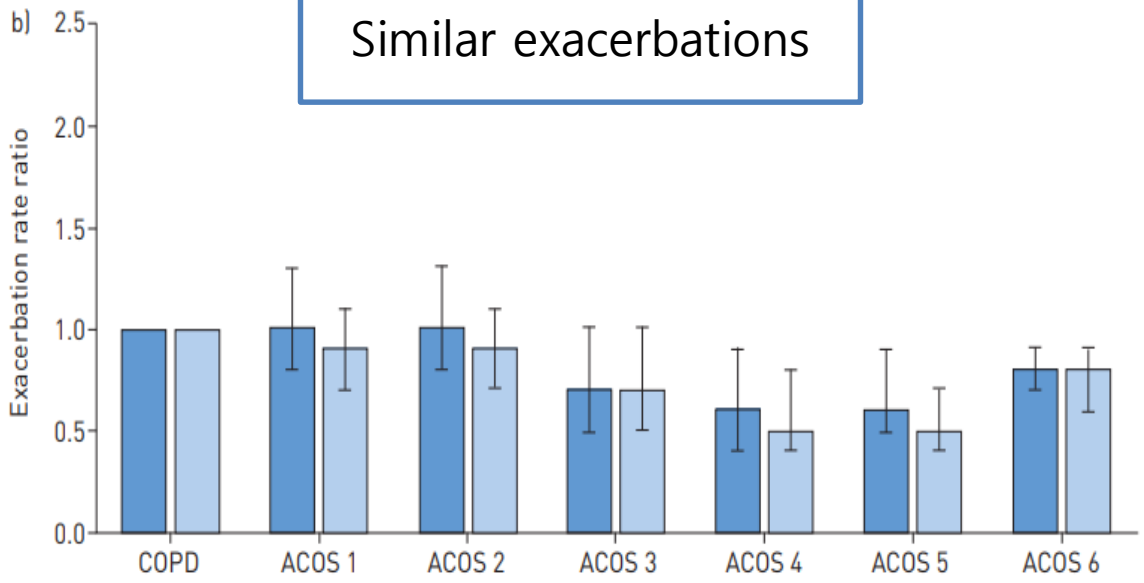
**Younger/Female**

**Less Smoking Hx**

**Worse HRQoL**

**More exacerbations†**

Similar exacerbations

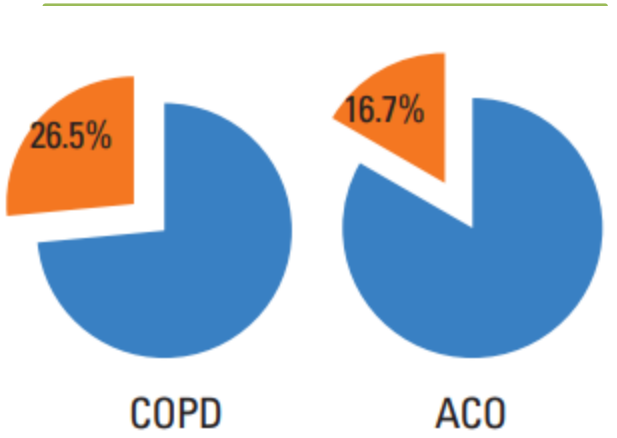



COPDGene Study/ECLIPSE Study
Italian Population Study
HIRA/SMC†

Netherlands
population Study
KOLD/CHAIN study

# ACO Clinical features

| ACO | ACO |
| --- | --- |
| Younger/Female | |
| Less Smoking Hx* | ≠ |
| Worse HRQoL | |
| More exacerbations† | ~~More~~ exacerbations |




COPDGene Study/ECLIPSE Study
Italian Population Study
HIRA/SMC†

KOCCOS

# ACO Clinical outcomes

**Lung Function Change**

Worse — Better

| | |
|---|---|
| **COPD** | **Asthma = ACO** |

European Hearth Survey

| | |
|---|---|
| **COPD** | **ACO** |

KOCCOS/KOLD/Hokkaido

**Asthma = ACO = COPD**

Australia

**ACO with late onset BA → COPD → Asthma=ACO with early onset BA**

Copenhagen City Heart study

# ACO Clinical outcomes

**Mortality**

Worse — Better

| | |
|---|---|
| **COPD** | **ACO** |

Japan/Italian Nationwide database/Spain/KOLD/Hokkaido

**ACO=COPD**

SA.R.A.(Italy)

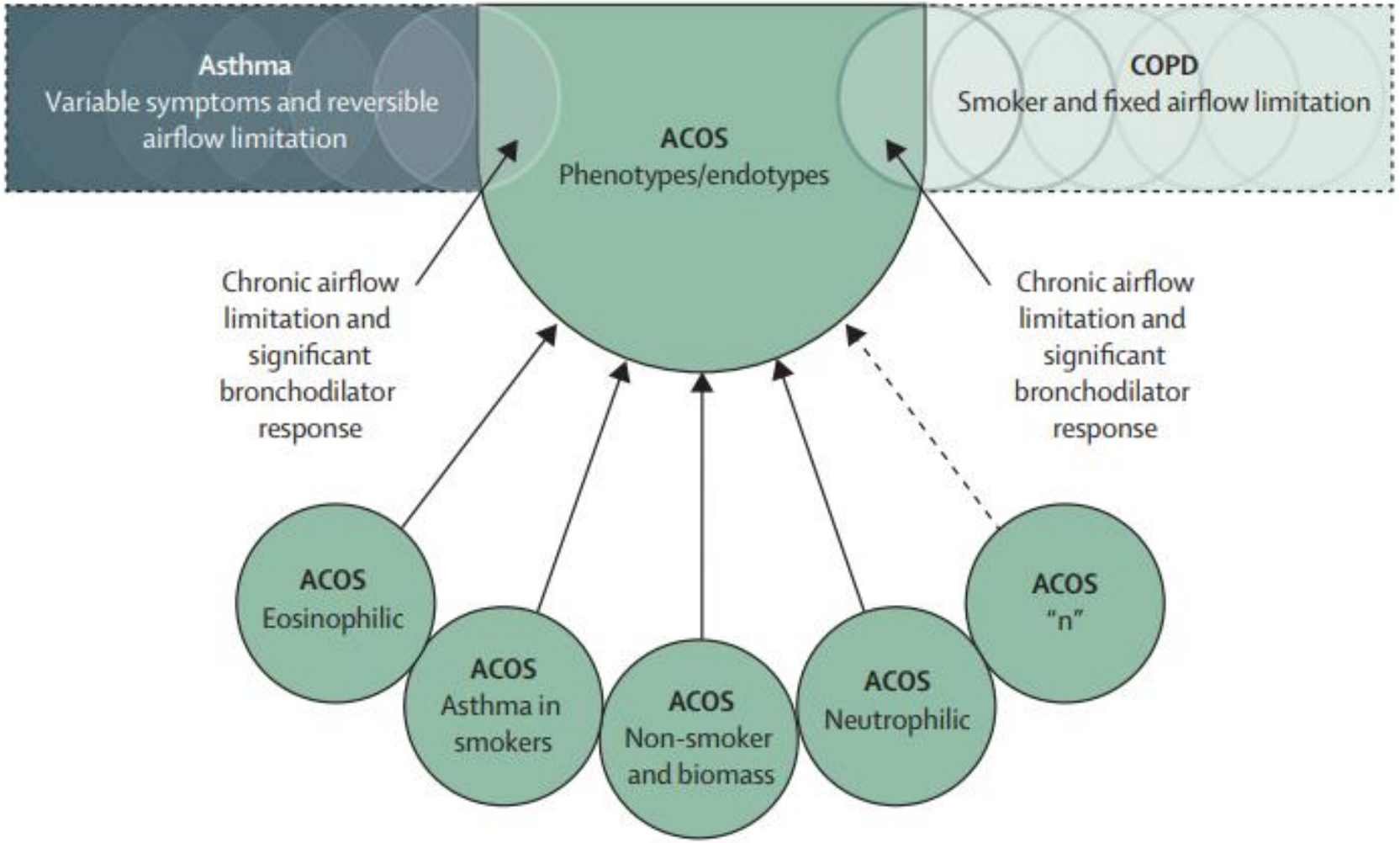
| | |
|---|---|
| **ACO** | **COPD** |

ASAN/US NHANES

**ACO with late onset BA → COPD → ACO with early onset BA → Asthma**

Copenhagen City Heart study

# Heterogeneity of ACO




*Lancet Respiratory Medicine. 2015;3(9):719-28*

# Why ACO is not a single discrete disease?

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# ACO

## Asthma

## COPD

ICS + Bronchodilators

# Treatment of COPD and Asthma

## Asthma

ICS-/+LABA

↓

Add LAMA

Biologic Agent

## COPD

Bronchodilators

↓

Add ICS

*GINA/GOLD Guideline*

# Treatment of COPD and Asthma

## Asthma

ICS-/+LABA

↓

Add LAMA

Biologic Agent

## COPD

Bronchodilators

↓

Add ICS

Use of ICS:

up to 60% of patients

in GOLD Group A/B

*GINA/GOLD Guideline*

# ICS withdrawal?!

## LAMA/LABA 출현

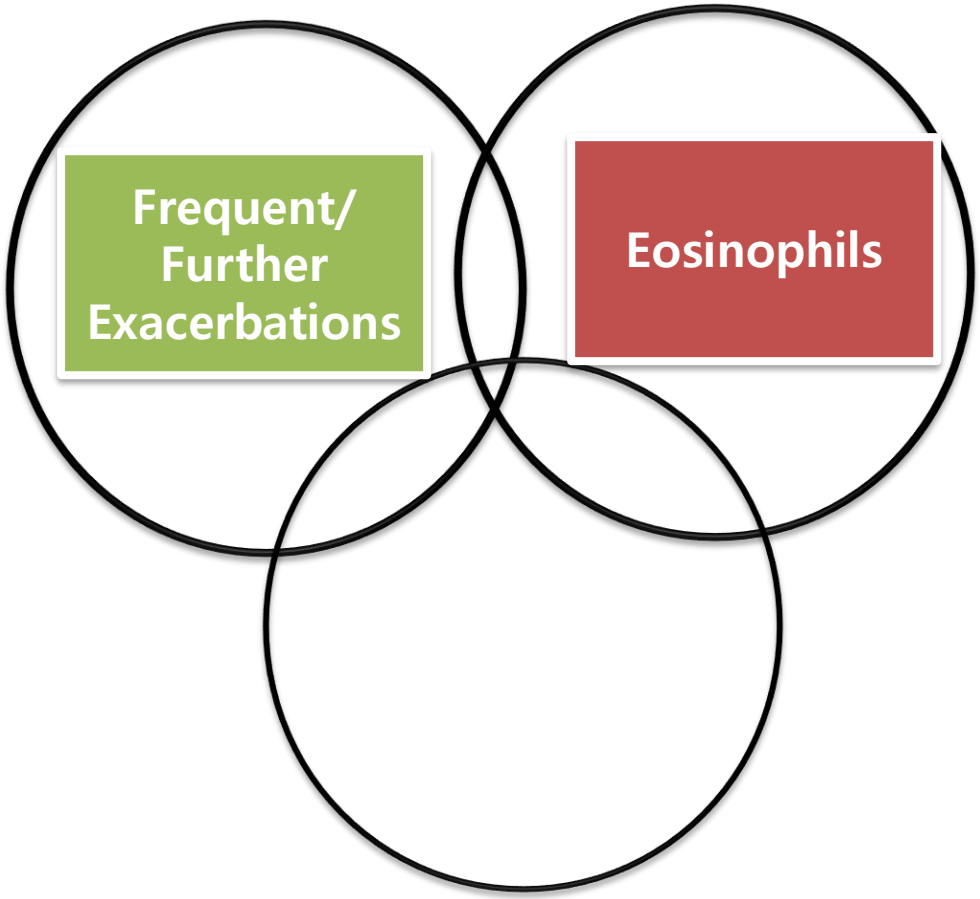
**Potential side effects associated with ICSs for patients with COPD**

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

*FVI (200 μg FF) group showed increased non-traumatic Fracture.

*Price et al. Prim Care Respir J 2013*

# Use of ICS in COPD



The NEW ENGLAND JOURNAL of MEDICINE

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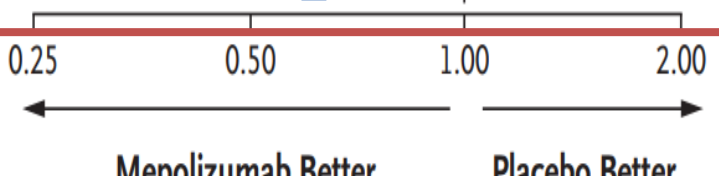
# Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

I.D. Pavord, P. Chanez, G.J. Criner, H.A.M. Kerstjens, S. Korn, N. Lugogo, J.-B. Martinot, H. Sagara, F.C. Albers, E.S. Bradford, S.S. Harris, B. Mayer, D.B. Rubin, S.W. Yancey, and F.C. Sciurba

| 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) |



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**ACO ?**

Exclusion
: patients with a current diagnosis of asthma
: nonsmokers with a history of asthma

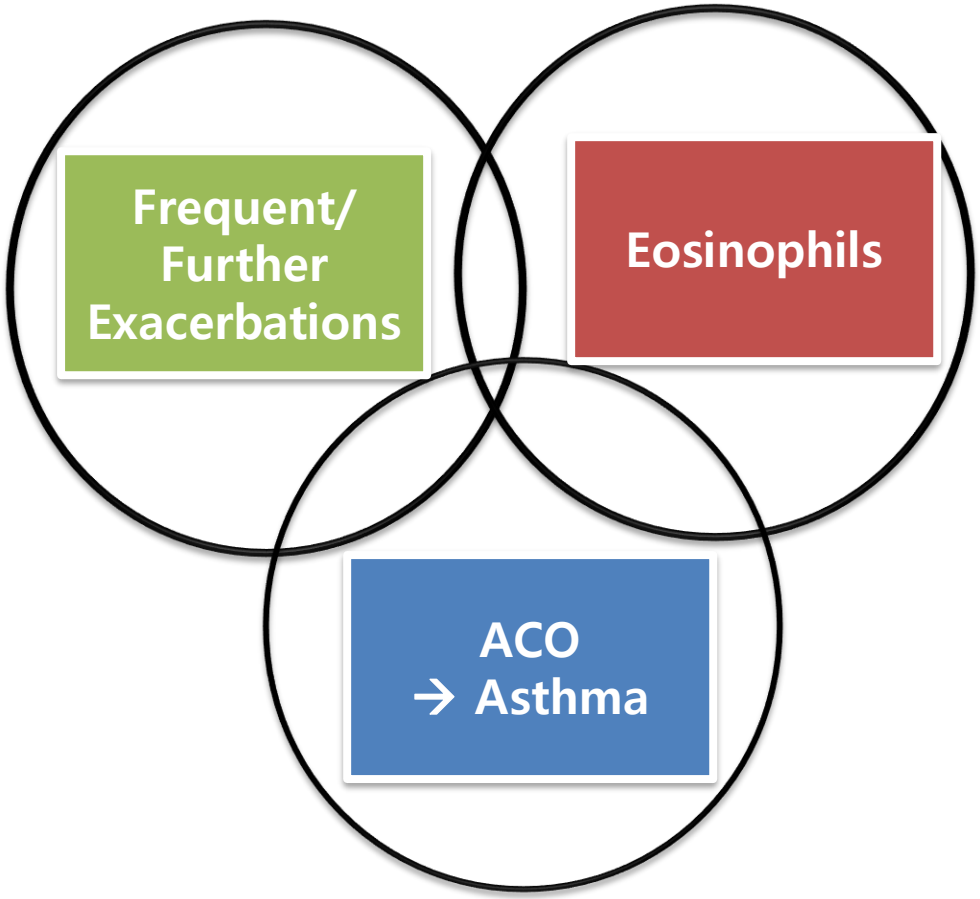
Table 1. I

| $FEV_1$ Rev | | | | s |
|---|---|---|---|---|
| | | | | th enotype ) |
| Yes | | | | |
| No. o | | | | |
| Blood [illegible] | [illegible] | [illegible] | [illegible] | [illegible]6 |
| No | | | | |
| No. of patients (%) | 391 (85) | 715 (86) | 565 (84) | 956 (84) |
| Blood eosinophil count — cells/mm³‡ | 260±0.566 | 140±0.943 | 230±0.854 | 240±0.752 |

We found no relationship
between $FEV_1$ reversibility after bronchodilator use
and blood eosinophil counts.

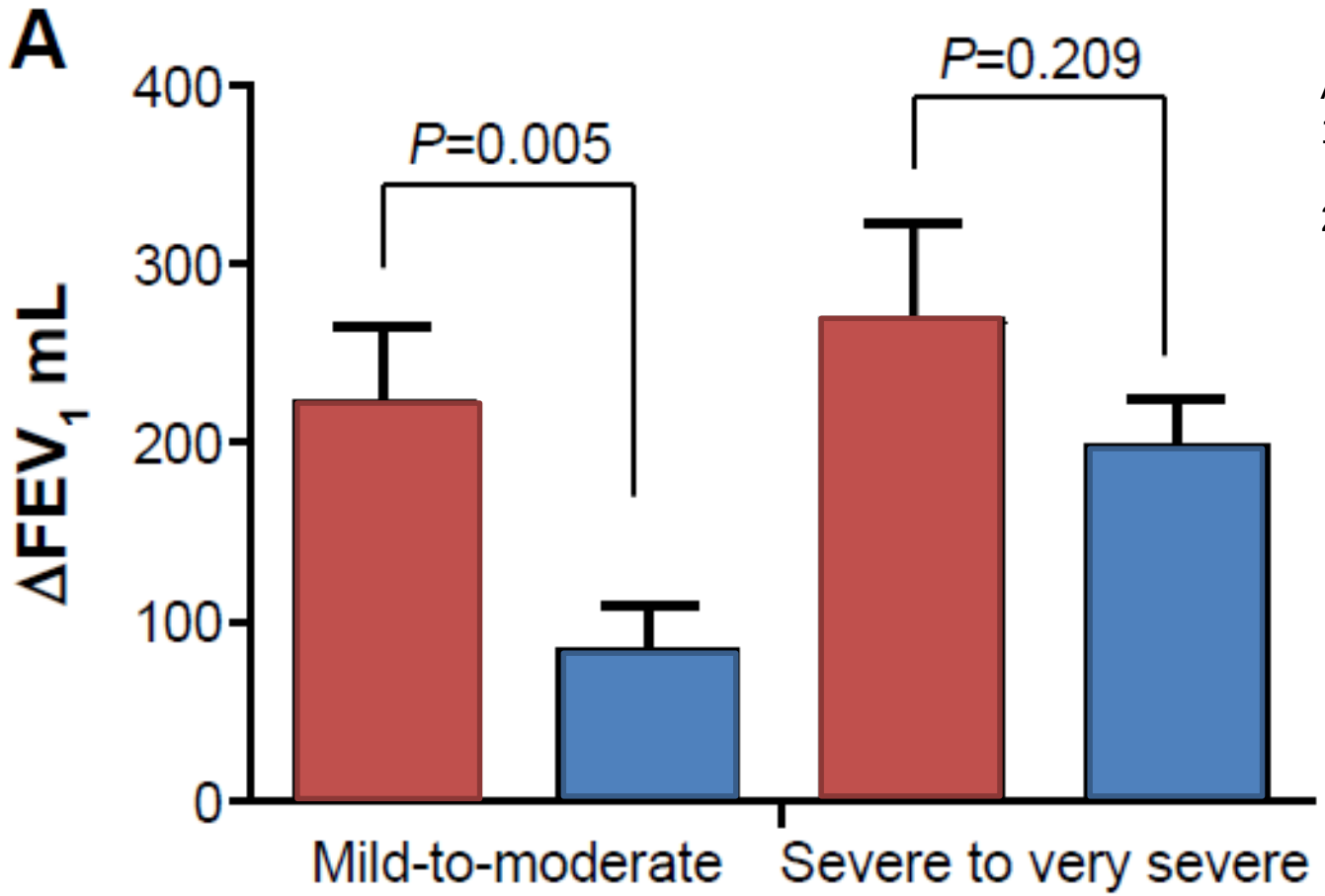
Eosinophilic COPD: treatable trait

# Use of ICS in COPD



# ICS responders

• 3 months, n=152,  stable COPD with washout and 3 months ICS/LABA Tx (KOLD cohort)




ACO: COPD +
1) Hx of BA and wheezing
2) + BD response

*Lee & Park et al. IJCOPD 2016*

# ICS effects on long-term?

**Lung Function Change** — **No Difference**

| | Total dataset (adjusted) | | PS-matched dataset | |
|---|---|---|---|---|
| | ΔFEV$_1$ (mL/y), mean (95% CI) | *P* value | ΔFEV$_1$ (mL/y), mean (95% CI) | *P* value |
| ICS | −9.61 (−20.51 to 1.29) | .598 | −12.88 (−34.49 to 8.73) | .972 |
| Non-ICS | −15.68 (−35.41 to 4.06) | | −12.37 (−31.15 to 6.41) | |

Seoul National University Airway Registry, AAAI

| | Crude<br>mL/y, mean (95% CI) | Adjusted<br>mL/y, mean (95% CI) | *P for interaction*† |
|---|---|---|---|
| **ICS** | -10.44 (-26.34, 5.46) | -10.22 (-26.12, 5.70) | 0.47 |
| **No ICS** | -21.73 (-47.76, 4.30) | -21.53 (-47.56, 4.50) | 0.47 |

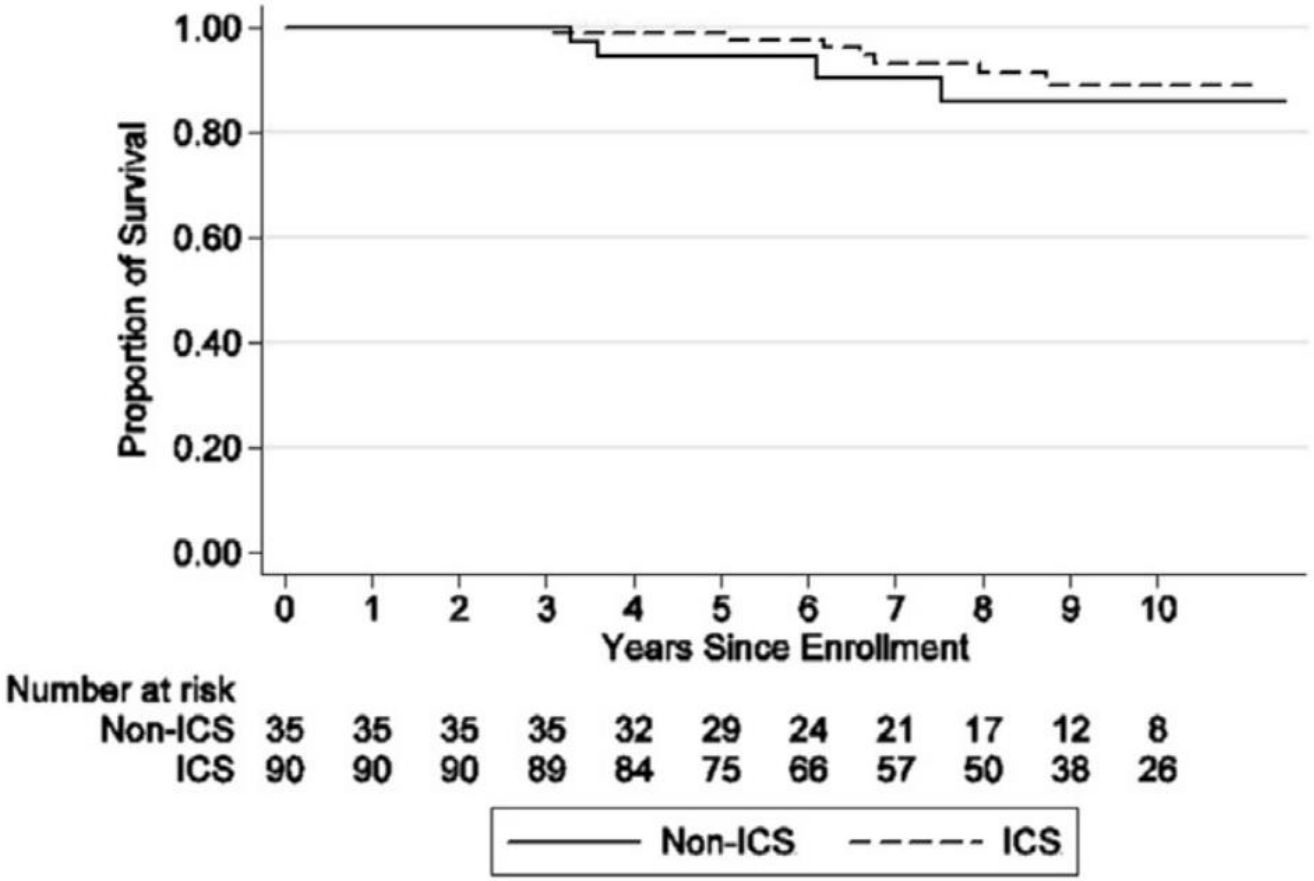
KOLD, Respiratory Research

# ICS effects on long-term?

**Mortality**

**No Difference**

*P*= 0.467



## COPD and MI: a bad combination

▲ Salisbury AC, Reid KJ, Spertus JA. Impact of chronic obstructive pulmonary disease on post-myocardial infarction outcomes. *Am J Cardiol* 2007;**99**:636–41.

In this observational prospective multicentre study that enrolled 2481 patients, the authors tried to highlight the relationship between chronic obstructive pulmonary disease (COPD) and a number of outcomes following an acute myocardial infarction (MI).

One-year mortality and rehospitalisation rates were significantly higher in patients with COPD than without (15.8% vs 5.7%) and (48.7% vs 38.6%), respectively. In addition, patients with COPD had worse health status at baseline as well as at 1 year and a trend toward a higher prevalence of angina at 1 year. Not surprisingly, patients with COPD had fewer coronary

selective agents, in the study population could have led to a better 1 year survival than observed and possibly a lower prevalence of angina, again at 1 year.

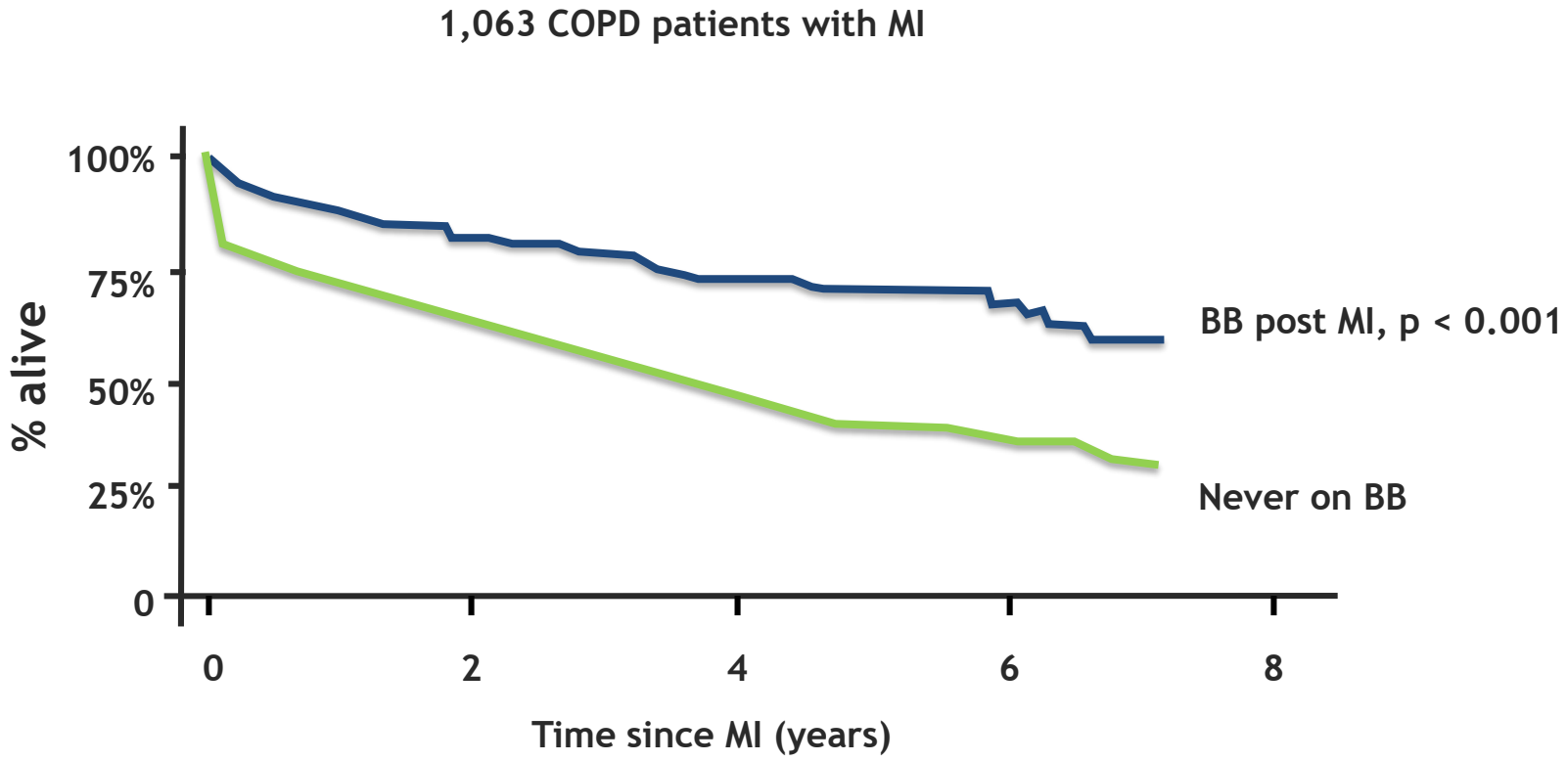
by the severity of COPD, which the authors were unable to classify. Nevertheless, the data suggest that patients with acute MI and COPD have a substantially worse prognosis in terms of mortality and health status. This cohort of patients therefore warrants careful attention and closer follow-up.

mortality and health status. This cohort of patients therefore warrants careful attention and closer follow-up.

**Nabil M Al Lawati**
Clinical Fellow, University of British Columbia, Canada; drnabilm@yahoo.com

# Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records

## Beta Blockers (BB)




*J K Quint et al, BMJ, 2013;347:f6650*

# GOLD Guideline

No MCO or CMO

## Ischaemic heart disease (IHD)

► Ischaemic heart disease should be considered in all COPD patients depending on their risk factor profile. The cardiovascular risk may be assessed by the global risk calculator, which can be found on the US National Heart Blood Lung Institute website[19] and treatment initiated based on the current recommendations.

► During acute COPD exacerbations, there is an increased risk of myocardial damage in patients with concomitant ischemic heart disease. Patients who demonstrate abnormal cardiac troponins in isolation are at increased risk of adverse outcomes including short-term (30day) and long-term mortality.[20]

► The treatment of ischaemic heart disease should be according to guidelines irrespective of the presence of COPD and *vice versa*.

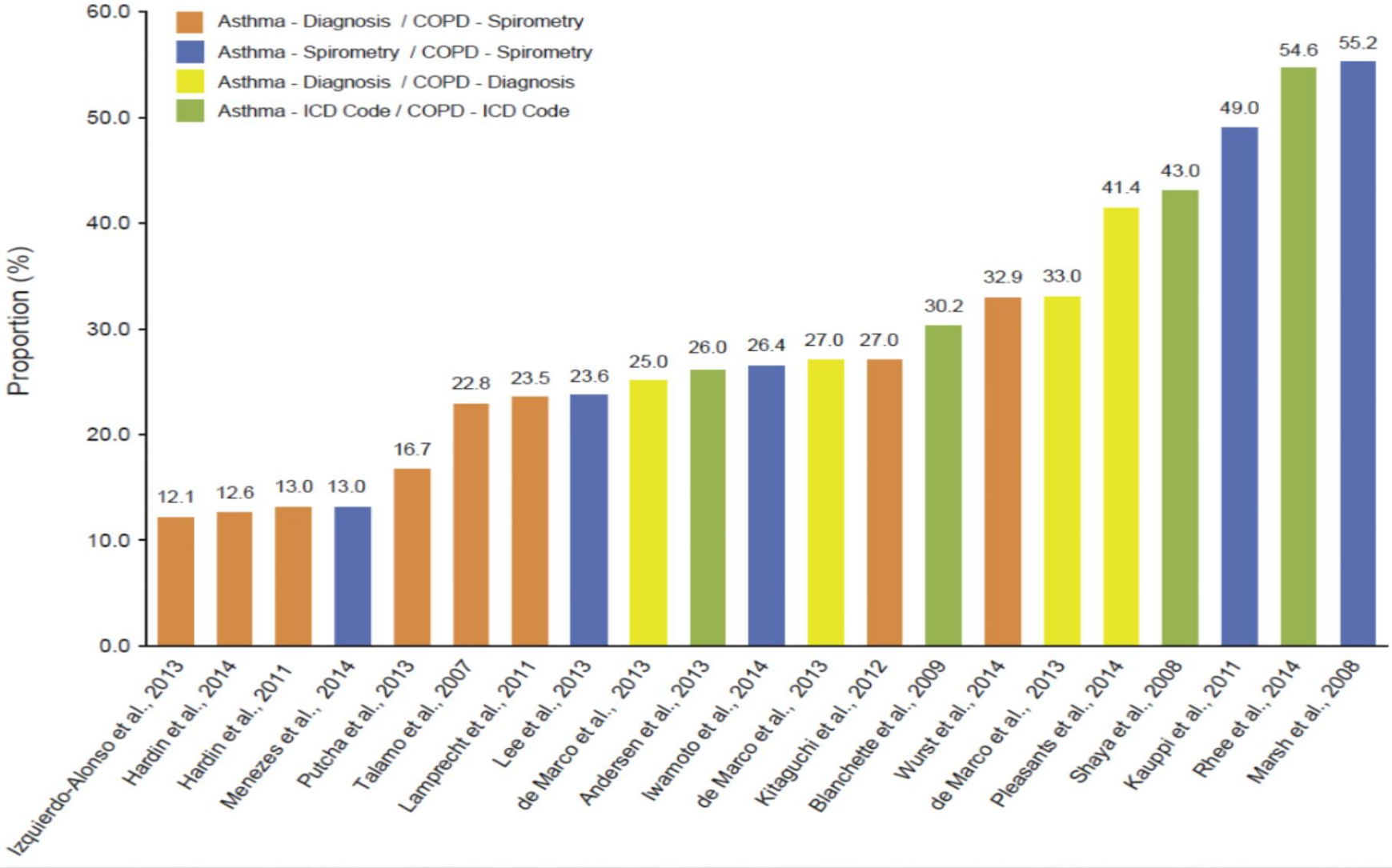
# Why ACO is not a single discrete disease?

- No single and universal definition/diagnosis
- Inconsistent outcomes
- Treatment remains uncertain

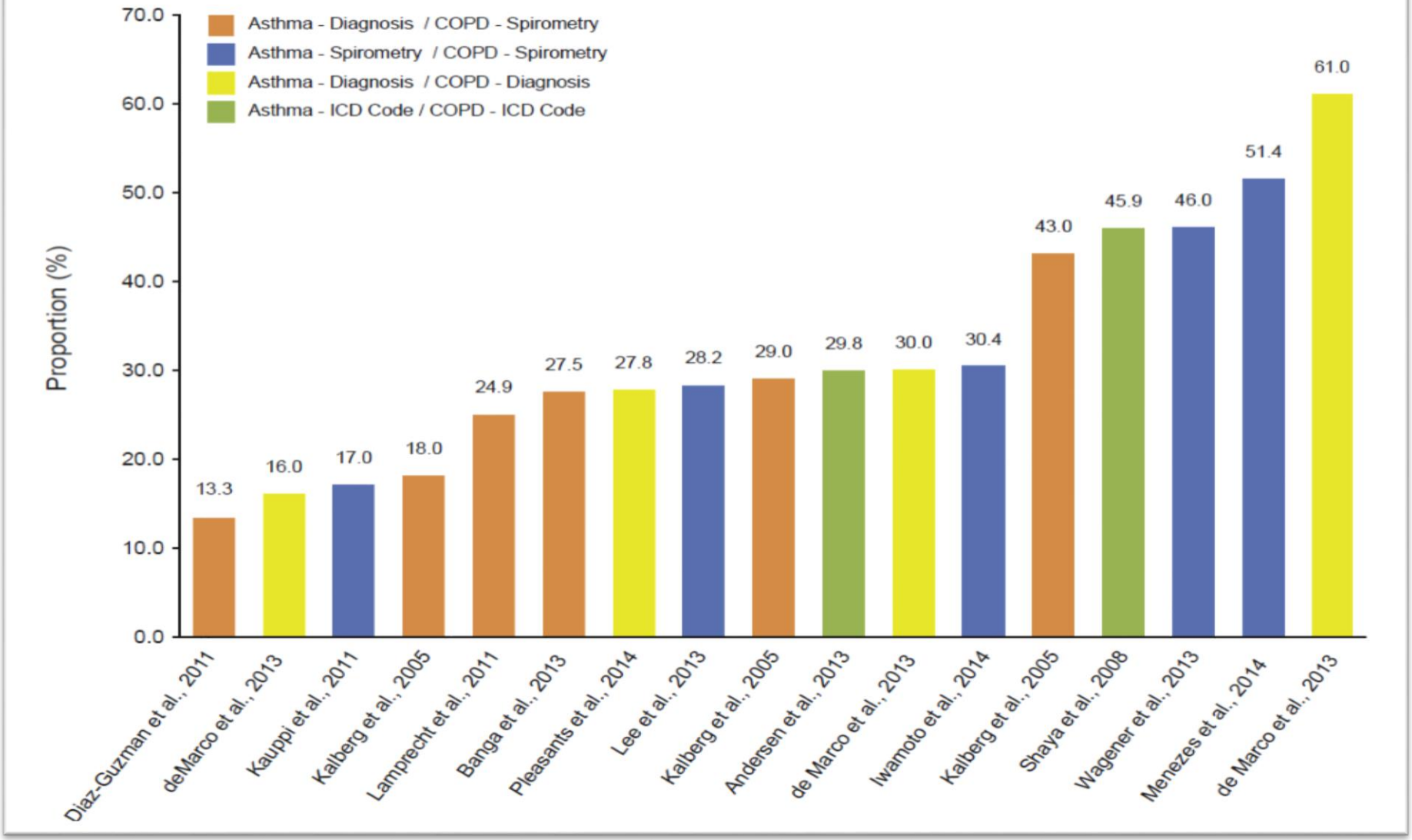
# ACO:

# Not a single discrete disease

# Prevalence among Asthma

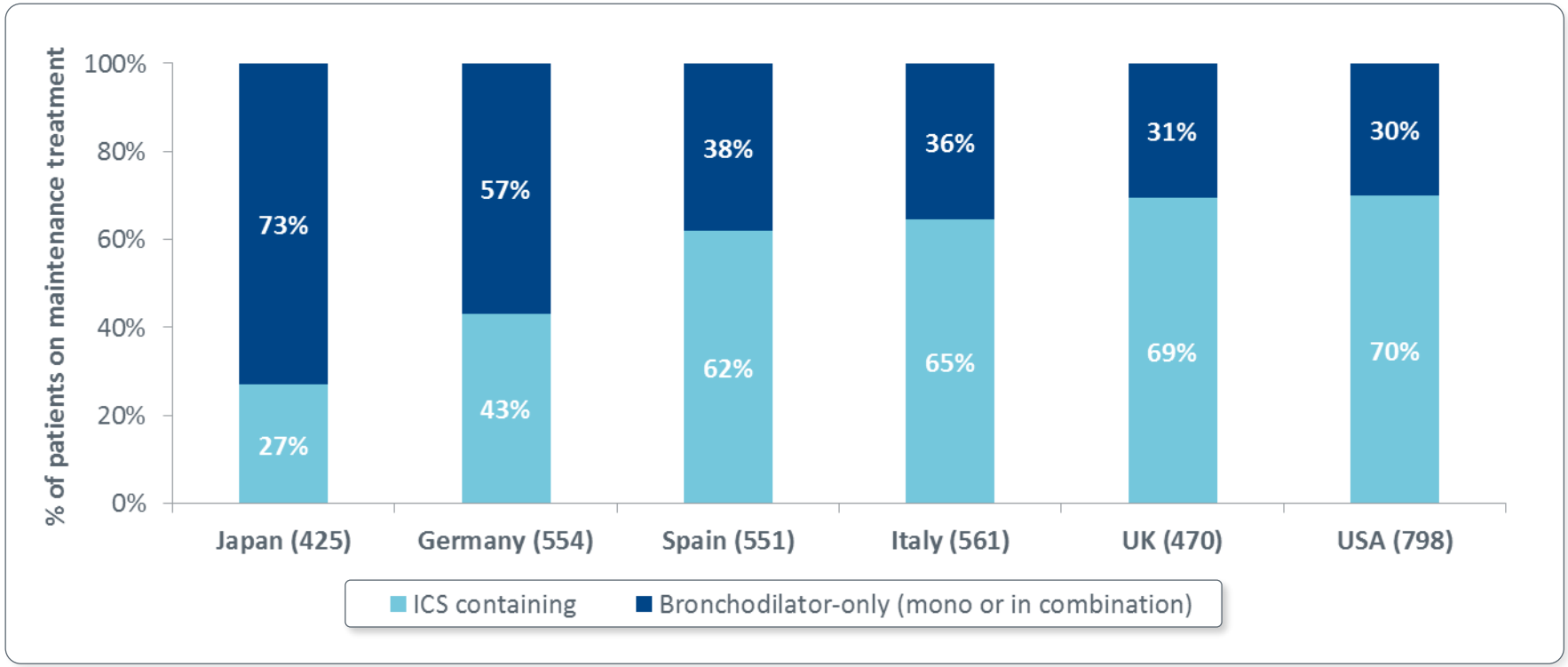


# Prevalence among COPD



# Prescribing patterns of ICS in COPD patients

## Maintenance regimen patient share trends
## UK and USA: 70% of patients are on an ICS-containing regimen




Base = EU4 + US + Japan COPD-only patients on a maintenance treatment; weighted
Source = Adelphi Respiratory DSP 2014/15, Macclesfield, UK; unpublished data.

# WISDOM Study
## LABA/LAMA/ICS
## ICS withdrawal vs. ICS continuation

Event Rates (Rate Ratios) over 9 months

| | 1 exacerbation | | | | | ≥ 2 exacerbation | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of patients | Adjusted event rate (per patient year) | Rate ratio | 95% CI | *P* value | No. of patients | Adjusted event rate (per patient year) | Rate ratio | 95% CI | *P* value |
| **≥ 300 cells/** | | | | | | | | | | |
| ICS | | | | | | | | | | |
| ICS withdrawal | | | | | | | | 75 | 1.09, 2.80 | 0.0205 |
| **≥ 400 cells/uL** | | | | | | | | | | |
| ICS | 77 | 0.77 | | | | 42 | 0.55 | | | |
| | | | 1.25 | 0.75, 2.09 | 0.3962 | | | 2.96 | 1.50, 5.83 | 0.0017 |
| ICS withdrawal | 84 | 0.96 | | | | 44 | 1.63 | | | |

Event rates, rate ratios, and corresponding 95% CIs and *P* values from negative binomial regression models.

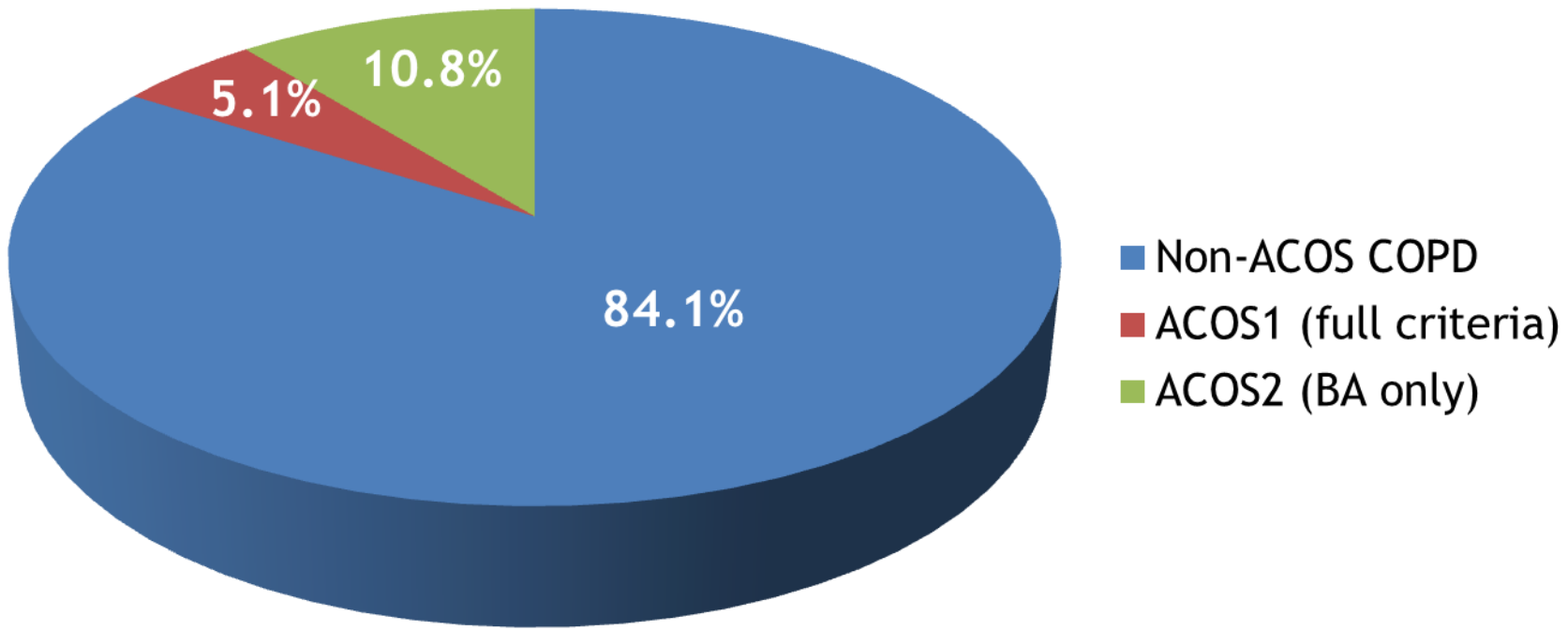
*Definition of abbreviations:* ICS = inhaled corticosteroid; CI = confidence interval.

**Previous frequent AE**

*Watz et al. Lancet Resp Med 2016;4:390-398*

# Previous diagnosis of asthma

Multicenter, observational, cross-sectional study
(n=3,125 COPD pts from primary clinics and specialized outpatient clinics)




*Barrecheguren et al.* Int J COPD 2015

# A previous diagnosis of BA

BA + other criteria

BA only

| Variable | ACOS 1 (n=158) | ACOS 2 (n=338) | P-value |
|---|---|---|---|
| Sex (men) | | 233 (68.9%) | 0.56 |
| Age (years) | | 65.1 (0.5) | 0.06 |
| BMI (kg/m$^2$) | | 28.2 (0.2) | 0.22 |
| Active smoker | 42 (26.6%) | 83 (26.9%) | 0.59 |
| Pack-years | 33.4 (1.9) | 31.9 (1.4) | 0.006 |
| Time walked pe | | | 0.62 |
| **Spirometry, p** | | | |
| FVC (L) | | | 0.53 |
| FVC% | | | 0.43 |
| $FEV_1$ (L) | | | 0.02 |
| $FEV_1$% | 63.0 (1.6) | 57.8 (1.2) | 0.012 |
| $FEV_1$/FVC | 56.1 (1.1) | 54.9 (0.6) | 0.09 |
| **Symptoms** | | | |
| mMRC, mean (SD) | 1.7 (0.07) | 1.6 (0.05) | 0.07 |
| Chronic cough | 130 (82.3%) | 259 (76.6%) | 0.33 |
| Daily expectoration | 113 (71.5%) | 212 (62.7%) | 0.08 |
| BODEx index, mean (SD) | 2.5 (0.1) | 2.5 (0.1) | 0.62 |
| Charlson Comorbidity Index | 1.6 (0.07) | 1.3 (0.06) | 0.005 |
| % blood eosinophilic count (mean, SD) | 4.9 (0.5) | 4.7 (0.6) | 0.14 |
| Number of exacerbations in the previous 12 months | 2.3 (0.1) | 1.9 (0.1) | 0.006 |
| Hospital admissions in the previous 2 years | 1.2 (0.1) | 1.1 (0.1) | 0.39 |

1/3

There were no significant differences in the demographic characteristics between two groups of patients with ACOS.

IJCOPD 2015

# Prevalence of ACOS

## Asthma – COPD overlap: Clinical evidence of genomic signatures of Type 2 inflammation in COPD

The 100 genes used to generate the airway epithelial Th2 Signature (T2S) Score

| | | | |
|---|---|---|---|
| AADAC | CST2 | KIT | SERPINB2 |
| ADRA2A | CST4 | KRT23 | SERPINB4 |
| AGR2 | CSTA | KRT6A | SF3B5 |
| ALOX15 | CXCL14 | LOC100288152 | SLC18A2 |
| ANXA3 | CYB5R2 | LOC100505495 | SLC22A16 |
| APOBEC3B | DHX35 | LOXL4 | SLC24A3 |
| ARL1 | DPYSL3 | LRRC31 | SLC25A39 |
| C12orf57 | EGFL6 | MFSD2A | SPRR1B |
| C16orf54 | FAM110C | MS4A2 | SPRR3 |
| C1orf186 | FAM3B | NEK6 | SRD5A2 |
| CAPN14 | FGFBP1 | NOS2 | TCN1 |
| CCBL1 | FOLH1 | OSTalpha | TFF1 |
| CCL26 | GCNT3 | P2RY14 | TFF3 |
| CD1C | GGH | PCP4L1 | TIMP1 |
| CD44 | GNPNAT1 | PDIA5 | TMEM111 |
| CD69 | GPX2 | PHLDB2 | TMEM190 |
| CDC42EP5 | HIST1H2BF | POSTN | TMEM200A |
| CDH26 | HIST1H2BG | PP14571 | TNC |
| CEACAM5 | HIST1H2BK | PRR4 | TPSAB1 |
| CEP72 | HPGDS | PRSS16 | UPK1B |
| CLC | IGF2BP3 | RPL18AP3 | UTP20 |
| CLCA1 | IGJ | S100A16 | VSIG2 |
| CNFN | IGKC | S100P | WBP5 |
| CPA3 | ITLN1 | SCGB2A1 | ZMAT4 |
| CST1 | KCNJ16 | SERPINB10 | ZNF467 |

**Approximately 20% of smokers with COPD have a Th2 high signature**

Christenson et al. AJRCCM 2015; 191:758-766

# Childhood asthma-adult COPD

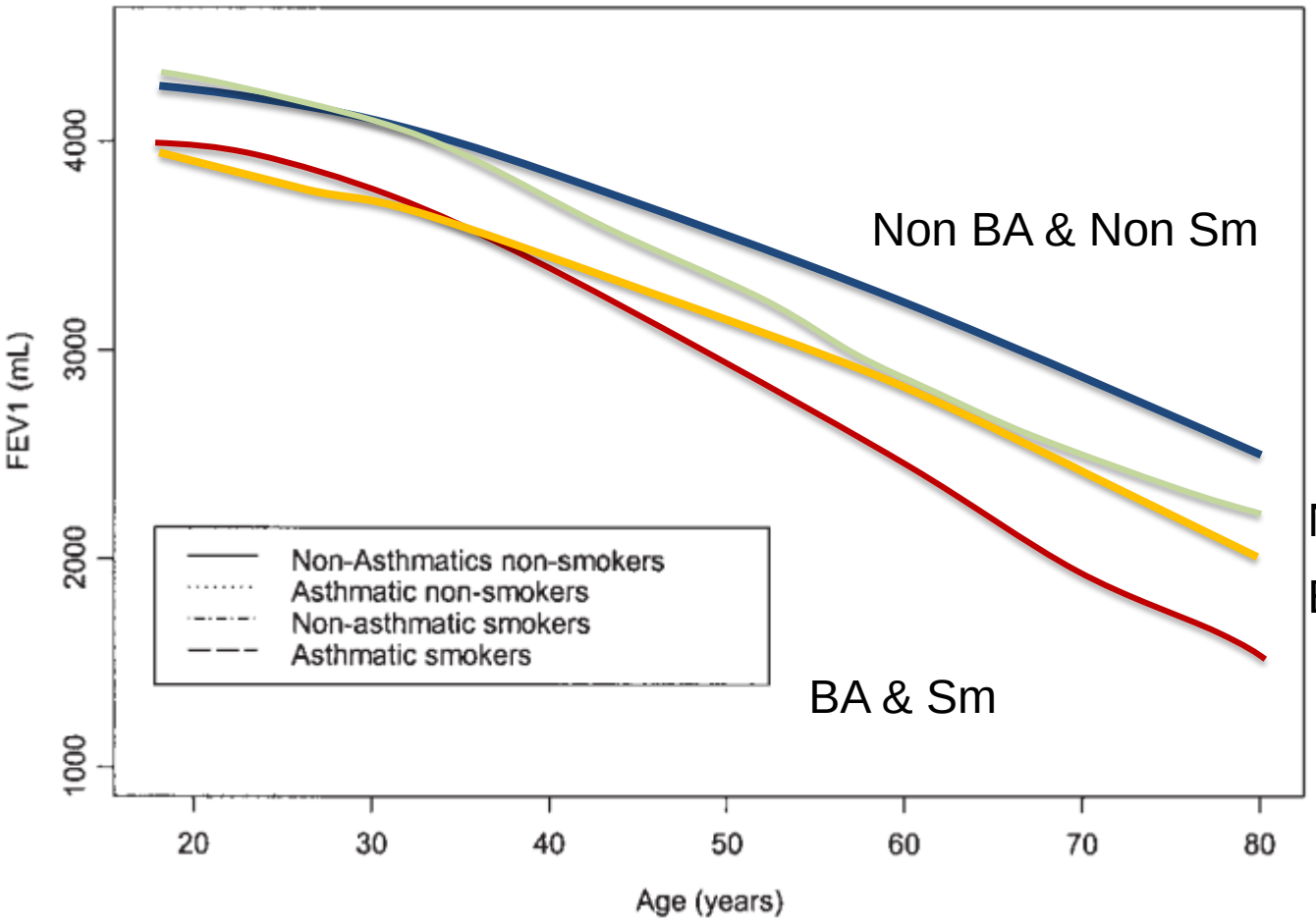
Longitudinal prospective study with 6-7 yr old children with asthma to 50 years of age n=346 → 197 completion

**Table 3** The childhood predictors of adult COPD

| | OR (95% CI) (univariate) | OR (95% CI) (multivariate) |
|---|---|---|
| Severe asthma | 37.1 (4.6 to 301) | 31.9 (3.4 to 269) |
| Asthma | 9.1 (1.1 to 76.4) | 9.6 (1.0 to 77) |
| Wheezy bronchitis | 3.5 (0.4 to 35.2) | |
| Mild wheezy bronchitis | 2.1 (0.1 to 35.8) | |
| Male sex | 2.4 (0.9 to 6.3) | |
| Ever smoker | 1.0 (0.5 to 2.3) | |
| Current smoker | 1.1 (0.5 to 2.4) | |
| Childhood hay fever | 1.0 (0.3 to 3.8) | |

*Tai A et al. Thorax 2014*

# Asthma = smoking for lung function decline




Non BA & Sm

BA & non Sm

*Alan L. James et al. AJRCCM, 2005*

# COPD alone vs. ACOS (spain)

| Variable | Non-ACOS (n=2,629) | ACOS | Total (n=3,125) | P-value |
|---|---|---|---|---|
| Sex (men) | 2,229 (84.8%) | | 2,575 (82.4%) | <0.001 |
| Age (years) | 67.4 (0.2) | | 66.9 (0.2) | <0.001 |
| BMI (kg/m$^2$) | 27.7 (0.1) | | 27.8 (0.1) | 0.003 |
| Active smoker | 601 (22.9%) | | 726 (23.2%) | 0.082 |
| Pack-years | 41.3 (0.5) | | 40.1 (0.5) | <0.001 |
| Time walked per day, minutes | 63.3 (2.1) | | 63.7 (2.0) | 0.36 |
| **Spirometry (postbronchodilator)** | | | | |
| FVC (L) | 2.8 (0.02) | | 2.9 (0.02) | 0.0001 |
| FVC% | 68.7 (0.4) | | 69.7 (0.4) | <0.001 |
| $FEV_1$ (L) | 1.5 (0.01) | | 1.6 (0.01) | <0.001 |
| $FEV_1$% | 51.9 (0.4) | | 53.0 (0.3) | <0.001 |
| $FEV_1$/FVC | 53.4 (0.2) | | 53.7 (0.2) | <0.001 |
| **Symptoms** | | | | |
| mMRC, mean (SD) | 1.7 (0.02) | 1.7 (0.04) | 1.7 (0.02) | 0.31 |
| Chronic cough | 1,939 (73.8%) | 389 (78.4%) | 2,328 (74.5%) | 0.07 |
| Daily expectoration | 1,650 (62.8%) | 325 (65.5%) | 1,975 (63.2%) | 0.38 |
| BODEx index | 2.9 (0.04) | 2.5 (0.08) | 2.9 (0.04) | <0.001 |
| Charlson Comorbidity Index | 1.4 (0.06) | | 1.4 (0.07) | 0.82 |
| Positive bronchodilator test ($FEV_1$ >12%, >200 mL) | 99 (3.9%) | | 155 (5.0%) | <0.001 |
| Very positive bronchodilator test* ($FEV_1$ >15%, >400 mL) | 231 (8.9%) | | 371 (11.9%) | <0.001 |
| % blood eosinophilic count (mean, SEM) | 2.9 (0.2) | | 3.4 (0.2) | <0.001 |
| Clinical/radiologic signs of emphysema | 1,035 (39.4 | | 1,196 (38.3%) | 0.007 |
| Number of exacerbations in the previous 12 months | 1.8 (0.03) | | 1.8 (0.03) | 0.0006 |
| Hospital admissions in the previous 2 years | 1.0 (0.03) | | 1.0 (0.03) | 0.03 |

Female

Younger

Smoked less

Better

Lung Function

(+) BD Response

Higher Eos

Less emphysema

# COPD alone vs. ACOS (COPD gene study)

TABLE 1 Subject characteristics

| | COPD | COPD and asthma | p-value |
|---|---|---|---|
| Subjects n | 3120 | 450 | |
| Age years | 64.0±8.4 | 60.0±8.7 | <0.001 |
| Females | 1335 (42.8) | 252 (56) | <0.001 |
| African–American | 627 (20.1) | 167 (37.1) | <0.001 |
| Pack-years | 54.2±27.8 | 45.7±25.1 | <0.001 |
| BMI kg·m$^{-2}$ | 27.9±6.1 | 28.8±6.9 | 0.006 |
| $FEV_1$ L | 1.45±0.63 | 1.40±0.62 | 0.16 |
| $FEV_1$ % predicted | 50.3±18.0 | 50.3±17.9 | 0.95 |
| $FEV_1/FVC$ | 0.49±0.13 | 0.51±0.13 | 0.02 |
| Emphysema | 13.54±12.95 | 9.93±11.5 | <0.001 |
| Bronchodilator responsiveness | 1120 (36.13) | 177 (39.42) | 0.19 |
| Absolute BDR L | 0.09±0.16 | 0.11±0.16 | 0.11 |

Female

Younger

Smoked less

Less emphysema

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: bronchodilator response (>200 mL and 12% change in $FEV_1$).

*Hardin et al*. ERJ 2014

# COPD alone vs. ACOS (COPD gene study)

TABLE 2 Clinical features of subjects with chronic obstructive pulmonary disease (COPD) and asthma compared to those with COPD alone

| | COPD | COPD and asthma | Effect size | p-value |
|---|---|---|---|---|
| **Females** | | | −1.95) | <0.001 |
| **African–American** | | | −2.18) | <0.001 |
| **Bronchodilator responsiveness** | | | −1.47) | 0.10 |
| **Absolute BDR L** | | | .008 | 0.03 |
| **BODE score** | 2.9±2.1 | 3.1±2.0 | 0.25±0.1 | 0.02 |
| **SGRQ score** | 39.7±21.5 | 47.4±22.7 | 6.81±1.1 | <0.001 |
| **Exacerbations per year** | 0.7±1.2 | 1.2±1.6 | 0.56±0.06 | <0.001 |
| **Severe exacerbations** | 646 (20.7) | 153 (34.0) | 1.70 (1.36–2.12) | <0.001 |
| **Hay fever** | 442 (17.8) | 186 (50.3) | 4.66 (3.68–5.90) | <0.001 |
| **High school graduates** | 1828 (58.6) | 261 (58.0) | 1.10 (-0.19–0.39) | 0.54 |
| **Maternal asthma** | 162 (7.0) | 57 (19.0) | 2.22 (1.59–3.12) | <0.001 |
| **Paternal asthma** | 123 (5.9) | 47 (17.5) | 2.64 (1.82–3.83) | <0.001 |

More exacerbations and poor QOL

Data are presented as n (%) or mean±SD, unless otherwise stated. Effect size data are presented as OR (95% CI) or β±SE. Linear and logistic regression models were adjusted for age, race, sex and pack-years. BDR: bronchodilator response (>200 mL and 12% change in forced expiratory volume in 1 s); BODE: body mass index, airflow obstruction, dyspnoea and exercise capacity; SGRQ: St George's Respiratory Questionnaire.

*Hardin et al*. ERJ 2014

# Why is ACOS important?

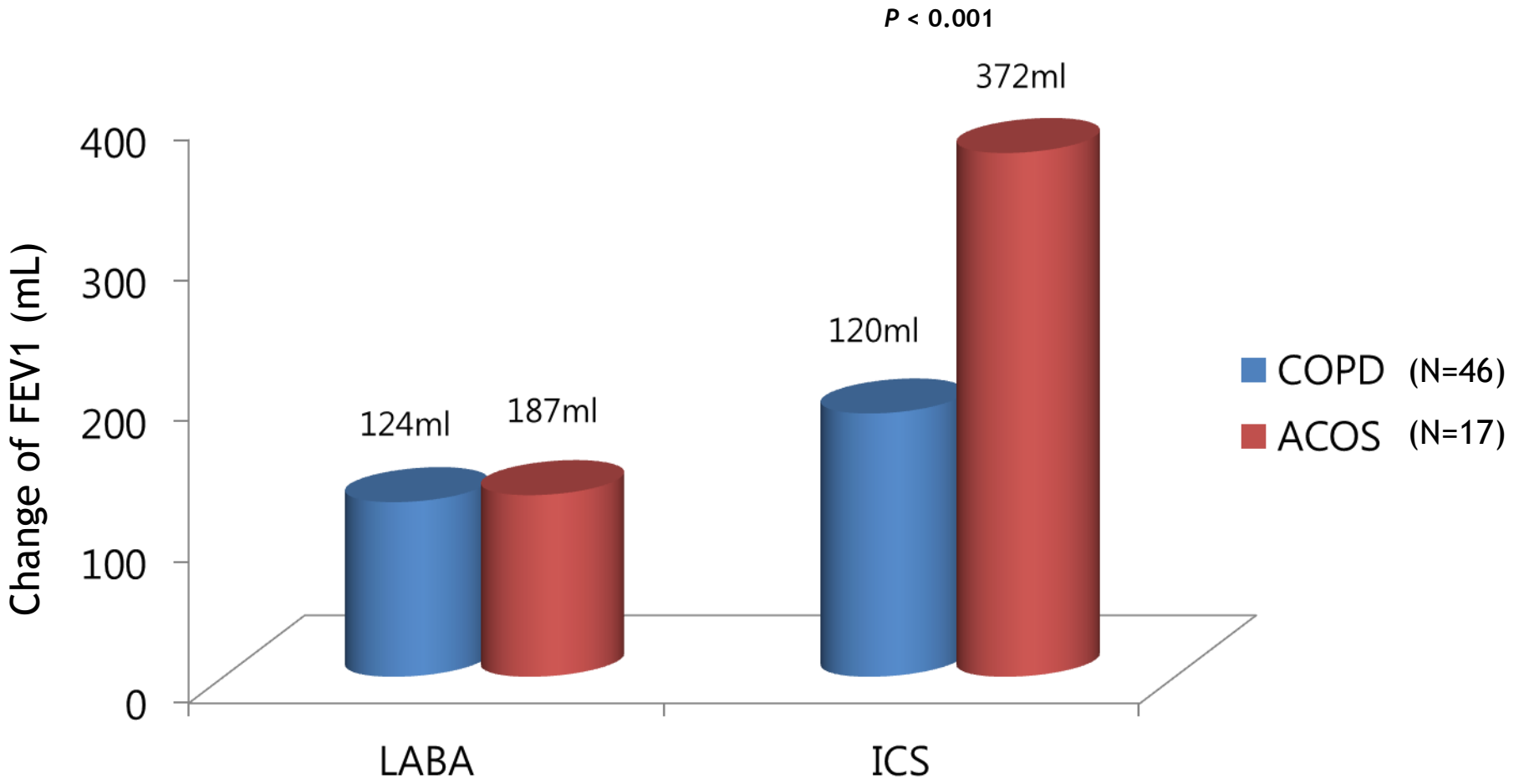
- 20% of patients with obstructive airway disease
- Increased illness burden

- Treatment implications

  – There is an increased response to ICS and LABA in COPD patients with asthma

  →ICS are the most commonly prescribed medications in clinical practice for patients with COPD

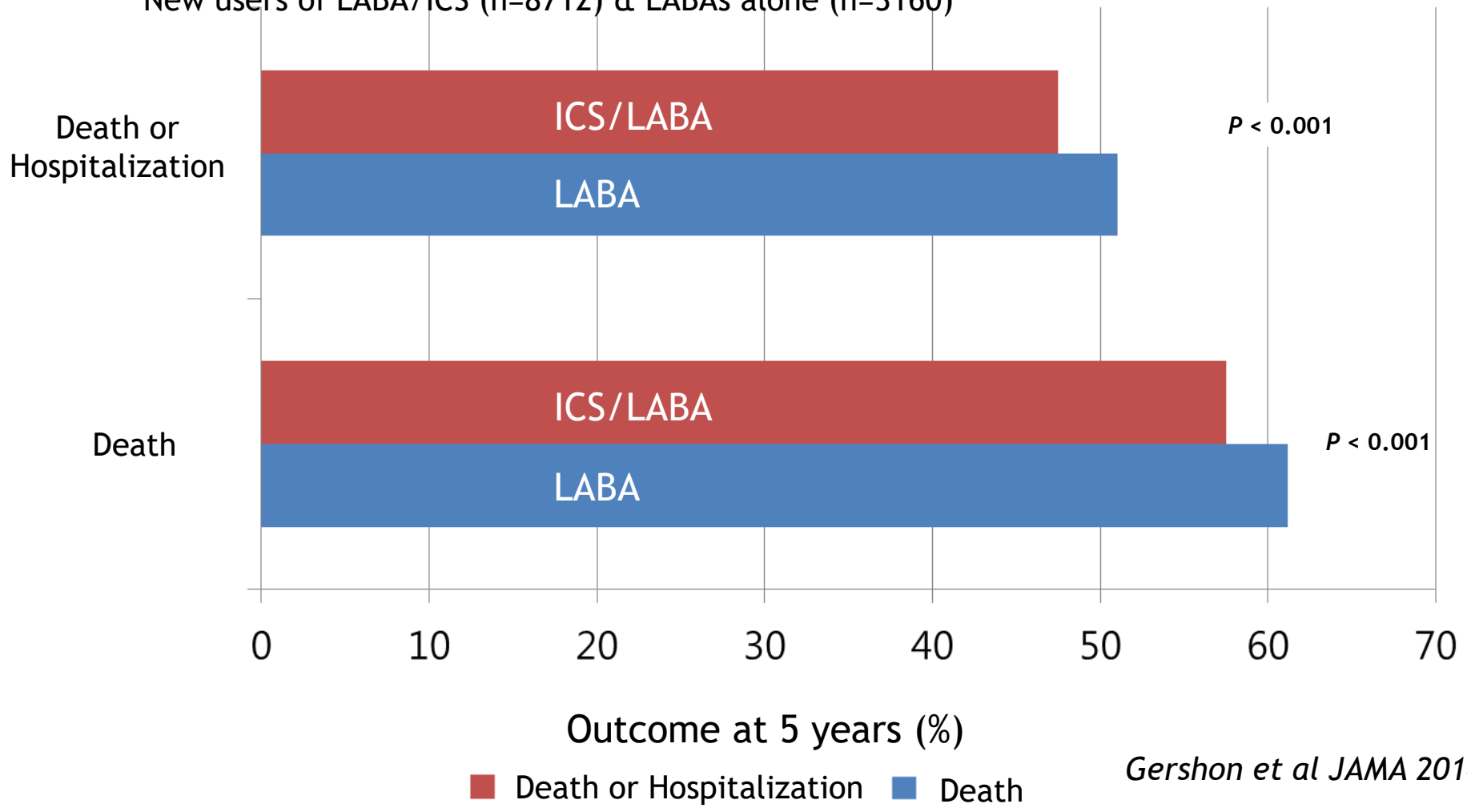
# Impact of ICS on ACOS




*Kitaguchi et al Int J COPD 2012*

# ICS/LABA vs. LABA in older COPD patient

Population-based, longitudinal cohort study in Ontario, Canada from 2003 to 2011
New users of LABA/ICS (n=8712) & LABAs alone (n=3160)




*Gershon et al JAMA 2014*

# Impact of ICS on ACOS

Population-based, longitudinal cohort study in Ontario, Canada from 2003 to 2011

New users of LABA/ICS (n=8712) & LABAs alone (n=3160)

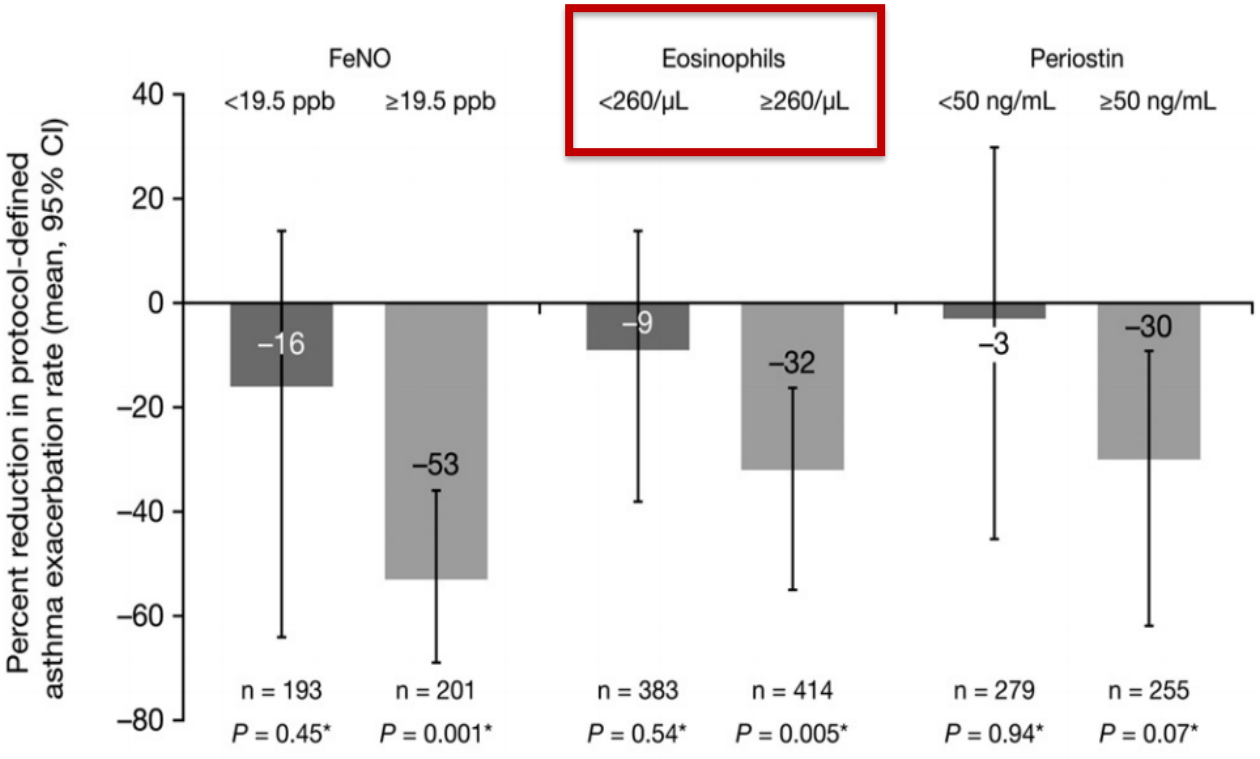
| Death or Hospitalization | No. With Outcome/Total (%) | | *P* Value for Interaction | Difference in Outcome at 5 y, % (95% CI) | Propensity Score–Matched Regression | |
|---|---|---|---|---|---|---|
| Stratifying Characteristics | New LABA and ICS Users | New LABA Alone Users | | | Hazard Ratio (95% CI)[a] | *P* Value |
| **Asthma** | | | | | | |
| No diagnosis of asthma | 4098/6237 (65.7) | 1532/2266 (67.6) | <.001 | −2.5 (−4.8 to −0.2) | 0.96 (0.90-1.01) | .13 |
| Diagnosis of asthma | 1496/2475 (60.4) | 597/894 (66.8) | | −6.5 (−10.3 to −2.7) | 0.84 (0.77-0.91) | <.001 |
| No diagnosis of asthma and no LAA receipt | 1148/1824 (62.8) | 484/692 (69.9) | .31 | −7.7 (−12.0 to −3.4) | 0.83 (0.73-0.92) | <.001 |
| No diagnosis of asthma and LAA receipt | 2798/4225 (66.2) | 1019/1541 (66.1) | | 0.6 (−2.2 to 3.4) | 1.05 (0.98-1.13) | .15 |
| Diagnosis of asthma and no LAA receipt | 549/1026 (53.5) | 249/380 (65.5) | | −9.5 (−15.4 to −3.6) | 0.73 (0.64-0.84) | <.001 |
| Diagnosis of asthma and LAA receipt | 818/1311 (62.4) | 328/489 (67.1) | | −5.8 (−10.9 to −0.7) | 0.88 (0.78-0.99) | .045 |
| Spirometry | | | | | | |
| No spirometry prior to index date | 2032/2987 (68.0) | 889/1214 (73.2) | <.001 | −6.0 (−9.1 to −2.9) | 0.87 (0.81-0.93) | <.001 |
| Spirometry prior to index date | 2967/5013 (59.2) | 1110/1801 (61.6) | | −2.7 (−5.4 to 0.0) | 0.95 (0.89-1.02) | .13 |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LAA, long-acting anticholinergic; LABA, long-acting β-agonist.

[a] Reflects the risk of outcome in new users of LABAs and ICSs compared with new users of LABAs alone.

*Gershon et al JAMA 2014*

# Eosinophils in asthma (Omalizumab)




| Exacerbation rates | | | | | | |
|---|---|---|---|---|---|---|
| | Low FeNO at baseline | High FeNO at baseline | Low eosinophils at baseline | High eosinophils at baseline | Low periostin at baseline | High periostin at baseline |
| Omalizumab | 0.60 | 0.50 | 0.65 | 0.70 | 0.73 | 0.66 |
| Placebo | 0.71 | 1.07 | 0.72 | 1.03 | 0.72 | 0.93 |

***Figure 2.*** Mean percent reduction (95% CI) in protocol-defined asthma exacerbation rate in the low- and high-biomarker subgroups (baseline fractional exhaled nitric oxide [$F_{ENO}$], peripheral blood eosinophils, and serum periostin). *Exacerbation reduction *P* values; omalizumab versus placebo in each biomarker subgroup. CI = confidence interval.

*Hanania et al*, AJRCCM 2013

# ACOS phenotype

**Table 1. Four Examples of Patients with Obstructive Airway Disease.***

| Characteristic | Patient with "Easy" Asthma | Patient with "Easy" COPD | Patient with ACOS Stemming from Asthma | Patient with ACOS Stemming from COPD |
|---|---|---|---|---|
| Age (yr) | 21 | 65 | 45 | 45 |
| Atopy | Yes | No | Yes | Yes |
| Current smoker | No | Yes | No | Yes |
| Pack-years | 0 | 95 | 0 | 20 |
| Dyspnea | Recurrent | Chronic | Chronic with flares | Chronic with flares |
| Wheezing | Yes | No | Yes | Yes |
| Reversible airway obstruction | Yes | No | No | Yes |
| Bronchial hyperresponsiveness | Yes | No | Yes | Yes or no |

* "Easy" asthma and "easy" COPD are the easily recognized extremes of asthma and COPD. The two patients with the asthma–COPD overlap syndrome (ACOS) have a similar age, and both have atopy. Despite not being a smoker, the patient with ACOS stemming from asthma has irreversible airway obstruction, which is accompanied by chronic dyspnea and flare-ups of wheezing and bronchial hyperresponsiveness. The patient with ACOS stemming from COPD has some reversibility of airway obstruction after bronchodilator use, chronic dyspnea, and flare-ups of wheezing, which may or may not be accompanied by hyperresponsiveness. In the two patients with ACOS, whether the syndrome stems from asthma or from COPD cannot be easily distinguished by their phenotype.

*Dirkje S. et al* NEJM 2015

# Distribution of blood eosinophil in COPD patients

|   | Proportion (%) of COPD patients with elevated blood eosinophil | | |
|---|---|---|---|
| GOLD | ≥200 (cells/uL) | ≥300 (cells/uL) | ≥400 (cells/uL) |
| I (n=53) | 67 | 42 | 21 |
| II (n=93) | 71 | 34 | 17 |
| III/IV (n=38) | 75 | 43 | 34 |
| Total | 70 | 38 | 21 |

# Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap

Increased induced sputum levels of NGAL might be a characteristic feature of overlap, suggesting enhanced neutrophilic airway inflammation and/or airway epithelial injury in COPD–asthma overlap.

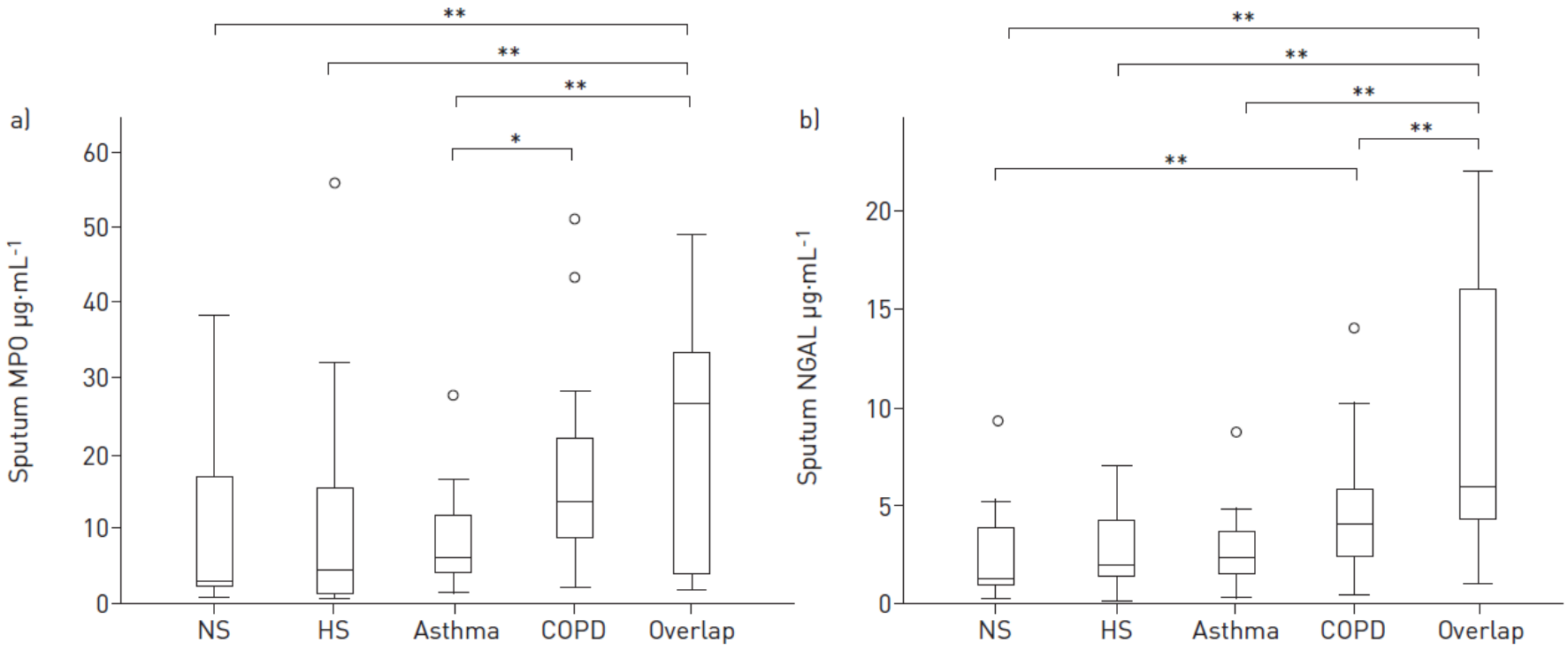



FIGURE 2 Sputum levels of a) myeloperoxidase (MPO) and b) neutrophil gelatinase-associated lipocalin (NGAL). The boxes represent the 25th to 75th percentiles, the solid lines within the boxes show the median values, the whiskers are the 10th and 90th percentiles, and the circles represent outliers. p-values were calculated by ANOVA followed by Fisher's protected least significant difference test. NS: nonsmoker; HS: healthy smoker; COPD: chronic obstructive pulmonary disease. *: $p<0.05$; **: $p<0.01$.

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