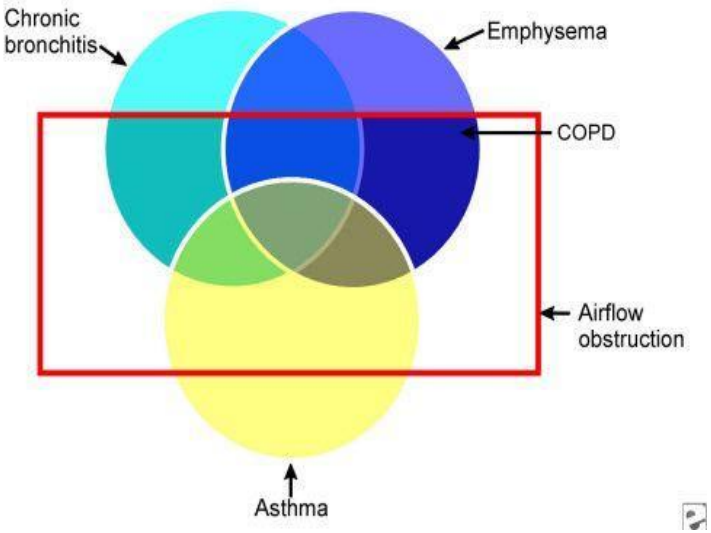
ACOS,

역사적 배경과 진단



동아 대학교 병원 호흡기 내과
엄수정

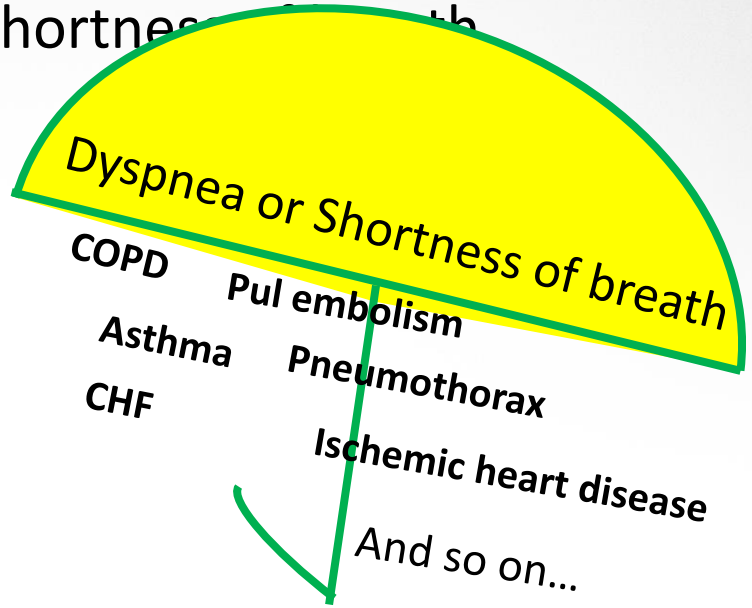
Content

1) **역사적 배경**
2) Suggested Definition review
3) Asthma Characteristics in COPD
4) Newly Evolving Definitions
5) Summary

History of COPD

Hippocrates(460~360BC) _ Dyspnea or Shortnes

2000 yrs

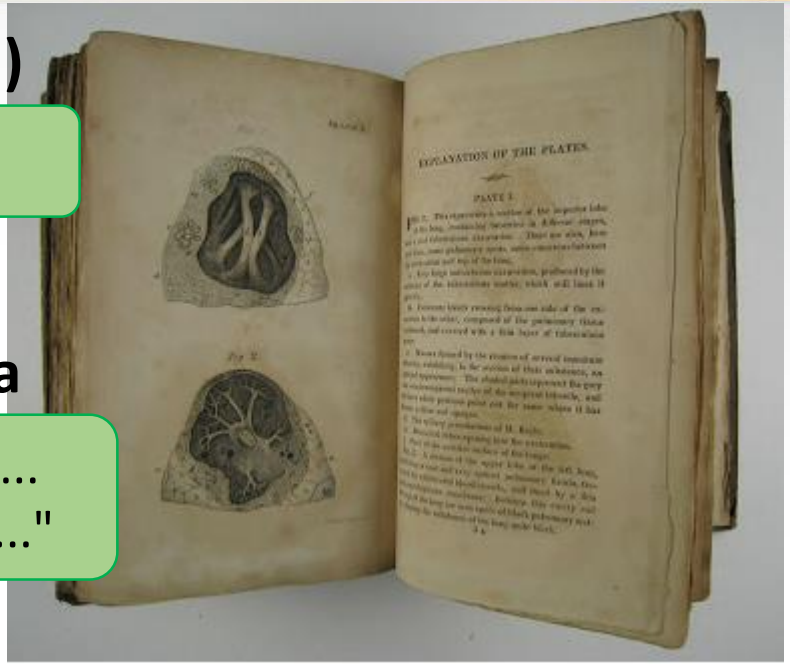


1679 Bonet _Voluminous Lung

History of COPD

1814 Badham defined **Bronchitis (catarrh)**

"chronic cough and mucous hypersecretion"



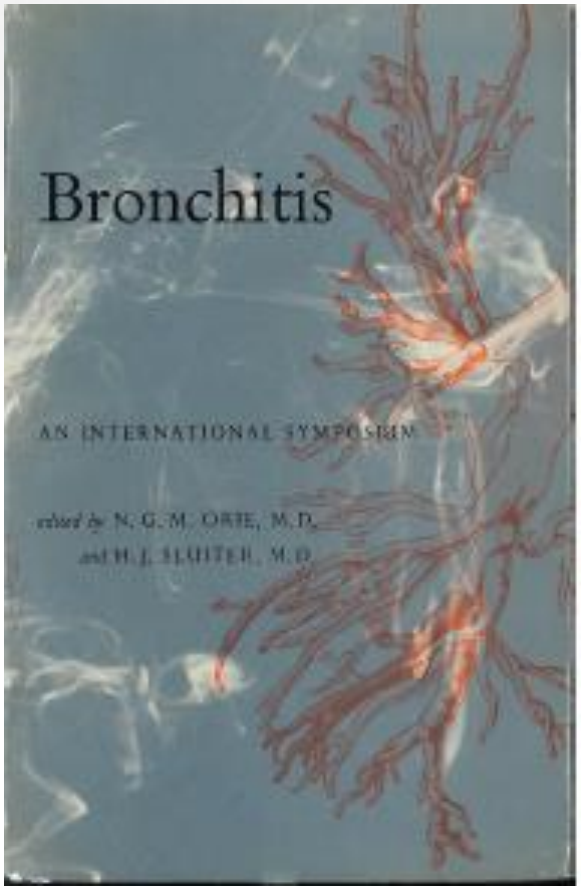
1821 Rene Laennec defined **Emphysema**

"lungs (that) do not collapse…. due to aging….. tissue damage in the peripheral air passage……"

Spirometry

1959 CIBA Guest symposium and ATS Committee on Diagnostic Standards 1962 defined COPD

Dutch Hypothesis

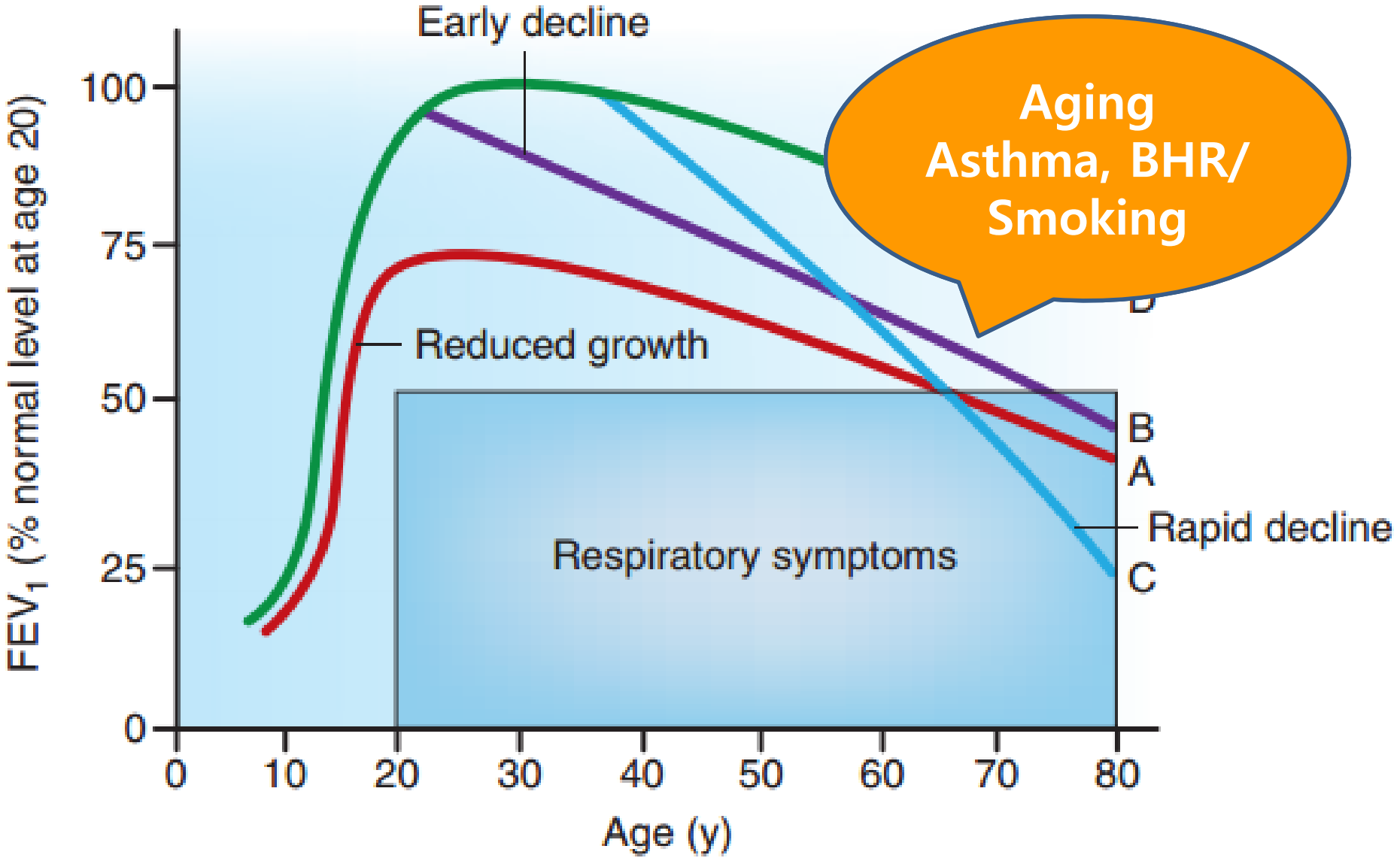


1961’

“bronchitis and asthma may be found in one patient at the same age ……
……development from bronchitis in youth to a more asthmatic picture in adults, which in turn, develops into bronchitis of elderly patients”

By Orie and Sluter

J Allergy Clin Immunol 2015;138:521



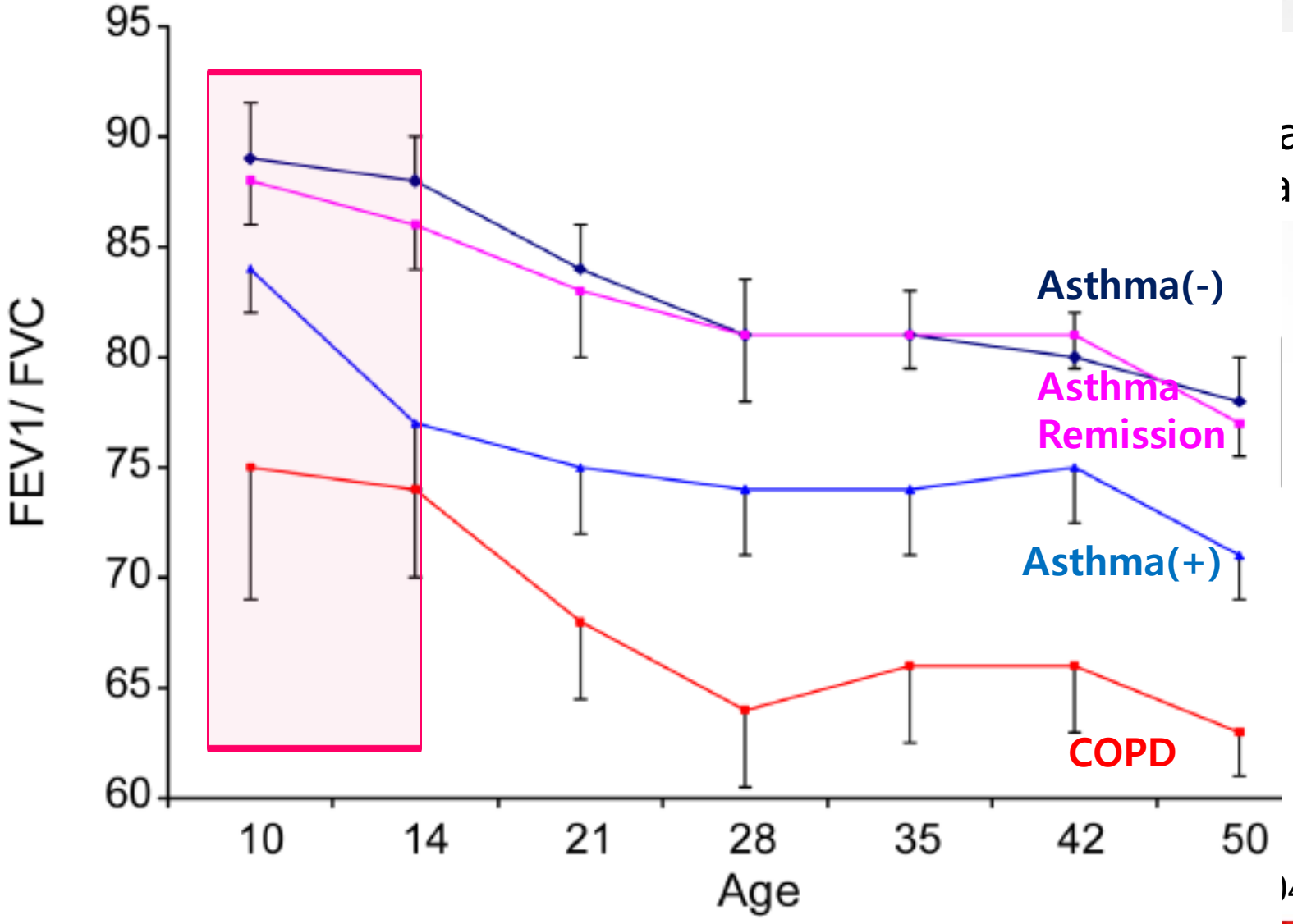
From Nature Genetics 2010;42:14~16

Childhood Asthma and Adult COPD

- N=197, Australia
- Longitudinal, prospective study of 6–7 year-old children with asthma has been regularly reviewed every 7 years to the current analysis at 50 years

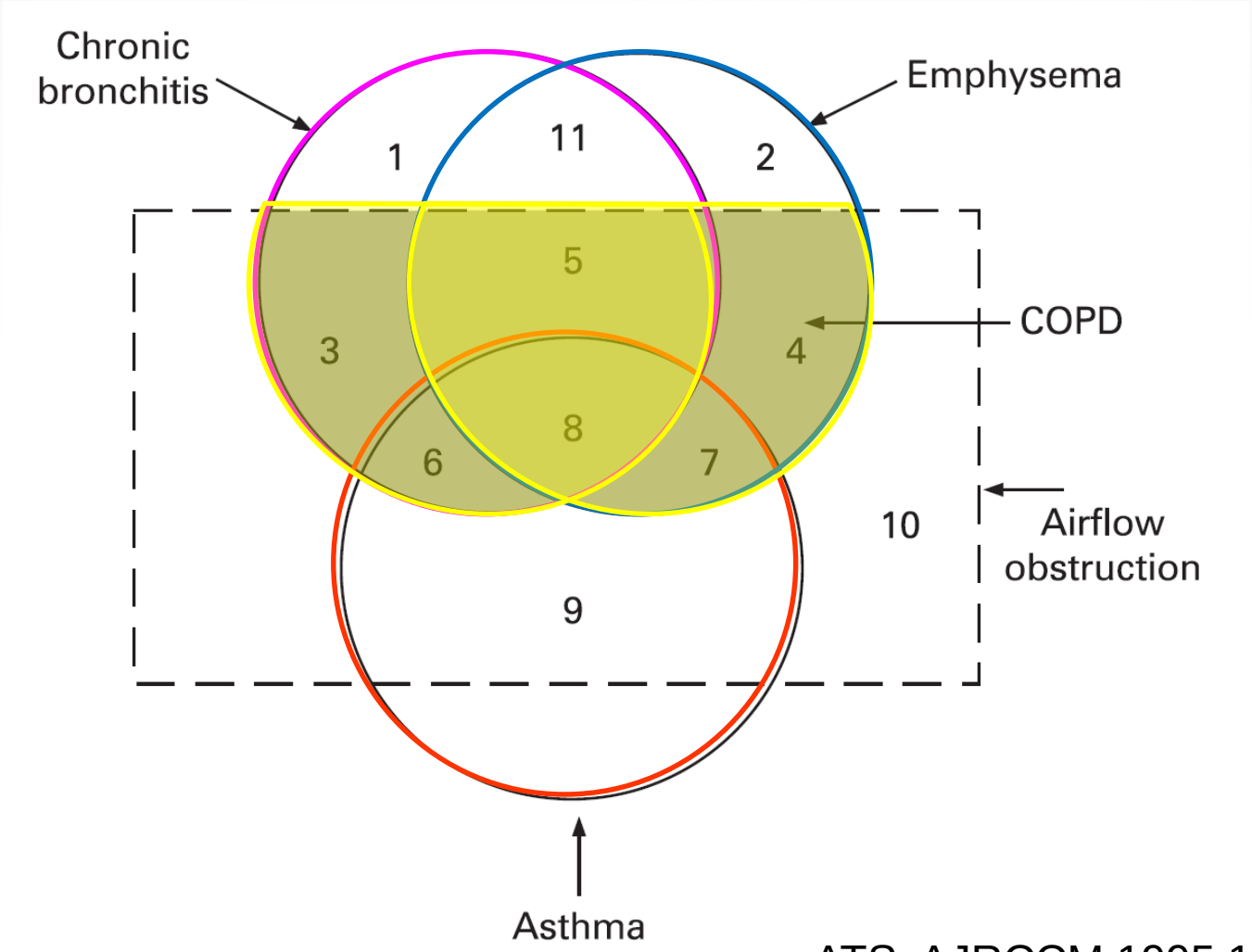
Andrew et al. Thorax 2014;0:1–6. doi:10.1136/thoraxjnl-2013-204815.

Childhood Asthma and Adult COPD



Overlapping Conditions

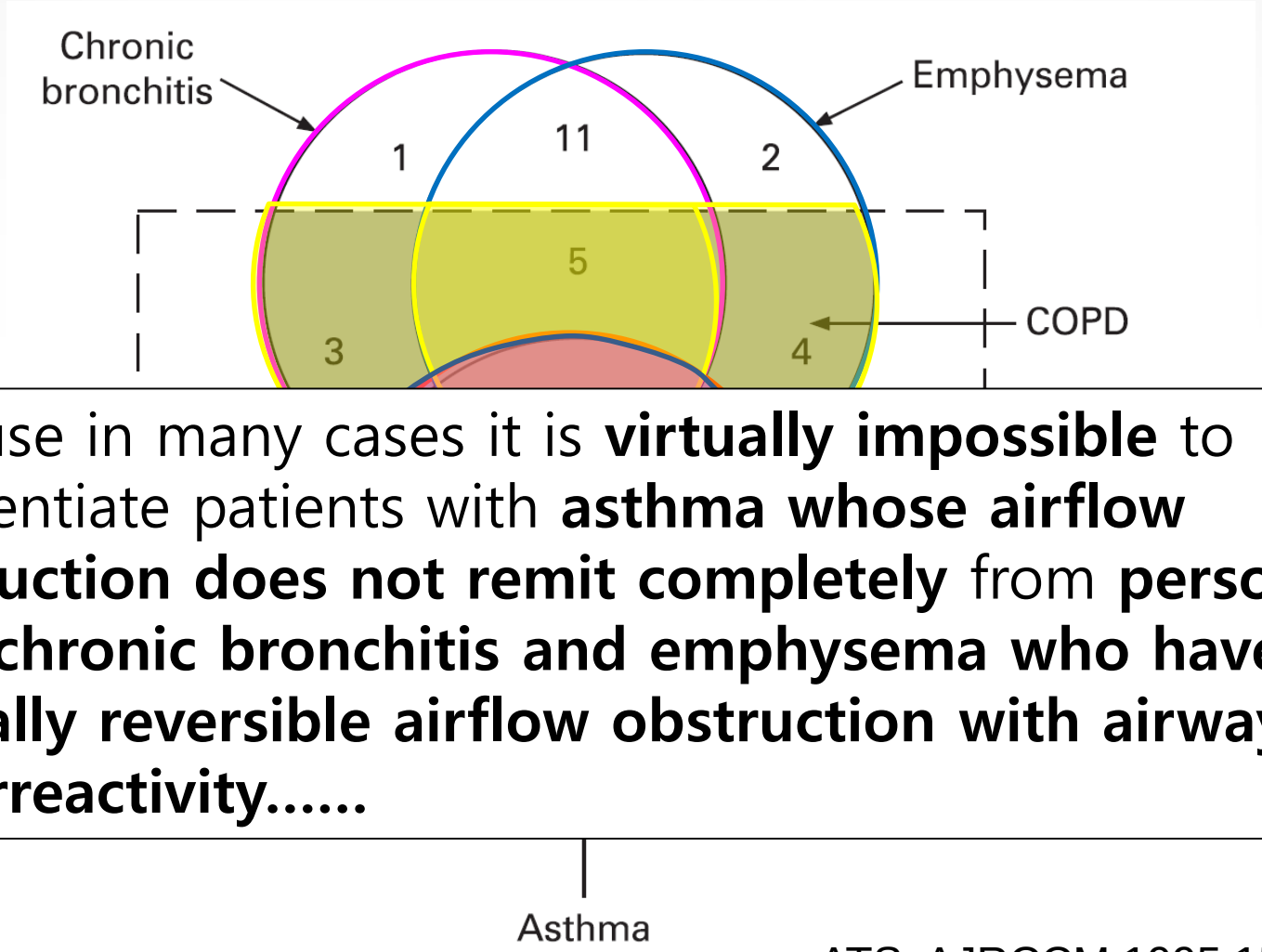
1995 ATS



ATS. AJRCCM 1995;152:s77

Overlapping Conditions

1995 ATS

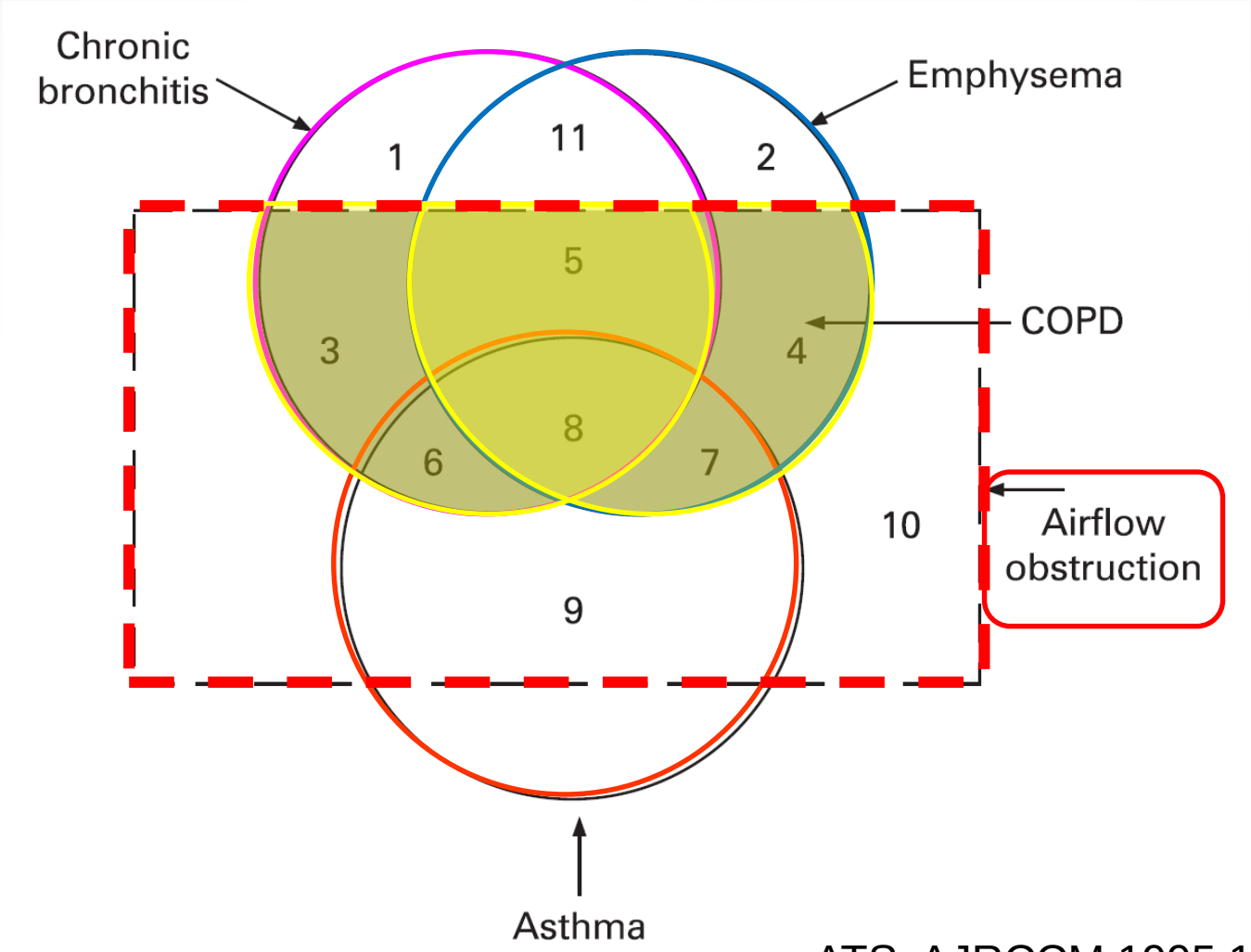


Because in many cases it is **virtually impossible** to differentiate patients with **asthma whose airflow obstruction does not remit completely** from **persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity……**

ATS. AJRCCM 1995;152:s77

Overlapping Conditions

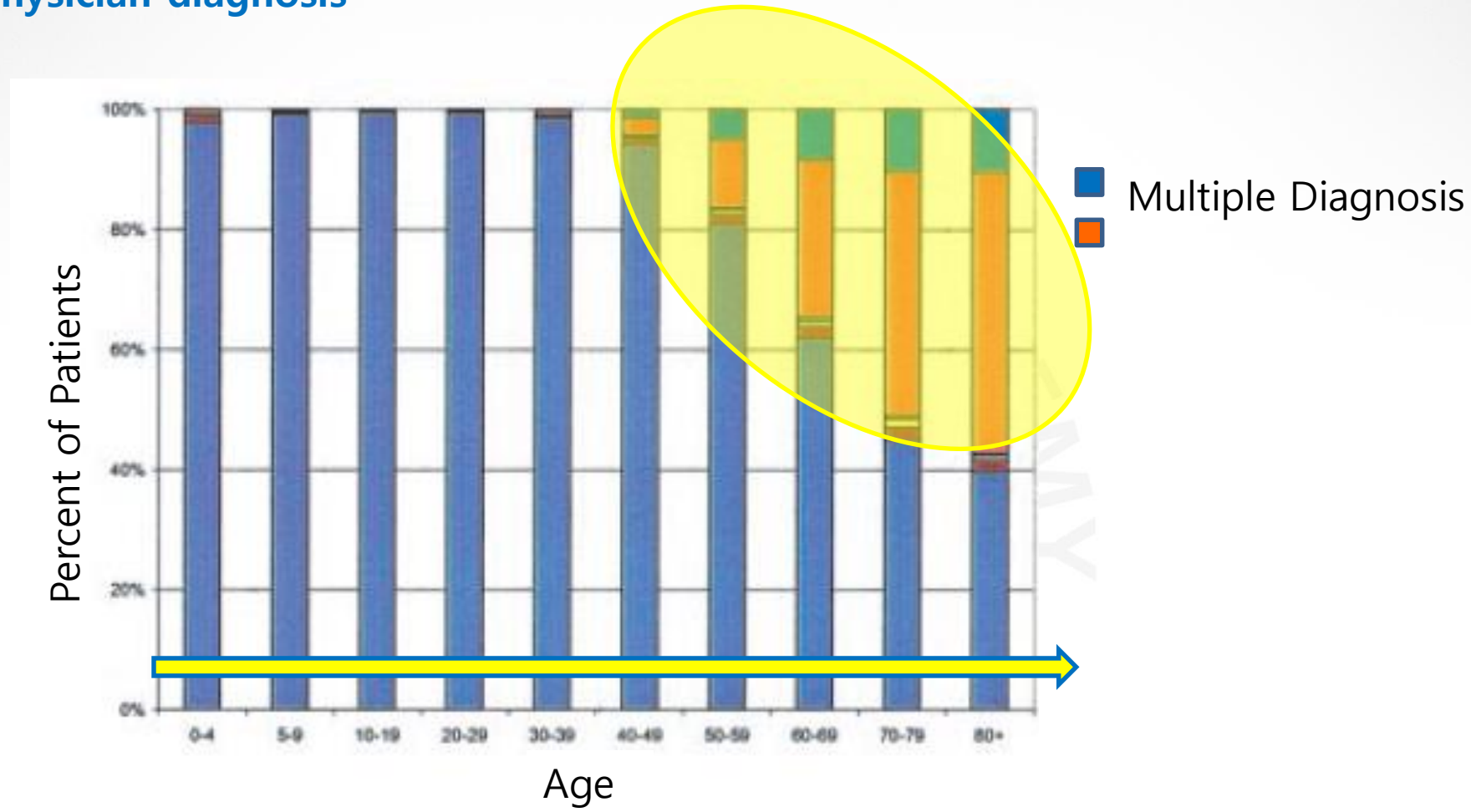
1995 ATS



ATS. AJRCCM 1995;152:s77

Ovelapping conditions in reality

- **United States (NHANES III surveys from 1988 to 1994)and UK(GPRD 1998)**
- **Physician diagnosis**

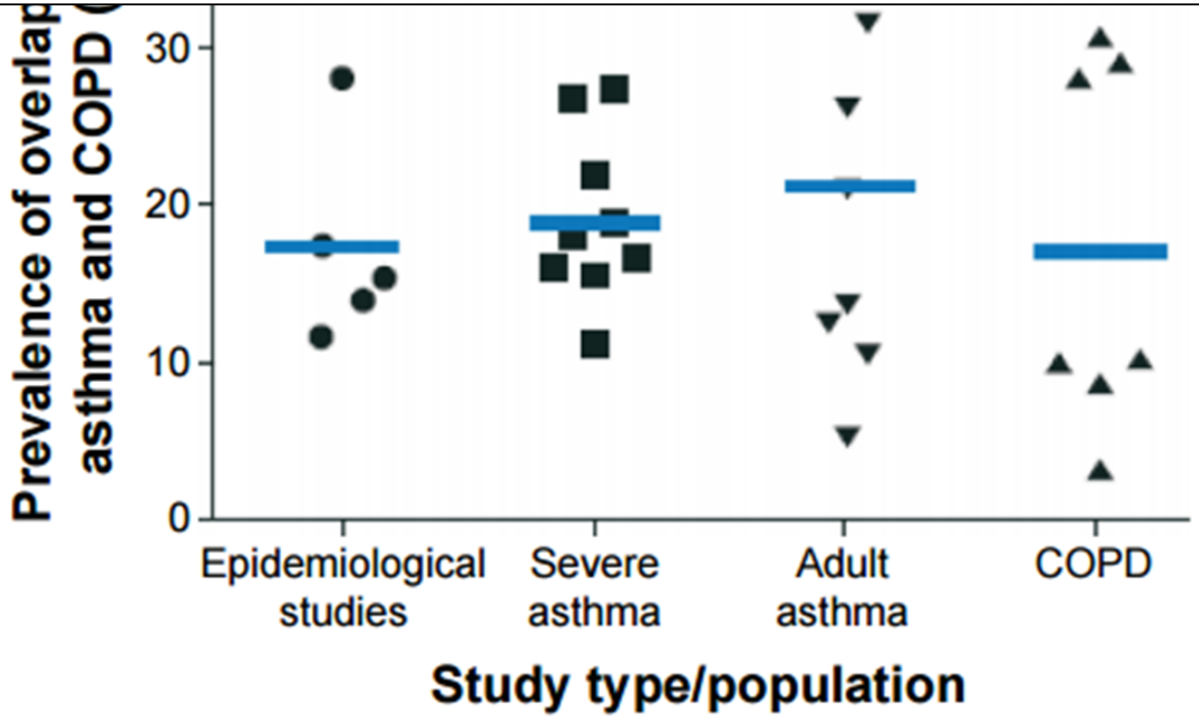


Soriano et al. Chest 2003; 124: 474

Definition, WHY?

Prevalence

20% of Obstructive airway disease
2% of adult population sample



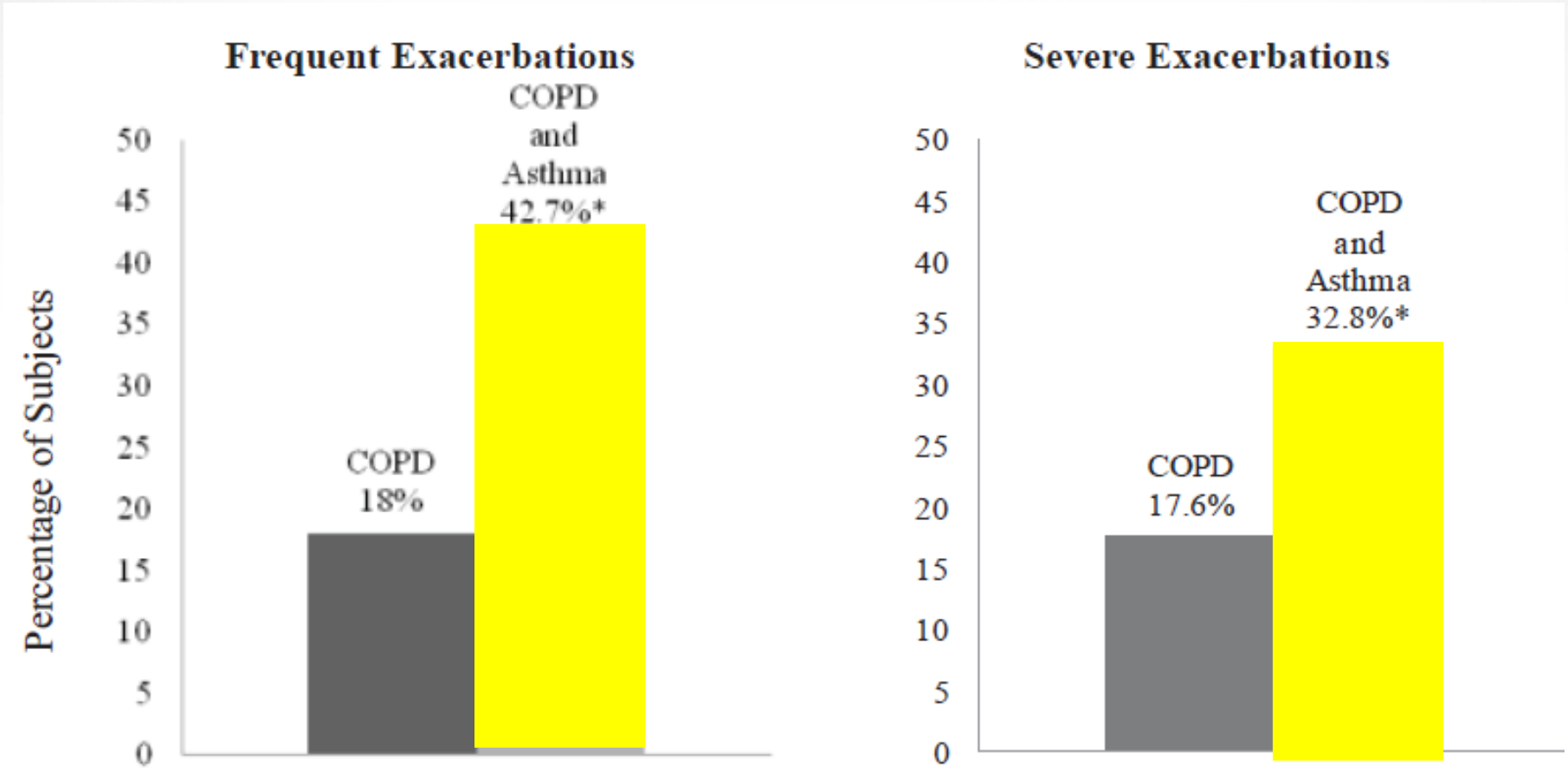
Gibson PG et al. Thorax 2015; 70: 683–691.

Definition of ACOS per study

Definition
Self-reported asthma and COPD
Combination of asthma and COPD
FEV_1/FVC ratio <0.7, self-reported wheezing
Previous diagnosis of asthma, postbronchodilator FEV_1/FVC ratio <0.7
History of asthma, postbronchodilator FEV_1/FVC ratio <0.7, previous positive bronchodilator response, <5 pack-
History and symptoms of COPD and asthma, postbronchodilator FEV_1/FVC ratio <0.7 and FEV_1 <80%, >30 pa
Previous diagnosis of asthma before age 40 y, postbronchodilator FEV_1/FVC ratio <0.7, postbronchodilator FEV smoking history
Symptoms of wheezing, postbronchodilator FEV_1/FVC ratio <0.7, bronchodilator response >12% + 200 mL
History of asthma, positive bronchodilator response ≥15%, FEV_1 <75% predicted despite ICSs or oral steroids, <10
Chronic symptoms of asthma, postbronchodilator FEV_1 <50%, previous variation obstruction >15% either sponta persistent obstruction (postbronchodilator FEV_1 had not varied by >10% when repeated within 3-6 mo)
Physician's diagnosis of asthma at age <30 y, diagnosis of COPD, postbronchodilator FEV_1/FVC ratio <0.7, post of predicted value, documented bronchodilator response (FEV_1 ≥200 mL and 12%), ICSs in previous year, >10
Diagnosis of obstructive airway disease, postbronchodilator FEV_1/FVC ratio <0.7, postbronchodilator FEV_1 <80 airway hyperresponsiveness (≥15% FEV_1 decrease from baseline after inhalation of 4.5% hypertonic saline) o (FEV_1 ≥200 mL and 12%)
History of asthma, postbronchodilator FEV_1/FVC ratio <0.7, bronchodilator response >12% in FEV_1 or >15% in P in PEF, airway hyperresponsiveness, long-term smoking
Major criteria: previous history of asthma, FEV_1 >15% and 400 mL after salbutamol; *minor criteria*: IgE >100 separated bronchodilator responses to salbutamol >12% and 200 mL, blood eosinophils >5%; among patients

Exacerbations COPD vs ACOS

COPDGene study
ACOS : Asthma Hx before 40yrs



Hardin et al. Respiratory Research 2011, 12:127

Definition, WHY?

- Significant clinical consequences (Prevalence, Exacerbations, Mortality..)
- Confusion to use of diagnostic label
- Exclusion from the Randomized controlled study, especially major therapeutic trial

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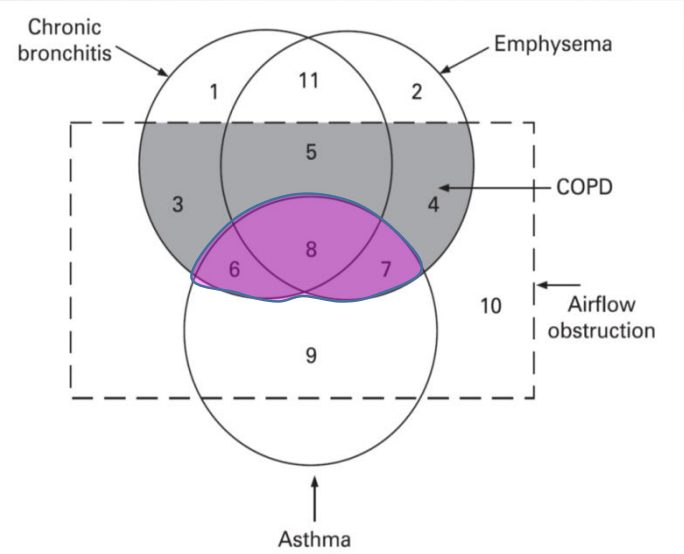
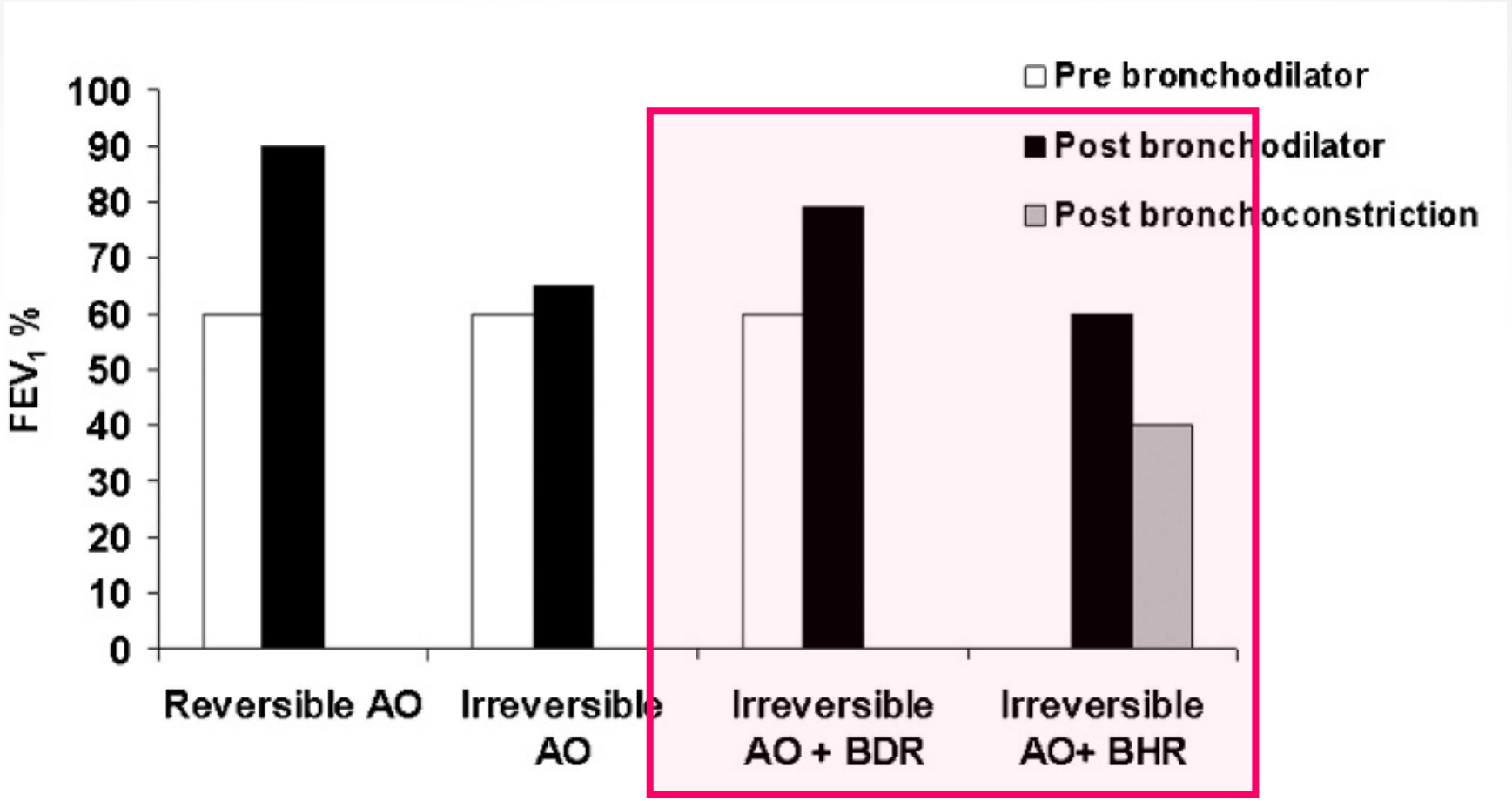


- Asthma and smoker
- COPD with BHR and/or BDR
- Asthma and fixed airway obstruction

ACOS - Physiologic Patterns



Gibson et al. Thorax 2009;64:728–735

Definition of ACOS

Persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.

ACOS is therefore identified by the features that it shares with both asthma and COPD.

Features that (when present) favor asthma or COPD

Feature	Favors asthma	Favors COPD
Age of on		
Pattern o respirato symptom		
Lung fun		
Past hist family his		
Time cou	Symptoms vary seasonally, or from year to year ❑ May improve spontaneously, or respond immediately to BD or to ICS over weeks	(progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	❑ Severe hyperinflation

Syndromic diagnosis of airways disease

The shaded columns list features that, when present, best distinguish between asthma and COPD.

For a patient, count the number of check boxes in each column.

- If **3 or more boxes** are checked for either asthma or COPD, that diagnosis is suggested.
- If there are **similar numbers** of checked boxes in each column, the diagnosis of **ACOS** should be considered.

Spanish guideline for ACOS

Diagnostic Criteria of the Mixed COPD/Asthma phenotype	Type of Criterion
Very positive bronchodilator test (increase of FEV1 ≥15% and ≥400 ml over baseline)	Major
Eosinophilia in sputum	Major
Personal history of asthma (history before the age of 40)	Major
High total IgE	Minor
Personal history of atopy	Minor
Positive bronchodilator test (increase in FEV1 ≥12% and ≥200 ml over baseline) on 2 or more occasions	Minor

2 major criteria or

1 major and 2 minor criteria

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

Czech Guideline

Diagnostic Criteria of the Asthma-COPD overlap	Type of Criterion
Very positive bronchodilator test (increase of FEV1 ≥15% and ≥400 ml over baseline)	Major
Positive BCT (Bronchoconstrictor test)	Major
FeNO ≥ 45-50 ppb and/or Sputum eosinophil ≥ 3%	Major
History of Asthma	Major
Mild BDT (FEV1 ≥12% and ≥200 ml)	Minor
Total Ig E ↑	Minor
History of atopy and definite COPD diagnosis	Minor

2 major criteria or
1 major and 2 minor criteria

Koblizek V et al.Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013;157:189–201.

ACOS Definition

- Persistent air flow limitation
- ≥ 40yo
- Significant smoking

+

Asthmatic Characteristics

1) History of atopy and asthma
2) BDR /BHR
3) Blood or Sputum Eosinophil count
3) other Biomarker of Asthma (FeNO, Ig E, ICS responsiveness ,etc ..)

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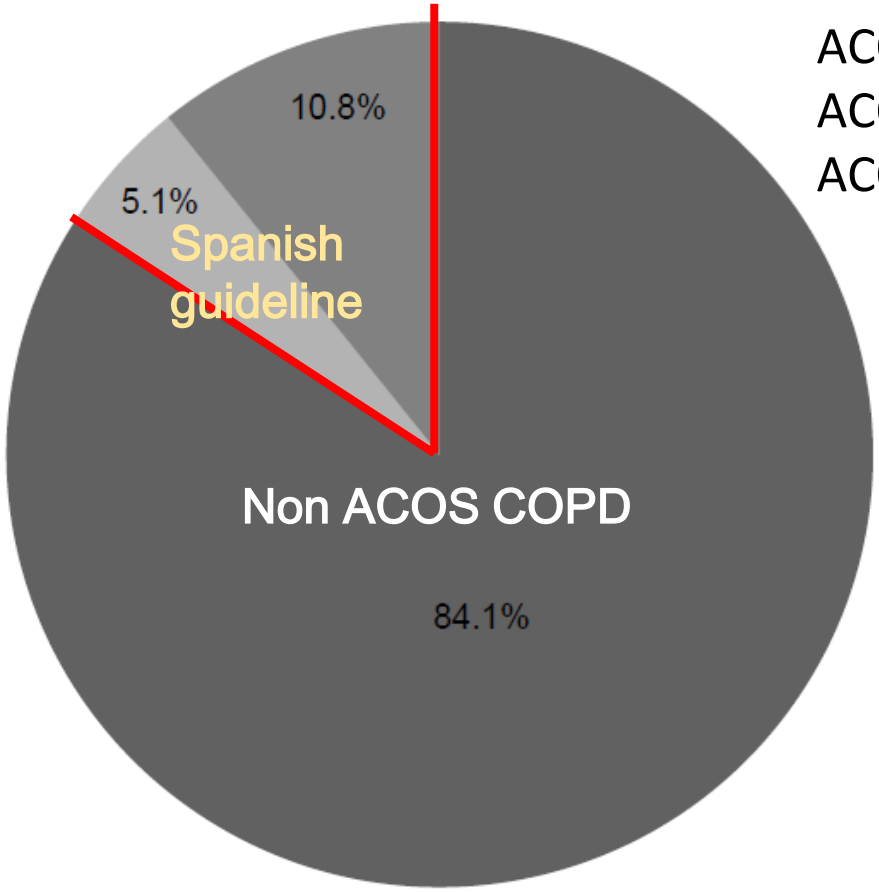
Asthma Characteristics

- **History of Asthma or atopy**
- **BDR /BHR**
- **Blood or Sputum Eosinophil count**
- **other Biomarker of Asthma**

  (FeNO, Ig E, ICS responsiveness ,etc ..)

Asthma Hx before Age 40

Previous diagnosis of asthma before the age of 40 years vs the diagnostic criteria of the Spanish guidelines of COPD



ACOS ; Asthma Hx before 40 yo
ACOS 1 ; Spanish guideline
ACOS 2 ; the rest of ACOS

International Journal of COPD 2015:10 1745–1752

ACOS Vs Non-ACOS

Variable	Non-ACOS (n=2,629)	ACOS (n=496)	Total (n=3,125)	P-value
Sex (men)	2,229 (84.8%)	346 (69.8%)	2,575 (82.4%)	<0.001
Age (years)	67.4 (0.2)	64.6 (0.4)	66.9 (0.2)	<0.001
BMI (kg/m^2)	27.7 (0.1)	28.3 (0.2)	27.8 (0.1)	0.003
Active smoker	601 (22.9%)	125 (25.2%)	726 (23.2%)	0.082
Pack-years	41.3 (0.5)	32.3 (1.2)	40.1 (0.5)	<0.001
Time walked per day, minutes	63.3 (2.1)	66.1 (2.12)	63.7 (2.0)	0.36
Spirometry (postbronchodilator)				
FVC (L)	2.8 (0.02)	3.02 (0.04)	2.9 (0.02)	0.0001
FVC%	68.7 (0.4)	75.2 (0.9)	69.7 (0.4)	<0.001
FEV_1 (L)	1.5 (0.01)	1.7 (0.03)	1.6 (0.01)	<0.001
FEV_1%	51.9 (0.4)	59.4 (1.0)	53.0 (0.3)	<0.001
FEV_1/FVC	53.4 (0.2)	55.3 (0.6)	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)	1.4 (0.07)	0.82
Positive bronchodilator test (FEV_1 >12%, >200 mL)	99 (3.9%)	56 (11.3%)	155 (5.0%)	<0.001
Very positive bronchodilator test* (FEV_1 >15%, >400 mL)	231 (8.9%)	140 (22.2%)	371 (11.9%)	<0.001
% blood eosinophilic count (mean, SEM)	2.9 (0.2)	4.8 (0.4)	3.4 (0.2)	<0.001
Clinical/radiologic signs of emphysema	1,035 (39.4%)	161 (32.5%)	1,196 (38.3%)	0.007
Number of exacerbations in the previous 12 months	1.8 (0.03)	2.0 (0.07)	1.8 (0.03)	0.0006
Hospital admissions in the previous 2 years	1.0 (0.03)	1.2 (0.08)	1.0 (0.03)	0.03

Spanish guideline Vs Asthma Hx

Variable	Spanish ACOS 1 (n=158)	Asthma Hx ACOS 2 (n=338)	P-value
Sex (men)	113 (71.5%)	233 (68.9%)	0.56
Age (years)	63.4 (0.7)	65.1 (0.5)	0.06
BMI (kg/m^2)	28.7 (0.3)	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 per day, minutes	65.7 (2.1)	66.3 (2.0)	0.62
Spirometry, postbronchodilator			
FVC (L)	3.1 (0.07)	3.0 (0.05)	0.53
FVC%	76.3 (1.6)	74.8 (1.1)	0.43
FEV_1 (L)	1.8 (0.05)	1.7 (0.04)	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

International Journal of COPD 2015:10 1745–1752

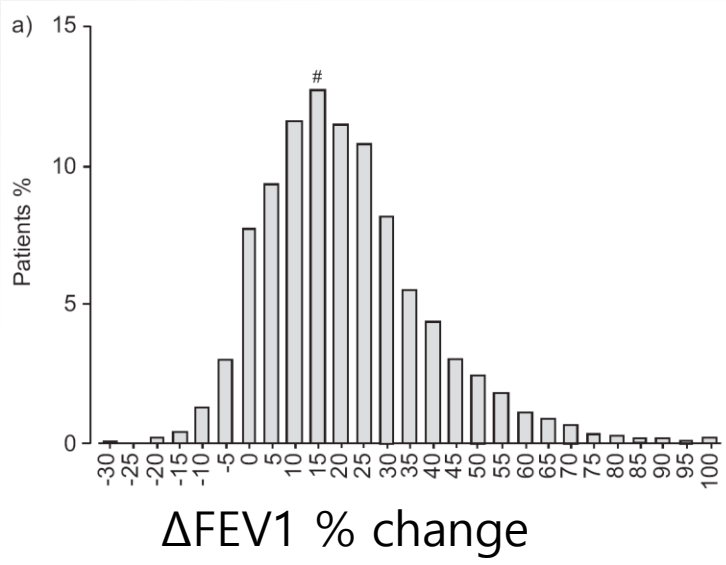
Asthma Characteristics

- History of Asthma or atopy
- **BDR** /BHR
- Blood or Sputum Eosinophil count
- other Biomarker of Asthma

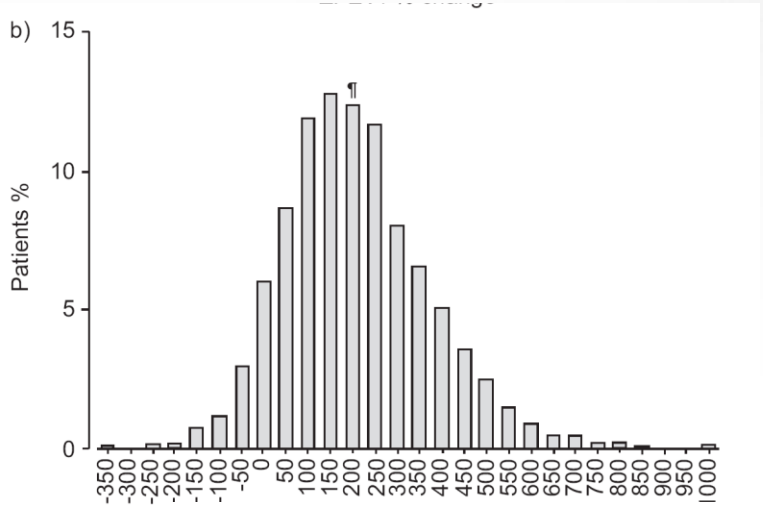
  (FeNO, Ig E, ICS responsiveness ,etc ..)

BDR

UPLIFT



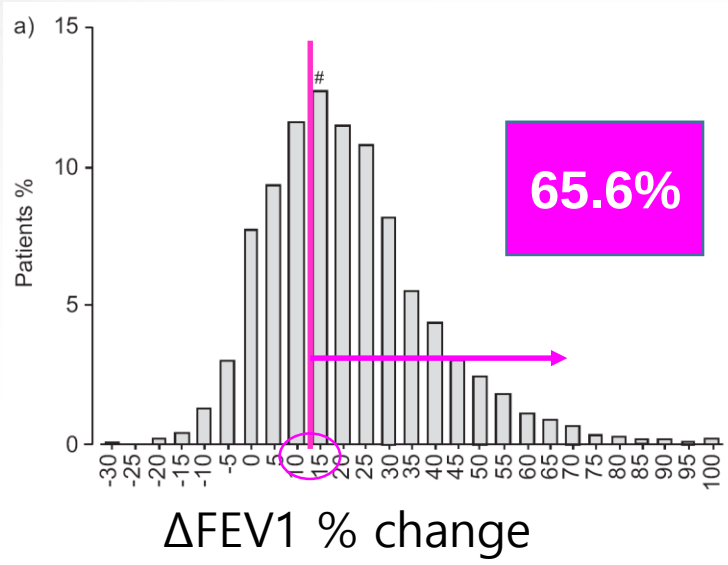
ΔFEV1 % change

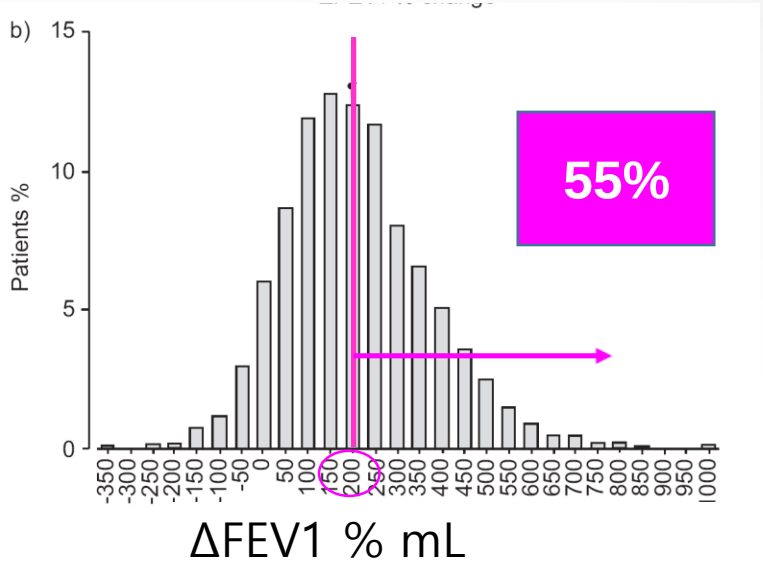


ΔFEV1 % mL

BDR

UPLIFT

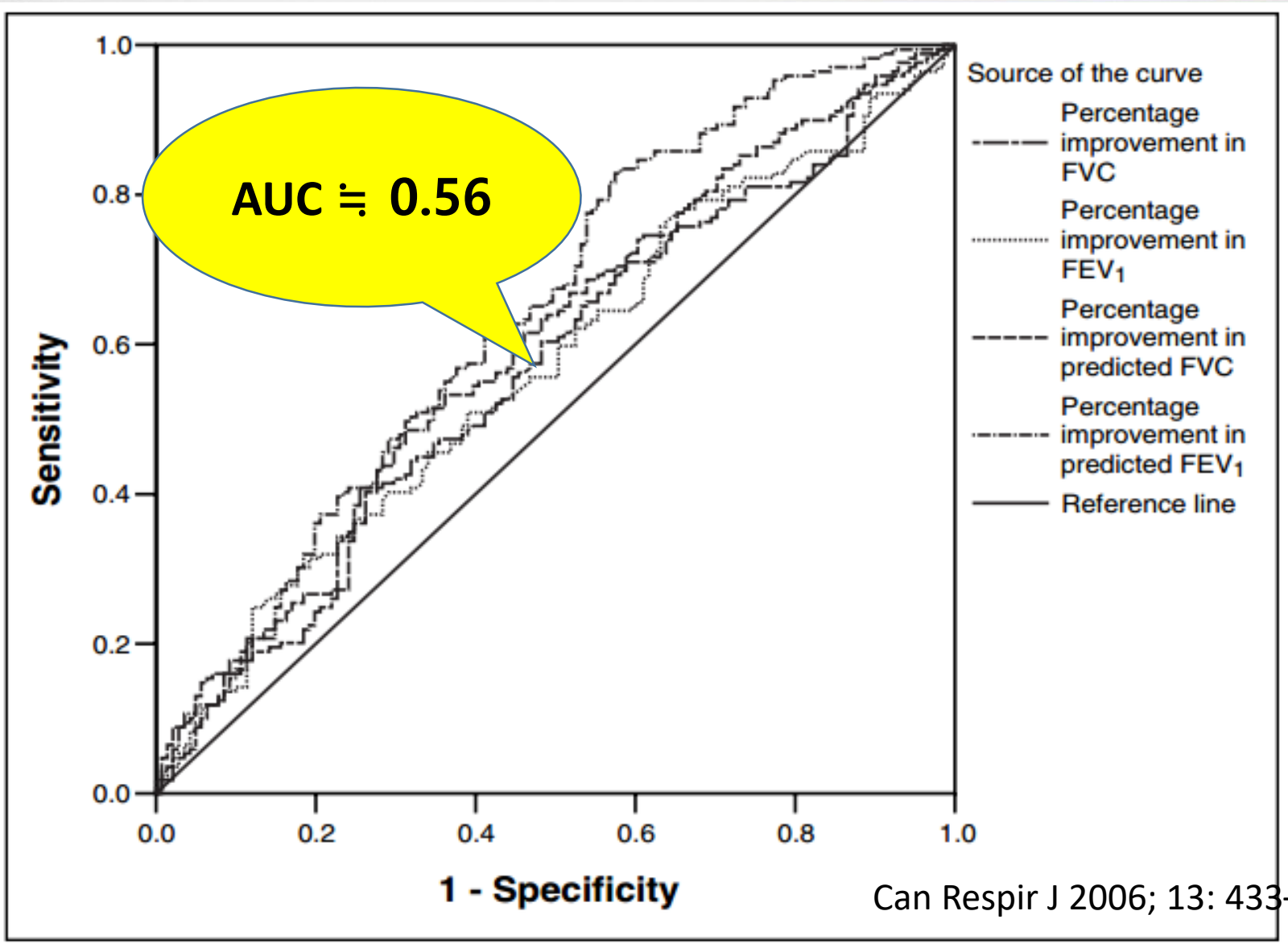




Over half of Pt. showed **Reversible Airway Obstruction** among moderate to severe COPD Pt.

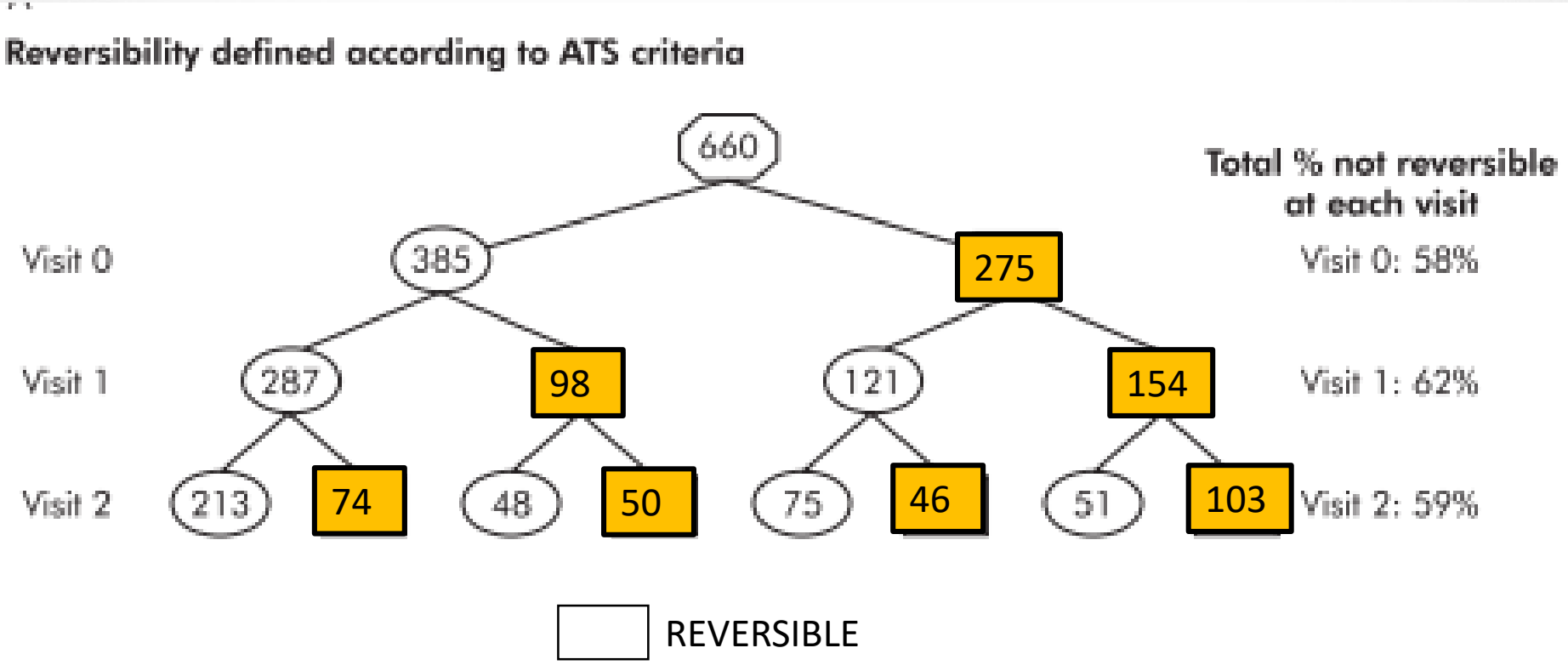
Tashkin et al. Eur Respir J 2008; 31: 742–750

BDR in Differential Diagnosis of Asthma and COPD



Can Respir J 2006; 13: 433–437.

BDR in COPD patients



Calverley et al. Thorax 2003;58:659-664

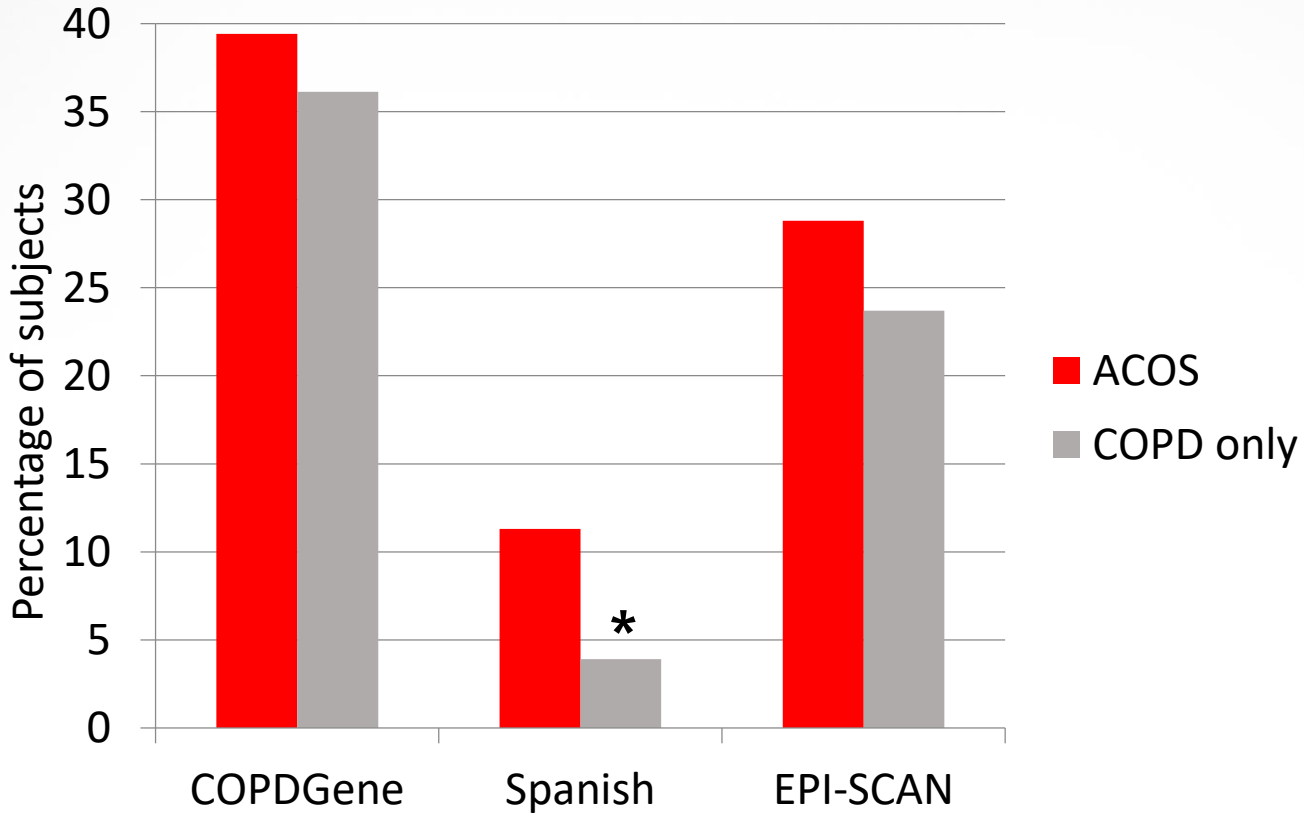
BDR in COPD

- **not reproducible**
- **not related to other typical asthma features**
- **not predict ICS responsiveness**
- **not specific for the asthma–COPD phenotype**

Fingleton J et al. J Allergy Clin Immunol. 2015 Published Online
Albert P et al. Thorax 2012;67:701–8.

BDR in COPD cohorts

- 40세 이전 asthma 병력 – ACOS



Hardin et al. Eur Respir J 2014;44:341-350
Barrecheguren et al. Int J COPD 2015;10:1745-52
Miravitlles et al. Resp Med 2013;107:1053-60

Asthma Characteristics

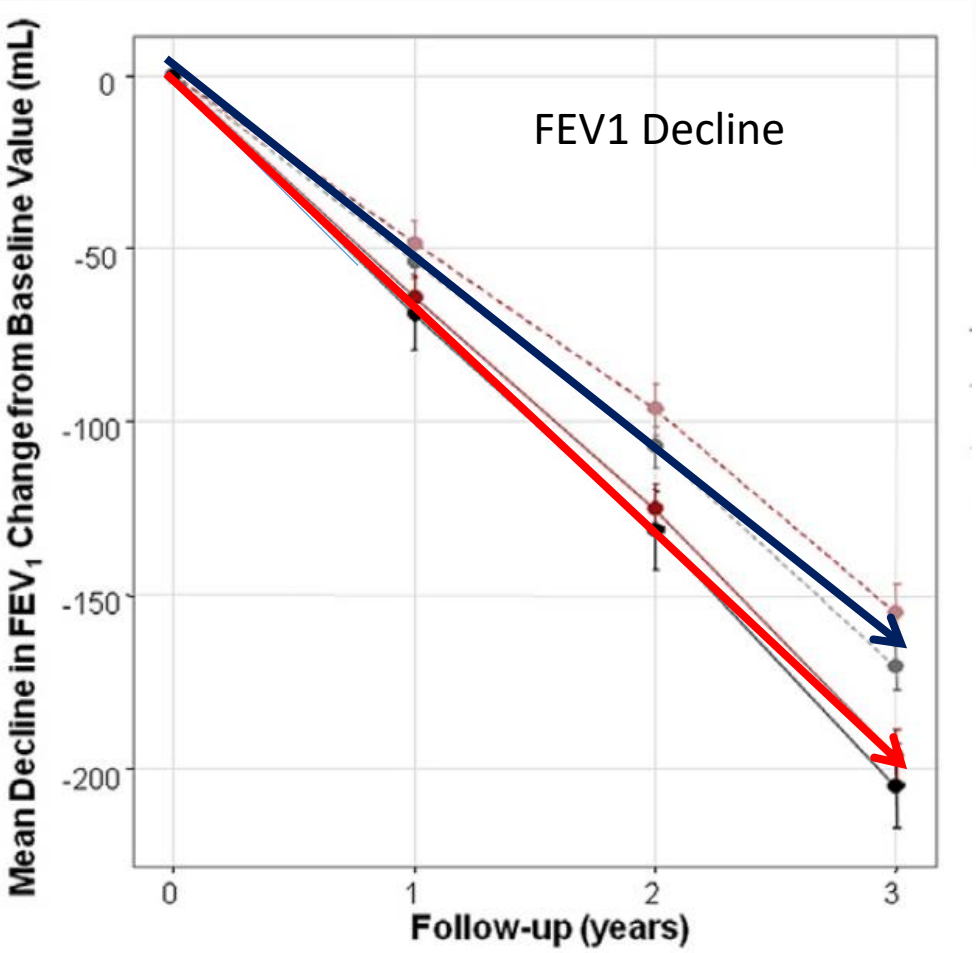
- History of Asthma or atopy
- BDR /**BHR**
- Blood or Sputum Eosinophil count
- other Biomarker of Asthma

  (FeNO, Ig E, ICS responsiveness ,etc ..)

BHR in COPD

Lung Health Study
GLUCOLD study
N= 5887

BHR : 24% of COPD patients



No AHR

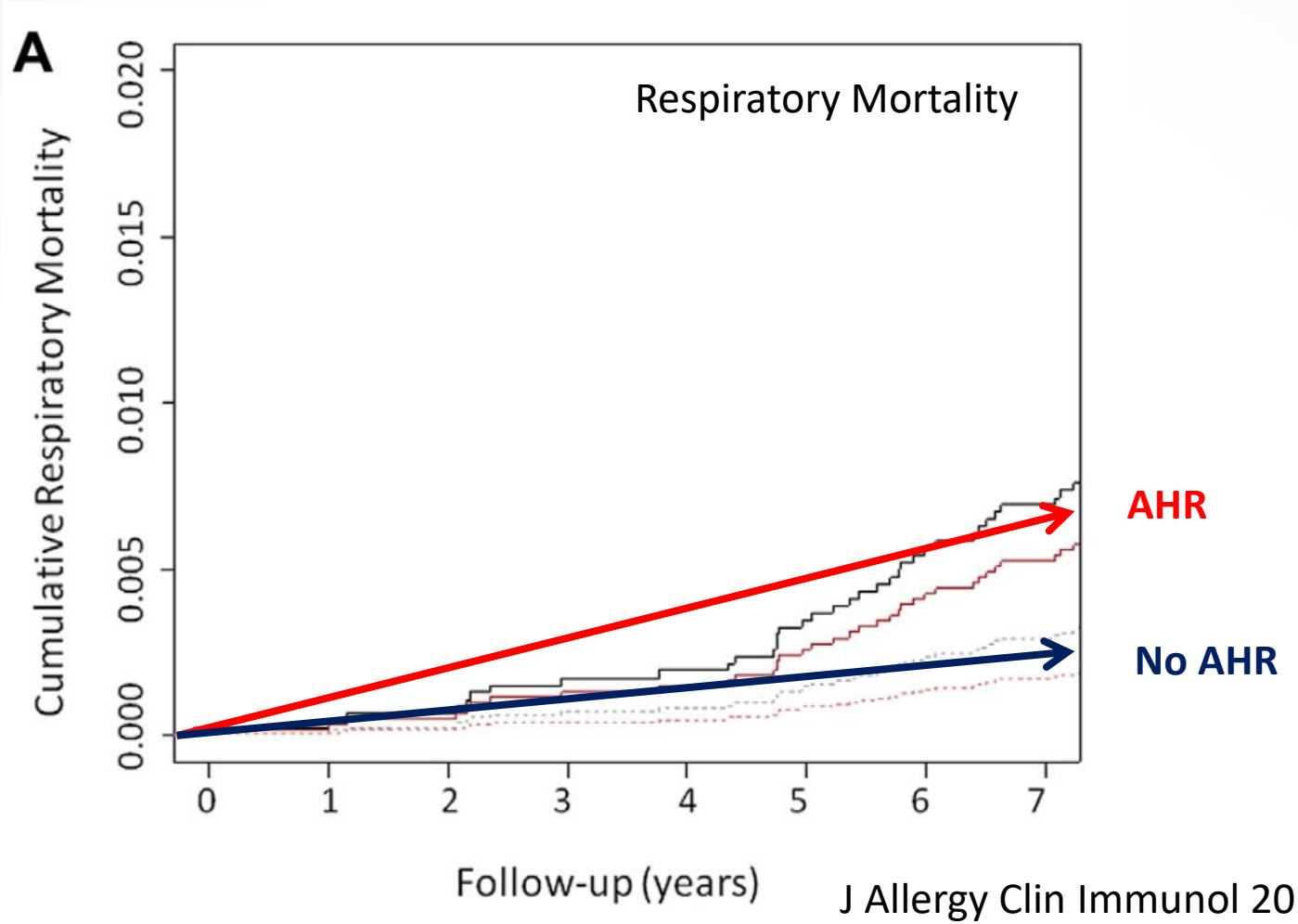
AHR

J Allergy Clin Immunol 2016 in press

BHR in COPD

BHR : 24% of COPD patients

Lung Health Study
GLUCOLD study
N= 5887



J Allergy Clin Immunol 2016 in press

Asthma Characteristics

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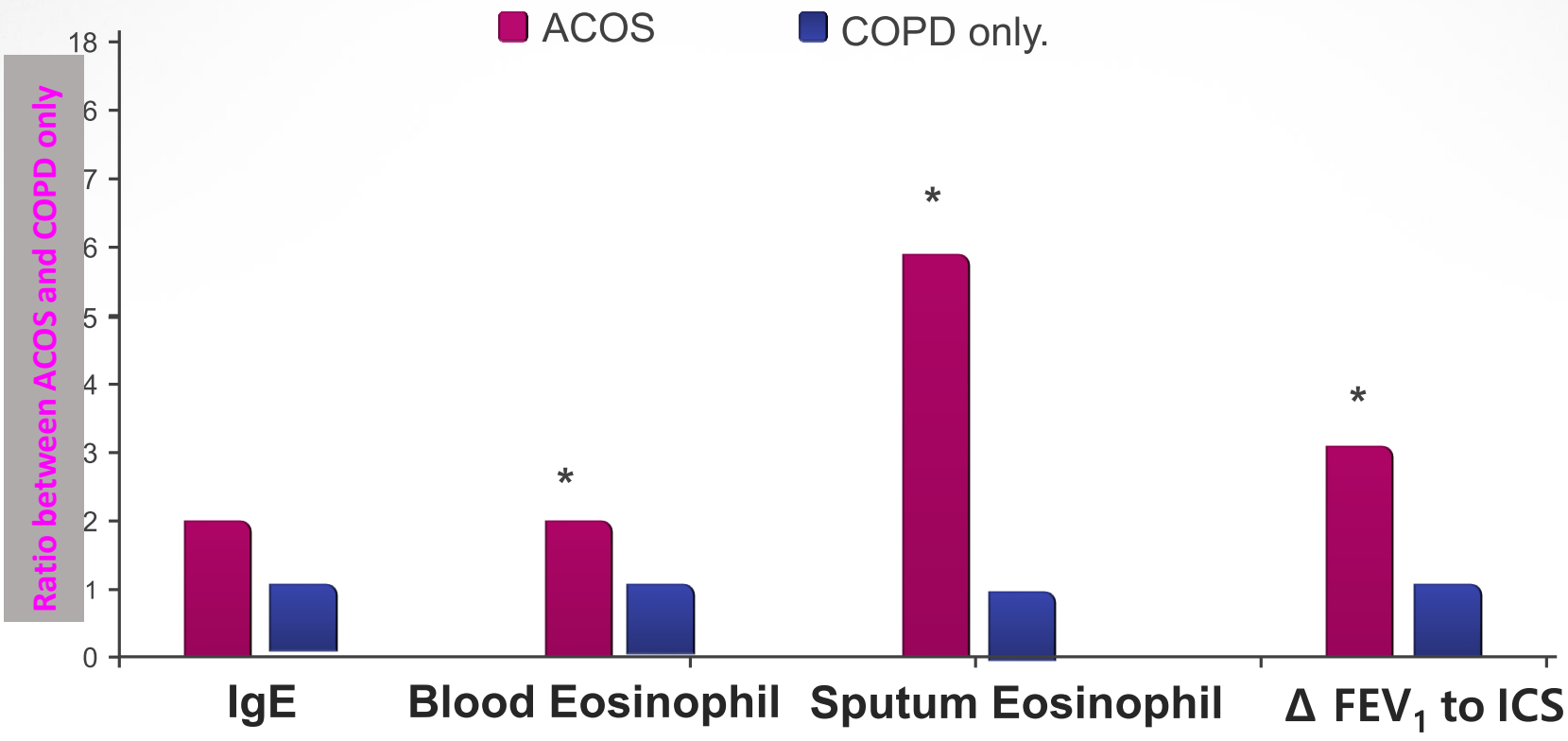
- **Blood or Sputum Eosinophil count**
- other Biomarker of Asthma

  (FeNO, Ig E, ICS responsiveness ,etc ..)

Blood or sputum Eosinophil



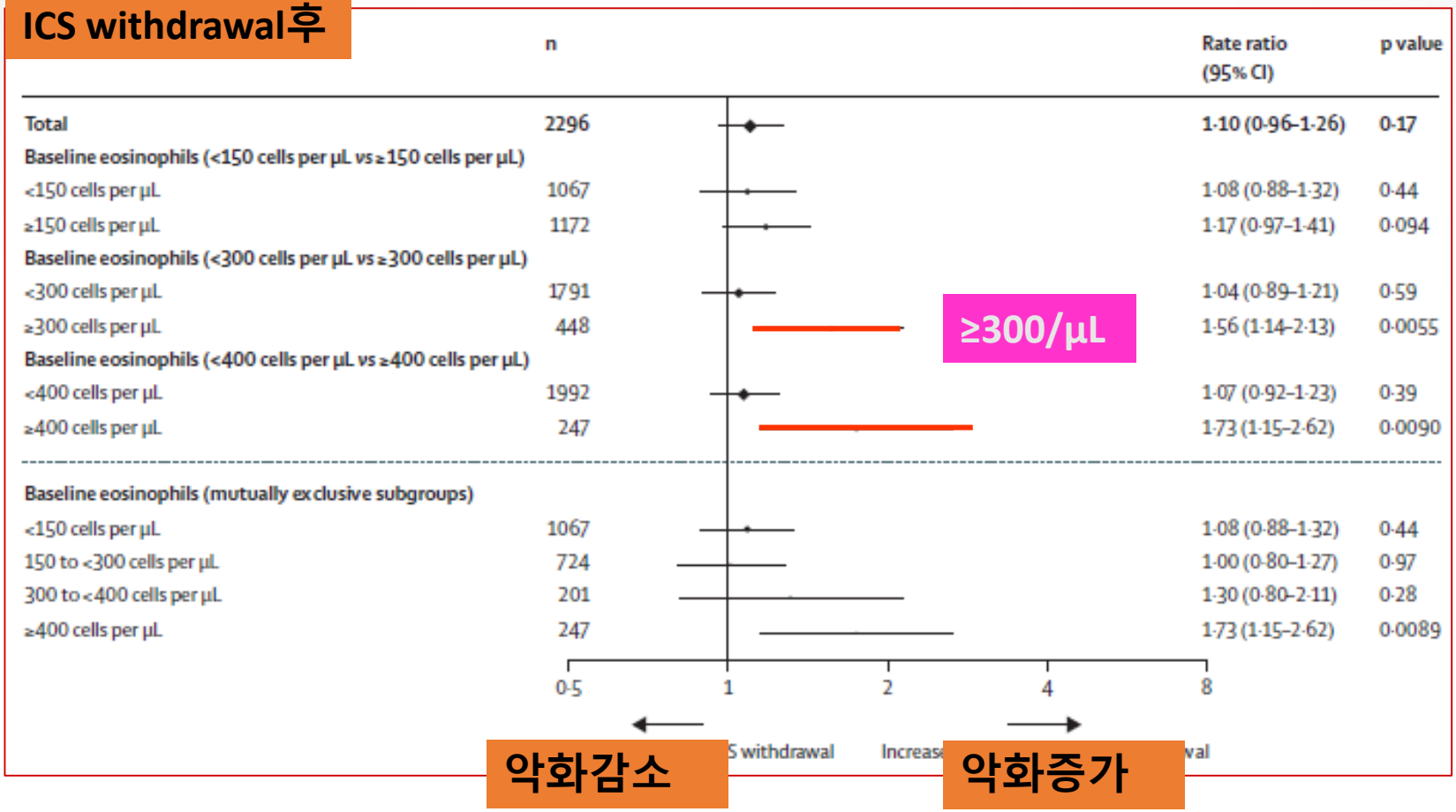
*p<0.05 versus chronic obstructive pulmonary disease without asthma

Kitaguchi Y. Int J Chron Obstruct Pulmon Dis 2012;7:283-289.

Post-hoc analysis of the WISDOM trial

Exacerbation rate ratios by eosinophil absolute count subgroup

ICS withdrawal후



Lancet Respir Med 2016; 4: 390–98

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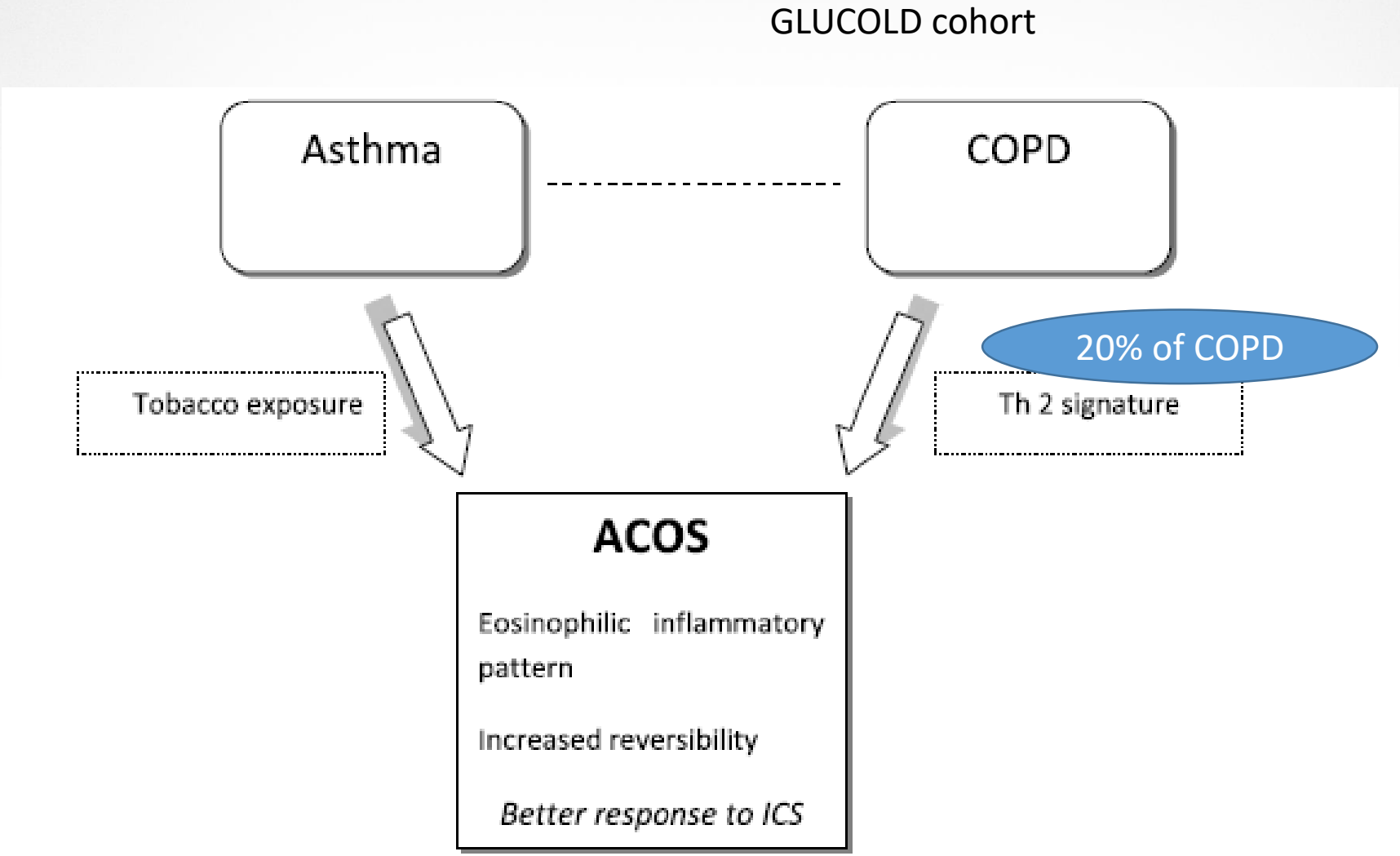
- **other Biomarker of Asthma**

  (FeNO, Ig E, ICS responsiveness ,etc ..)

Th-2 related gene expression



Christenson SA et al. Am J Respir Crit Care Med.2015;191:758–66.

Content

1) 역사적 배경
2) Suggested Definition review
3) Asthma Characteristics in COPD
4) **Newly Evolving Definitions**
5) Summary

New Guideline (suggested by ACOS working group)

- Persistent air flow limitation (FEV1/FVC <70%)
- ≥ 40yo
- Significant smoking or **biomass exposure**

+

MAJOR CRITERIA	+	MINOR CRITERIA (NEED 1 OF THESE)
	Major + 1 Minor	
Documented history of asthma before age 40 OR BDR >400 ml		**1. History of atopy or allergic rhinitis** **2. BDR ≥200 ml and 12% from baseline on 2 or more visits** **3. Peripheral blood eosinophils of ≥300 cells/uL**

Modified Spanish criteria

- Persistent air flow limitation (FEV1/FVC <70%)
- ≥ 40yo
- Significant smoking

✚

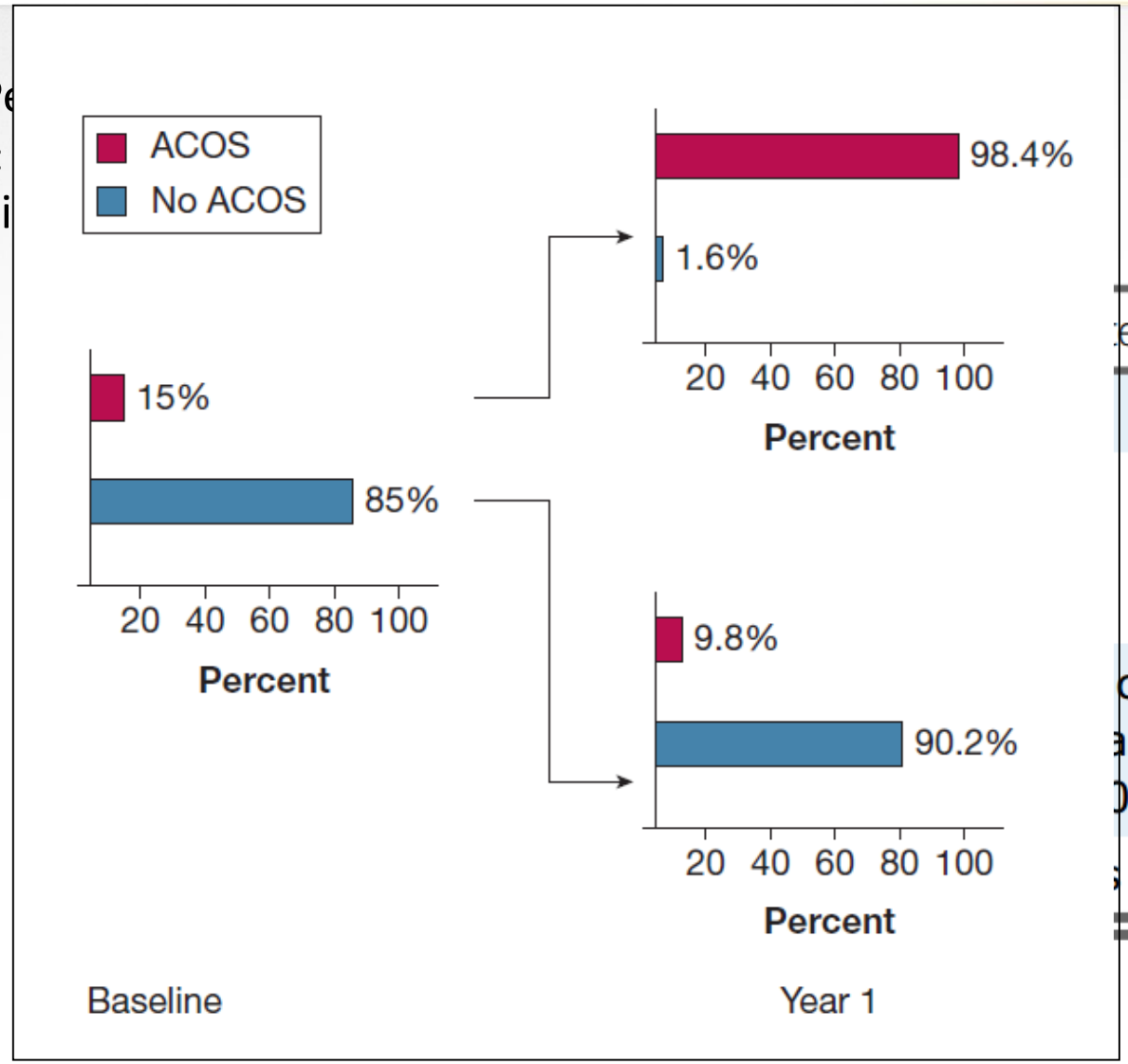
Major Criteria	Minor Criteria
Previous history of asthma	IgE > 100 IU, or
Bronchodilator response to salbutamol > 15% and 400 mL	History of atopy,
	2 separated bronchodilator responses to salbutamol > 12% and 200 mL
	Blood eosinophils > 5%

1 major or two minor

Cosio BG. Chest 2016; 149: 45.

Modified Spanish criteria

- Pe
- ≥
- Si



eria

chodilator
albutamol
) mL
> 5%

Cosio BG. Chest 2016; 149: 45.

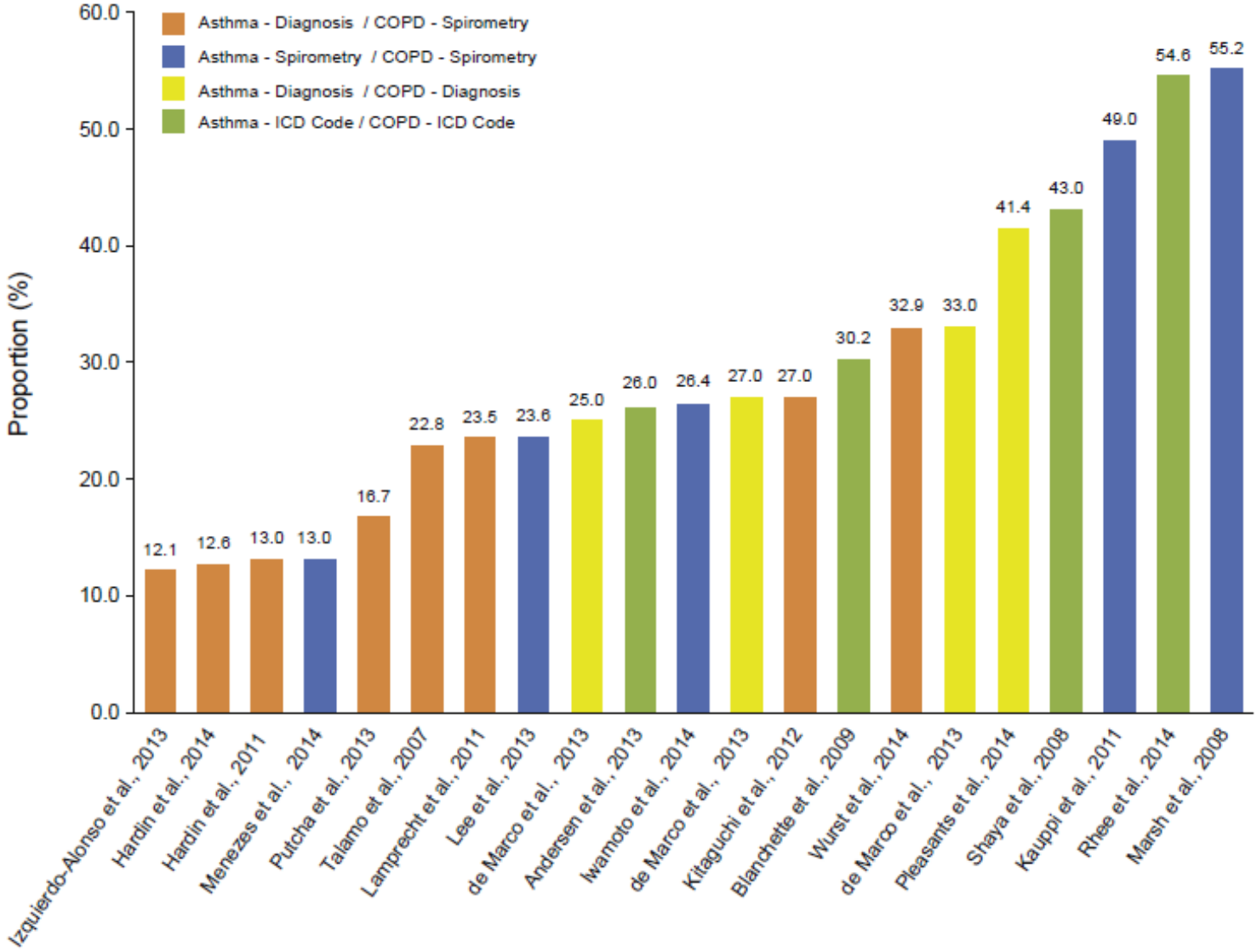
Diagnostic criteria sould be…

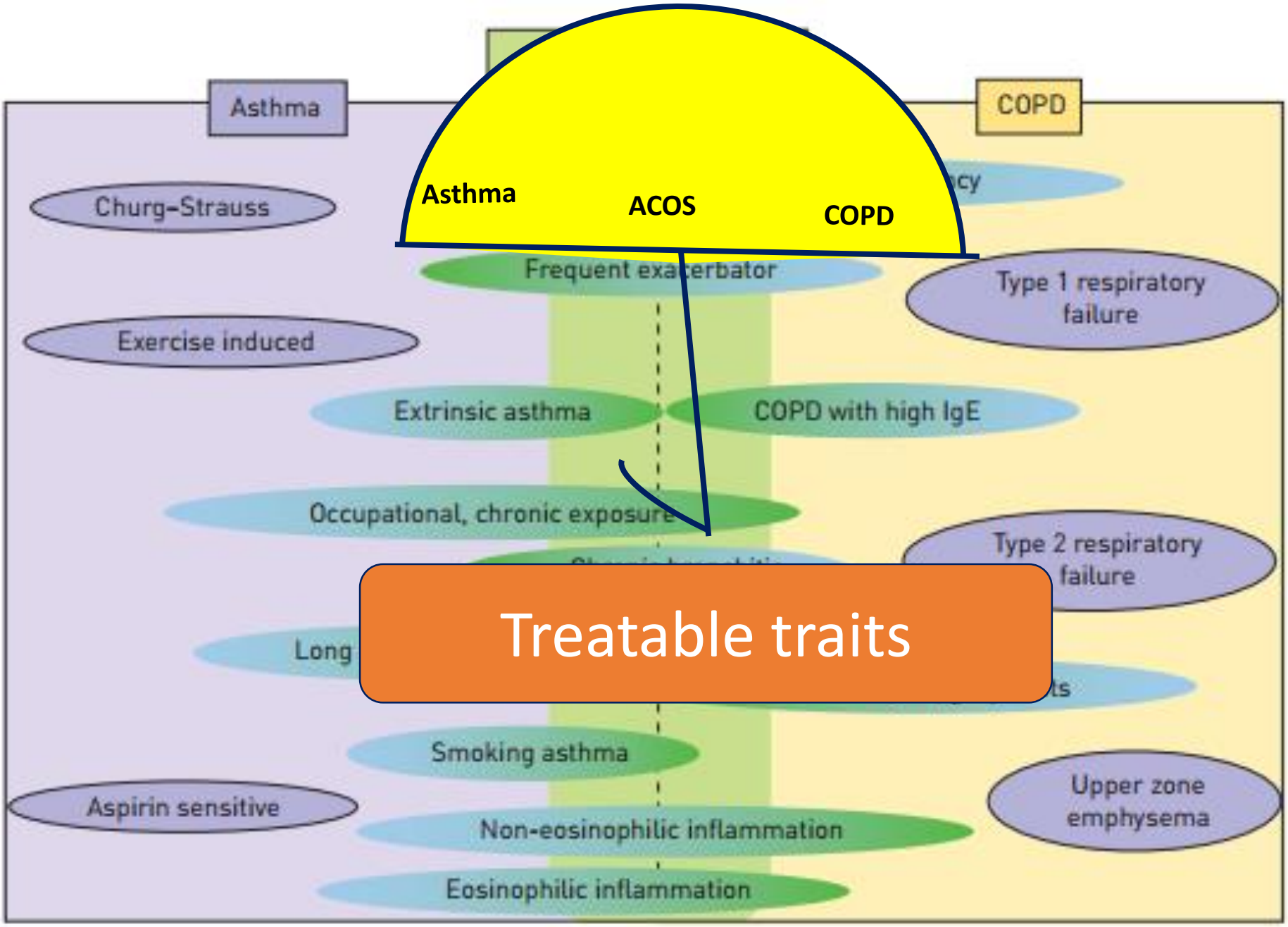
Fasting glucose ≥ 126 mg/dl

≥ 140 or ≥ 90

Easily applicable
Clear –Cut
Reproducible

ACOS prevalence among COPD patients according to similar definitions





Eur Respir Rev 2015;24:283-98

Remained Questions

Heterogeneity of ACOS

Asthmatics with fixed airflow limitation

Smoking asthmatics

COPD with significant airflow reversib

Beta-Blocker use for Cardiologic comorbidities

Long-term ICS use and side effect

Biological therapies

Safety of LABA monotherapy

?

Summary

- ACOS 는 흔하고 임상적으로 중요하다
- ACOS 는 COPD 환자 중 asthma 특징이 있는 환자를 말한다
- ACOS 정의와 진단 기준은 주로 전문가 의견에 의한 것이며 근거는 빈약하다.
- 공통된 정의와 진단기준이 필요하다