Άσθμα ως συνοσηρότητα στη ΧΑΠ

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Το ACOS έγινε ACO

GINA 2017

- The word ‘syndrome’ has been removed from the previous term ‘asthma-COPD overlap syndrome (ACOS)’ because:
  - This term was being commonly used in the respiratory community as if it was a single disease (‘the asthma-COPD overlap syndrome’)
  - There are two medically-accepted definitions of ‘syndrome’
  - This distracted from the key messages for clinicians and regulators
- The aim is to focus attention back on the original issues
  - These patients are commonly seen in clinical practice
  - They are almost always excluded from the RCTs that provide the evidence base for treatment recommendations, and from studies of underlying mechanisms
  - Current guidelines have opposite safety-based recommendations
    - Asthma: never use LABA without ICS
    - COPD: start treatment with LABA and/or LAMA, without ICS

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Asthma-COPD overlap

GINA 2018

- "Asthma-COPD overlap" does not mean a single disease entity
  - It includes patients with several different forms of airways disease (phenotypes) caused by a range of different underlying mechanisms
- Persistent airflow limitation may be found in:
  - Some children with asthma *(McGeachie NEJM 2016)*
  - Many adults with a history of asthma *(Lange NEJM 2015)*
  - Patients with low lung function in early adulthood with normal decline over time *(Lange NEJM 2015)*
  - Patients with normal lung function in early adulthood but rapid decline over time *(Lange NEJM 2015)*

Table 3. Stratified Associations of Death or Hospitalization for COPD Among New Users of LABA-ICS Combination Therapy Compared With New Users of LABAs Alone

Stratifying Characteristics	No. With Outcome/Total (%)		*P* Value for Interaction	Difference in Outcome at 5 y, % (95% CI)	Propensity Score-Matched Regression	
	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

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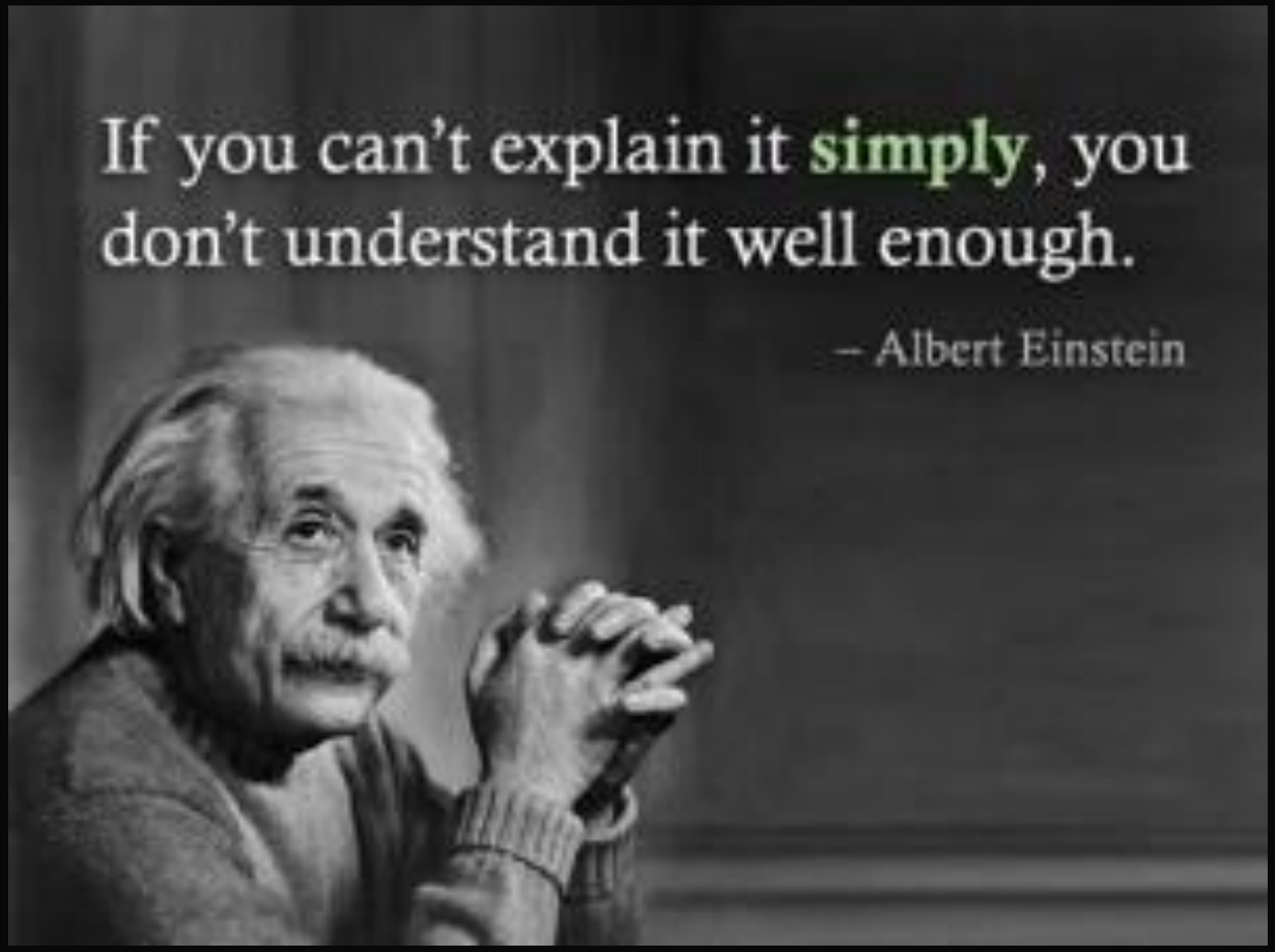
ACO = Δεν Υπάρχει ξεκάθαρος ορισμός που περιγράφει με σαφήνεια τα ιδιαίτερα χαρακτηριστικά του συνδρόμου και της φλεγμονής που επικρατεί



Asthma and chronic obstructive pulmonary disease overlap: asthmatic chronic obstructive pulmonary disease or chronic obstructive asthma?

Ther Adv Respir Dis

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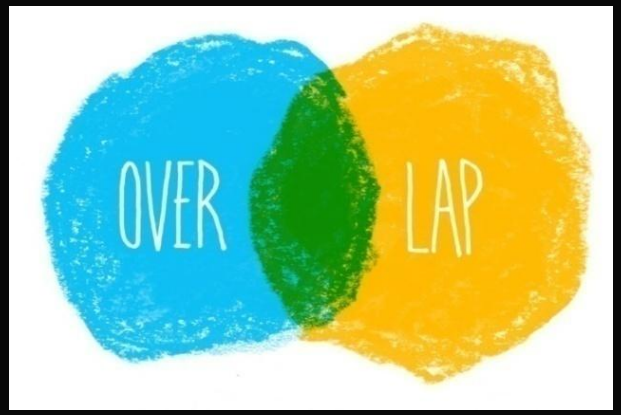
Annelies Slats and Christian Taube

Αλληλοεπικάλυψη Άσθματος και ΧΑΠ: ACO ή CAO;



ACO: Από ποια βασική πάθηση ξεκινάμε;

- Άσθμα ή ΧΑΠ;
- Στην καθημερινή κλινική πρακτική, η πλειοψηφία των ασθενών που διερευνώνται για την ύπαρξη ACO ξεκινούν συνήθως από τη ΧΑΠ
- Οι θέσεις ομοφωνίας αποφεύγουν να πάρουν θέση
- Η ισπανική άποψη θεωρεί ως δεδομένο την ύπαρξη ΧΑΠ και αναζητά στοιχεία που συνηγορούν υπέρ της συνύπαρξης άσθματος

Η ισπανική άποψη

Mixed COPD/Asthma Phenotype: 2 μείζονα κριτήρια ή 1 μείζον και 2 ελάσσονα κριτήρια

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

Cataluna J, et al. *Arch Bronconeumol* 2012; 48: 331-37.

Πληθυσμοί ασθενών που χαρακτηρίζονται ότι πάσχουν από ACO

Διαφορετικοί φαινότυποι, όπως:

- Ασθενείς με ΧΑΠ και ηωσινοφιλική φλεγμονή
- Ασθενείς με άσθμα και σοβαρή νόσο (κυρίως ουδετεροφιλική φλεγμονή)
- Ασθενείς με άσθμα που καπνίζουν (κυρίως ουδετεροφιλική φλεγμονή)
- Ασθενείς με άσθμα και μόνιμη απόφραξη των αεραγωγών χωρίς αναστρεψιμότητα (λόγω δομικών αλλαγών)

CHEST 2016

Asthma-COPD Overlap

Peter J. Barnes, Master FCCP
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PODCAS

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

Κατηγοριοποίηση της σπουδαιότητας και της εφαρμογής των κριτηρίων

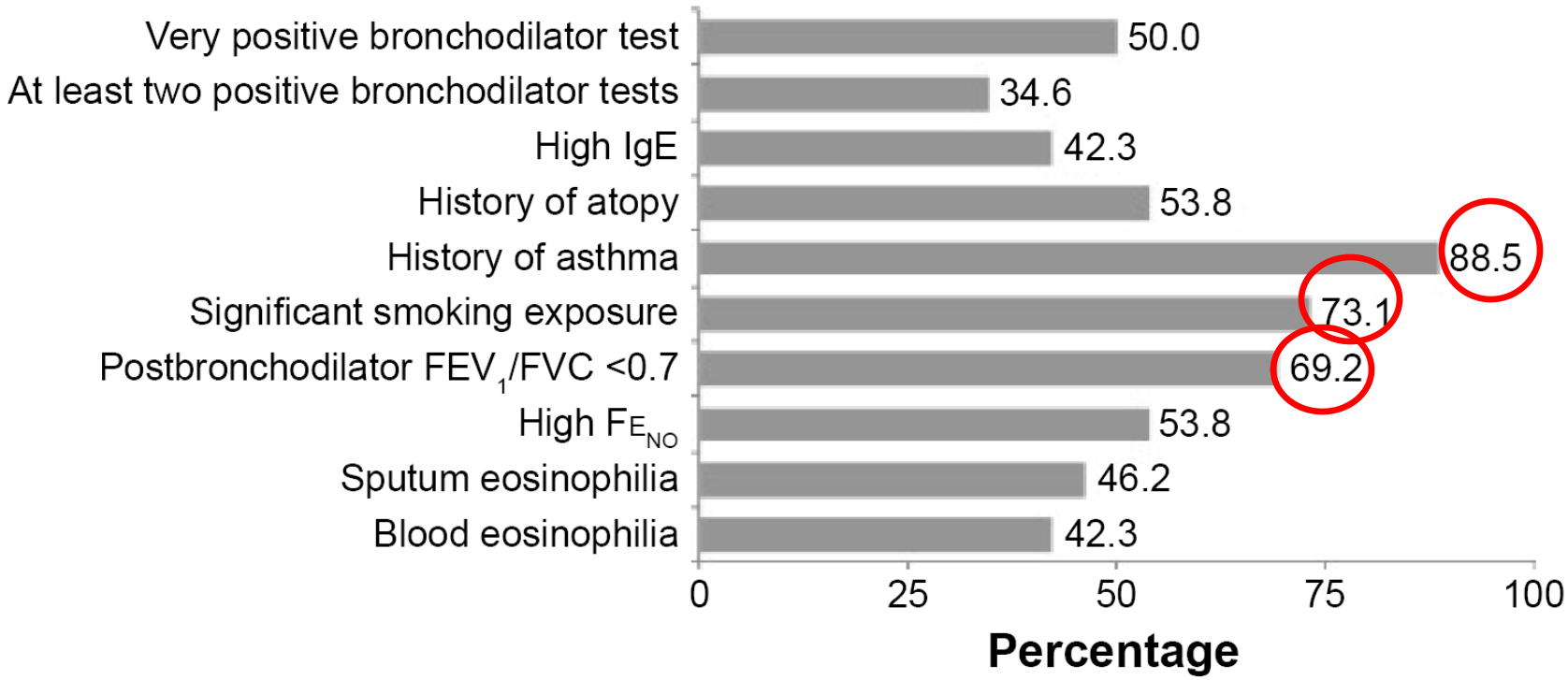
(13 ειδικοί στο άσθμα – 13 ειδικοί στη ΧΑΠ)

	Very important criteria	Important criteria	Less important criteria
Specialized care			
Very applicable	Very positive bronchodilator test (increase in FEV_1 ≥15% and ≥400 mL compared to basal value) Previous history of asthma before 40 years of age	Positive bronchodilator test on two or more occasions Blood eosinophilia Total IgE Positive methacholine test History of atopy Rhinitis of any type	Positive bronchodilator test Family history of atopy and/or asthma Positive skin tests
Quite applicable	Elevated FE_{NO}		
Not very applicable	Eosinophilia in sputum Positive oral corticosteroid test		Increased or seasonal variability of symptoms Variability of peak flow >20%
Primary care			
Very applicable	Previous history of asthma before 40 years of age	Eosinophilia in blood	
Quite applicable	Very positive bronchodilator test	Rhinitis of any type Elevated total IgE Personal history of atopy	Family history of asthma and/or atopy
Not very applicable	Eosinophilia in sputum Elevated FE_{NO} Positive oral corticosteroid test	Positive bronchodilator test on two or more occasions Positive methacholine test	Increased or seasonal variability of symptoms Positive skin tests Variability in peak flow >20% Positive bronchodilator test

Miravitlles M, et al. *International Journal of COPD* 2015; 10: 1321–30.

What pulmonologists think about the asthma–COPD overlap syndrome

Κριτήρια που προτιμούνται από τους πνευμονολόγους για τη διάγνωση του ACO

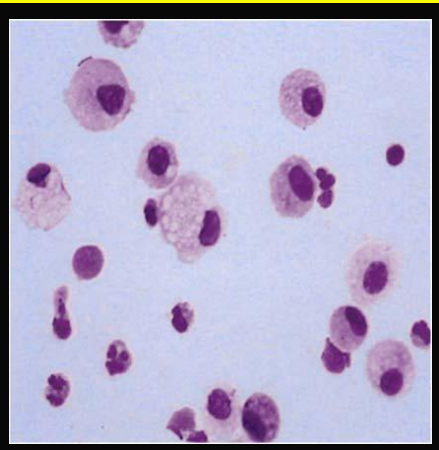


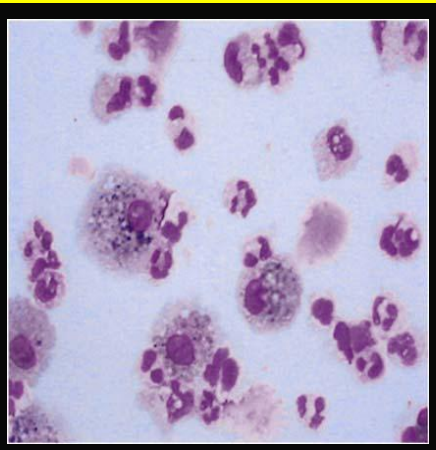
Miravitlles M, et al. *International Journal of COPD* 2015; 10: 1321–30.

Asthma COPD Overlap (ACO): Αλλάζει το φλεγμονώδες πρότυπο;

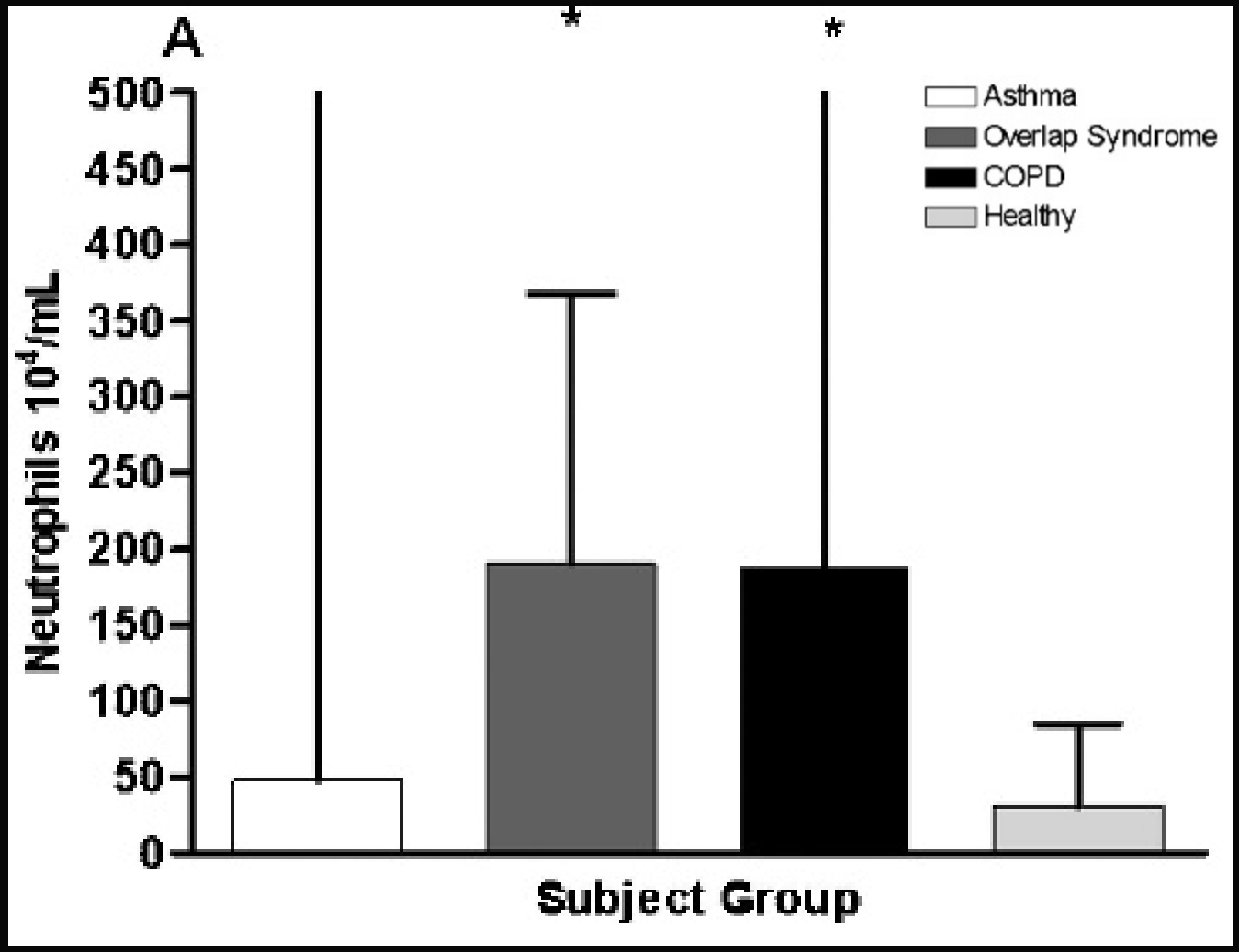
- GINA/Ισπανικές θέσεις: θεωρούν ως το σημαντικότερο στοιχείο την ηωσινοφιλική φλεγμονή, που μπορεί να ορίζεται είτε με τη μέτρηση του εκπνεόμενου FeNO είτε με την αξιολόγηση των ηωσινοφίλων στα πτύελα

Διαφορετικό φλεγμονώδες πρότυπο, με μικτά χαρακτηριστικά (πλησιάζουν πιο πολύ στη ΧΑΠ), χωρίς να γνωρίζουμε ποιο ακριβώς είναι αυτό το πρότυπο





Overlap vs Asthma: ↑ Ουδετερόφιλα (πτύελα)

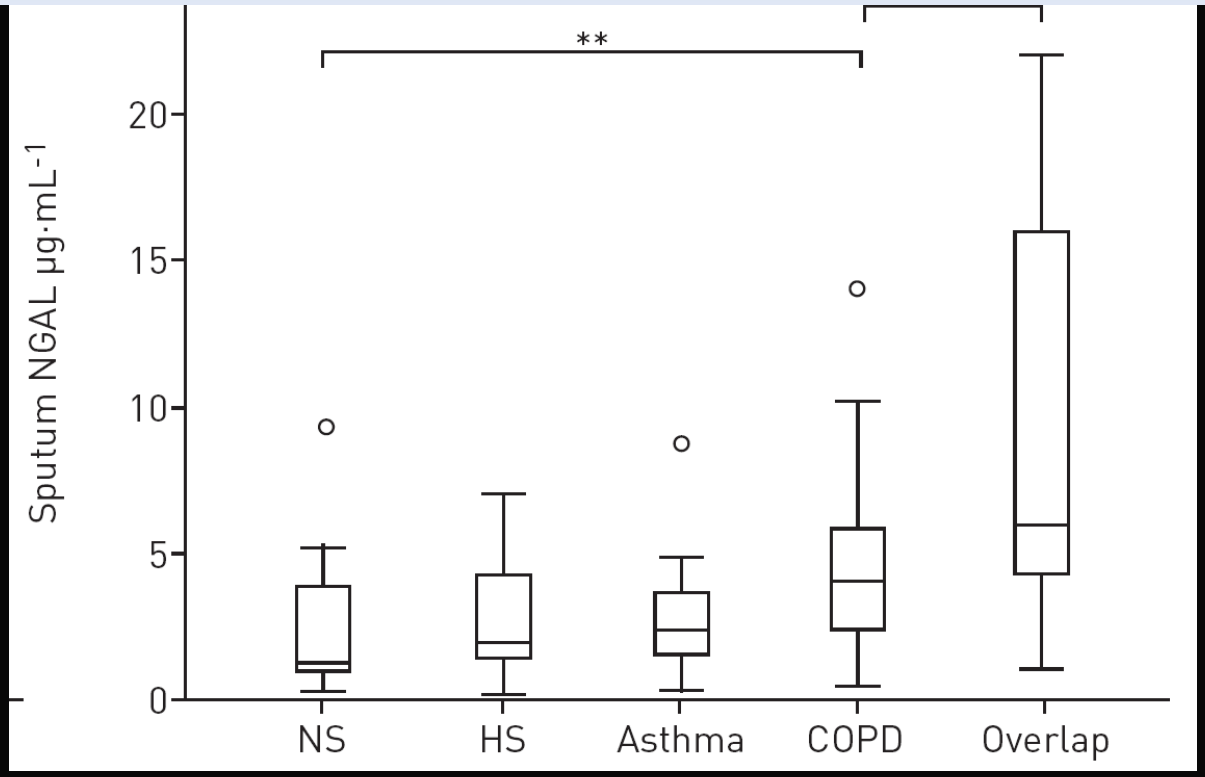


Gibson PG, et al. *Thorax* 2009; 64: 728–35.

Differences in plasma and sputum biomarkers between COPD and COPD–asthma overlap

neutrophil gelatinase-associated lipocalin (NGAL): neutrophil-derived molecule

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.



Iwamoto H, et al. *Eur Respir J* 2014; 43: 421–29.

Asthma COPD Overlap (ACO) - προκλητά πτύελα: ↑ ηωσινόφιλα, ↑ ουδετερόφιλα

	NS	HS	Asthma	COPD	Overlap
Subjects n	26	23	32	39	14
Females/males n	10/16	11/12	16/16	13/26	5/9
Age years	46.9±2.6	47.6±2.5	58.3±1.5	62.4±1.1	61.2±1.5
BMI kg·m^{-2}	28.2±1.0	26.9±1.0	27.5±1.0	25.5±0.7	28.3±1.9
Smoking status					
Former smoker	0	0	17 (53)	13 (33)	8 (57)
Current smoker	0	23 (100)	4 (13)	26 (67)	6 (43)
Pack-years	0	25.8±3.7	16.1±3.8	47.8±3.8	36.9±6.1
Allergy	4 (15)	9 (40)	18 (56)	11 (28)	5 (36)
ICS use	0	0	28 (88)	13 (33)	14 (100)
Postbronchodilator					
FVC L	4.7±0.2	4.4±0.3	3.5±0.2	3.2±0.2	3.2±0.3
FEV1 L	3.9±0.2	3.5±0.2	2.6±0.1	1.9±0.1	1.9±0.2
FEV1 % pred	103.8±2.1	96.0±3.6	77.0±3.0	57.9±3.2	55.3±3.1
FEV1/FVC	83.9±1.1	80.1±1.3	80.9±1.7	62.6±2.4	69.9±4.1
*D*LCO % pred	93.8±4.6	89.4±2.8	87.8±5.6	62.9±4.2	66.8±5.2
ΔFEV1# mL	110±31	78±38	173±36	109±30	203±49
ΔFEV1# %	3.1±0.9	2.4±1.1	7.8±1.6	7.5±1.3	13.0±4.0
PEF diurnal variability %			28.1±2.0	17.2±1.8	37.9±4.8
Differential sputum cell counts %					
Eosinophils	1.5±0.8	0.9±0.6	6.3±1.9	1.4±0.5	8.3±3.5
Neutrophils	34.7±2.7	41.9±5.4	53.4±4.6	63.1±3.6	68.2±4.1
Macrophages	59.11±3.3	54.3±5.6	41.3±4.4	32.9±3.7	21.8±3.5

Iwamoto H, et al. *Eur Respir J* 2014; 43: 421–29.

Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease

- 86 ασθενείς με σοβαρό άσθμα – 75 με μέτρια/σοβαρή ΧΑΠ
- Cluster analyses - 18 κυτταροκίνες στα πτύελα
- Οι υποπληθυσμοί επικυρώθηκαν σε μία ανεξάρτητη ομάδα με σοβαρό άσθμα (n=166) και μία ομάδα με ΧΑΠ (n=58)

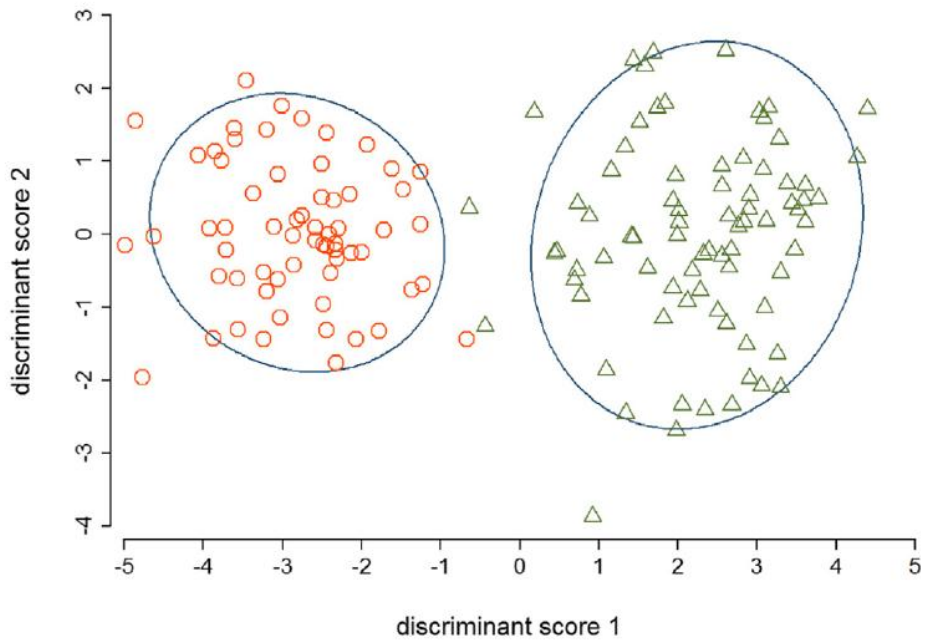
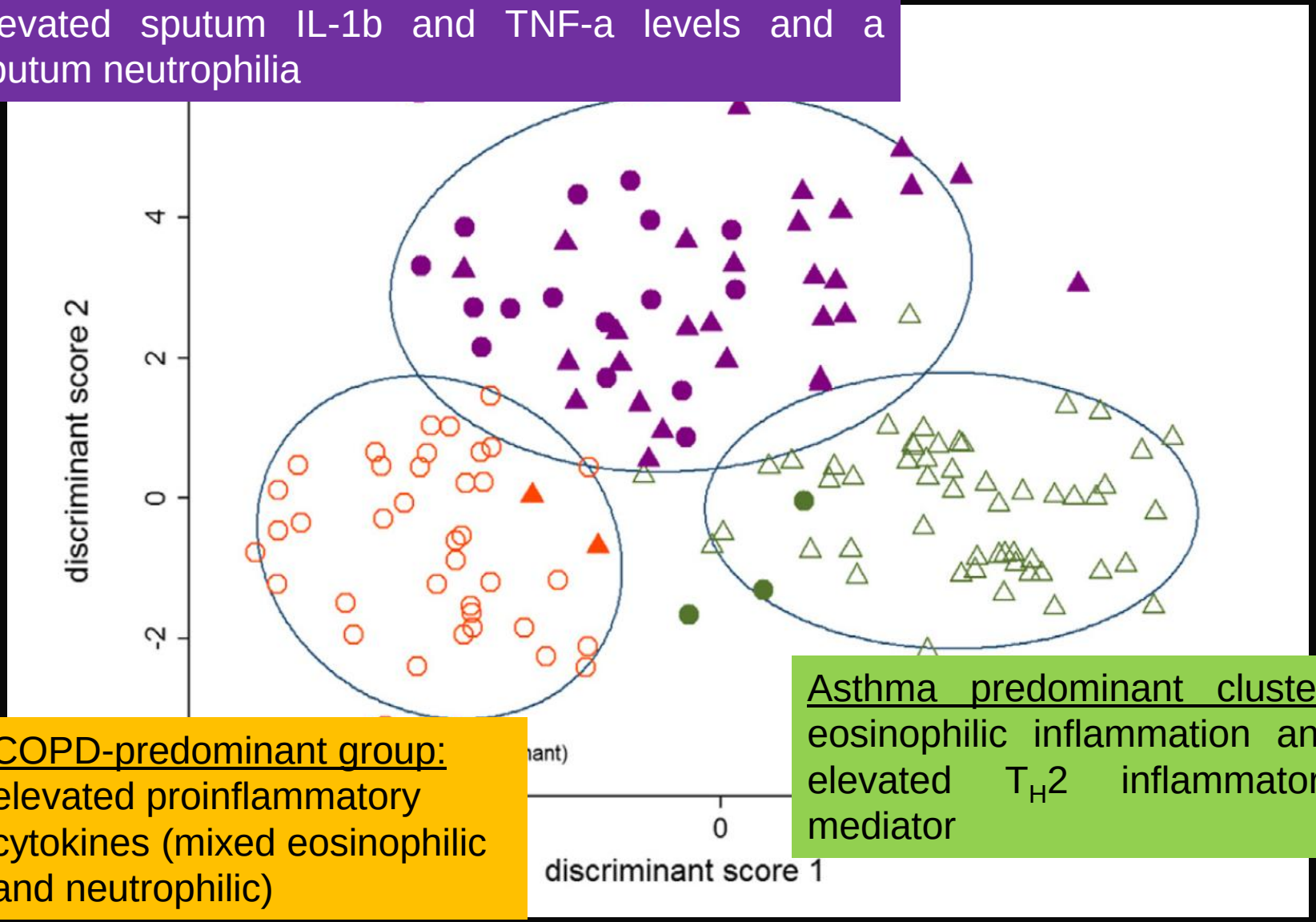


FIG 1. Discriminant function of demographic, clinical, lung function, and sputum cytokines characteristics across asthma and COPD. *Hollow triangles* indicate asthma and *hollow circles* indicate COPD.

Ghebre MA, et al. *J Allergy Clin Immunol* 2014

Asthma and COPD overlap group that clinically had: chronic bronchitis, increased bacterial colonization, elevated sputum IL-1b and TNF-a levels and a sputum neutrophilia



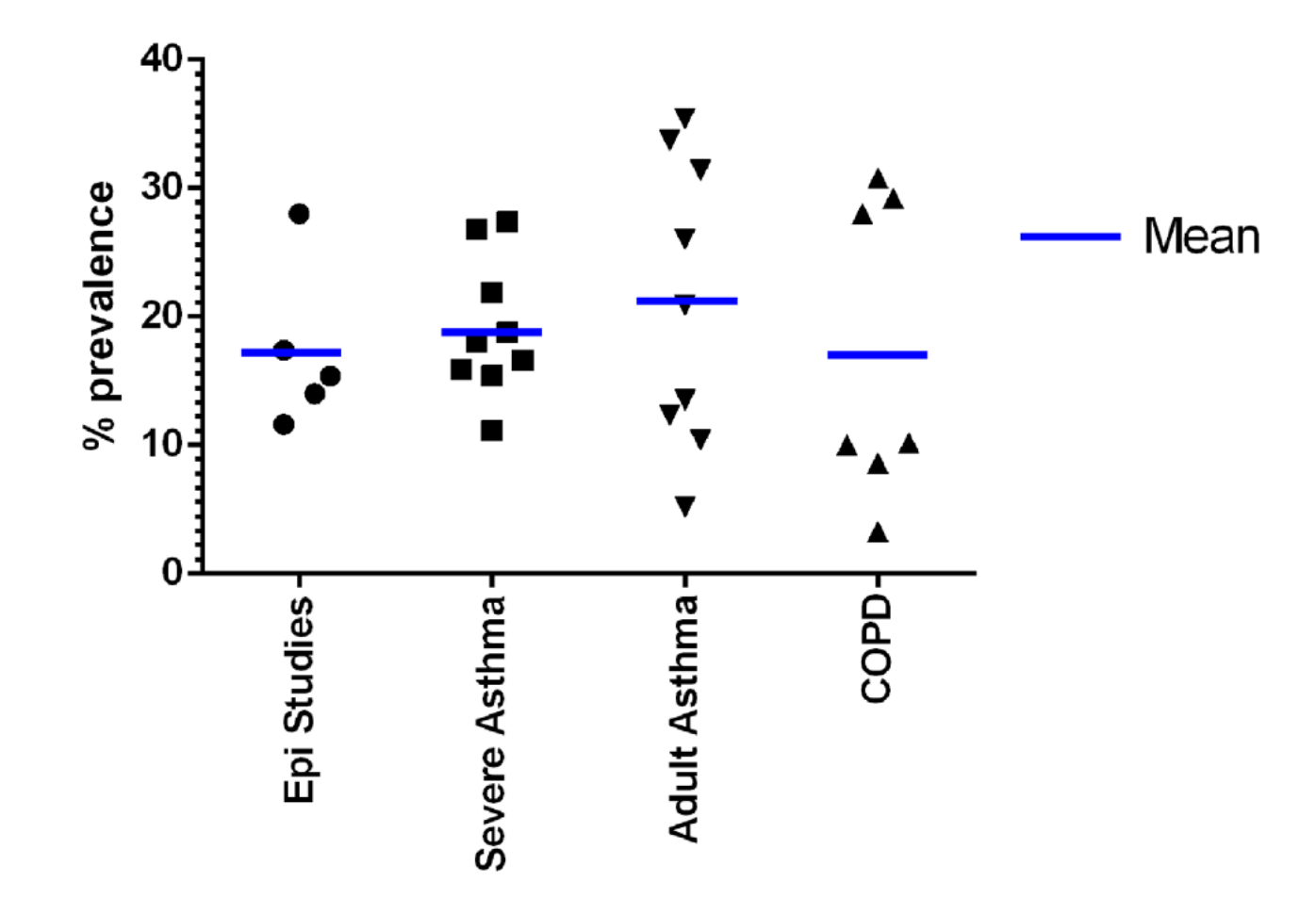
COPD-predominant group: elevated proinflammatory cytokines (mixed eosinophilic and neutrophilic)

Asthma predominant cluster: eosinophilic inflammation and elevated T_H2 inflammatory mediator

Ghebre MA, et al. *J Allergy Clin Immunol* 2014

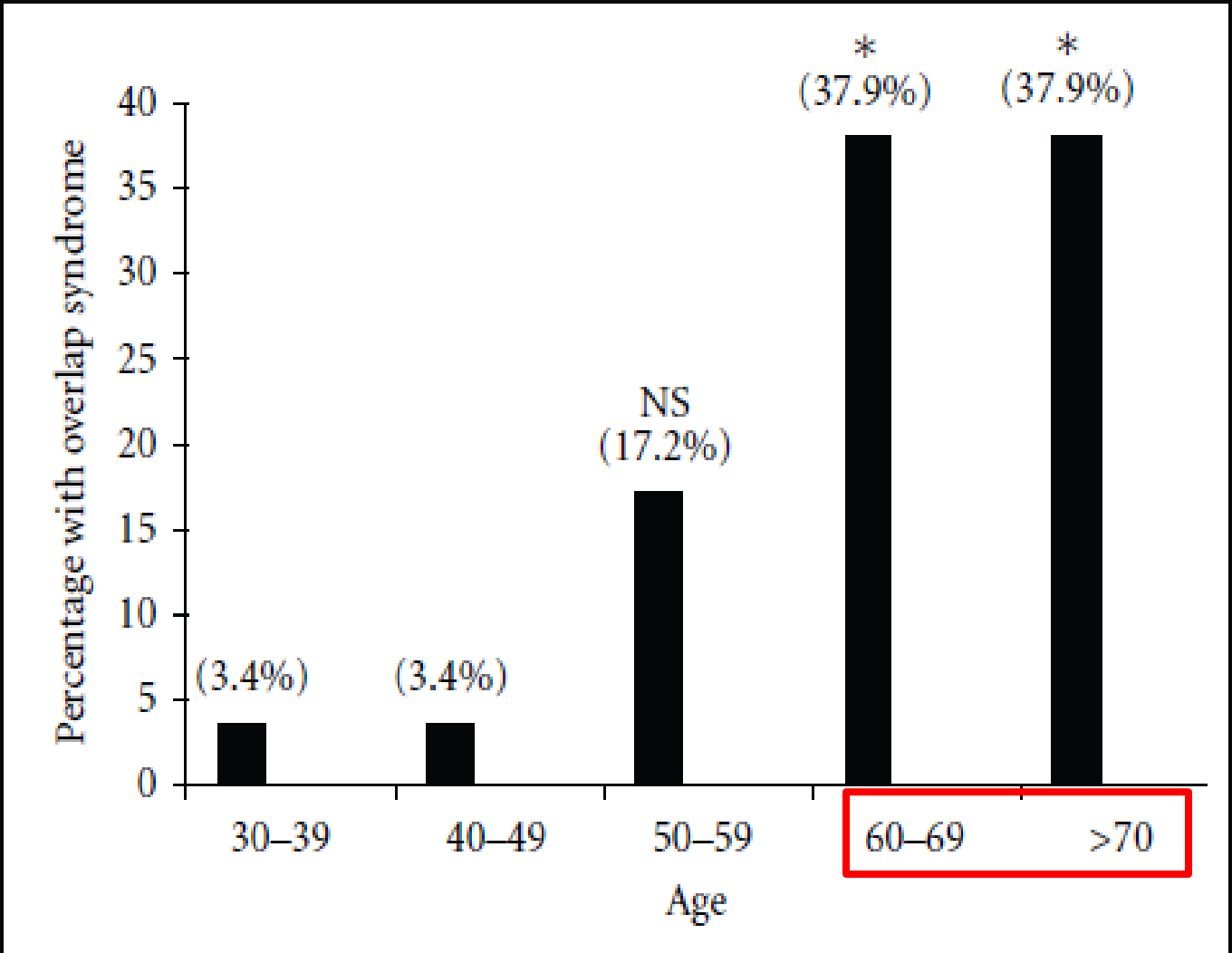
Asthma COPD Overlap (ACO):
Επίπτωση που ποικίλει σε μελέτες διαφορετικού σχεδιασμού, αύξηση της επίπτωσης με την ηλικία (ιδιαίτερα σε καπνιστές με ηλικία > 60 ετών)

Επίπτωση ACO σε μελέτες διαφορετικού σχεδιασμού



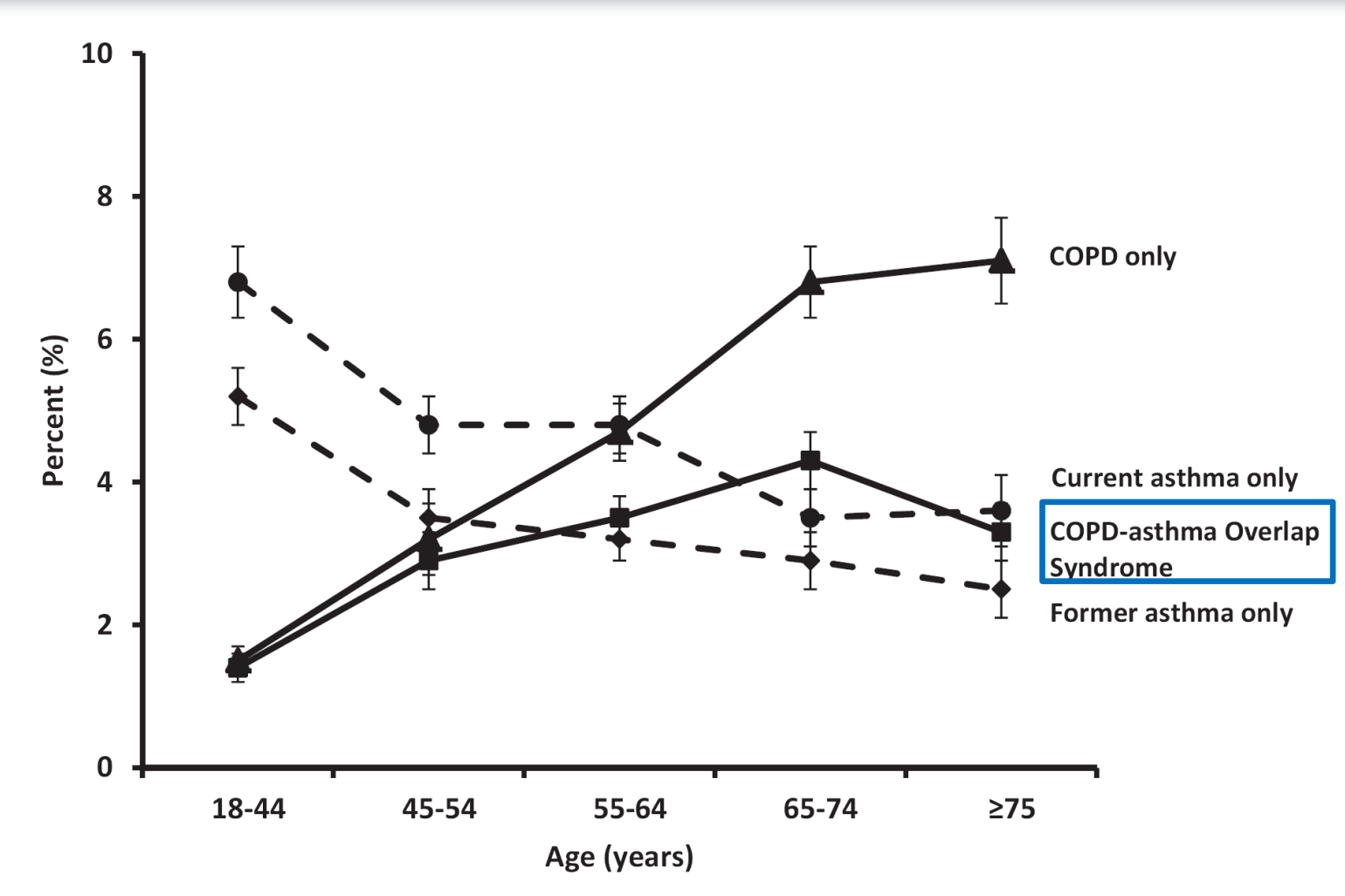
Gibson PG, et al. *Thorax* 2015; 70: 683–91.

Asthma COPD Overlap (ACO) : συχνότερο σε ηλικία > 60 έτη



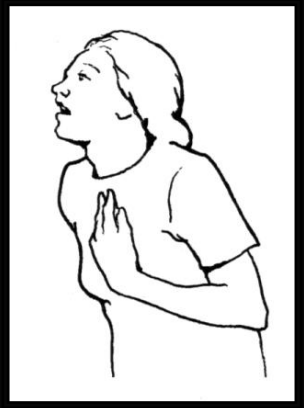
Zeki AA, et al. *J Allergy* 2011

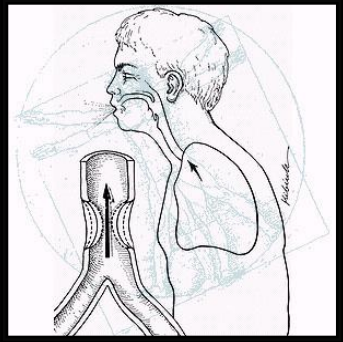
CAO: ↑ επίπτωσης με την ηλικία



Pleasants RA, et al. *COPD* 2014; 11: 256–66.

Asthma COPD Overlap (ACO) = Περισσότερες γυναίκες, χαμηλότερο μορφωτικό επίπεδο, περισσότερα συμπτώματα και χειρότερη ποιότητα ζωής σε σχέση με τους ασθενείς με άσθμα ή ΧΑΠ





ACO: Παράγοντες κινδύνου

Table 4. Factors associated with the diagnoses of asthma, COPD, and the asthma–COPD overlap syndrome.

	Asthma only	Asthma+COPD	COPD only
Gender males	1	1	1
females	0.87 (0.72–1.04)	**1.63 (1.15–2.31)**	1.15 (0.92–1.44)
Age [20–44]	1	1	1
[45–64]	**0.60 (0.47–0.77)**	1.12 (0.75–1.69)	**1.57 (1.20–2.07)**
[65–85]	**0.48 (0.3–0.77)**	1.43 (0.76–2.70)	**5.50 (3.75–8.08)**
Smoking habits non-smoker	1	1	1
current smoker	**1.27 (1.02–1.58)**	**1.70 (1.12–2.60)**	**3.16 (2.41–4.16)**
ex smoker	0.99 (0.78–1.26)	**1.56 (1.04–2.35)**	**1.56 (1.16–2.08)**
Education compulsory	1	1	1
high school	1.26 (0.99–1.6)	**0.45 (0.31–0.65)**	**0.70 (0.55–0.90)**
college/university	**1.61 (1.24–2.09)**	**0.30 (0.17–0.51)**	**0.38 (0.26–0.57)**
Industries nearby	1.00 (0.78–1.27)	0.91 (0.55–1.50)	1.30 (0.98–1.73)
Heavy traffic occasional/none	1	1	1
frequent	1.00 (0.78–1.27)	0.91 (0.55–1.50)	**1.30 (0.98–1.73)**
constant	**1.38 (1.07–1.77)**	1.57 (0.98–2.50)	**1.67 (1.24–2.24)**

de Marco R, et al. *PLOS ONE* 2013

ACO: ↑ συμπτώματα

Table 3. Prevalence* (% with 95%CI) of respiratory symptoms or conditions in subjects who did and did not report a diagnosis of asthma and/or COPD.

Respiratory symptoms or conditions	no asthma, no COPD %(95%CI)	asthma only %(95%CI)	asthma+COPD overlap %(95%CI)	COPD only %(95%CI)
Wheezing	9.9 (9.2–10.6)	43.4 (39.2–47.7)	78.7 (71.3–84.5)	42.7 (37.6–47.9)
Asthma attacks	0.7 (0.5–0.9)	38.8 (34.6–43.2)	56.9 (48.7–64.8)	4.4 (2.7–6.9)
Antiasthmatic drugs	0.3 (0.2–0.4)	29.8 (25.8–34)	55.4 (47–63.5)	2 (1.1–3.8)
Allergic rhinitis	18.2 (17.3–19.1)	59.2 (54.9–63.4)	53.5 (45.5–61.3)	23.9 (19.7–28.6)
Cough or phlegm	10.2 (9.5–10.9)	23.1 (19.6–26.9)	61.7 (53.7–69.1)	54 (48.7–59.2)
MRC† ≥3	3.8 (3.3–4.3)	9.3 (7.1–12.2)	38.8 (31.1–47.1)	20.8 (17–25.2)
Hospitalizations	0.4 (0.2–0.5)	1.1 (0.5–2.4)	3.1 (1.4–6.7)	2.5 (1.4–4.5)

*Adjusted for gender, age (class), season, % of answers to the questionnaire, type of survey (postal/telephone), and centre.
†MRC: Medical Research Council dyspnea score.
doi:10.1371/journal.pone.0062985.t003

de Marco R, et al. *PLOS ONE* 2013

Overlap COPD/asthma vs COPD: ↓ ποιότητα ζωής

	COPD	COPD and asthma	Effect size	p-value
Females	1335 (42.8)	252 (56.0)	1.59 (1.29–1.95)	<0.001
African–American	627 (20.1)	167 (37.1)	1.74 (1.39–2.18)	<0.001
Bronchodilator responsiveness	1120 (36.1)	177 (39.4)	1.19 (0.97–1.47)	0.10
Absolute BDR L	0.09±0.16	0.11±0.16	0.02±0.008	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

Hardin M, et al. *Eur Respir J* 2014; 44: 341–50.

Αποφρακτικά νοσήματα των αεραγωγών

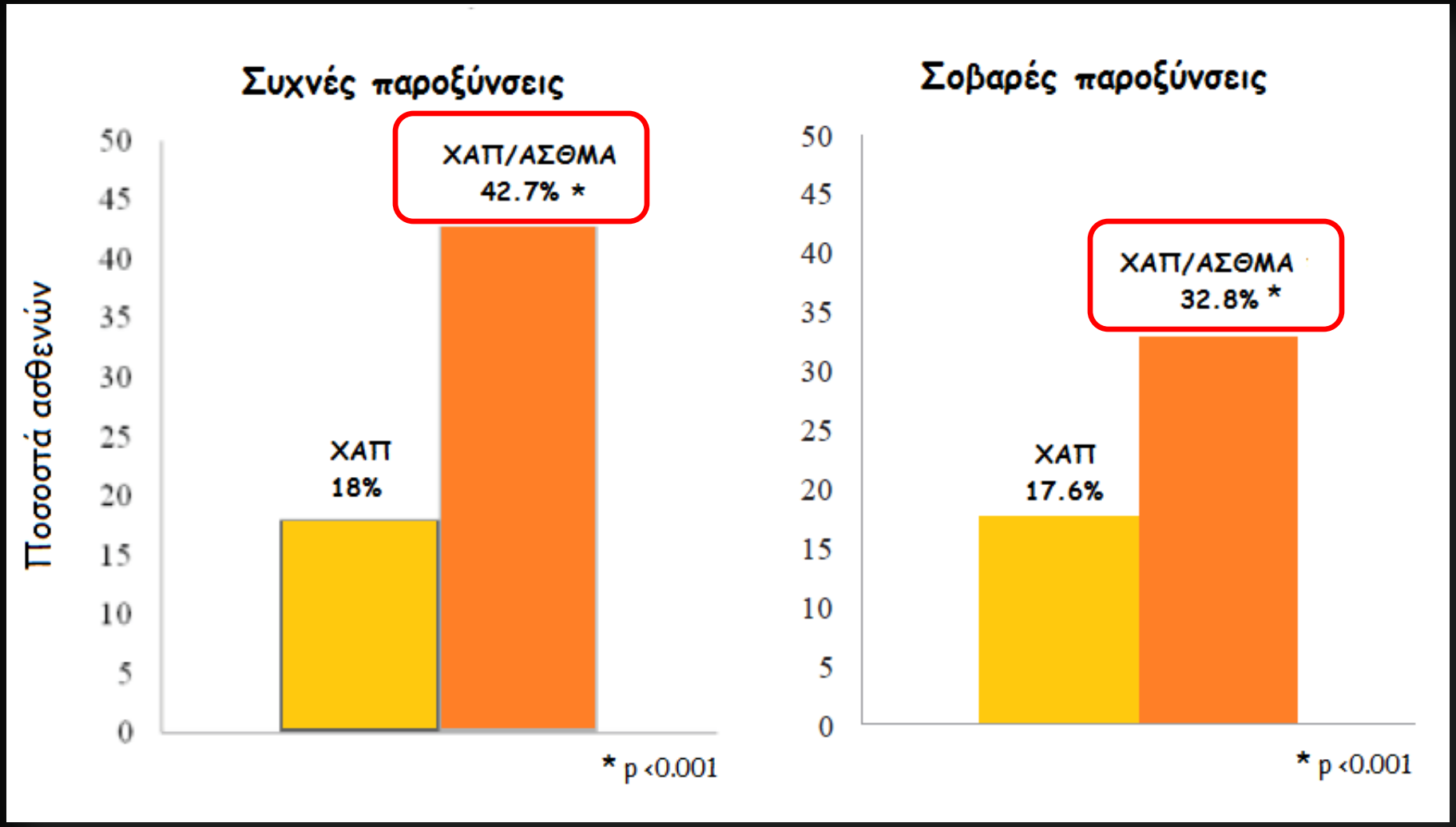
Table 1. Four Examples of Patients with Obstructive Airway Disease.*

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

Postma DS, et al. *N Engl J Med* 2015; 373: 1241-9.

Asthma COPD Overlap (ACO) = περισσότερες/σοβαρότερες παροξύνσεις, περισσότερες νοσηλείες, χειρότερη αναπνευστική λειτουργία

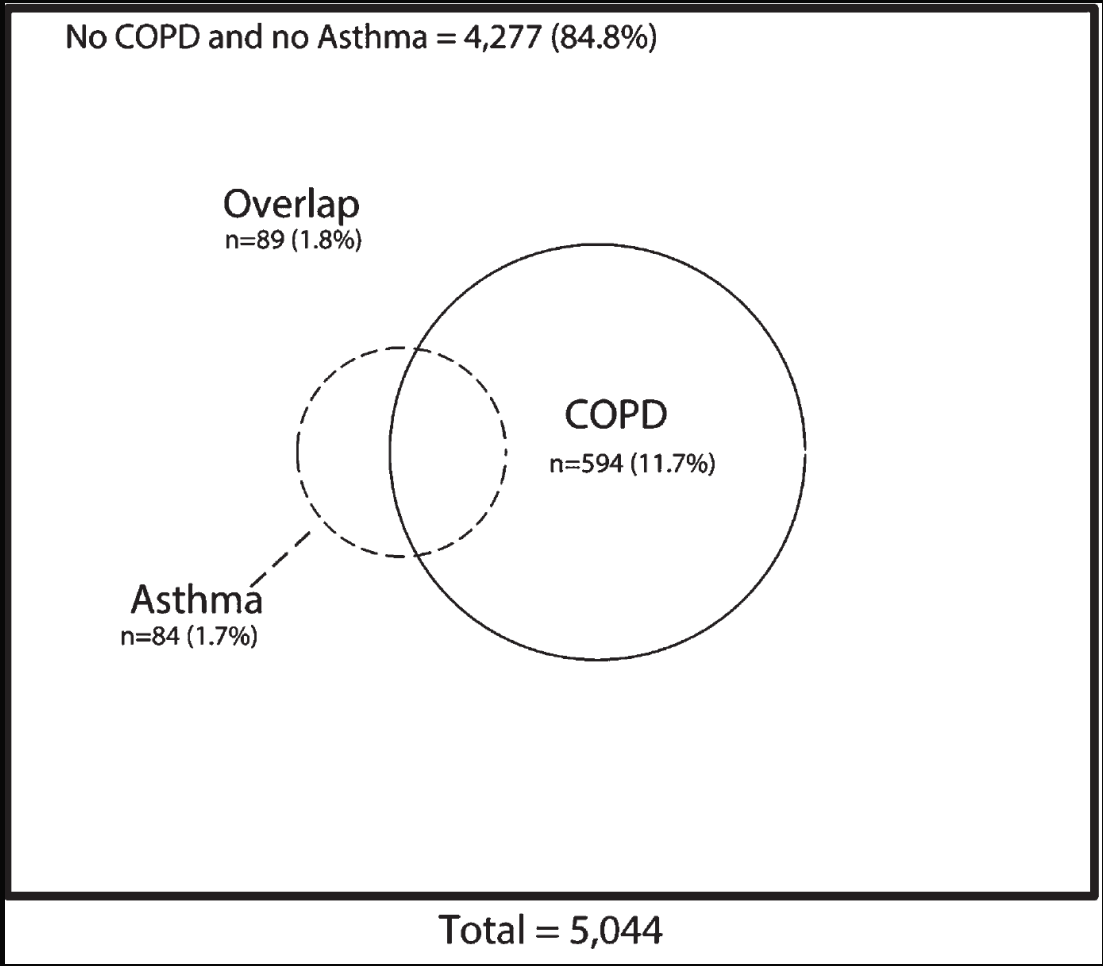
ΧΑΠ/ΑΣΘΜΑ έναντι ΧΑΠ:
Πιο συχνές, πιο σοβαρές παροξύνσεις



Hardin M, et al. *Res Res* 2011; 12: 127.

Increased Risk of Exacerbation and Hospitalization in Subjects With an Overlap Phenotype

COPD-Asthma



Menezes AM, et al; PLATINO Team. *Chest* 2014; 145: 297-304.

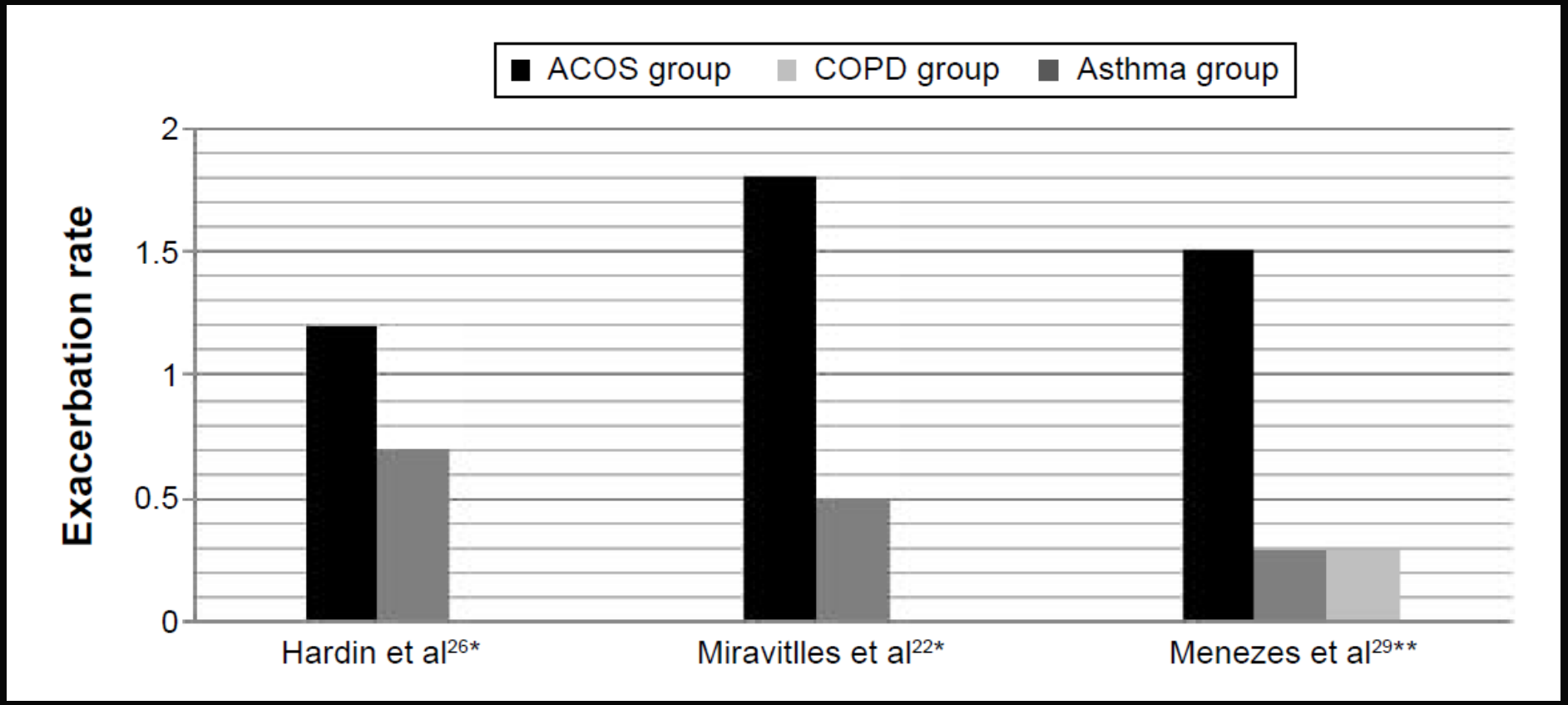
COPD-Asthma Overlap: ↓ FEV_1, ↑ παροξύνσεις, ↑ νοσηλείες

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)
Prebronchodilator FEV_1, L	2.0 ± 0.6	2.1 ± 0.8	1.7 ± 0.6
Prebronchodilator FEV_1, % predicted	79.9 ± 17.2	81.4 ± 20.0	63.5 ± 18.9
Postbronchodilator FEV_1, L	2.5 ± 0.8	2.2 ± 0.8	2.0 ± 0.7
Postbronchodilator FEV_1, % predicted	94.0 ± 17.8	82.0 ± 19.2	72.1 ± 18.9

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)
Exacerbations past year			
Unadjusted, PR (95% CI)	2.54 (1.42-4.52)	1.00 (Ref)	3.01 (1.74-5.21)
Adjusted,[a] PR (95% CI)	1.65 (0.93-2.92)	1.00 (Ref)	2.11 (1.08-4.12)
Number of exacerbations past year			
Unadjusted, RR (95% CI)	1.04 (0.40-2.69)	1.00 (Ref)	5.48 (1.74-17.22)
Adjusted,[a] RR (95% CI)	0.98 (0.32-3.02)	1.00 (Ref)	4.20 (1.05-16.62)
Hospitalizations past year			
Unadjusted, PR (95% CI)	[b]	1.00 (Ref)	4.76 (1.70-13.31)
Adjusted,[a] PR (95% CI)	[b]	1.00 (Ref)	4.11 (1.45-11.67)
Number of hospitalizations past year			
Unadjusted, RR (95% CI)	[b]	1.00 (Ref)	5.90 (1.74-20.01)
Adjusted,[a] RR (95% CI)	[b]	1.00 (Ref)	5.24 (1.49-18.38)

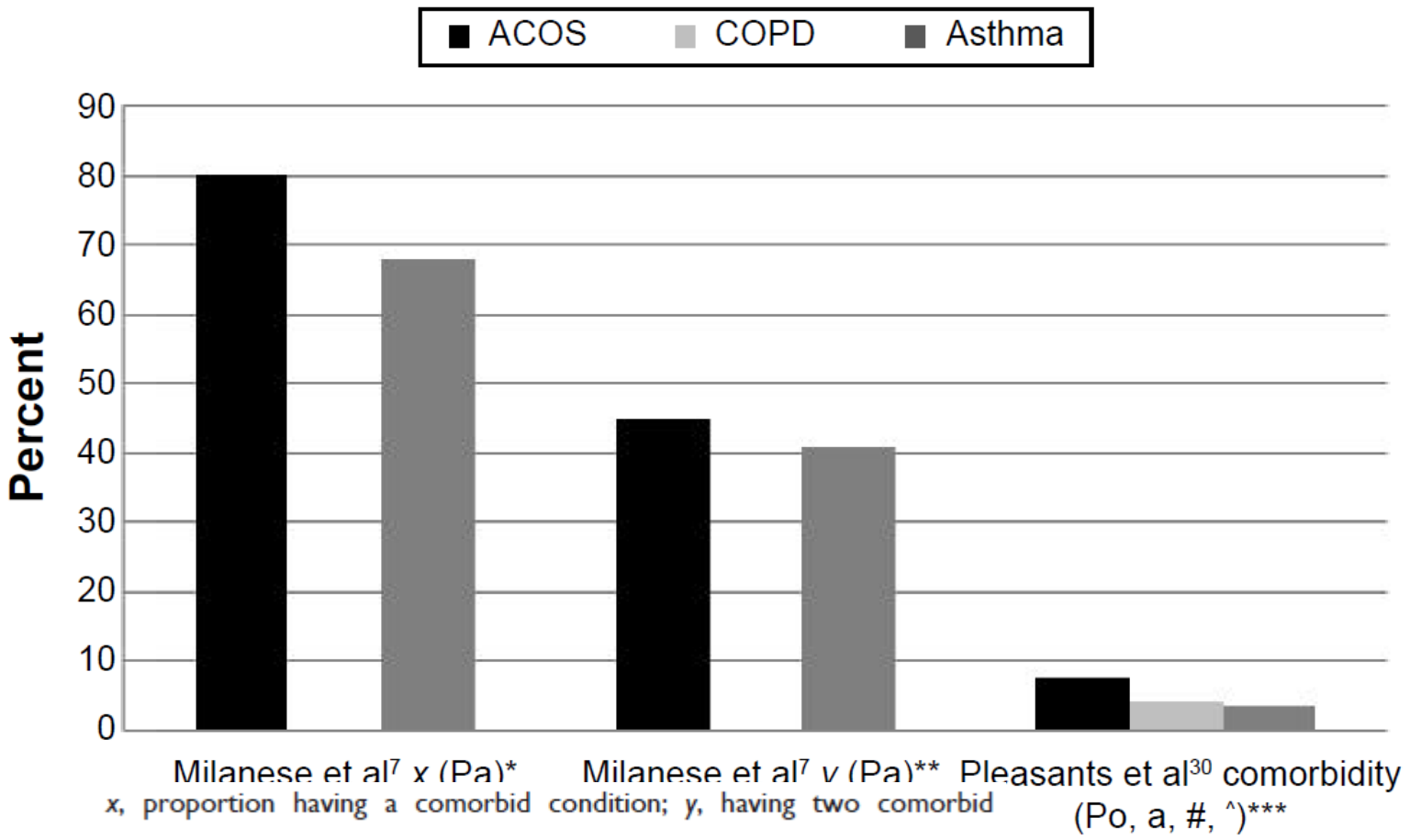
Menezes AM, et al; PLATINO Team. *Chest* 2014; 145: 297-304.

ACO έναντι Άσθματος και ΧΑΠ: ↑ Παροξύνσεις



Nielsen M, et al. *Inter J COPD* 2015

ACO: περισσότερα συνοδά νοσήματα σε σχέση με τους ασθενείς με άσθμα ή ΧΑΠ



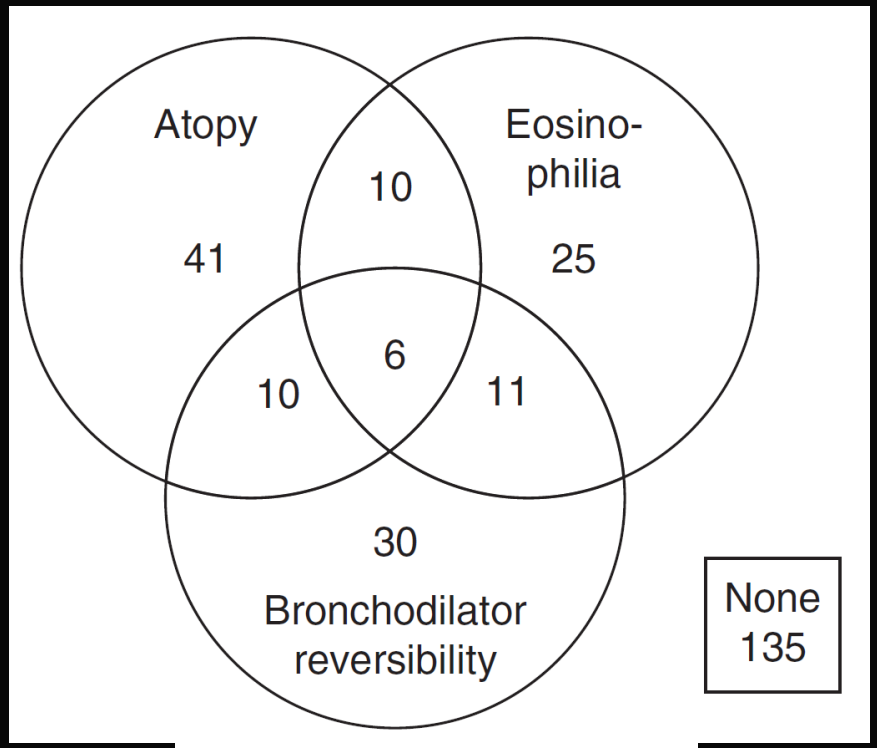
Nielsen M, et al. *Inter J COPD* 2015

Asthma-like Features and Clinical Course of Chronic Obstructive Pulmonary Disease

An Analysis from the Hokkaido COPD Cohort Study

Masaru Suzuki, Hironi Makita, Satoshi Konno, Kaoruko Shimizu, Hiroki Kimura, Hirokazu Kimura, and Masaharu Nishimura; for the Hokkaido COPD Cohort Study Investigators

First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan



$DFEV_{1\geq}$>12% and>200ml

- 268 ασθενείς με ΧΑΠ
- Καταγραφή των ετήσιων αλλαγών στον FEV_1 και παροξύνσεων τα πρώτα 5 έτη
- Θνητότητα: 10 έτη παρακολούθησης

Suzuki M, et al. *AJRCCM* 2016; 194: 1358–65.

Χαρακτηριστικά ασθενών

Characteristic	All-Negative	Reversibility	Eosinophilia	Atopy
Number of subjects	135	57	52	67
Age, yr	70 ± 8	70 ± 7	67 ± 8	68 ± 8
Female sex, n (%)	11 (8)	2 (4)	2 (4)	3 (4)
Body mass index, kg/m^2	22 ± 3	23 ± 3	24 ± 3	22 ± 3
Current smoker at entry, n (%)	40 (30)	11 (19)	9 (17)	25 (37)
Smoking index at entry, pack-years	61 ± 31	67 ± 32	67 ± 30	61 ± 26
Chronic bronchitis, n (%)	17 (13)	8 (14)	5 (10)	7 (10)
Serum total IgE, IU/ml	49 (18–113)	69 (25–225)	85 (37–250)*†	190 (45–393)*†
Blood eosinophils, cells/μl	132 (86–190)	195 (102–347)*†	387 (345–462)*†	180 (112–295)*†
Post-bronchodilator FEV_1, % predicted	64 ± 22	60 ± 15	65 ± 21	68 ± 23
Reversibility of FEV_1, %	8 ± 7	26 ± 11*‡	14 ± 14*‡	12 ± 13*‡
D_{LCO}, % predicted	74 ± 26	82 ± 22*‡	79 ± 20	81 ± 25
K_{CO}, % predicted	62 ± 25	65 ± 22	68 ± 23	64 ± 24
CT emphysema score	1.2 (0.7–2.2)	1.1 (0.6–2.0)	1.1 (0.7–2.0)	1.0 (0.7–1.7)
SGRQ total score	31 ± 17	36 ± 17*‡	30 ± 19	30 ± 18
Any cardiovascular disease, n (%)	29 (21)	16 (28)	12 (23)	14 (21)
Ischemic heart disease, n (%)	6 (4)	5 (9)	6 (12)	5 (7)
Diabetes, n (%)	7 (5)	2 (4)	3 (6)	4 (6)

Suzuki M, et al. *AJRCCM* 2016; 194: 1358–65.

Ασθενείς με «ασθματικά χαρακτηριστικά» vs ασθενείς με «αμιγή ΧΑΠ»: μεγαλύτερη αναλογία ασθενών σε ICS

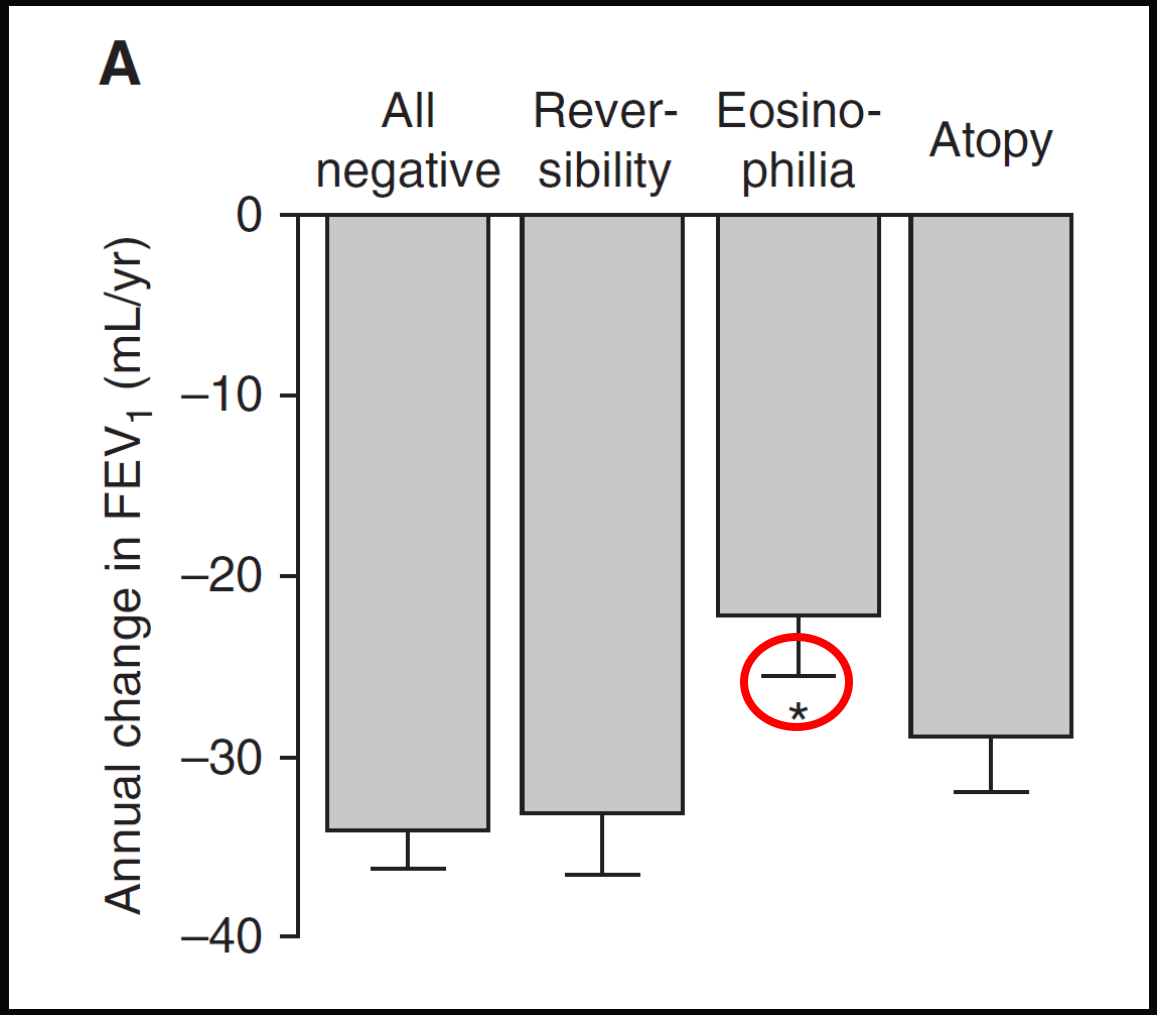
Ασθενείς με αναπόκριση στη βρογχοδιαστολή: περισσότερα βρογχοδιασταλτικά φάρμακα

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

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

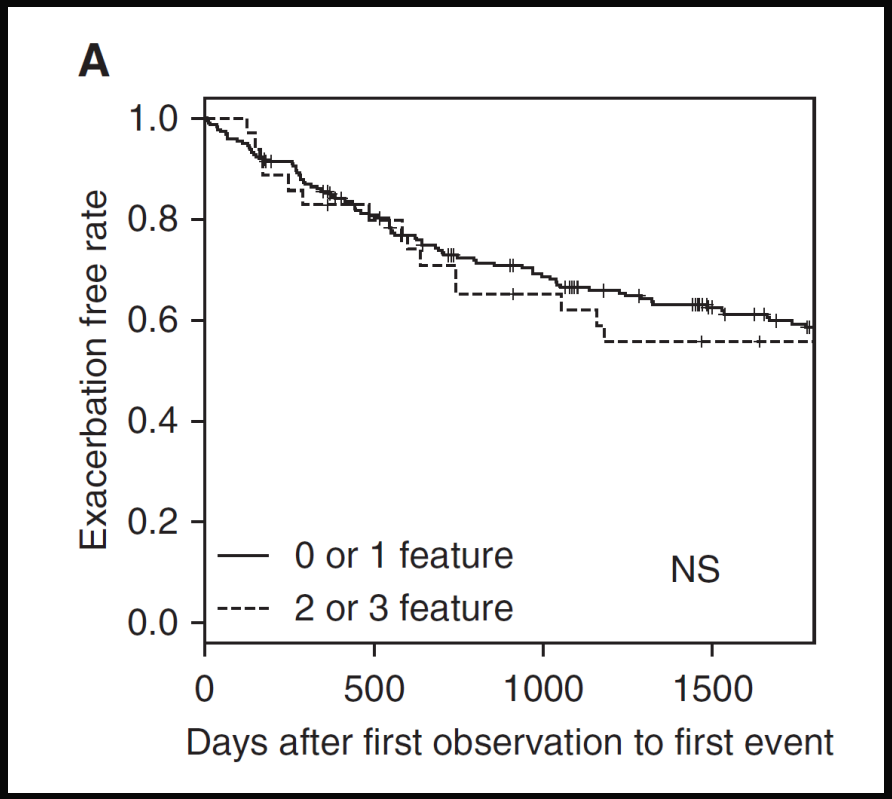
Suzuki M, et al. *AJRCCM* 2016; 194: 1358–65.

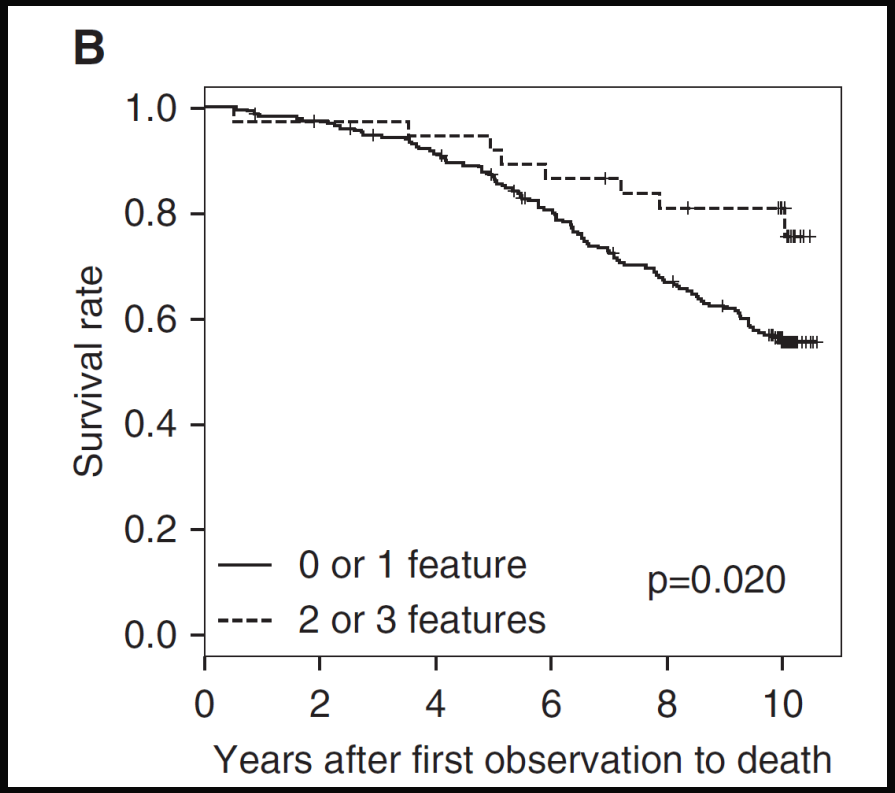
Ασθενείς με ΧΑΠ και ηωσινοφιλία: μικρότερη ετήσια έκπτωση αναπνευστικής λειτουργίας



Suzuki M, et al. *AJRCCM* 2016; 194: 1358–65.

«Ασθματικά χαρακτηριστικά» = καμία διαφορά στις παροξύνσεις, μικρότερη θνητότητα





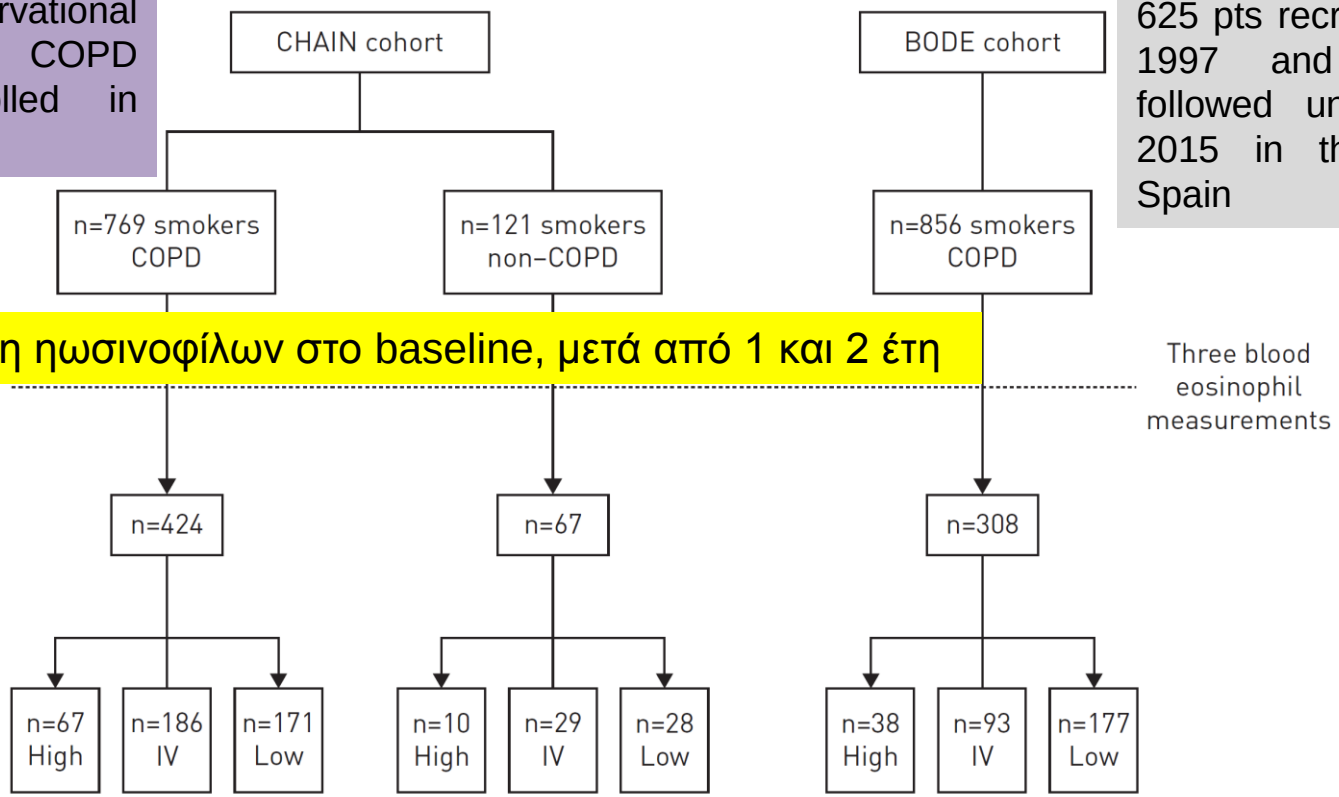
Suzuki M, et al. *AJRCCM* 2016; 194: 1358–65.

Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD

ongoing observational study of 24 COPD cohorts enrolled in Spain

625 pts recruited between 1997 and 2011 and followed until December 2015 in the USA and Spain

Μέτρηση ηωσινοφίλων στο baseline, μετά από 1 και 2 έτη



Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

TABLE 2 Baseline characteristics of blood eosinophil longitudinal patterns in patients with chronic obstructive pulmonary disease (COPD) (CHAIN cohort) using ⩾300 cells·μL^{-1} as the cut-off point

	Persistently high ⩾300 cells·μL^{-1}	Intermittently variable	Persistently low <300 cells·μL^{-1}	p-value
Patients n	67	186	171	
Male	60 (90)	156 (84)	139 (81)	0.298
Age years	66±8	68±9	67±9	0.148
Pack-years	55±29	55±28	57±31	0.779
Active smoking	31	29	27	0.729
BMI kg·m^{-2}	29.8±5.5	28.2±4.9	28.2±4.7	0.114
FEV_1 L	1.80±0.63	1.63±0.64	1.69±0.62	0.150
FEV_1 % pred	61±18	60±20	60±19	0.949
$P_{a}O_2$ mmHg	69.6±7.4	67.5±9.0	68.9±9.3	0.446
FVC L	3.37±0.94	3.08±0.92	3.15±0.93	0.094
FVC % pred	87±22	86±24	86±22	0.974
FEV_1/FVC	54±11	53±11	54±10	0.704
6MWD m	461±95	438±99	451±89	0.175
Dyspnoea mMRC	1 (0–3)	1 (0–4)	1 (0–3)	0.212
BODE index	1 (0–5)	2 (0–6)	1 (0–5)	0.346
IC/TLC	0.36±0.09	0.34±0.09	0.35±0.09	0.091
K_{CO} % pred	82±25	73±23	74±24	0.059
Charlson index	1 (0–5)	1 (0–4)	1 (0–4)	0.158
Inhaled anticholinergic	64	76	71	0.172
Inhaled β_2-agonist	73	75	70	0.483
Inhaled corticosteroid	64	68	59	0.233
CAT	11 (1–27)	12 (2–27)	10 (2–24)	0.297
IgE total U·L^{-1}	50 (8–1158)	62 (7–690)	26 (5–504)	<0.001

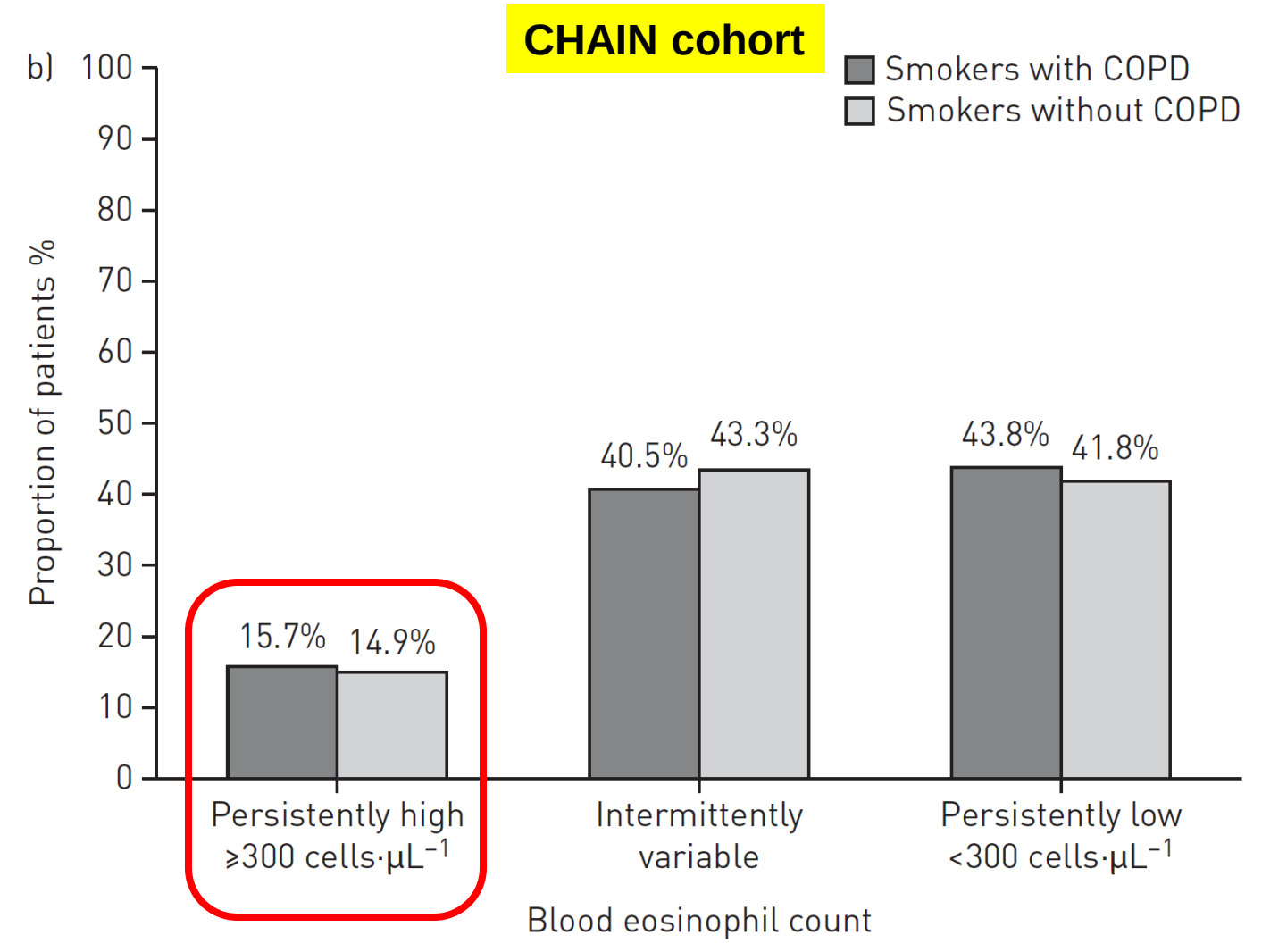
Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

TABLE 3 Baseline characteristics of blood eosinophil longitudinal patterns in patients with chronic obstructive pulmonary disease (BODE cohort) using ⩾300 cells·μL^{-1} as the cut-off point

	Persistently high ⩾300 cells·μL^{-1}	Intermittently variable	Persistently low <300 cells·μL^{-1}	p-value
Patients n	38	93	177	
Male	30 (79)	76 (82)	143 (81)	0.930
Age years	63±8	66±9	65±9	0.386
Pack-years	64±33	59±30	61±33	0.701
Active smoking	42	33	29	0.298
BMI kg·m^{-2}	28.2±6.1	28.2±4.9	27.8±4.7	0.655
FEV_1 L	1.58±0.53	1.52±0.56	1.56±0.68	0.877
FEV_1 % pred	60±18	60±22	59±22	0.959
FVC L	2.92±0.76	3.02±0.80	2.98±0.85	0.839
FVC % pred	84±18	84±22	85±24	0.874
FEV_1/FVC	53±12	51±13	50±13	0.289
6MWD m	397±131	379±132	418±115	0.058
Dyspnoea mMRC	1 (0–4)	1 (0–4)	1 (0–3)	0.340
BODE index	1 (0–7)	1 (0–6)	1 (0–6)	0.384
IC/TLC	0.34±0.05	0.34±0.11	0.33±0.11	0.913
***K*CO % pred**	74±23	74±20	72±20	0.718
Charlson index	2 (0–4)	1 (0–5)	1 (0–4)	0.624
Inhaled anticholinergic	60	65	65	0.853
Inhaled β_2-agonist	65	58	65	0.529
Inhaled corticosteroid	65	55	58	0.563

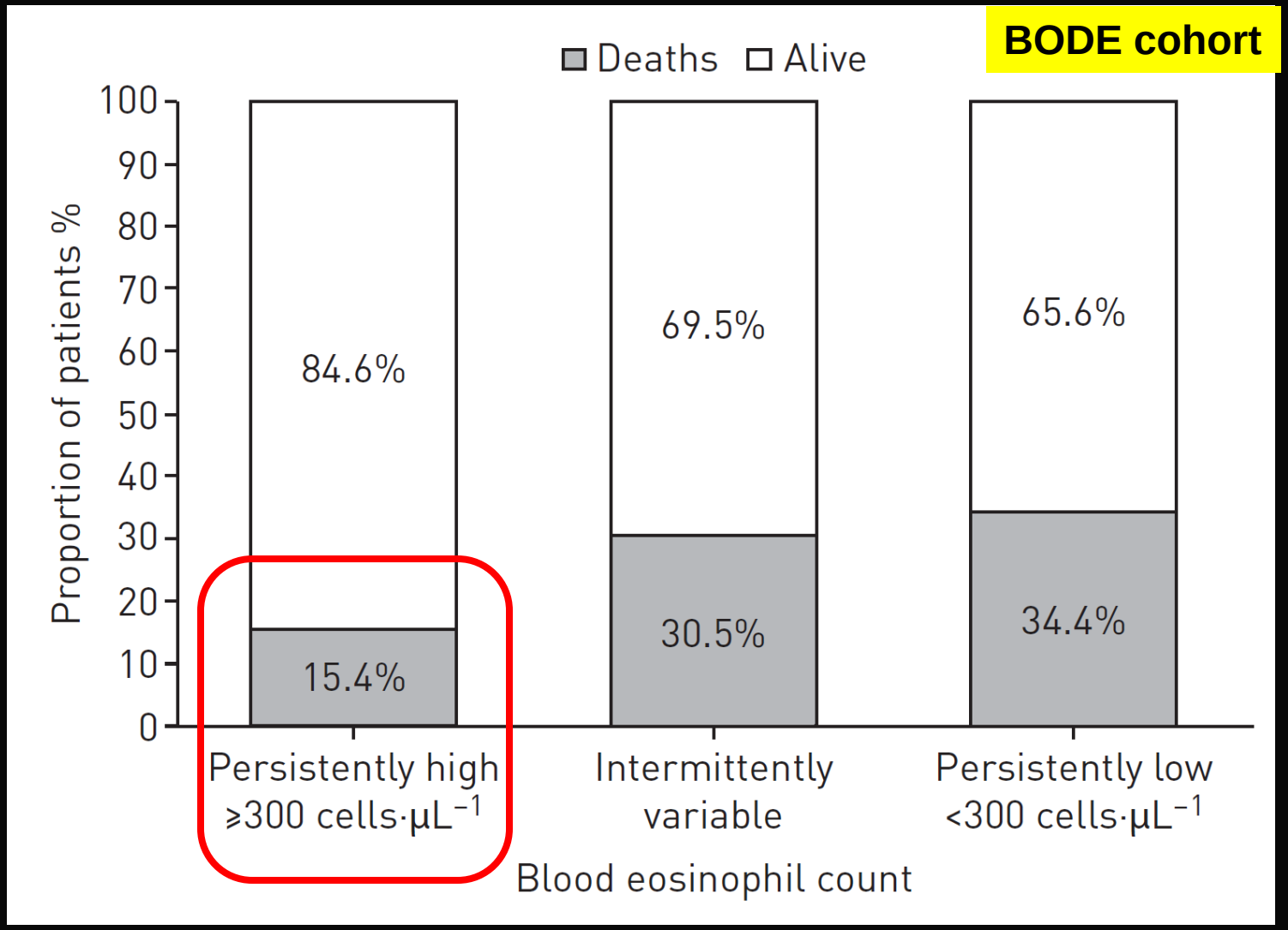
Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

Καπνιστές με ή χωρίς ΧΑΠ: το 15% έχει «σταθερή» ηωσινοφιλία



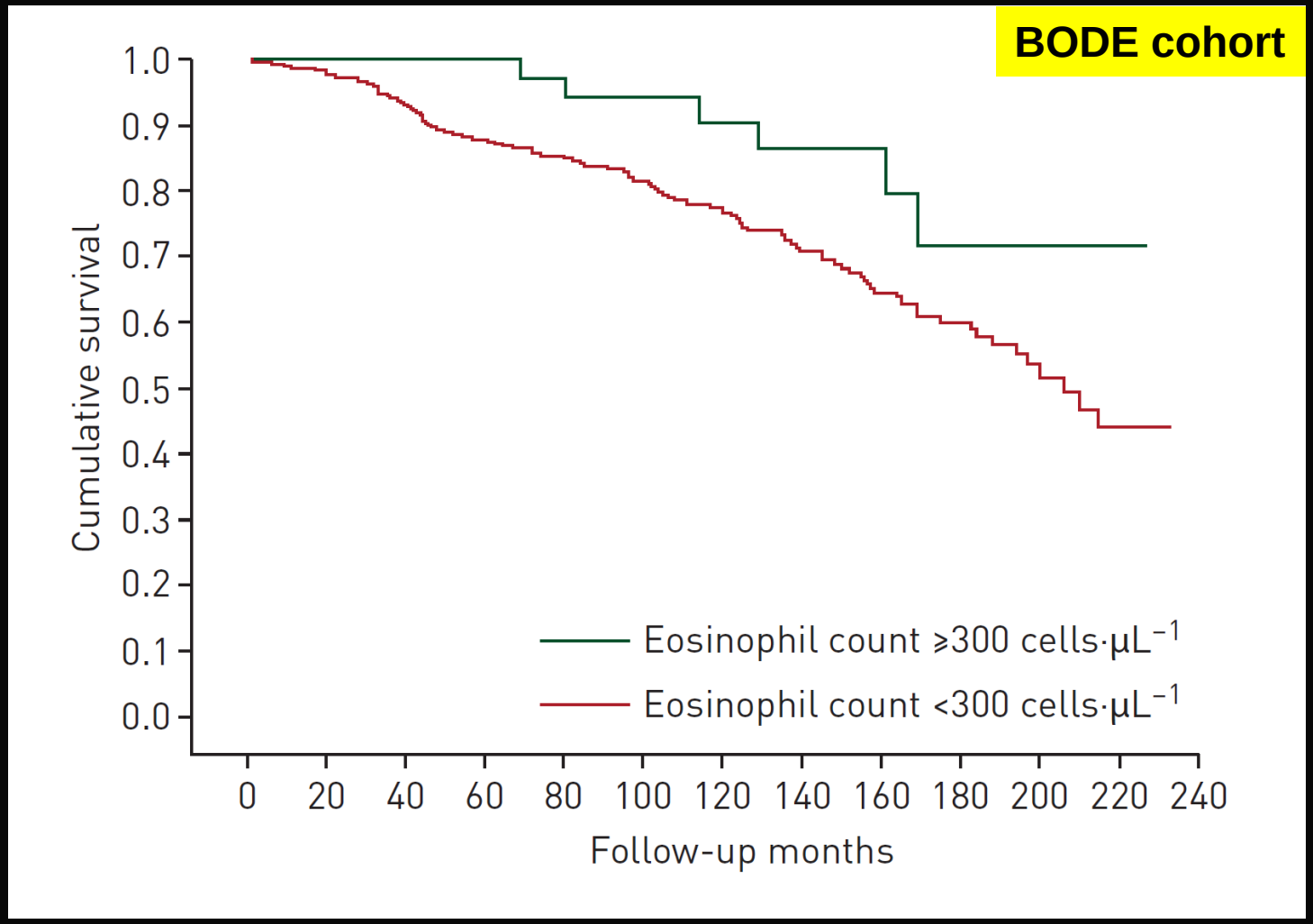
Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

Καπνιστές με ΧΑΠ: το 15% έχει «σταθερή» ηωσινοφιλία και μικρότερη θνητότητα



Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

ΧΑΠ και Ηωσινόφιλα 300 ≥ cells·μL^{-1} = συσχέτιση με καλύτερη επιβίωση



Casanova C, et al. *Eur Respir* J 2017; 50: 1701162.

Asthma–COPD Overlap

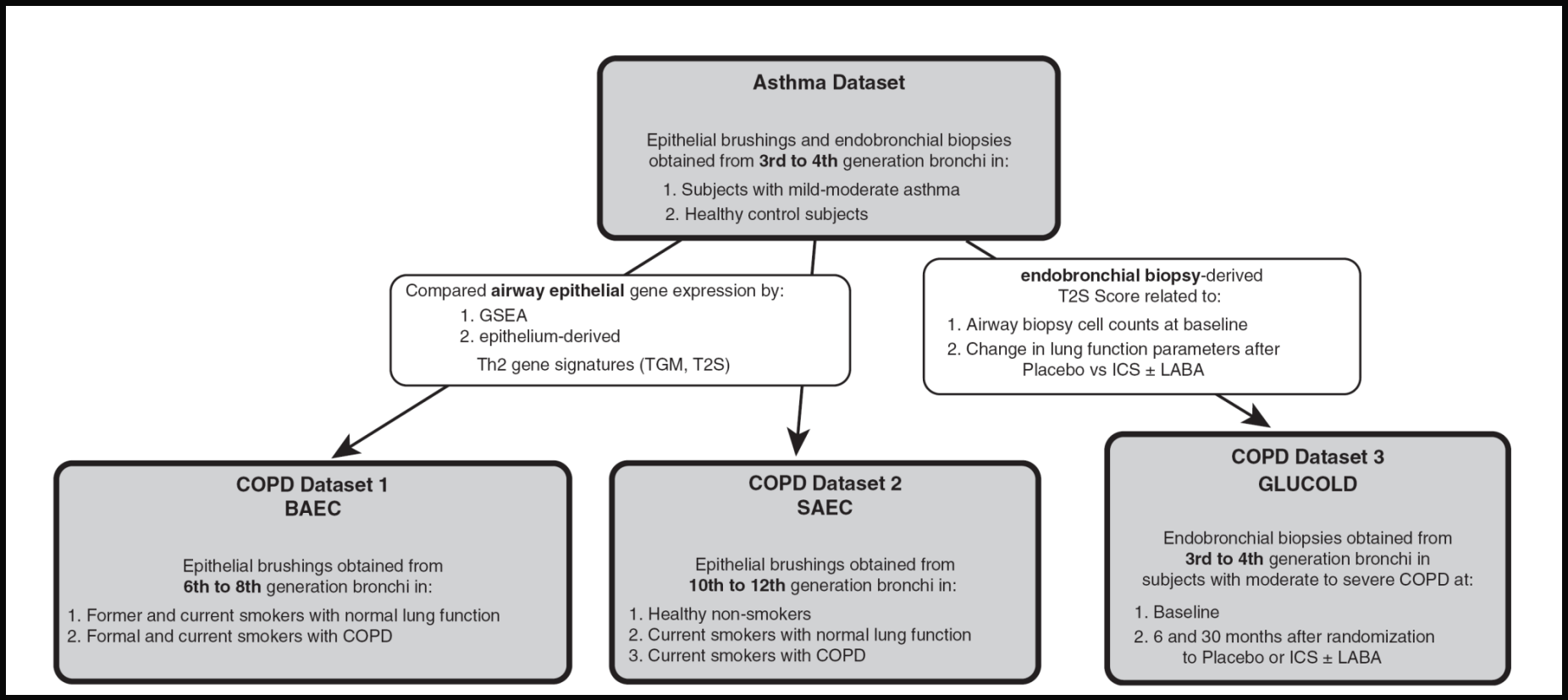
Clinical Relevance of Genomic Signatures of Type 2 Inflammation in Chronic Obstructive Pulmonary Disease

Stephanie A. Christenson[1,2], Katrina Steiling[3,4], Maarten van den Berge[5,6], Kahkeshan Hijazi[7], Pieter S. Hiemstra[8], Dirkje S. Postma[5,6], Marc E. Lenburg[3,4,9], Avrum Spira[3,4,9], and Prescott G. Woodruff[1,2]

- Υπόβαθρο μελέτης
- Μερικοί ασθενείς με ΧΑΠ παρουσιάζουν κλινική αλληλεπικάλυψη με το άσθμα, υποδεικνύοντας πως φλεγμονώδεις διαδικασίες σχετιζόμενες με το άσθμα πιθανώς παίζουν σημαντικό ρόλο σε αυτό το υποσύνολο των ασθενών με ΧΑΠ
- Σε αυτό το υποσύνολο των ασθενών με ΧΑΠ πιθανώς η θεραπεία με ICS να είναι περισσότερο αποτελεσματική
- Σκοπός μελέτης
- Η ανεύρεση «γονιδιακών υπογραφών σχετιζόμενων με άσθμα» σε ασθενείς με ΧΑΠ

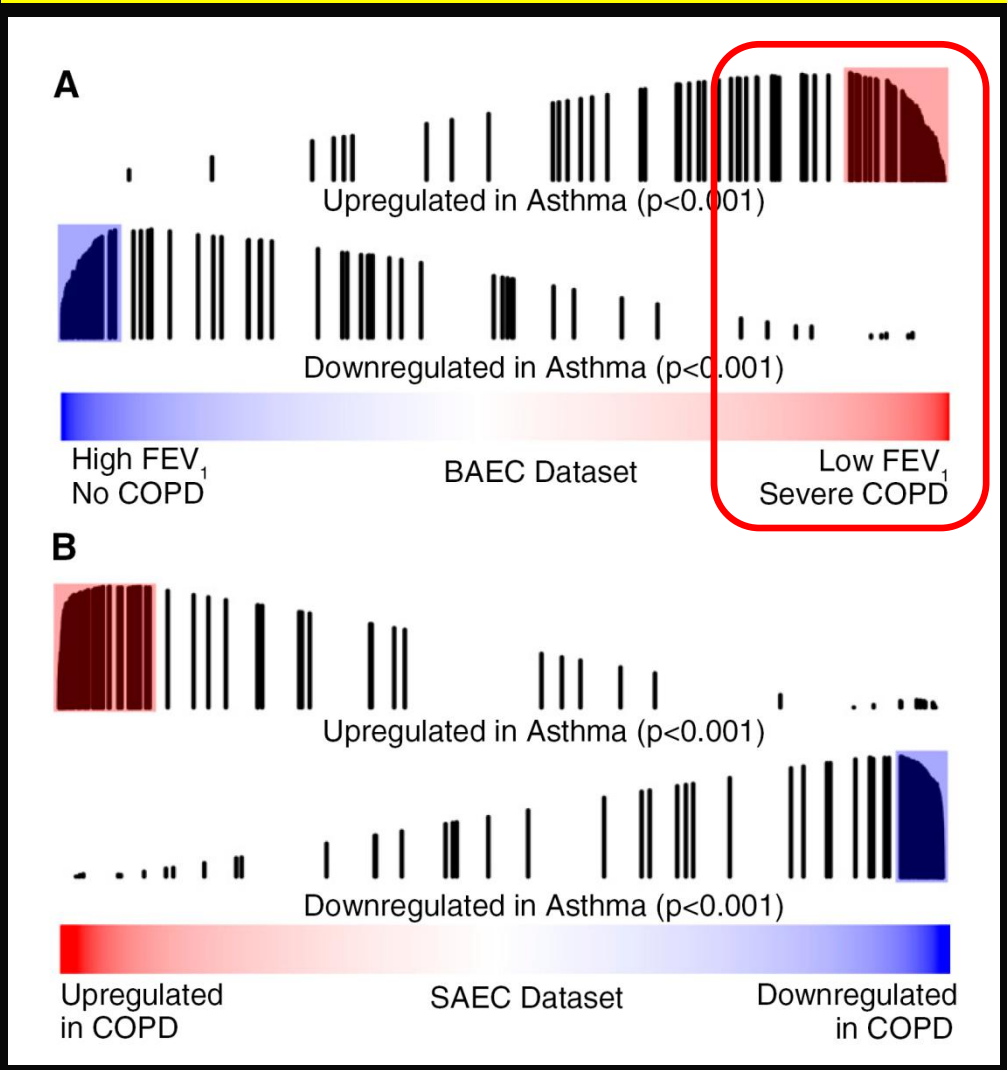
Christenson SA, et al. *AJRCCM* 2015; 191: 758-66.

Υλικό μελέτης



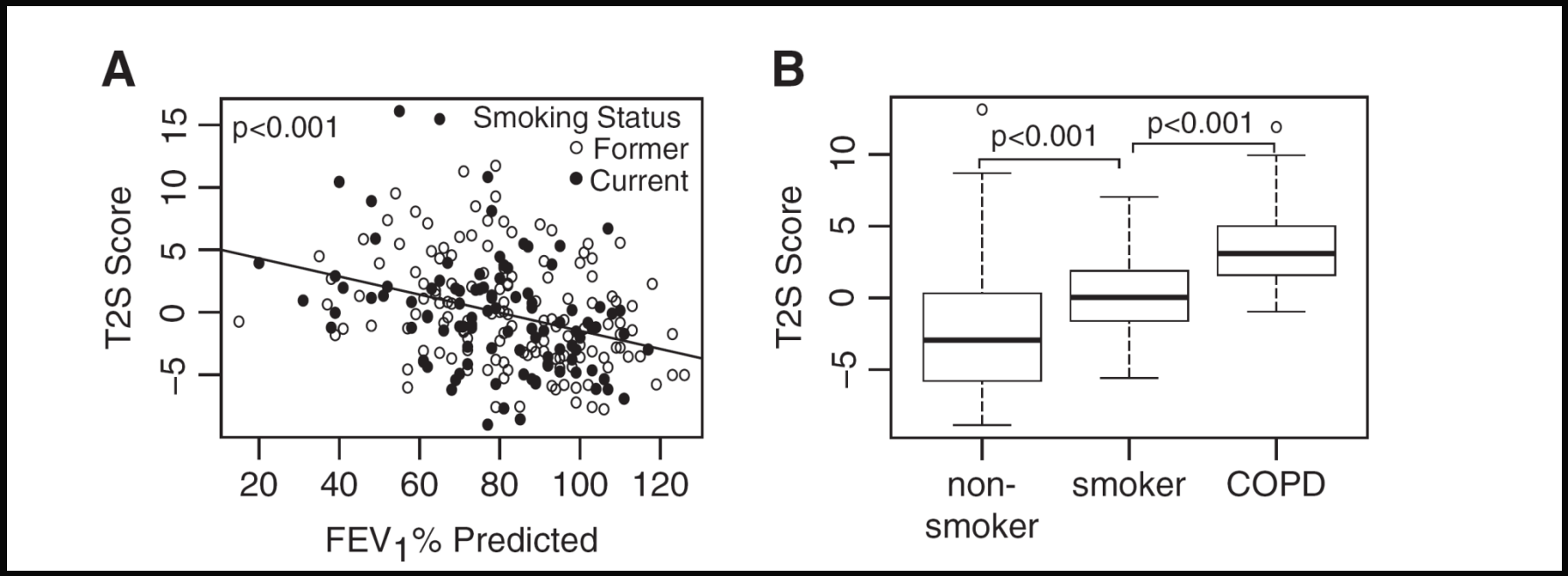
Christenson SA, et al. *AJRCCM* 2015; 191: 758-66.

Τα 100 πιο υπερεκφρασμένα γονίδια στο επιθήλιο των αεραγωγών στο άσθμα υπερεκφράζονται και στο επιθήλιο ασθενών με σοβαρή ΧΑΠ



Genes most altered in the airway epithelium in asthma evaluated in COPD using gene set enrichment analysis (GSEA). The length of the lines represents the magnitude of the GSEA running enrichment score

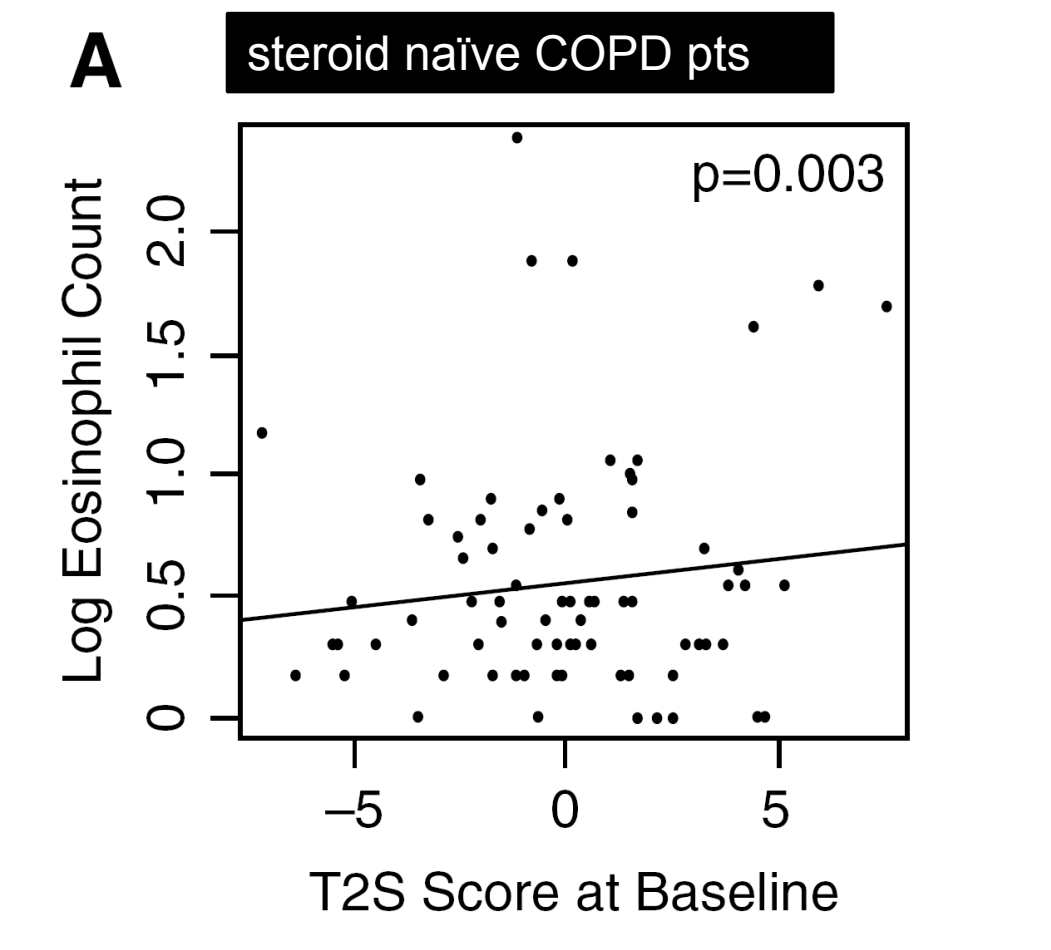
↑T2S (T_H2 φλεγμονή): Θετική συσχέτιση με ↓ FEV_1



The T_H2 signature (T2S) score, a gene expression metric induced in Th2-high asthma, was evaluated in these COPD cohorts.

Christenson SA, et al. *AJRCCM* 2015; 191: 758-66.

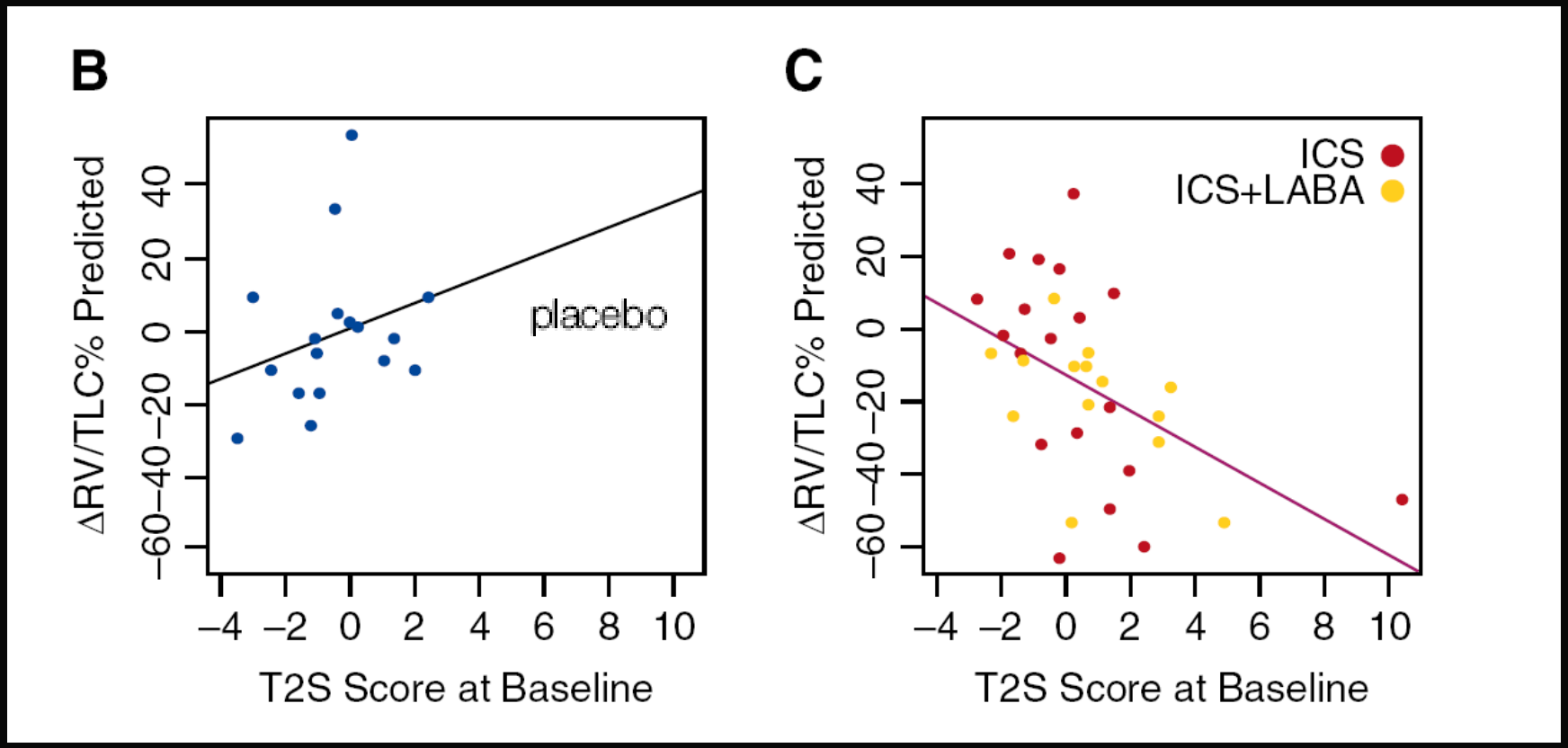
↑T2S (T_H2 φλεγμονή) : θετική συσχέτιση με ηωσινοφιλική φλεγμονή



•The T2S score derived from endobronchial biopsy data

Christenson SA, et al. *AJRCCM* 2015; 191: 758-66.

ICS: μικρότερη υπερδιάταση σε ασθενείς με ΧΑΠ και ↑T2S (T_H2 φλεγμονή)

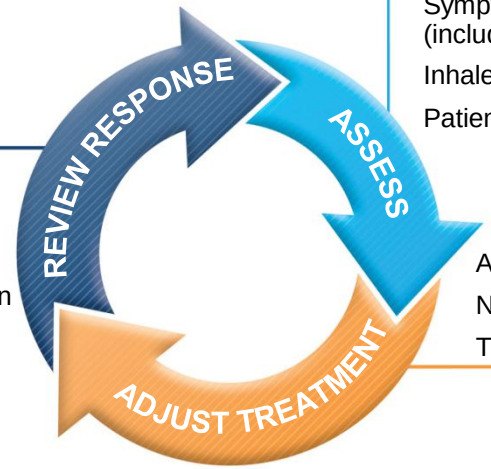


Christenson SA, et al. *AJRCCM* 2015; 191: 758-66.

Stepwise management - pharmacotherapy

ACO = Σοβαρό άσθμα (βήμα 4, 5)

GINA 2018



Diagnosis

Symptom control & risk factors (including lung function)

Inhaler technique & adherence

Patient preference

Symptoms

Exacerbations

Side-effects

Patient satisfaction

Lung function

Asthma medications

Non-pharmacological strategies

Treat modifiable risk factors

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA)* *Low dose theophylline**	*Med/high dose ICS* *Low dose ICS + LTRA (or + theoph*)*	*Add tiotropium*†* *Med/high dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta2-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

© Global Initiative for Asthma

Ουδετεροφιλικό άσθμα: Μακρολίδες;

- Μακροχρόνια χορήγηση μακρολιδών στο μη ηωσινοφιλικό άσθμα: μείωση παροξύνσεων και διάρκειας οξέων συμβαμάτων

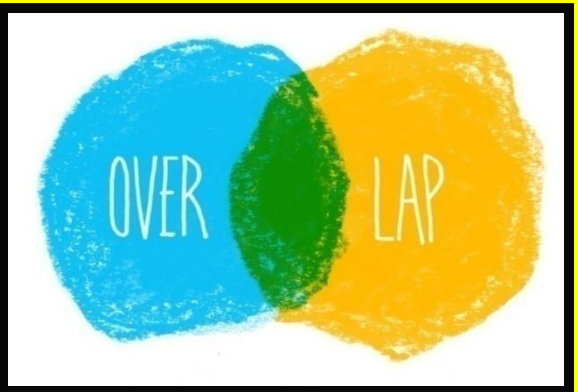
Brusselle GG, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013; 68: 322- 9.

- Μακροχρόνια χορήγηση μακρολιδών στο μη ηωσινοφιλικό άσθμα: καμία επίδραση στις παροξύνσεις, στην αναπνευστική λειτουργία και στον έλεγχο του άσθματος

Cameron EJ, et al. *Eur Respir J* 2013; 42: 1412-5.
Sutherland ER, et al. *J Allergy Clin Immunol* 2010; 126:n747-53.
Kostadima E, et al. *Eur Respir J* 2004; 23: 714-7.
Black PN, et al. *Am J Respir Crit Care Med* 2001; 164: 536-41.
Amayasu H,et al.. *Ann Allergy Asthma Immunol* 2000; 84: 594-8.
Shoji T, et al. *Clin Exp Allergy* 1999; 29: 950-6.
Strunk RC, et al. *J Allergy Clin Immunol* 2008; 122: 1138- 44.

ACO: Από την μεριά της ΧΑΠ

CAO



(COPD Asthma Overlap)

Ασθενής με CAO

Σύγκριση με ασθενή με ΧΑΠ

- Χειρότερη αναπνευστική λειτουργία
- Περισσότερα συμπτώματα
- Συχνότερες παροξύνσεις
- Σοβαρότερες παροξύνσεις
- Συχνότερη χρήση υπηρεσιών υγείας/ ↑ νοσηλείες
- Χειρότερη ποιότητα ζωής

} **D**

Ανάγκη για εντατικοποίηση θεραπείας

Επιβεβαίωση της διάγνωσης με σπιρομέτρηση → **Εκτίμηση του περιορισμού της ροής του αέρα** → **Εκτίμηση των συμπτωμάτων/κινδύνου παρόξυνσης**

Μετά βρογχοδιαστολή $FEV_1/FVC < 0.7$

	FEV_1
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

Ιστορικό μέτριων/σοβαρών παροξύνσεων

- **≥ 2 ή ≥ 1 που οδηγεί σε νοσηλεία**
- **0 ή 1 (που δεν οδηγεί σε νοσηλεία)**

(C)	(D)
(A)	(B)

mMRC 0-1	mMRC ≥ 2
CAT < 10	CAT ≥ 10

Συμπτώματα

GOLD 2019

Μη φαρμακευτική διαχείρηση της ΧΑΠ

Ομάδα	Απαραίτητα	Συνιστώμενα	Εξαρτώνται από τις τοπικές κατευθυντήριες οδηγίες
A	Διακοπή καπνίσματος (μπορεί να περιλαμβάνει και φαρμακευτική θεραπεία)	Σωματική άσκηση	Αντιγριπικός εμβολιασμός Αντιπνευμονιοκοκκικός εμβολιασμός
B, C, D	Διακοπή καπνίσματος (μπορεί να περιλαμβάνει και φαρμακευτική θεραπεία) Πνευμονική αποκατάσταση	Σωματική άσκηση	Αντιγριπικός εμβολιασμός Αντιπνευμονιοκοκκικός εμβολιασμός

GOLD 2019

Group D

- In some patients, initial therapy with LABA/ICS may be the first choice.
- This treatment has the greatest likelihood of reducing exacerbations in patients with blood eosinophil counts ≥ 300 cells/μL.
- LABA/ICS may also be first choice in COPD patients with a history of asthma.
- ICS may cause side effects such as pneumonia, so should be used as initial therapy only after the possible clinical benefits versus risks have been considered.

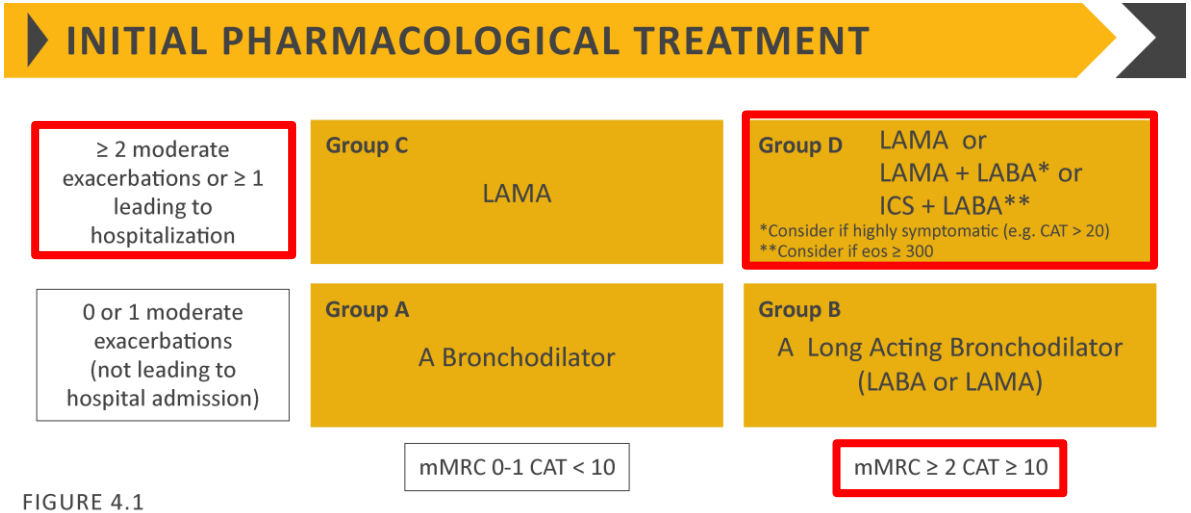


FIGURE 4.1

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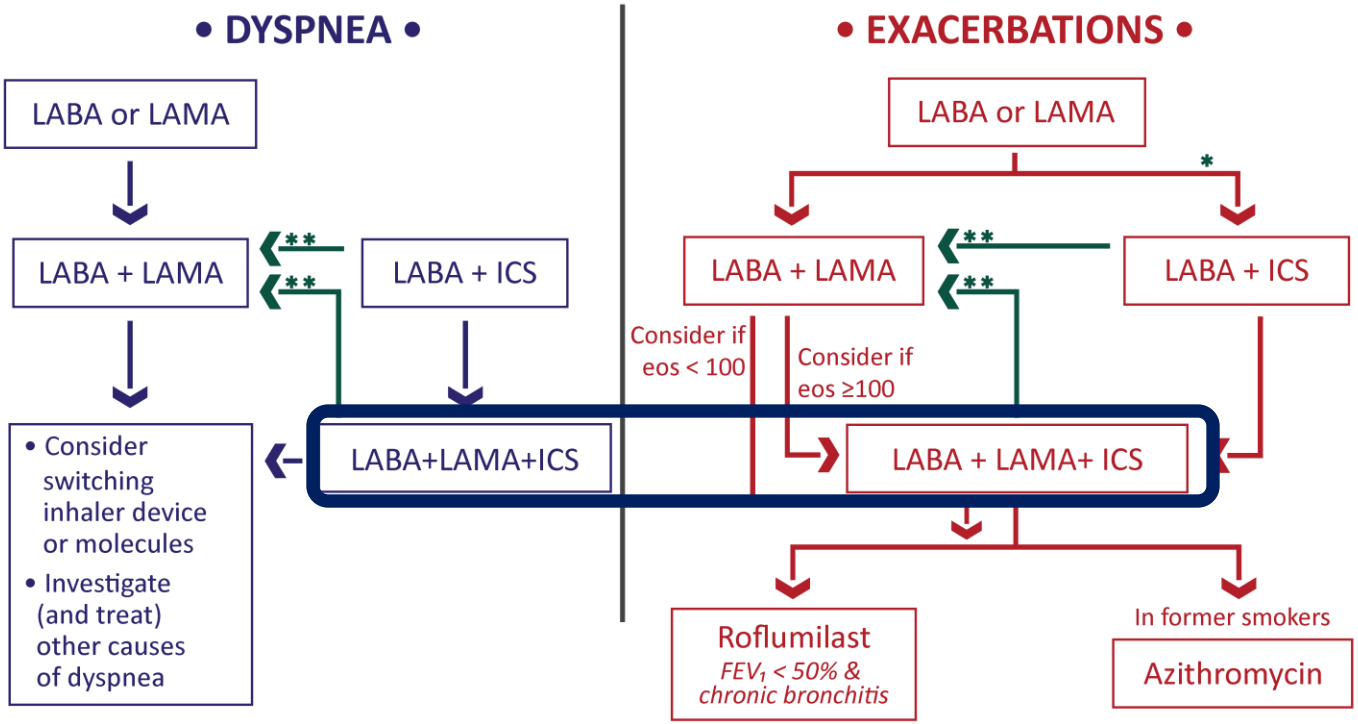
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



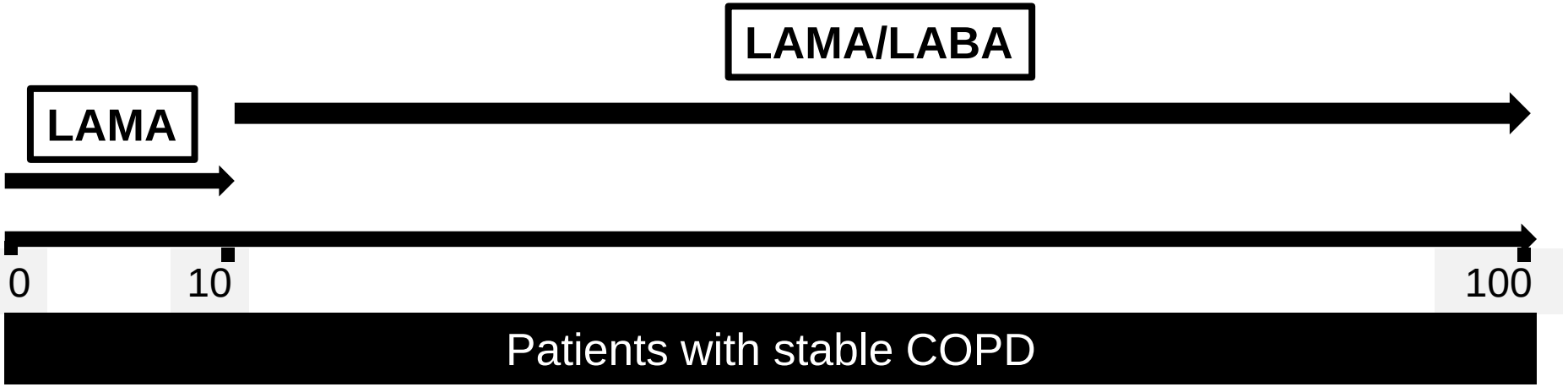
eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

GOLD 2019

1. **ACO**
2. Blood eosinophils (≥ 4%, ≥ 300 per µL) + Exacerbations
3. Frequent Exacerbations (≥ 2 per year, ≥ 1 leading to hospital admission) despite therapy with LAMA/LABA
4. Symptomatic pts with FEV_1 < 50% pred and ≥ 1 moderate/severe exacerbation

ICS as add-on therapy



G. Hillas

Πως η ΧΑΠ γίνεται CAO?

1. Ευαισθητοποίηση (αλλεργιογόνα)

2. Βρογχική υπεραντιδραστικότητα

3. Ηωσινοφιλική T_H2 φλεγμονή

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 4. Blood eosinophils >5%	1 major criteria OR 2 minor criteria
Sin, 2016[17]	**COPD plus:** 1. Persistent airflow limitation (post-bronchodilator FEV_1/FVC <0.7 or LLN in patients ≥40 years of age) 2. ≥10 pack years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure 3. Documented history of asthma before 40 years of age OR bronchodilator reversibility >400 mL in FEV_1	**COPD plus:** 1. Documented history of atopy or allergic rhinitis 2. Bronchodilator reversibility of FEV_1 ≥200 mL and 12% from baseline on ≥2 visits 3. Peripheral blood eosinophil count of ≥300 cells/mL	3 major criteria AND 1 minor criteria
Cataldo, 2017[23]	**ACOS in a COPD patient:** 1. High degree of variability in airway obstruction over time: FEV_1 variation ≥400 mL 2. High degree of response to bronchodilators: >200 mL and 12% above baseline	**ACOS in a COPD patient:** 1. Personal or family history of atopy and/or IgE sensitivity to one or more airborne allergens 2. Elevated blood or sputum eosinophils or increased FeNO 3. Asthma diagnosed before the age of 40 4. Symptom variability 5. Age (in favour of asthma)	2 major criteria AND 1 minor criterion
	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	

Janice M Leung, Don D Sin. *BMJ* 2017; 358: j3772.

Ειδικές στοχευμένες θεραπείες με μονοκλωνικά αντισώματα;

- Anti-IgE θεραπείες (omalizumab)
- Anti-IL-5/IL-5Rα θεραπείες (mepolizumab, reslizumab, benralizumab)
- Anti-IL-13/IL-4Rα θεραπείες (lebrikizumab/tralokinumab target IL-13, dupilumab target both IL-13 and IL-4)

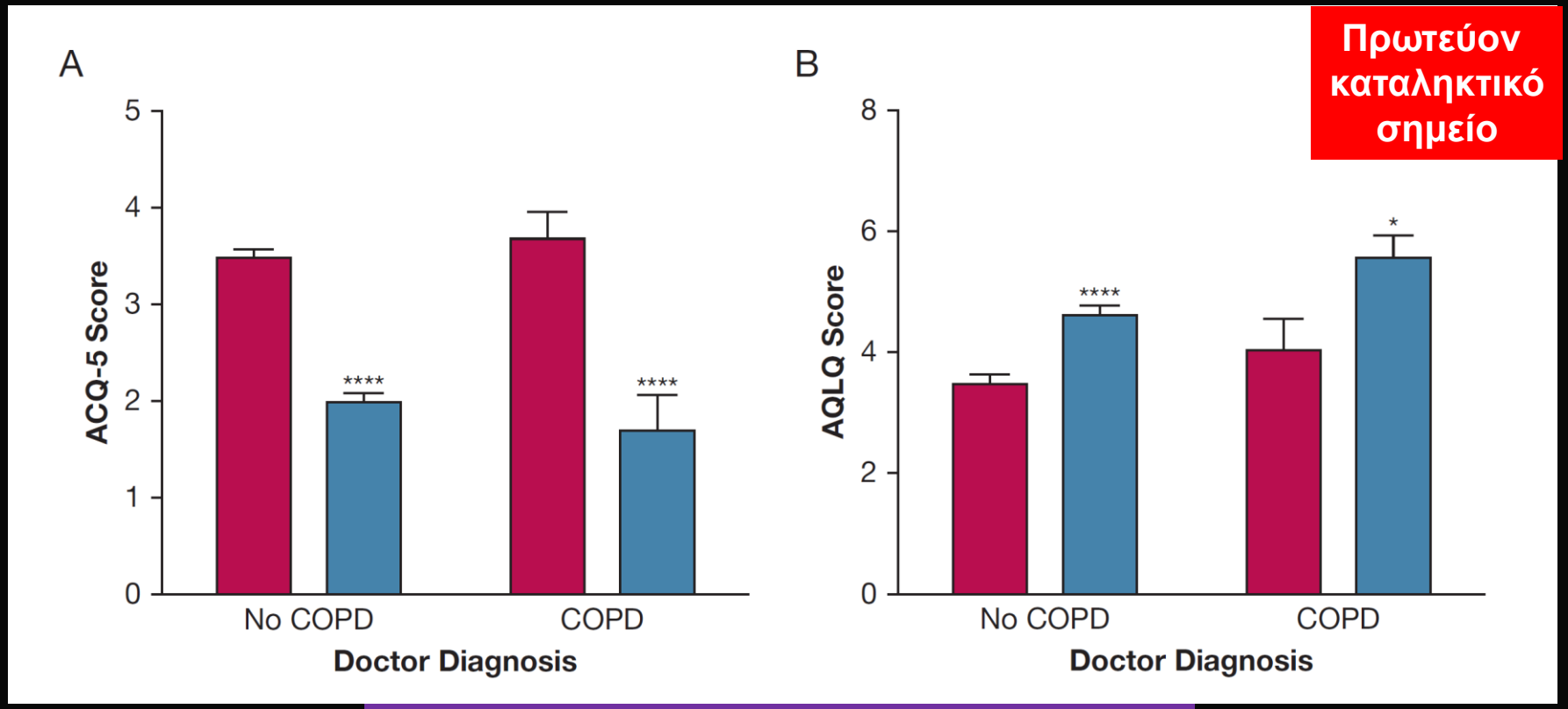
Omalizumab Treatment Response in a Population With Severe Allergic Asthma and Overlapping COPD

- Δεδομένα από το Australian Xolair Registry: σύγκριση της θεραπευτικής ανταπόκρισης σε ασθενείς με σοβαρό άσθμα/ΧΑΠ και ασθενείς με σοβαρό άσθμα
- Διαφορετικοί ορισμοί για ACO

1. Προηγούμενη διάγνωση ΧΑΠ ή όχι
2. Σπιρομέτρηση (baseline) FEV_1 < 80% pred μετά βρογχοδιαστολή ή όχι
3. Εάν FEV_1 < 80%, περαιτέρω ανάλυση με βάση το ιστορικό καπνιστικής συνήθειας

Maltby S, et al. *CHEST* 2017; 151: 78-89.

ACO/Ομαλιζουμάμπη: βελτίωση ελέγχου της ασθματικής συνιστώσας



•baseline (red bars)
• 6-month follow-up of omalizumab therapy (blue bars)

Maltby S, et al. *CHEST* 2017; 151: 78-89.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

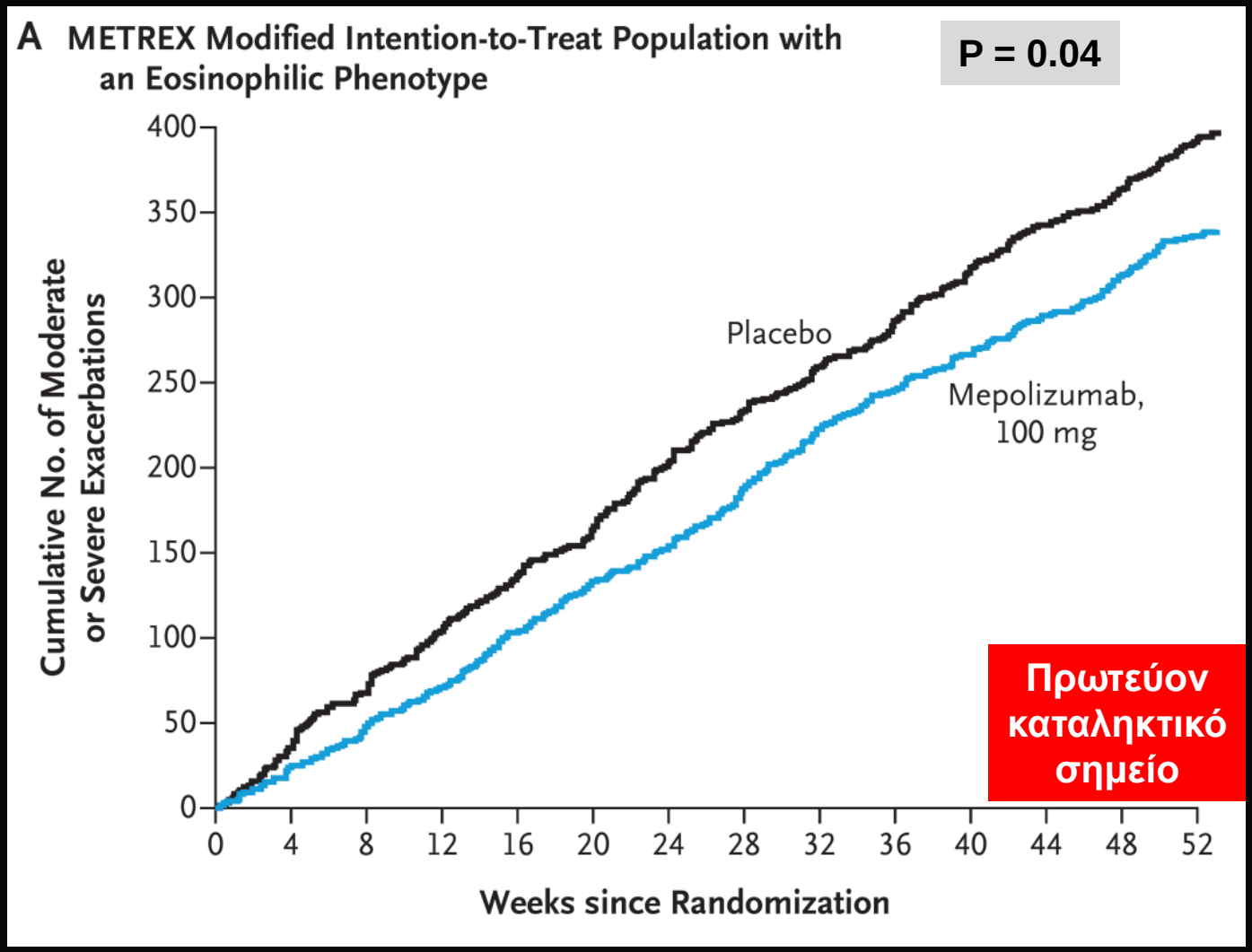
I.D. Pavord, P. Chanez, G.J. Criner, H.A.M. Kerstjens, S. Korn, N. Lugogo, J.-B. Martinot, H. Sagara, F.C. Albers, E.S. Bradford, S.S. Harris, B. Mayer, D.B. Rubin, S.W. Yancey, and F.C. Sciurba

Two phase 3, randomized, placebo-controlled, double-blind, parallel group

- Σύγκριση mepolizumab (100 mg - METREX, 100 ή 300 mg - METREO) με το εικονικό φάρμακο (υποδορίως) κάθε 4 εβδομάδες για 1 έτος σε ασθενείς με ΧΑΠ και ιστορικό μετρίων/σοβαρών παροξύνσεων παρά τη θεραπεία με ICS/LABA/LAMA
- (Ηωσινόφιλα αίματος ≥ 150 mm^3 ή ≥ 300 mm^3 το προηγούμενο έτος)
- Πρωτεύον καταληκτικό σημείο: Μέτριες σοβαρές παροξύνσεις

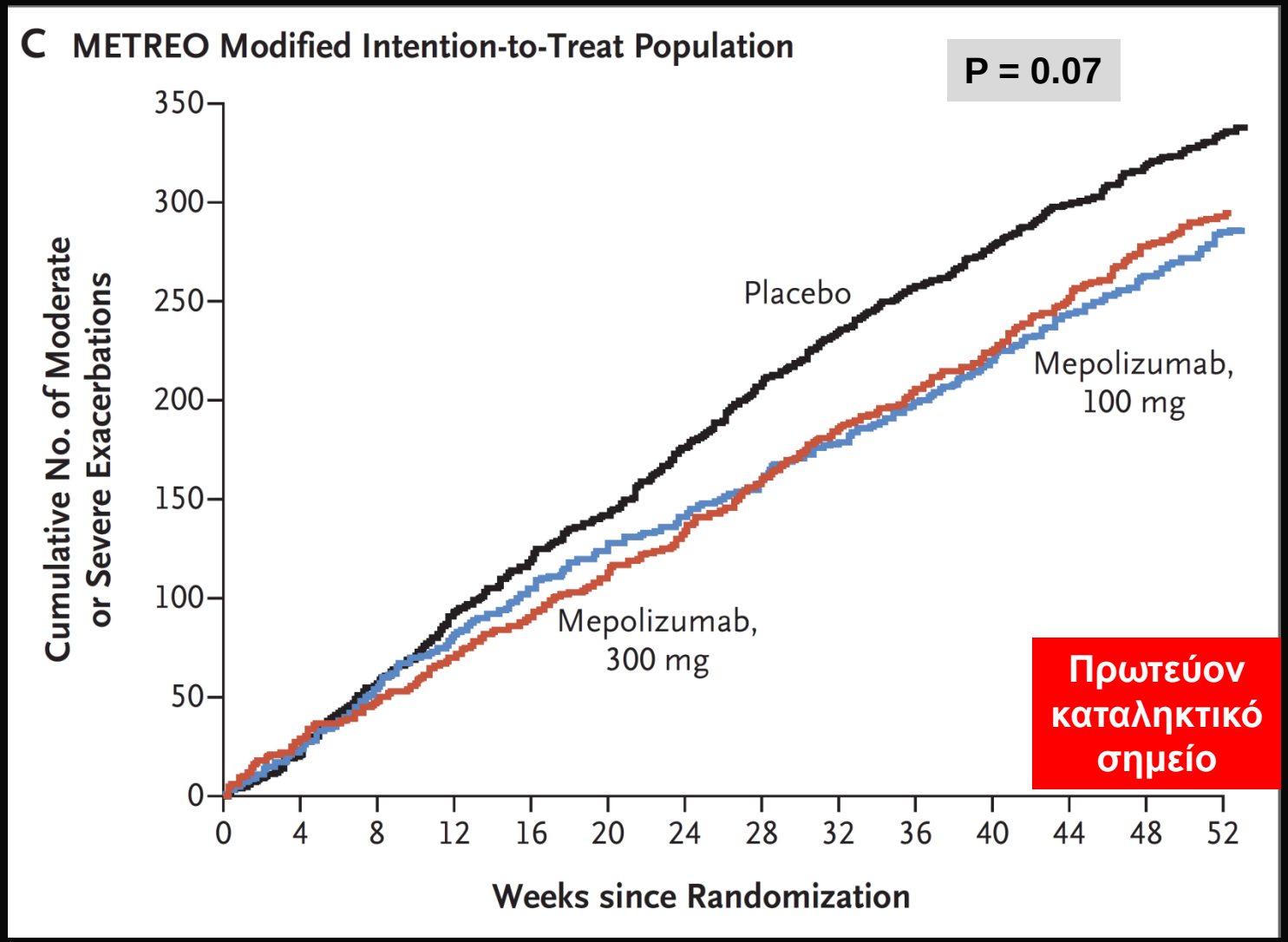
Pavord ID, et al. *NEJM* 2017

METREX: Υπεροχή μεπολιζουμάμπης στις μέτριες/σοβαρές παροξύνσεις



Pavord ID, et al. *NEJM* 2017

METREO: Καμία διαφορά στις μέτριες/σοβαρές παροξύνσεις



Pavord ID, et al. *NEJM* 2017

Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study

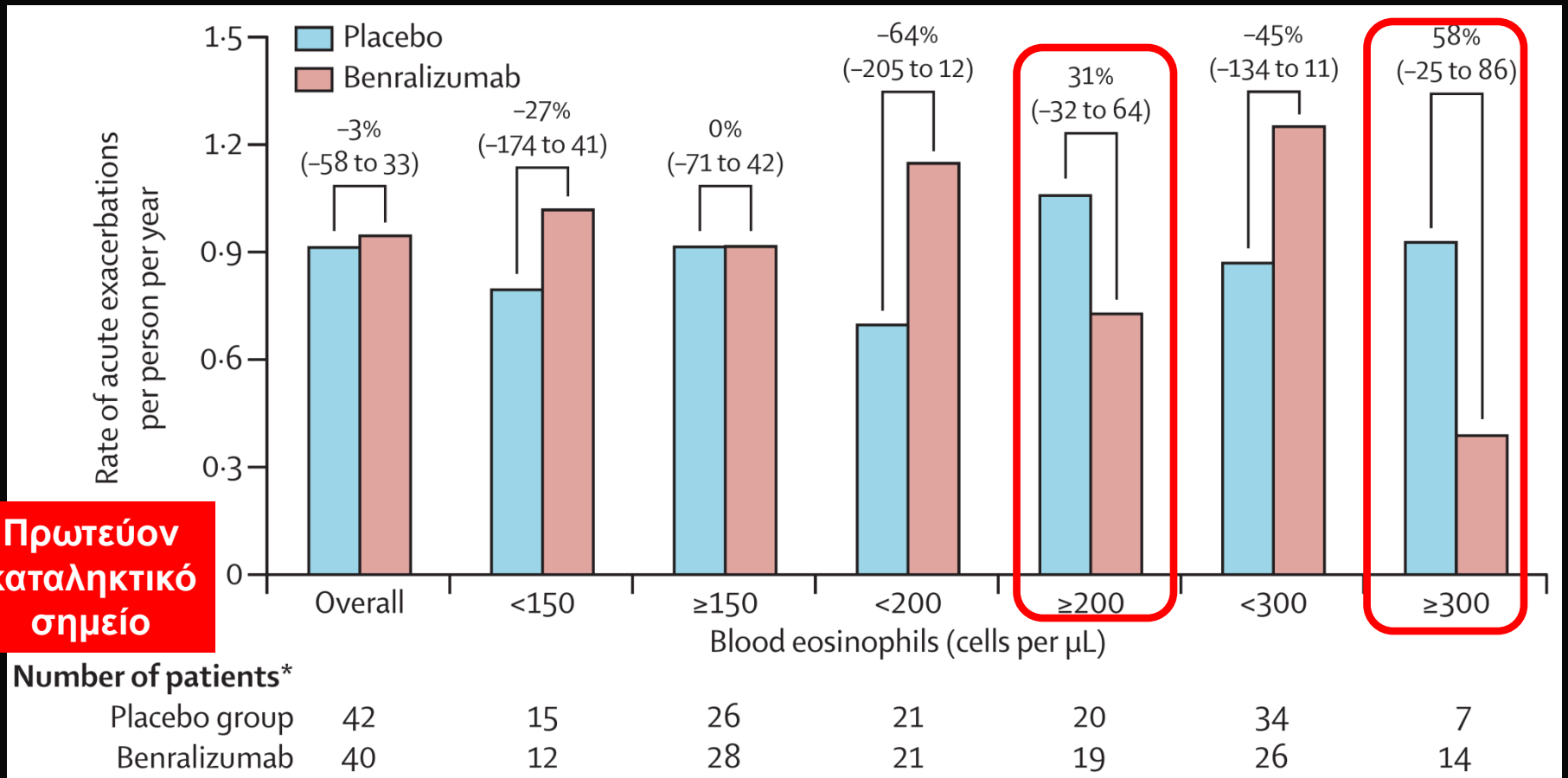
Christopher E Brightling, Eugene R Bleecker, Reynold A Panettieri Jr, Mona Bafadhel, Dewei She, Christine K Ward, Xiao Xu, Claire Birrell, René van der Merwe

Randomised, double-blind, placebo-controlled, phase 2a study

- Σύγκριση εικονικού φαρμάκου και benralizumab (anti-IL-5 receptor) 100 mg (υποδορίως) κάθε 4 εβδομάδες (3 δόσεις) και έπειτα κάθε 8 εβδομάδες (5 δόσεις) για 48 εβδομάδες σε ασθενείς με μέτρια/σοβαρή ΧΑΠ, ≥ 1 παρόξυνση, ηωσινόφιλα στα πτύελα ≥ 3% το προηγούμενο έτος
- Πρωτεύον καταληκτικό σημείο: Μέτριες σοβαρές παροξύνσεις την 56η εβδομάδα

Brightling CE, et al. *Lancet Respir Med* 2014; 2: 891–901

Καμία διαφορά μεταξύ στις μέτριες/σοβαρές παροξύνσεις μεταξύ Benralizumab και placebo

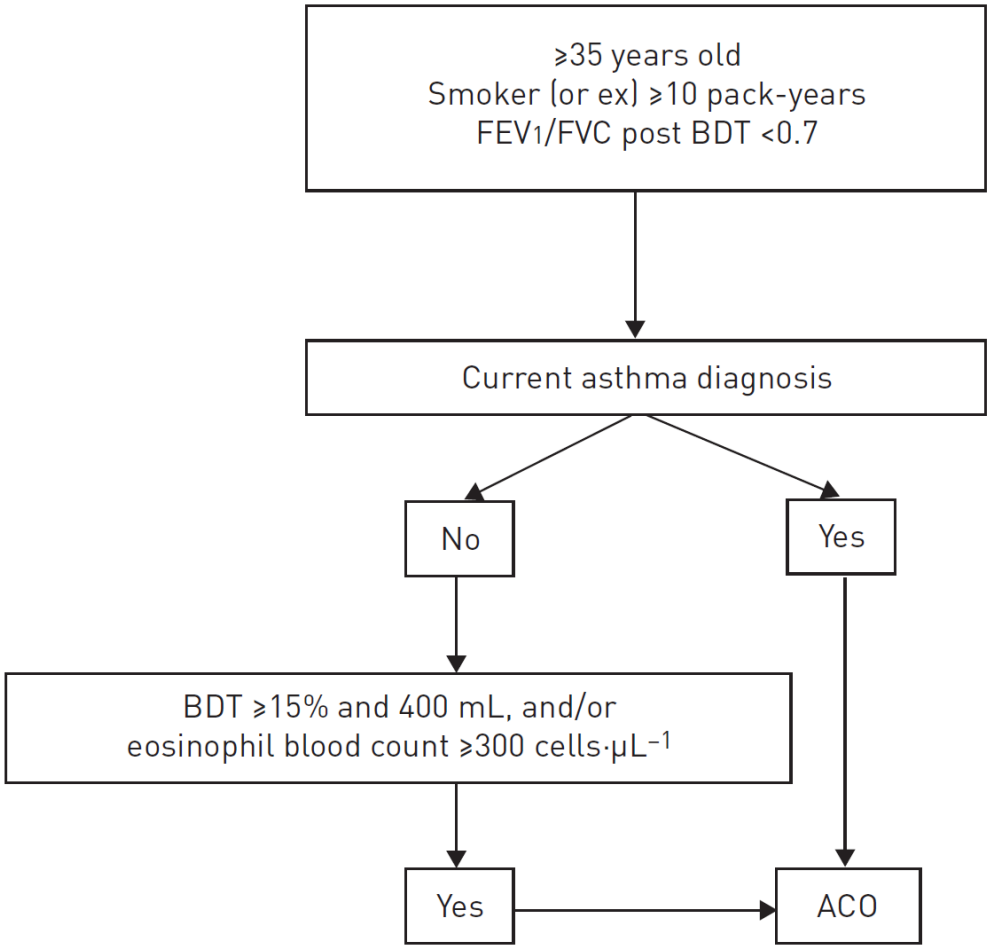


Πρωτεύον καταληκτικό σημείο

Rate of annualised moderate and severe acute exacerbations of COPD at week 56

Brightling CE, et al. *Lancet Respir Med* 2014; 2: 891–901

Algorithm for identification of asthma–COPD overlap: consensus between the Spanish COPD and asthma guidelines



Miravitlles M, et al. *Eur Respir J* 2017; 49: 1700O68.

Θεραπεία ACO/CAO

- Γενικά μέτρα

1. Διακοπή καπνίσματος
2. Αντιγριπικός – Αντιπνευμονιοκοκκικός εμβολιασμός
3. Πνευμονική αποκατάσταση (CAO)
4. Οξυγονοθεραπεία (όπου απαιτείται)

- Φαρμακευτική θεραπεία

Εντατικοποίηση φαρμακευτικής θεραπείας

ACO: Θεραπεία από τη μεριά του άσθματος

- Ασθενείς σε Θεραπεία βήματος 4, 5 (GINA) - Μέτριες/Υψηλές δόσεις ICS/LABA και προσθήκη Τιοτροπίου

ACO = ICS/LABA + Τιοτρόπιο

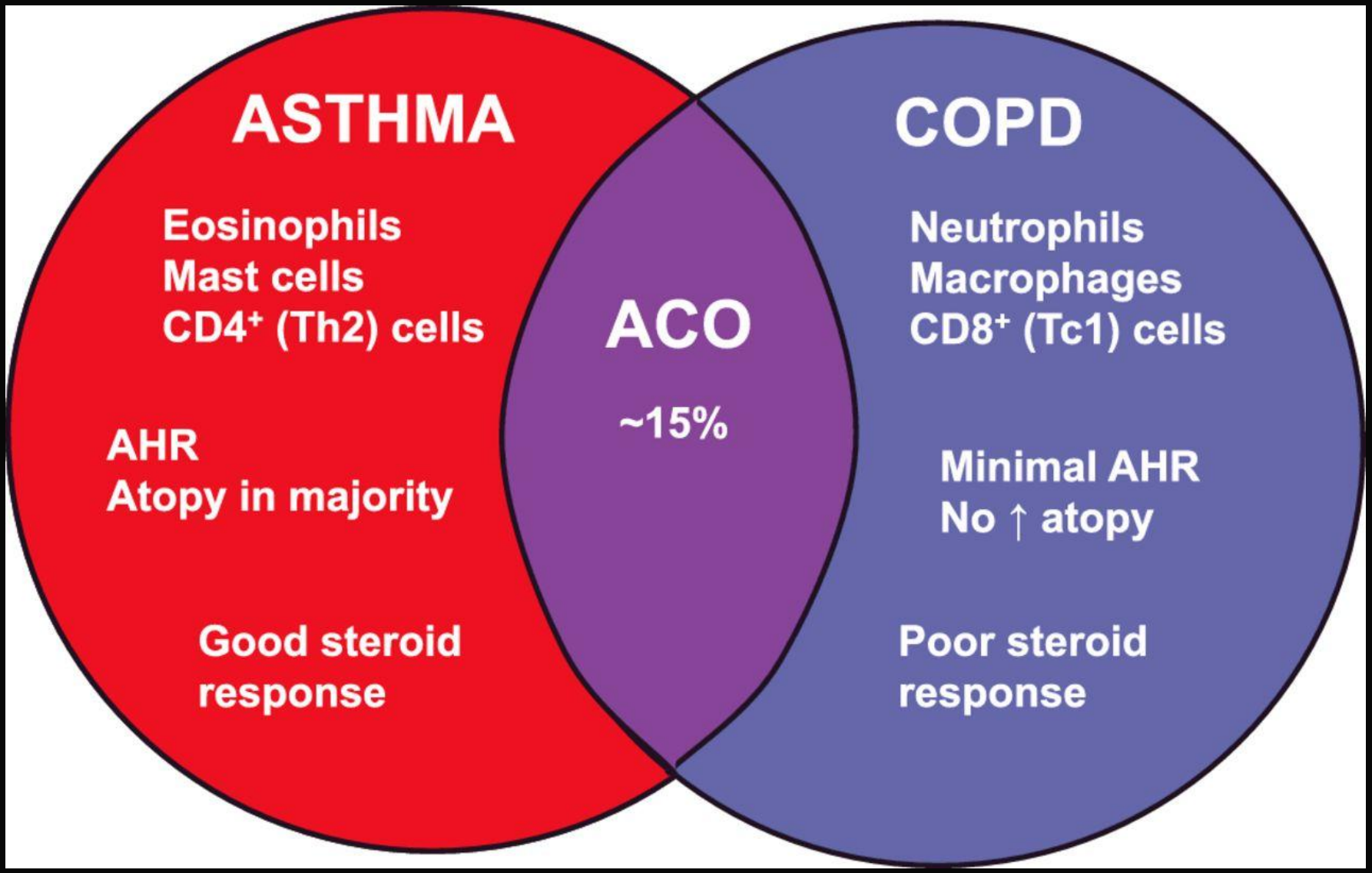
+ Μονοκλωνικά αντισώματα (;)

CAO: Θεραπεία από τη μεριά της ΧΑΠ

- Ασθενείς σταδίου D: Μέγιστη βρογχοδιαστολή (LAMA/LABA) + ICS

CAO = ICS/LABA/LAMA (Τριπλή θεραπεία)

+ Μονοκλωνικά αντισώματα (;)


ASTHMA
Eosinophils
Mast cells
CD4+ (Th2) cells
AHR
Atopy in majority
Good steroid response
ACO
~15%
COPD
Neutrophils
Macrophages
CD8+ (Tc1) cells
Minimal AHR
No ↑ atopy
Poor steroid response