Διπλή βρογχοδιαστολή στη ΧΑΠ πέρα από τα συμπτώματα και την πνευμονική λειτουργία

Στέλιος Λουκίδης MD phD FCCP

Ιατρική σχολή ΕΚΠΑ

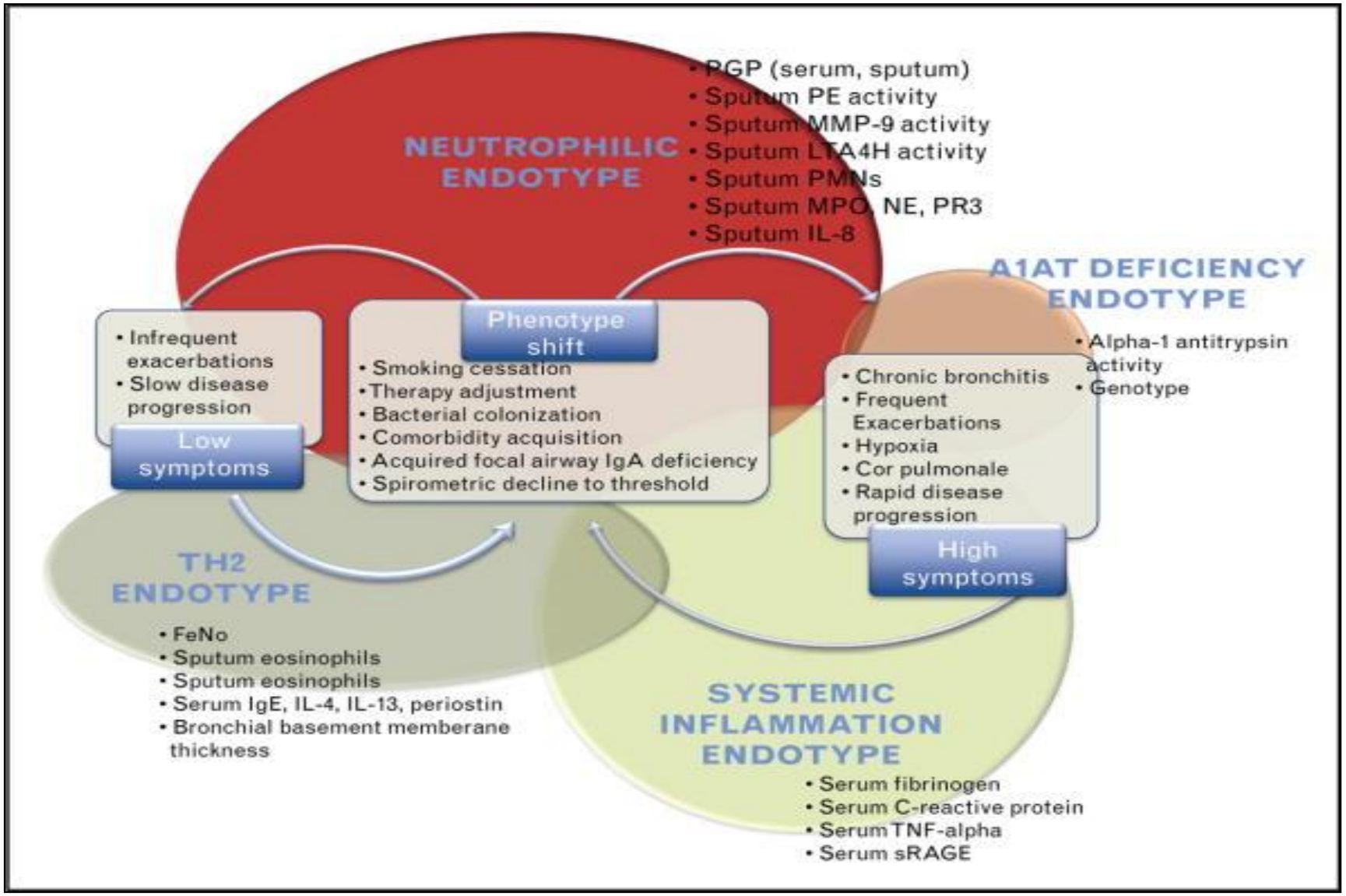
Conflicts [Honorarium fees]

- AstraZeneca Greece & Bulgaria & Poland
- Boehringer Ingelheim Greece& Europe
- Chiesi
- GlaxoSmithKline Greece & Denmark
- Elpen
- Menarini Helllas
- Novartis Hellas & Europe
- Pharmaten Hellas
- Vianex/MSD

Σχεδιασμός

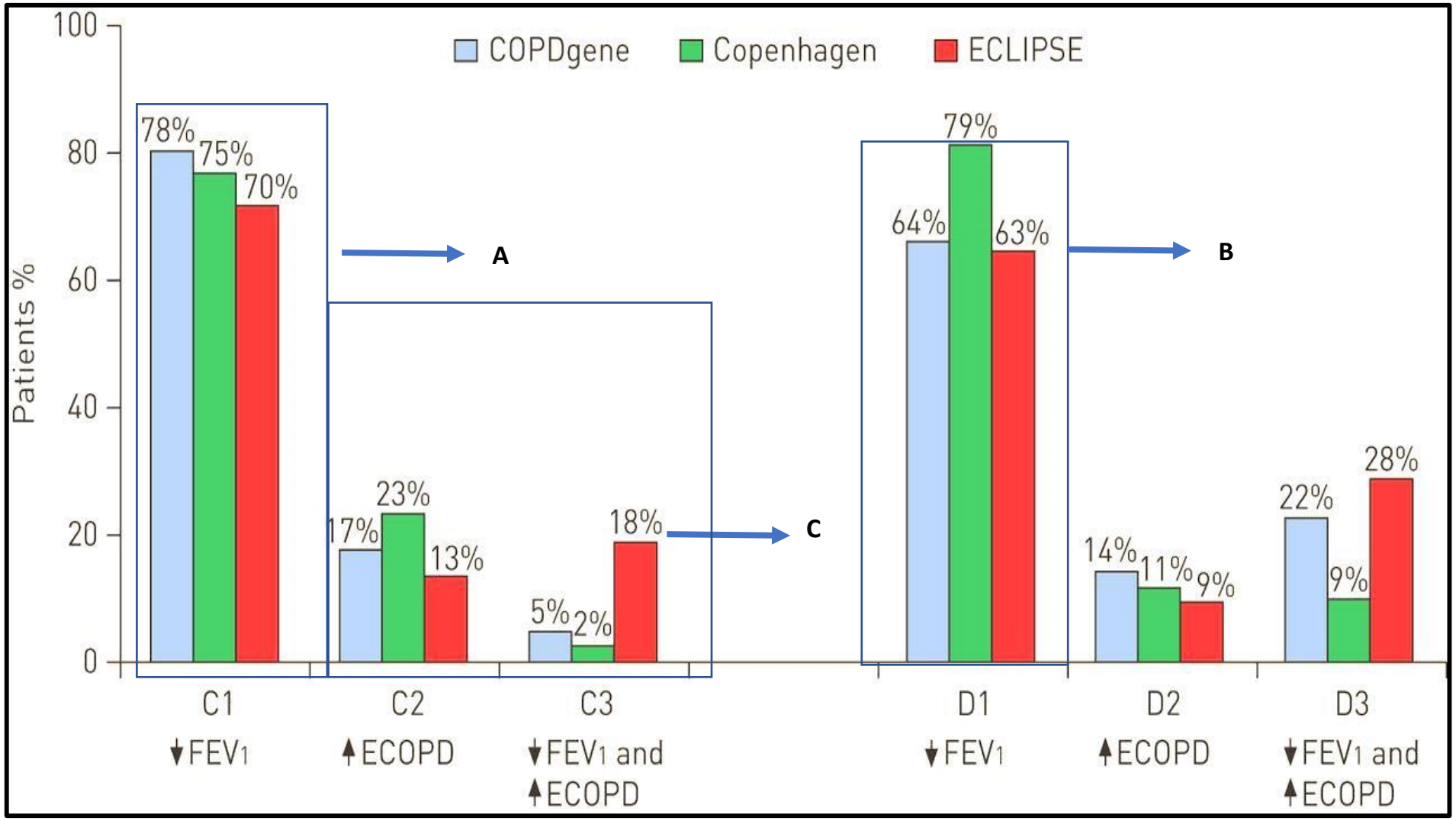
- Μερικά ενδιαφέροντα στοιχεία για να κτίσουμε την υπόθεση

Οι φλεγμονώδεις-θεραπευτικοί ενδότυποι



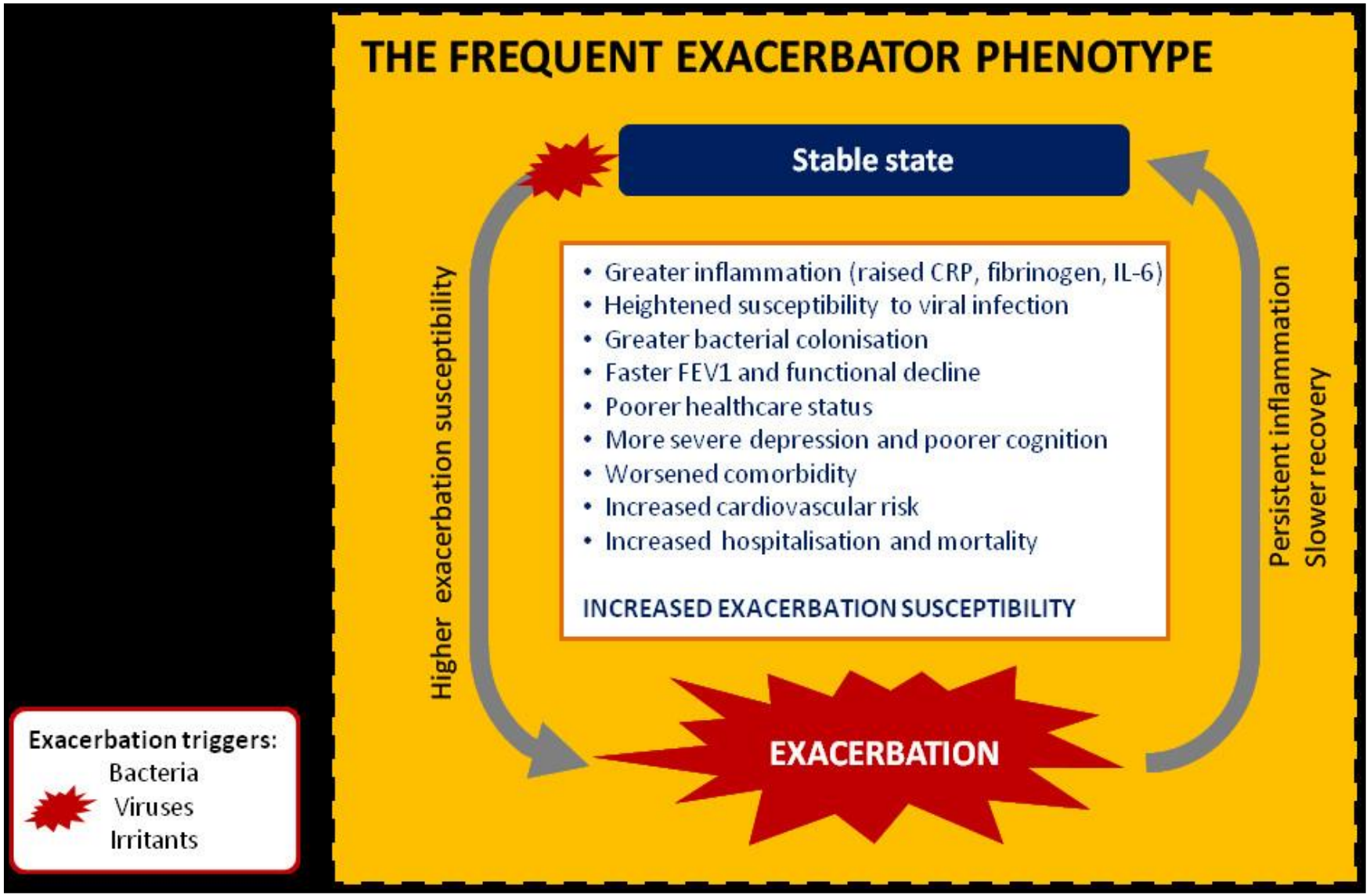
Russell, Derek; Wells, J; Blalock, J Current Opinion in Pulmonary Medicine. 22(2):91-99, March 2016.

Υπότυποι σταδίων κινδύνου: Οδηγός το σύμπτωμα οι παροξύνσεις ή ο FEV_1?



Alvar Agusti et al. Eur Respir J 2013

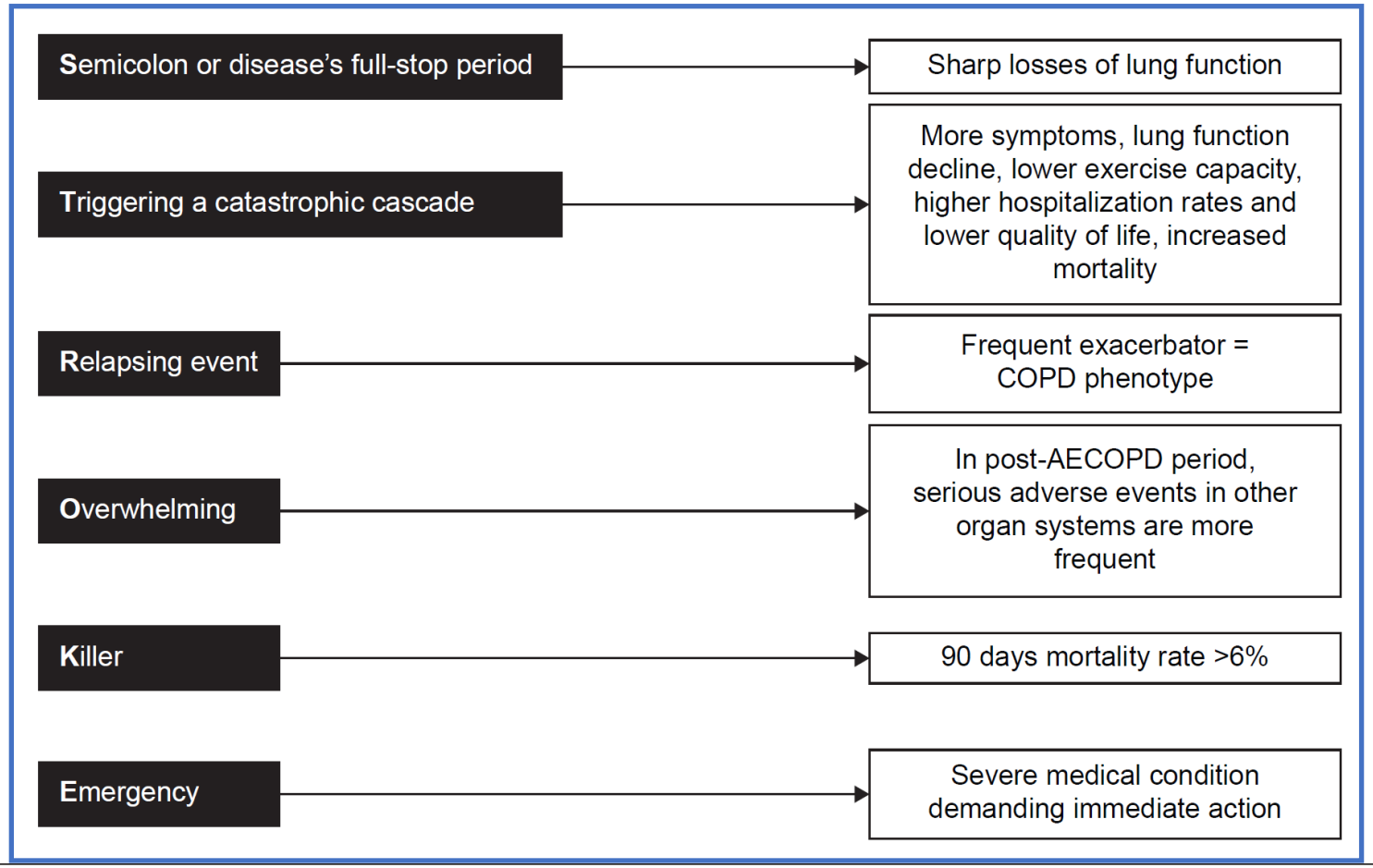
Ο συχνός παροξυντής πέρα από τη νοσηλεία



Wedzicha J A et al BMC Medicine 2013

Acute exacerbation of COPD: is it the "stroke of the lungs"?

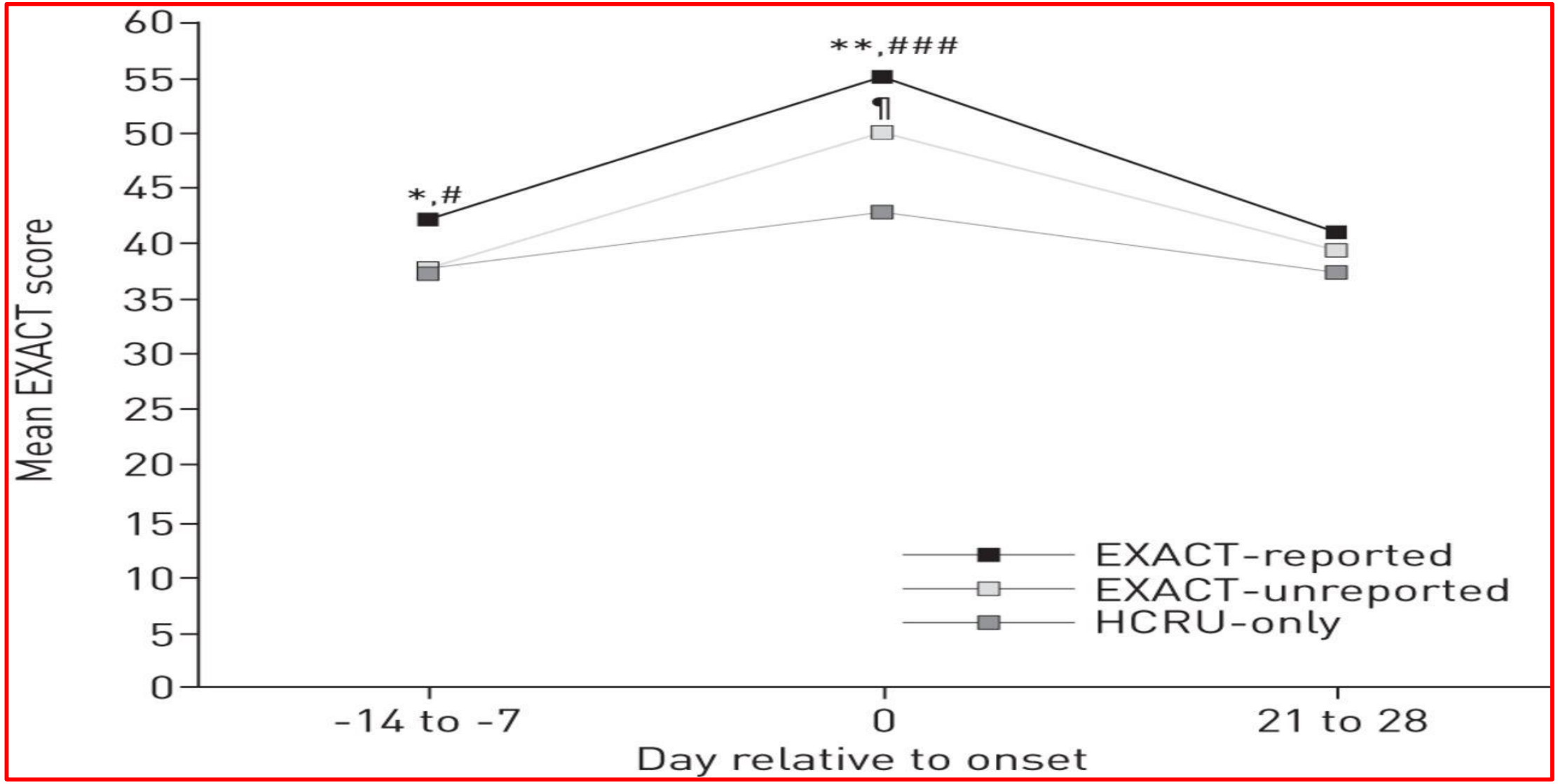
International Journal of COPD



Diseases	More symptoms	Higher hospitalization rates	Lower quality of life	Lower exercise capacity	Poorer prognosis
Coronary disease (myocardial infarctions)	√[30]	√[31]	√[32]	√[31]	√[33]
COPD (acute exacerbation)	√[14, 15]	√[35, 36]	√[37]	√[34]	√[38, 39]

Hillas G, et al. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1579-1586.

Δεν είναι όλες οι παροξύνσεις φανερές



Paul W. Jones et al. Eur Respir J 2014;44:1156-1165

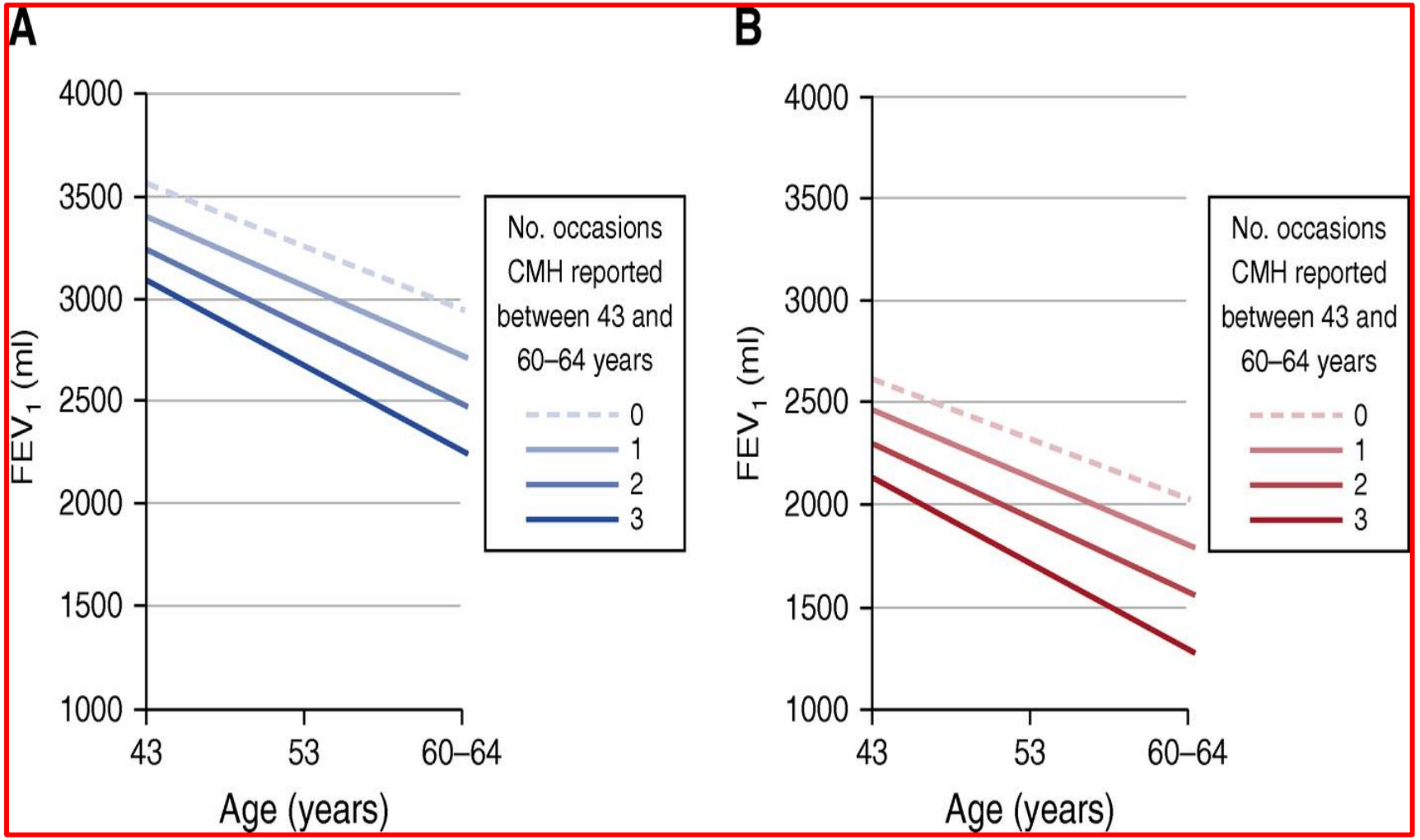
Αυξομειώσεις στη δύσπνοια οδηγούν τους ασθενείς σε μη προγραμματισμένες επισκέψεις στη ΠΦΥ

Variable	Total cohort	MRC grade (N=40,425)					across MRC grades
		1	2	3	4	5	
N	49,438	7392	15,378	10,529	5813	1313	
Females, n (%)	22,804 (46.1)	2915 (15.7)	7193 (38.8)	5035 (27.2)	2740 (14.8)	656 (3.5)	<0.001
Age, mean (SD)	69.2 (10.3)	66.4 (10.1)	68.4 (9.9)	70.1 (10.1)	71.3 (10.0)	73.2 (9.8)	<0.001
Current smoker, n (%)	16,341 (33.1)	2459 (18.3)	5249 (39.0)	3564 (26.5)	1817 (13.5)	379 (2.8)	0.377
Former smoker, n (%)	26,046 (52.7)	3795 (17.8)	7924 (37.2)	5510 (25.9)	3255 (15.3)	801 (3.8)	
Never smoker, n (%)	5066 (10.3)	855 (20.9)	1570 (38.4)	1032 (25.3)	531 (13.0)	98 (2.4)	
Other smoker, n (%)[a]	1985 (4.0)	283 (17.8)	635 (40.0)	423 (26.7)	210 (13.2)	35 (2.2)	
BMI <18.5, n (%)	2297 (4.7)	239 (13.4)	566 (31.8)	487 (27.4)	349 (19.6)	138 (7.8)	<0.001
BMI 18.5–24.9, n (%)	16,792 (34.0)	2689 (19.6)	5241 (38.2)	3438 (25.1)	1898 (13.8)	455 (3.3)	
BMI 25–29.9, n (%)	16,679 (33.7)	2880 (20.9)	5464 (39.6)	3437 (24.9)	1662 (12.1)	345 (2.5)	
BMI ≥30, n (%)	12,805 (25.9)	1467 (14.0)	3847 (36.7)	3012 (28.7)	1816 (17.3)	347 (3.3)	
Airflow limitation stage, n (%)							
Stage I (FEV_1≥80% pred.)	7356 (14.9)	1640 (28.0)	2369 (40.5)	1281 (21.9)	479 (8.2)	81 (1.4)	<0.001
Stage II (≥50% FEV_1<80% pred.)	24,815 (50.2)	4350 (21.0)	8673 (41.9)	5066 (24.5)	2276 (11.0)	337 (1.6)	
Stage III (≥30% FEV_1<50% pred.)	13,126 (26.6)	1101 (10.3)	3569 (33.4)	3318 (31.0)	2196 (20.5)	503 (4.7)	
Stage IV (FEV_1>30% pred.)	2911 (5.9)	110 (4.8)	445 (19.6)	641 (28.2)	726 (31.9)	352 (15.5)	
Moderate-to-severe COPD exacerbation in previous 12 months, n (%) with at least one event	22,088 (44.7)	2448 (14.0)	6103 (34.8)	4949 (28.2)	3187 (18.2)	847 (4.8)	<0.001
Severe COPD exacerbation rate, n (%) with at least one event	5092 (10.3)	490 (12.5)	1185 (30.2)	1102 (28.0)	880 (22.4)	273 (6.9)	<0.001
GP visits, all contacts with GP surgery, mean (SD)	45.4 (27.4)	36.6 (22.4)	41.4 (24.1)	47.0 (26.9)	52.8 (29.0)	60.1 (30.9)	<0.001
GP visits, contacts with GP, mean (SD)	12.3 (9.4)	10.4 (8.0)	11.6 (8.5)	12.9 (9.6)	13.9 (10.2)	13.6 (10.2)	<0.001

Percentages are based on row total. MRC scoring 1–5 equals to mMRC grades 0–4 with MRC 1 equals to mMRC 0.
[a]Other smoker: no record about smoking history or record of passive smoking.
Data on BMI were missing for 865 (1.7%) patients.
Data on GOLD grade were missing for 1002 (2%) patients.

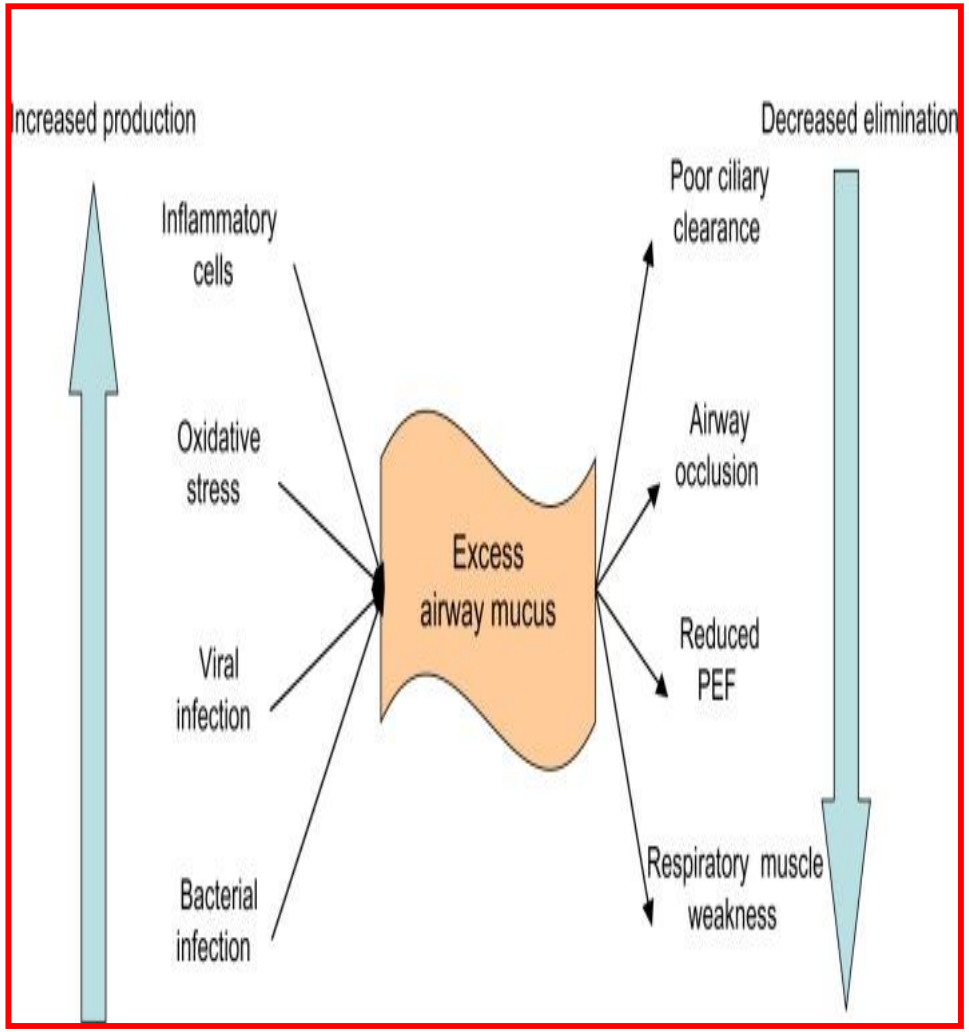
Müllerová H, Lu C, Li H, Tabberer M (2014) Prevalence and Burden of Breathlessness in Patients with Chronic Obstructive Pulmonary Disease Managed in Primary Care. PLoS ONE 9(1): e85540. d

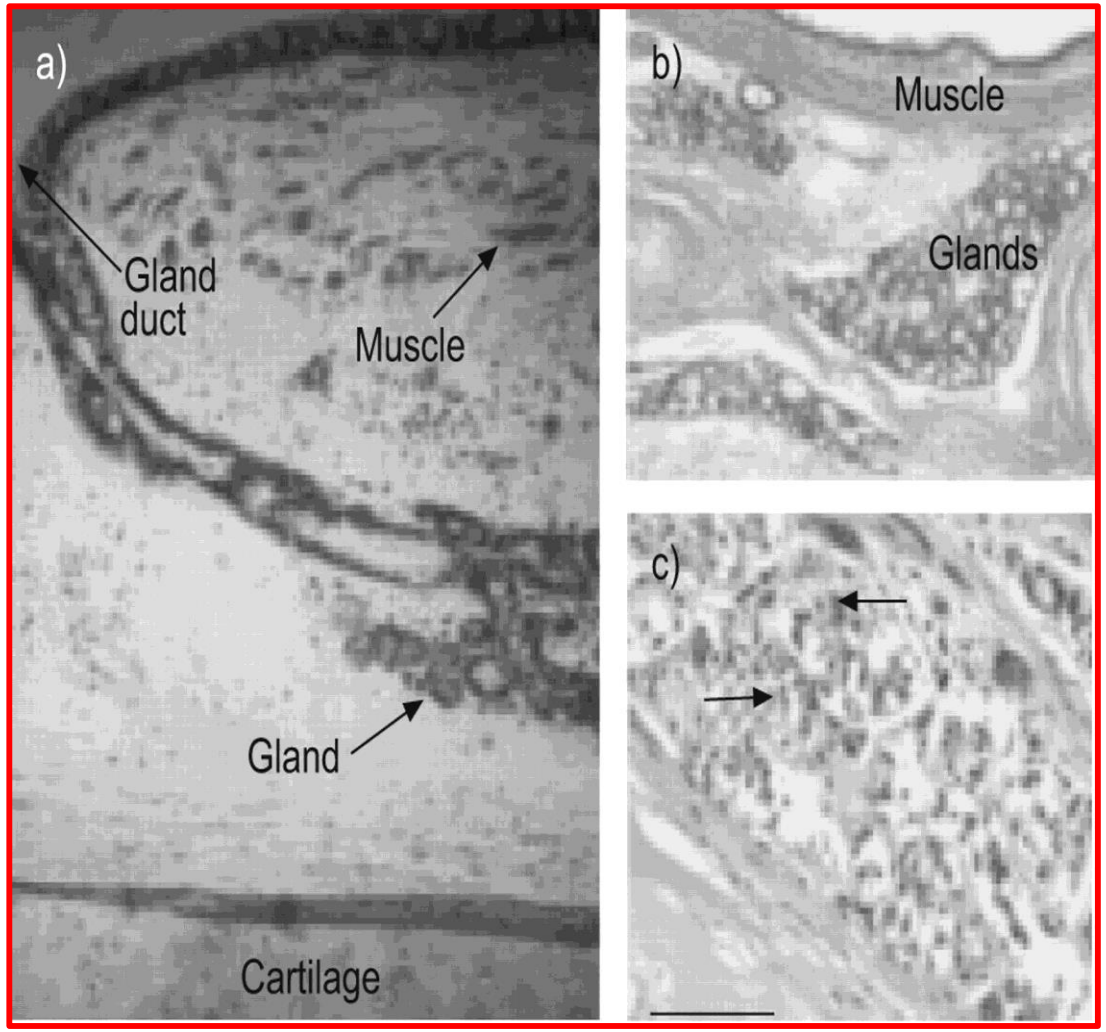
Ο παράγοντας βλέννα



James P. Allinson; Rebecca Hardy; Gavin C. Donaldson; Seif O. Shaheen; Diana Kuh; Jadwiga A. Wedzicha; *Am J Respir Crit Care Med* 2016 193, 662-672.

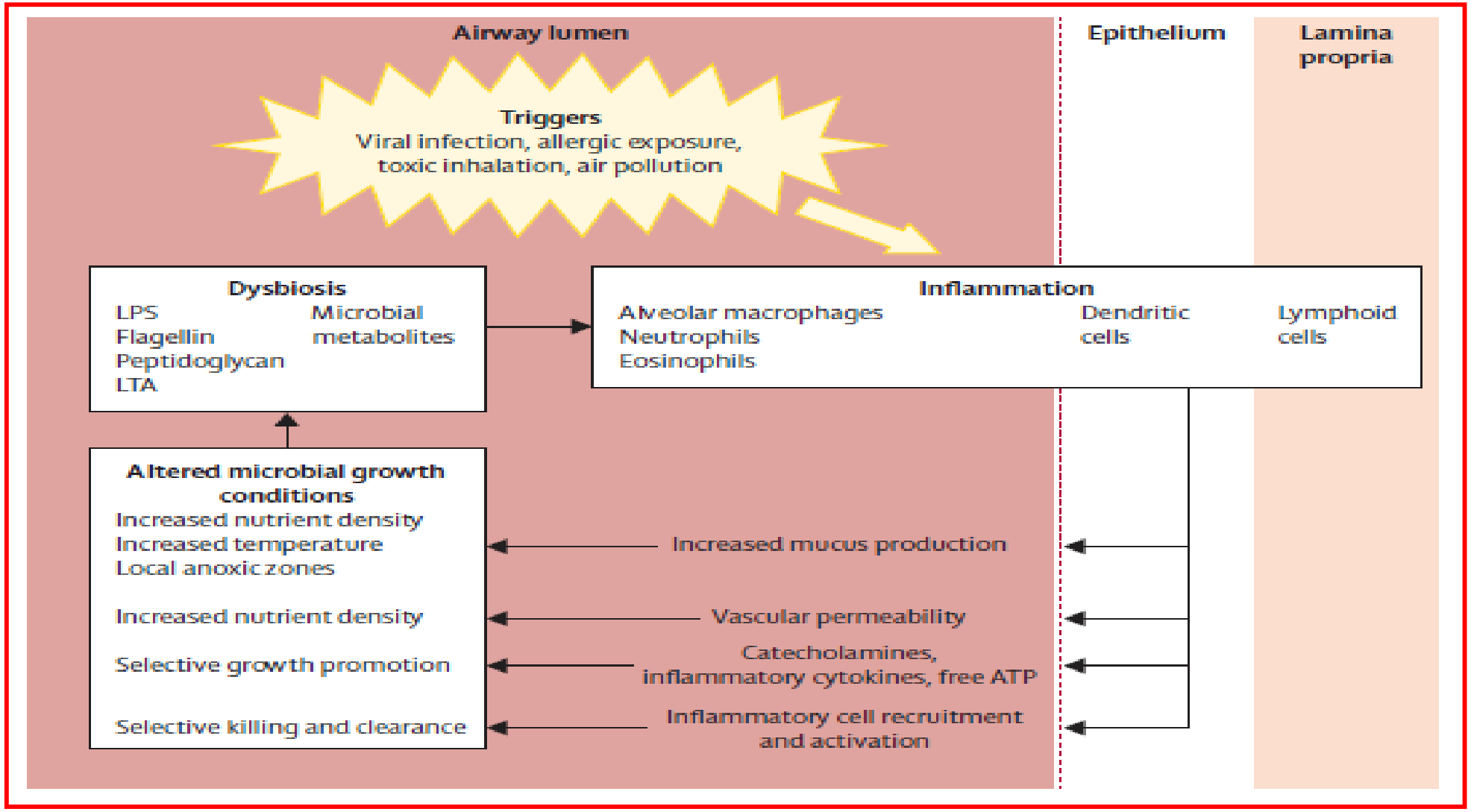
Ο παράγοντας βλέννα





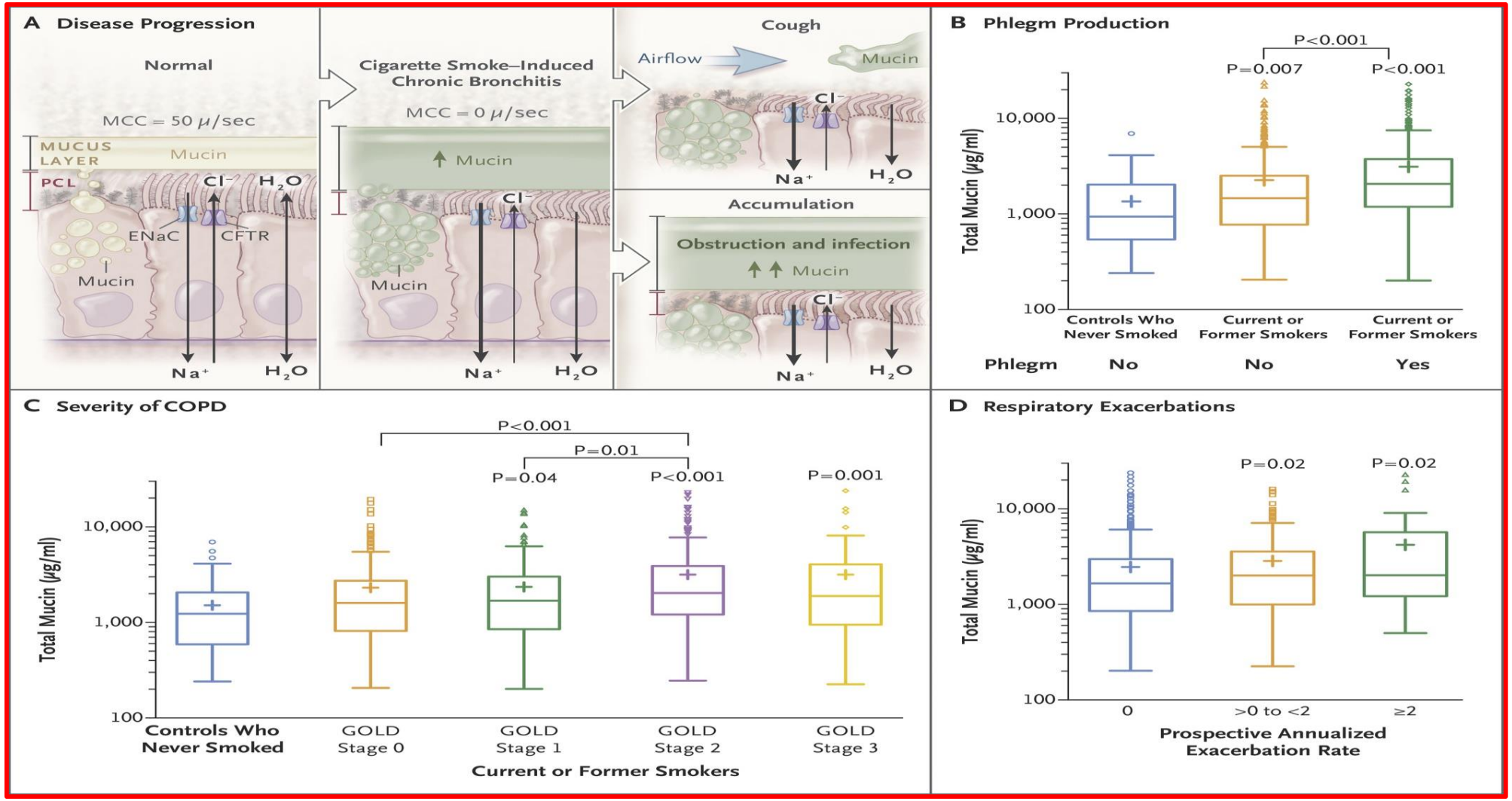
I. Cerveri, and V. Brusasco Eur Respir Rev 2010;19:109-112

Μικροβιακό φορτίο και παροξύνσεις



Robert P Dickson , Fernando J Martinez , Gary B Huffnagle The Lancet 2014

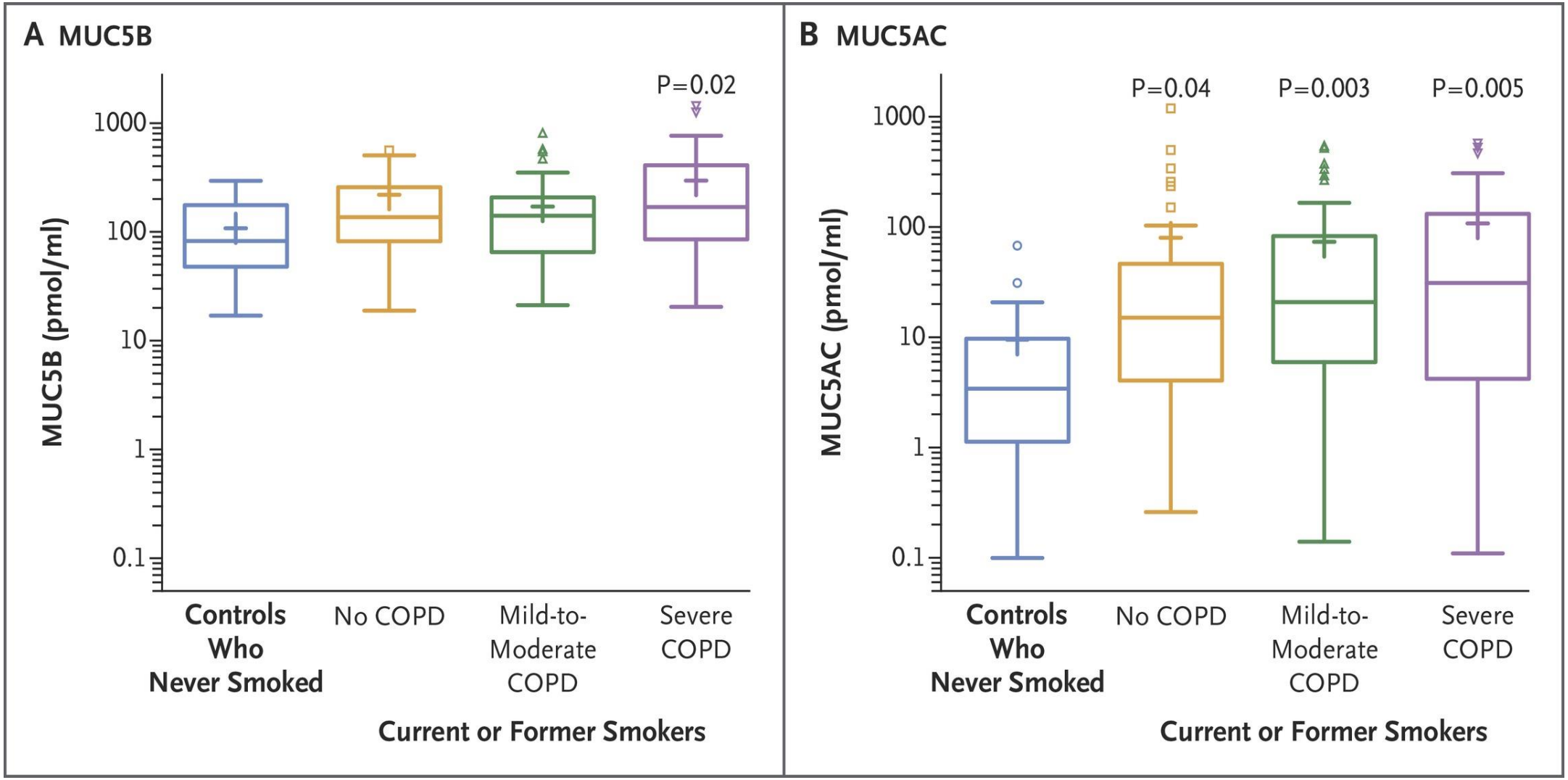
ΧΑΠ & Απόχρεμψη: Ξεπερνώντας τα κλασσικά



Kesimer M et al. N Engl J Med 2017;377:911-922

The NEW ENGLAND JOURNAL of MEDICINE

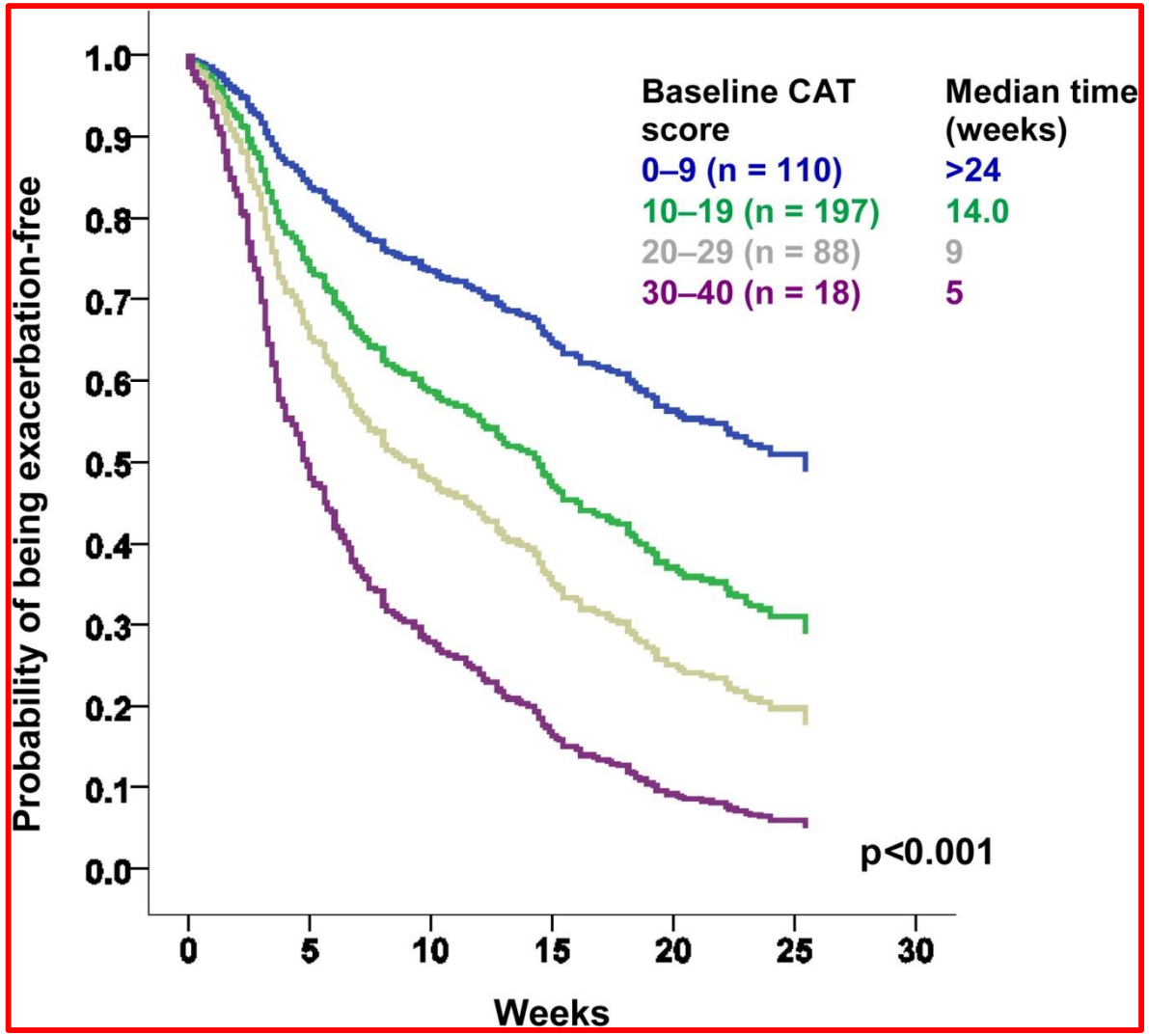
Επίπεδα MUC5B & MUC5AC σε ΧΑΠ: Βαρύτητα και σκέψεις



Kesimer M et al. N Engl J Med 2017;377:911-922

The NEW ENGLAND JOURNAL of MEDICINE

Τα συμπτώματα σχετίζονται με το κίνδυνο παροξύνσεων σε υψηλού & χαμηλού κινδύνου για παροξύνσεις ασθενείς με ΧΑΠ



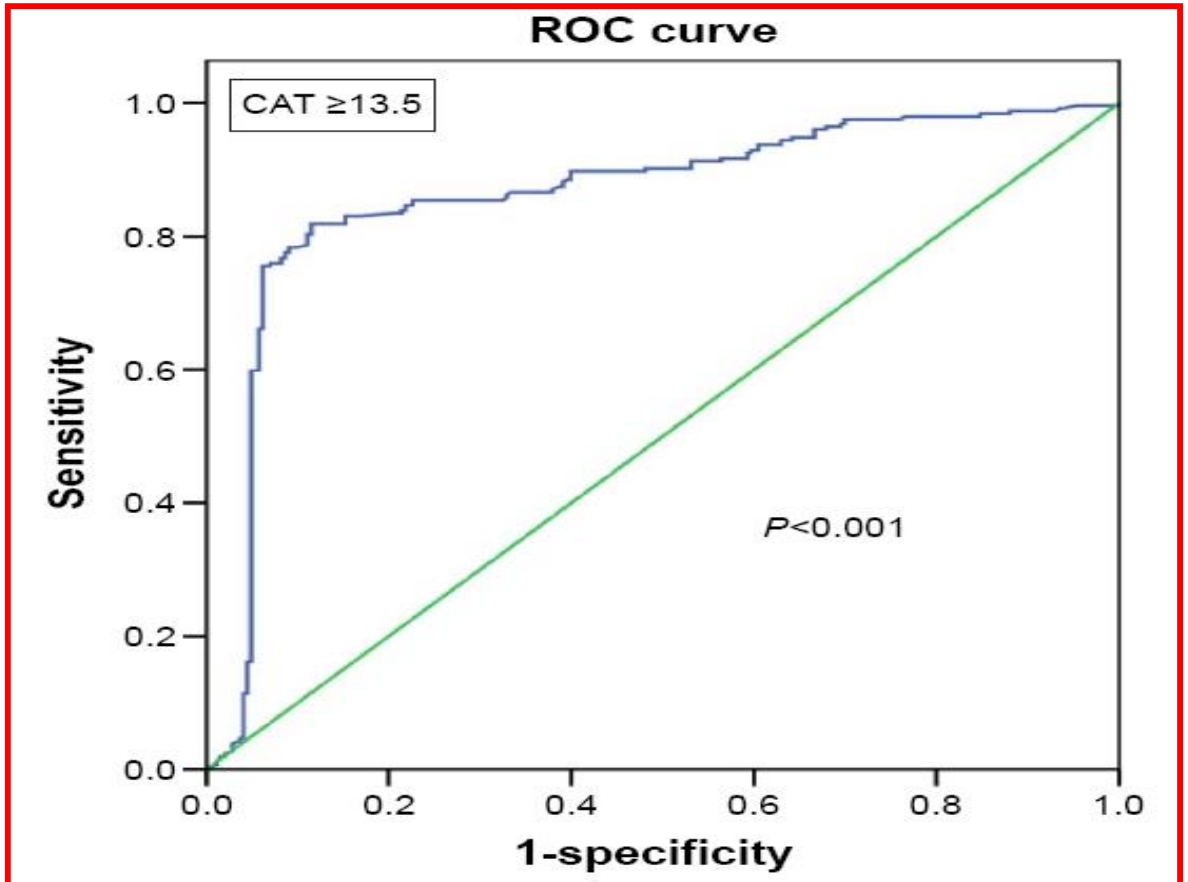
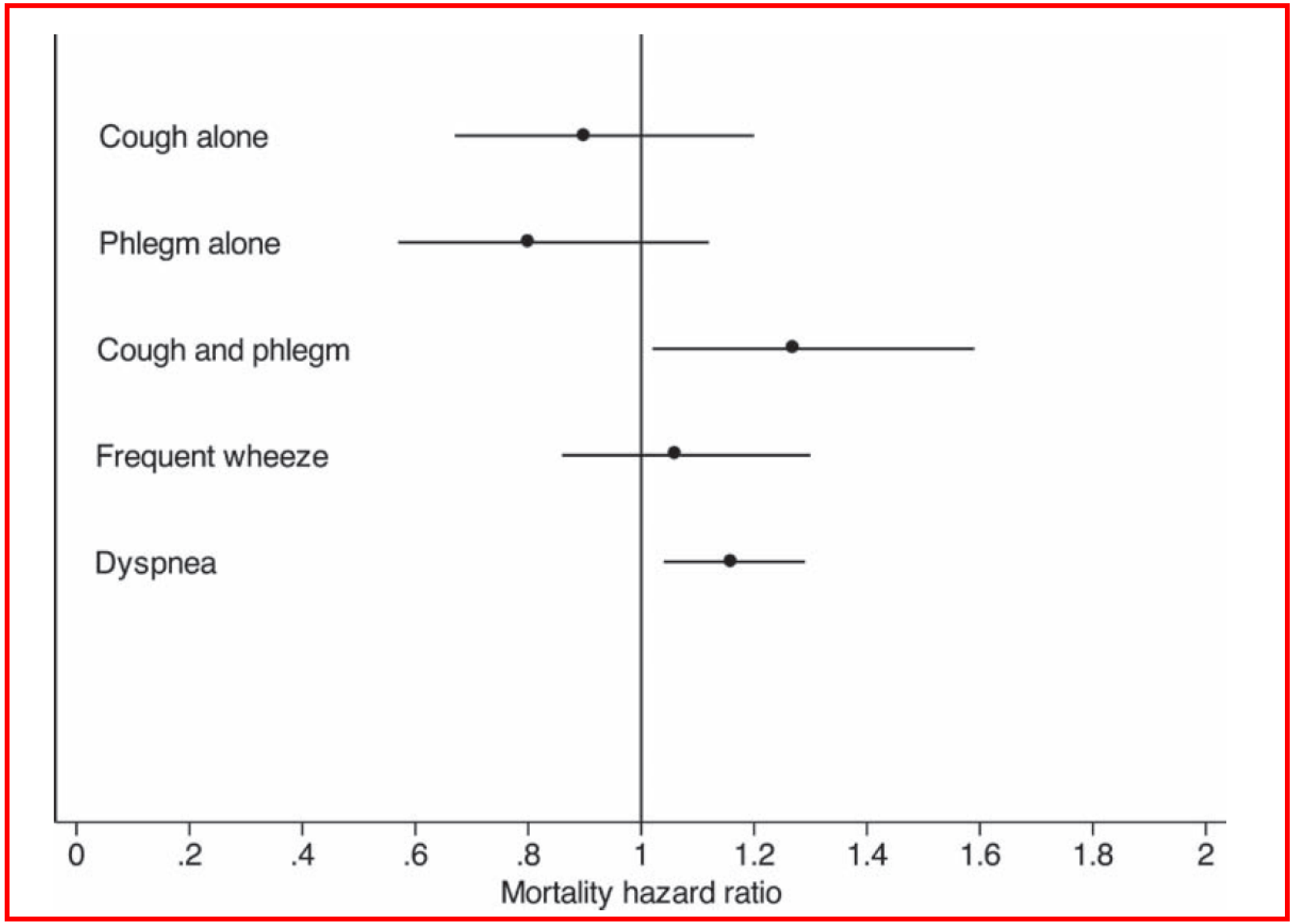


Figure 3 ROC analysis derived from the Cox regression model in its capacity to predict combined event. This model includes the number of exacerbations in the previous year and CAT ≥13.5 points (AUC =0.864, *P*<0.001).
Abbreviations: ROC, receiver operating characteristic; CAT, COPD Assessment Test; AUC, area under the curve.

Sang-Do Lee et al Respir Med 2014

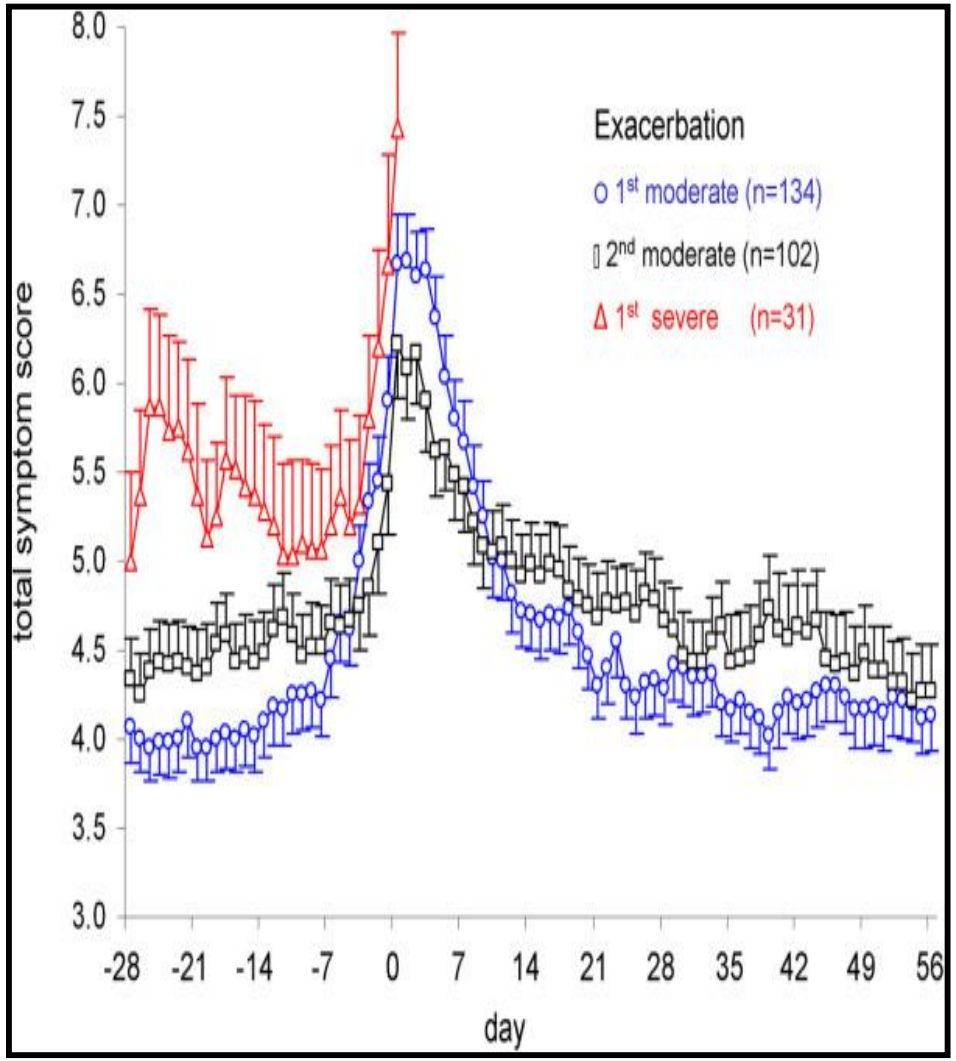
Miravitlles M et al Int J COPD 2015

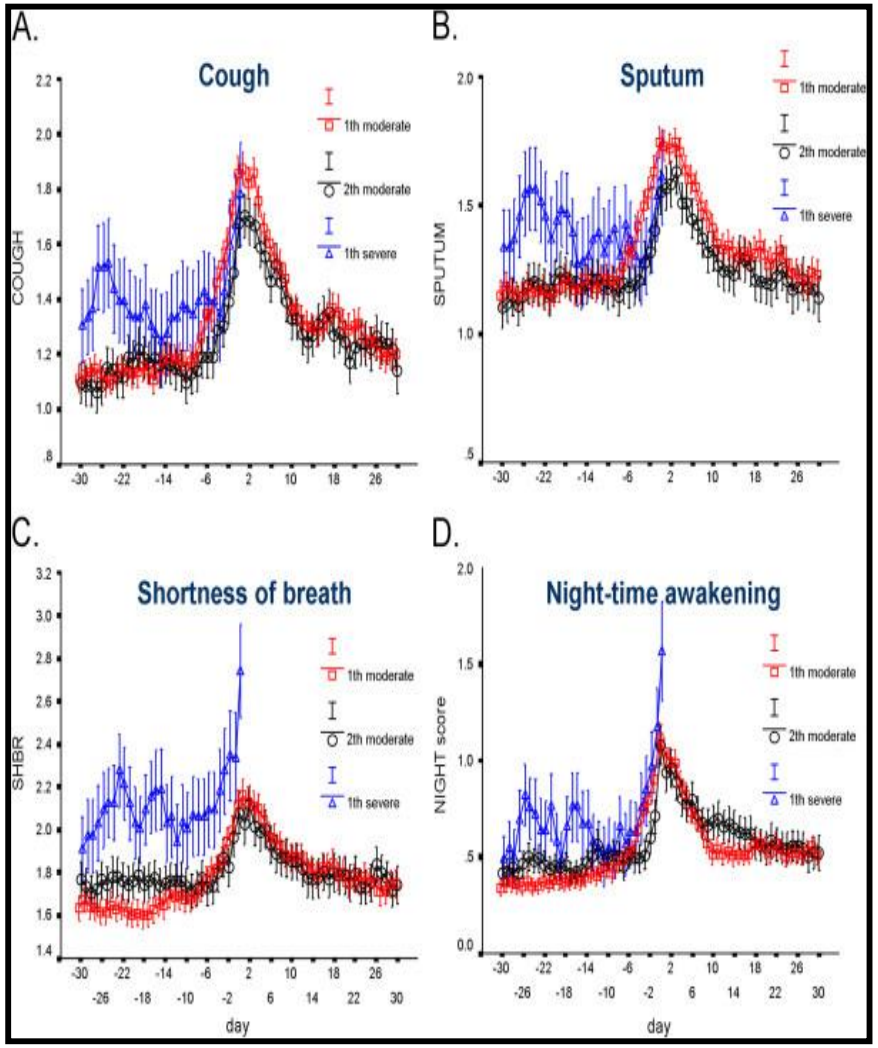
Συμπτώματα και κίνδυνος θανάτου στην πρώιμη ΧΑΠ



Putcha N, et al. *COPD* 2014 ;11:451-*8.*

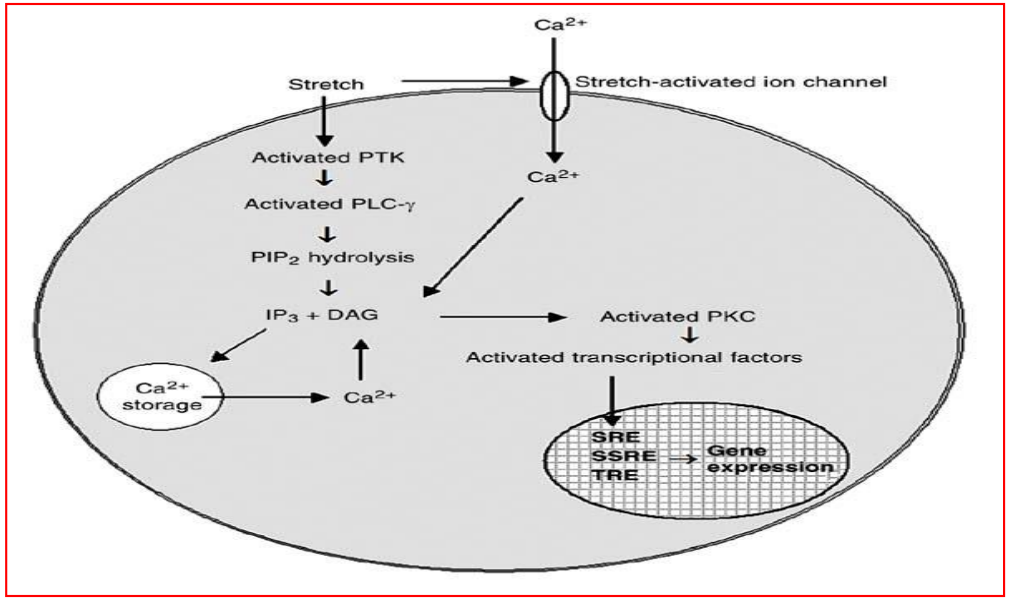
Η διακύμανση πριν από τη παρόξυνση

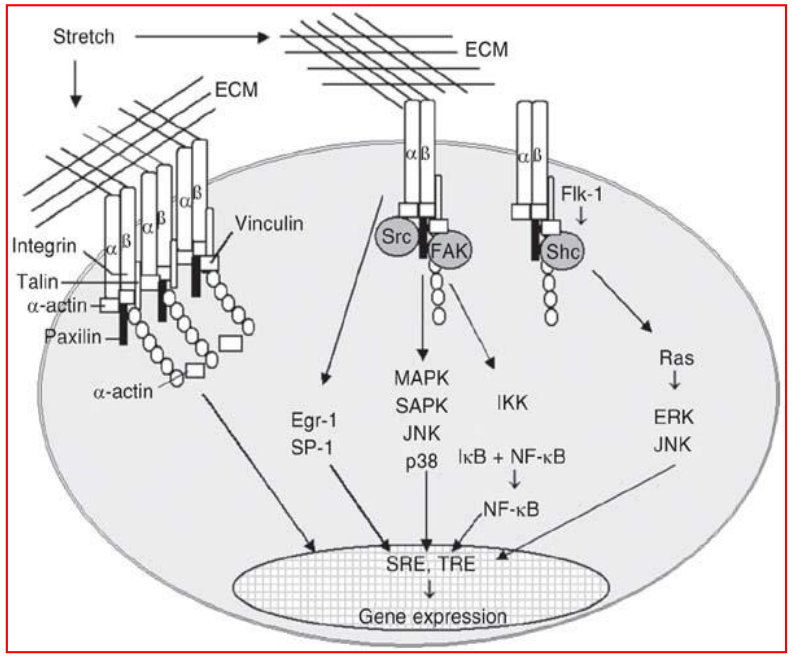


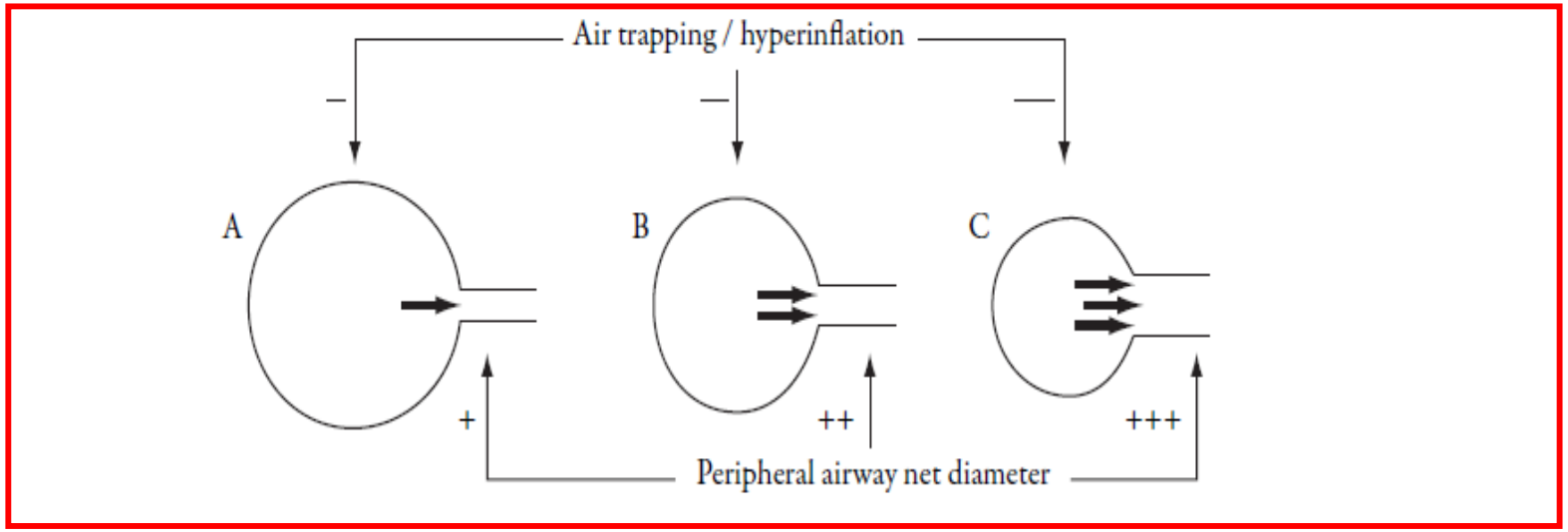


Van de Berge M et al Res Research 2012

Η φιλοσοφία των deflators

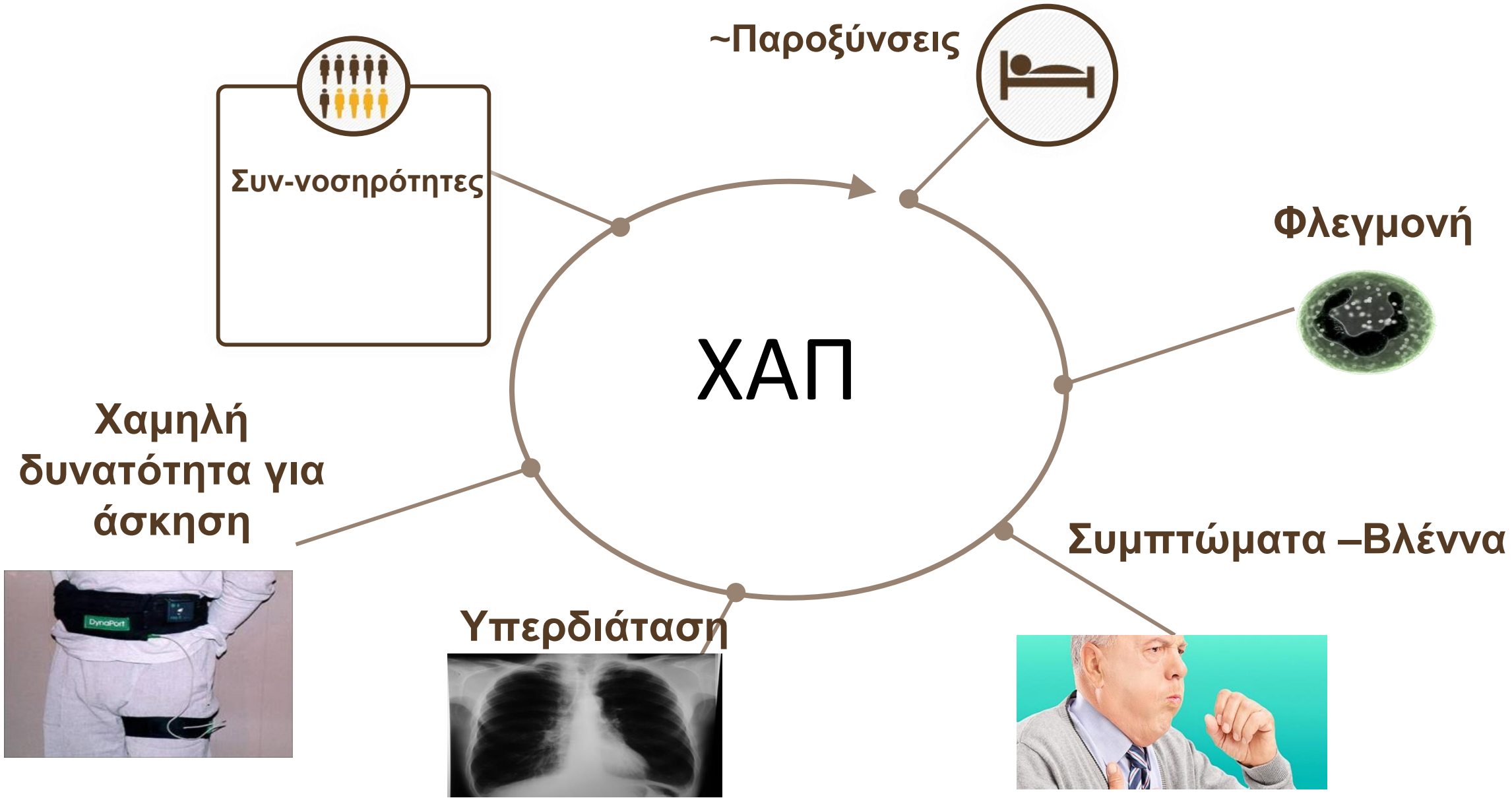






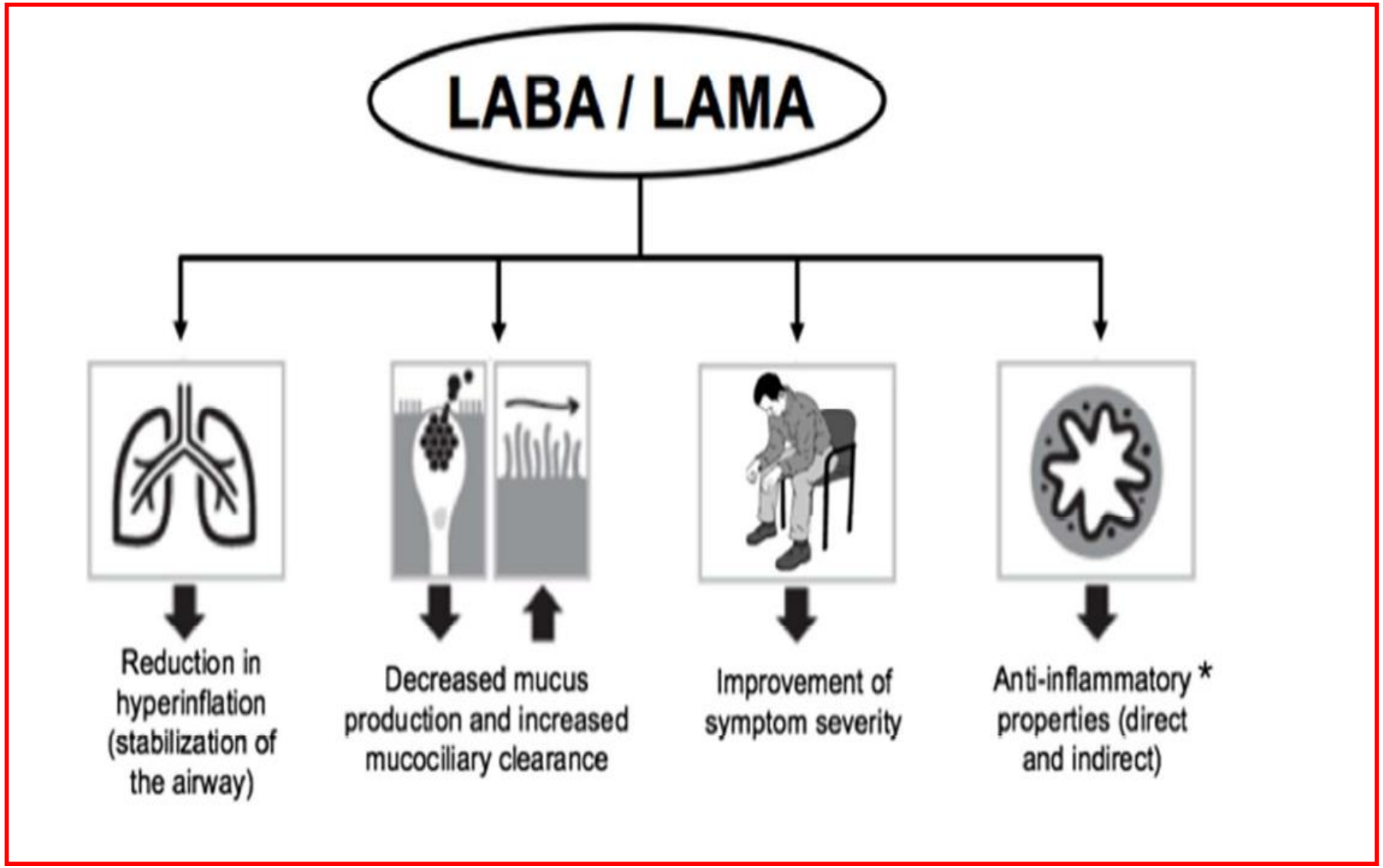
Bee K et al Adv Ther apy 2010

ΧΑΠ : Σκέψεις σε μια πολυπαραγοντική νόσο

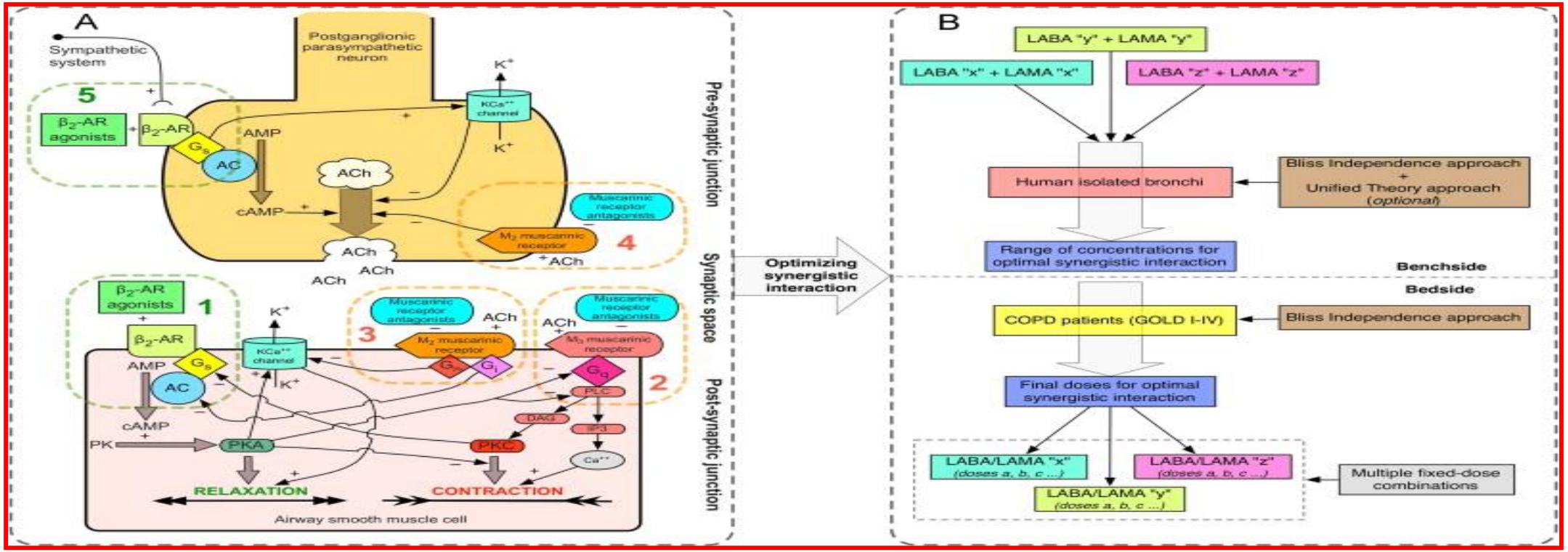


Σχεδιασμός

- Μερικά ενδιαφέροντα στοιχεία για να κτίσουμε την υπόθεση
- Έχει η υπόθεση μας θέση για τα LABA LAMA?


LABA / LAMA
Reduction in hyperinflation (stabilization of the airway)
Decreased mucus production and increased mucociliary clearance
Improvement of symptom severity
Anti-inflammatory * properties (direct and indirect)

Η θεωρία της συνέργειας



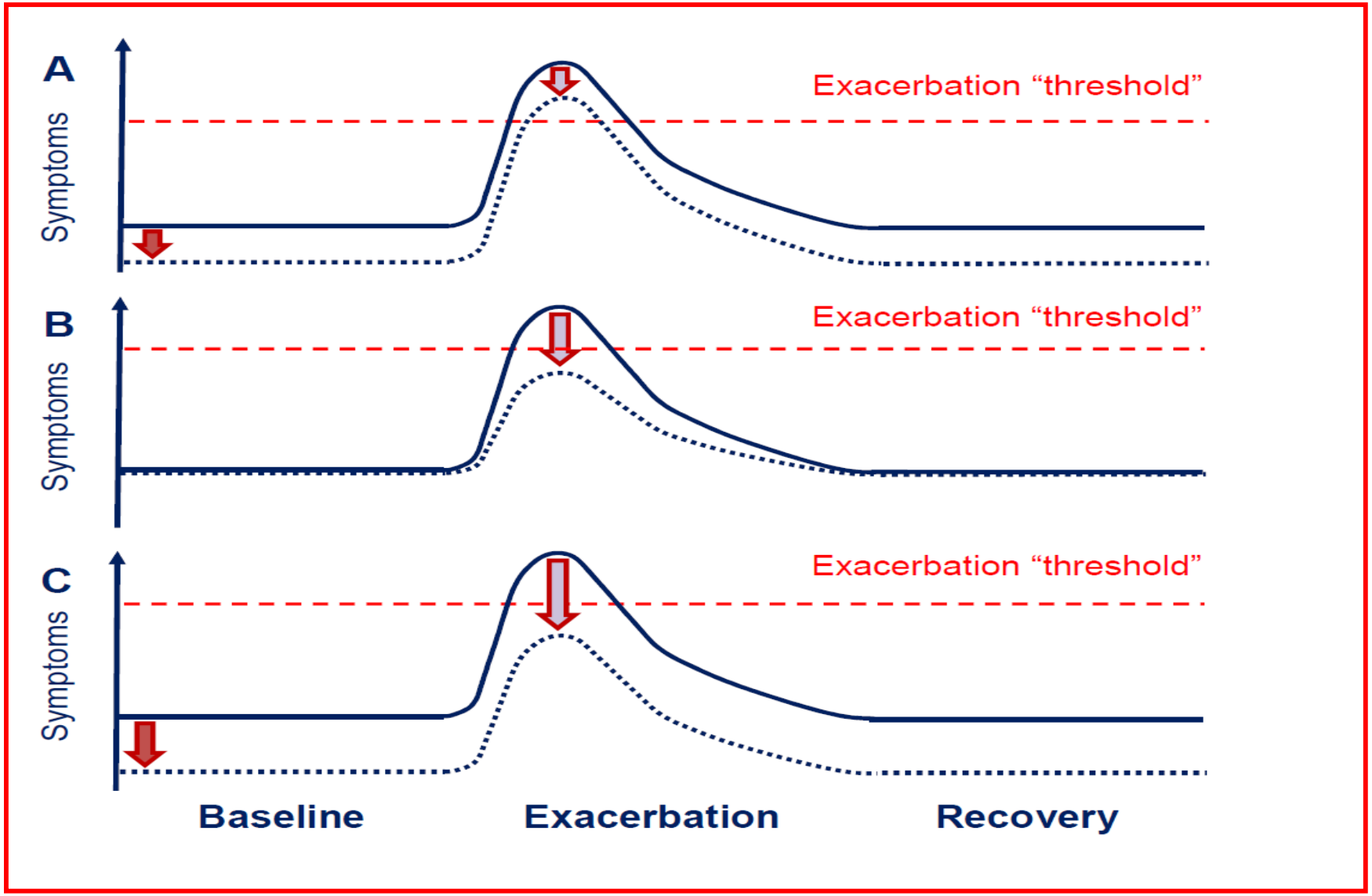
LABA and LAMA: important ***cross-talks inside ASM between cholinergic and adrenergic pathways***.

- ✓ stimulating β2-ARs, **LABA** can inactivate the signaling cascade underlying ACh-induced bronchoconstriction via an *effective inhibition of the activity of M3 muscarinic receptor* coupled Gq protein.

- ✓ **LAMA** can either *restore or potentiate and amplify the bronchodilating action of β2-adrenergic agonists* not only by inhibiting the IP3-dependent intracellular effects triggered by M3 receptor stimulation, but also by preventing the deleterious effects on β2-AR function elicited by the ACh-activated M3/Gq/PLC/DAG/PKC signaling pathway

Luigino Calzetta et al., Eur J Pharm, 2015

Η θεωρία των συμπτωμάτων

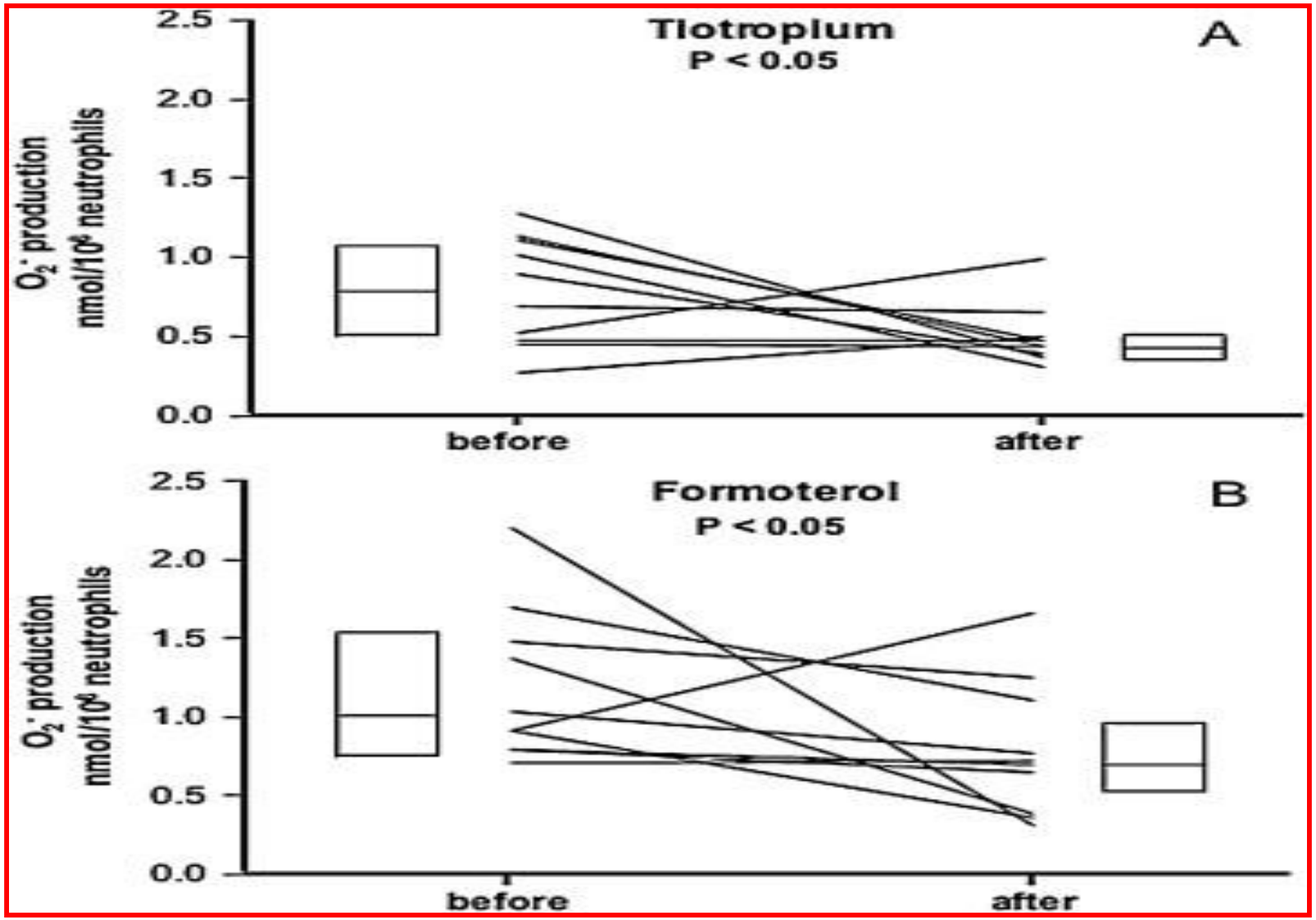


Bee K et al AGRCCM 2017

Σχεδιασμός

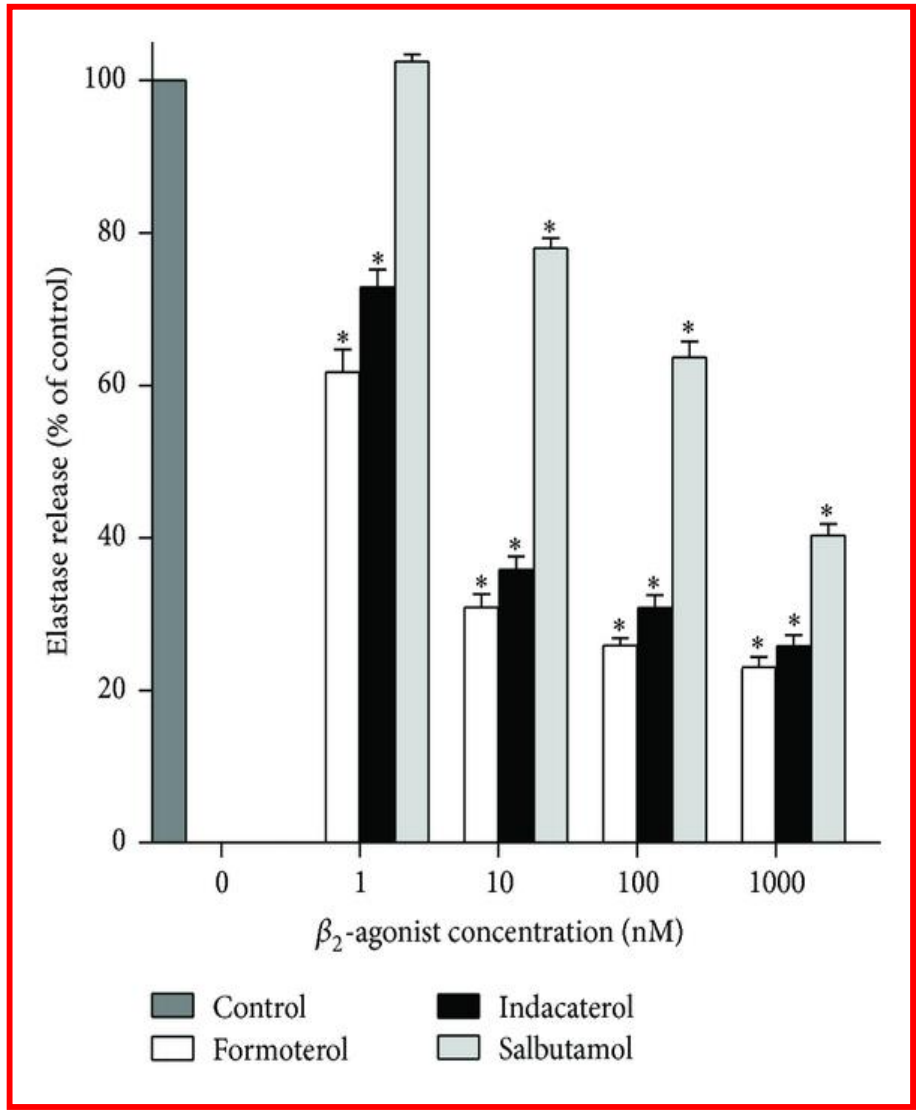
- Μερικά ενδιαφέροντα στοιχεία για να κτίσουμε την υπόθεση
- Έχει η υπόθεση μας θέση για τα LABA LAMA?
- Παρεμβάσεις και τροποποιήσεις

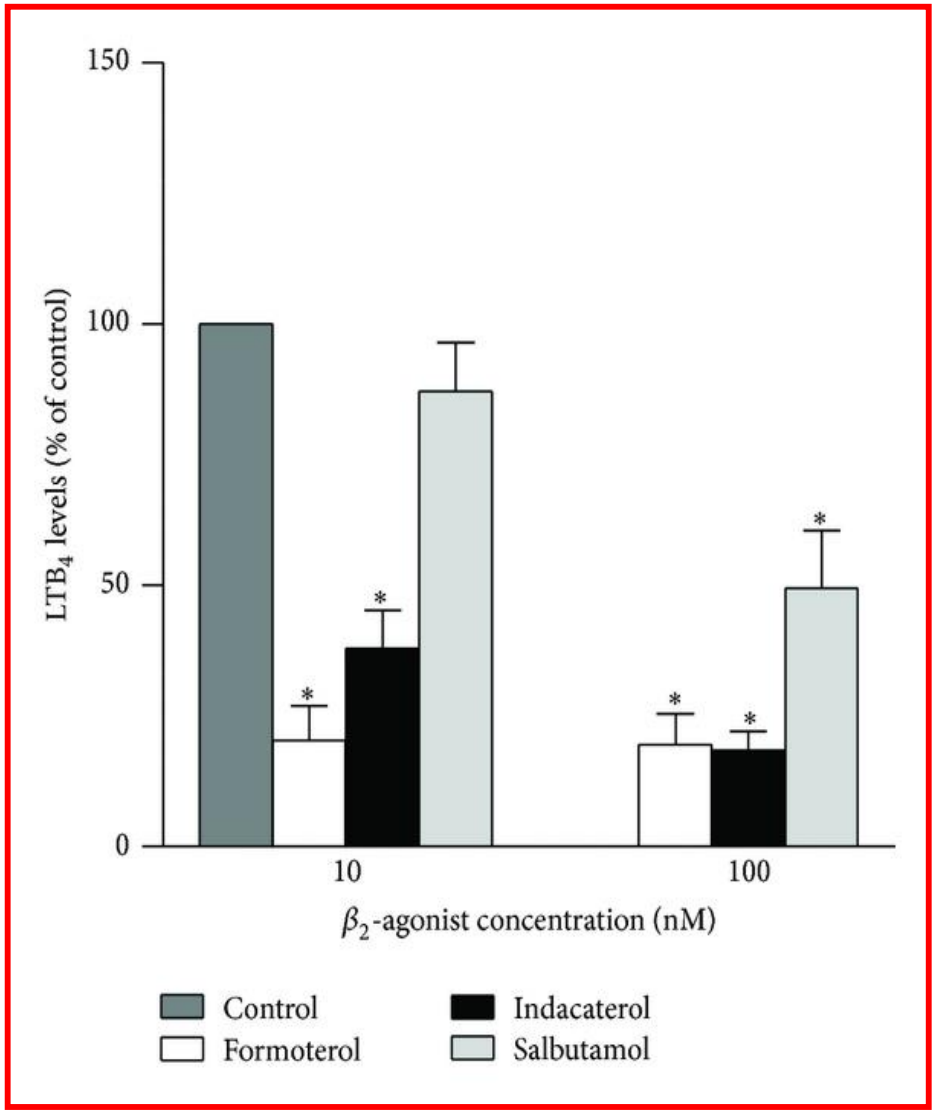
LABA –LAMA : Αντιφλεγμονώδης δράση



Pierachille Santus, et al Pharmacological Research, Volume 66, Issue 4, 2012, 343–348

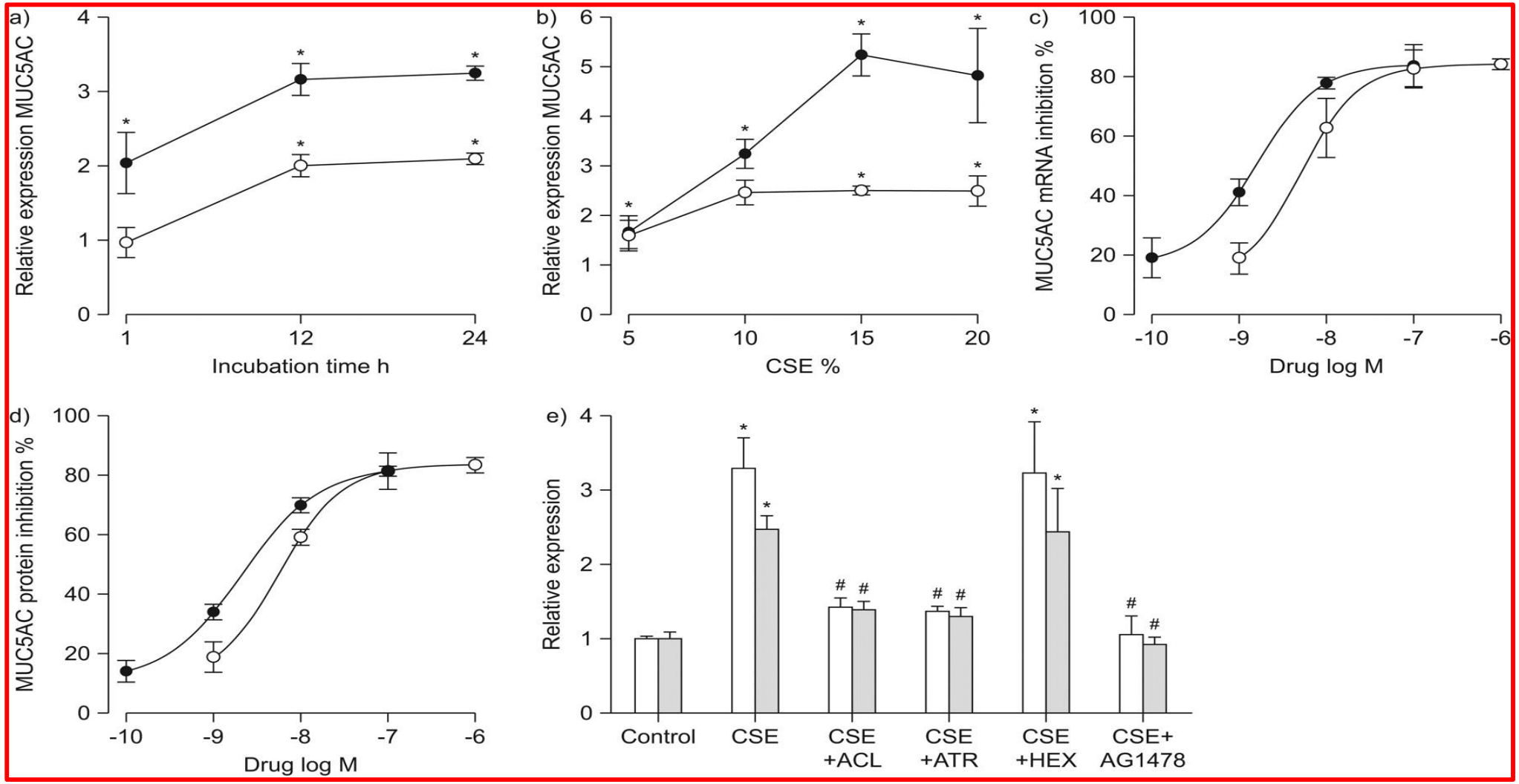
Ultra LABA: In vitro- καταστολή στην ουδετεροφιλική φλεγμονή





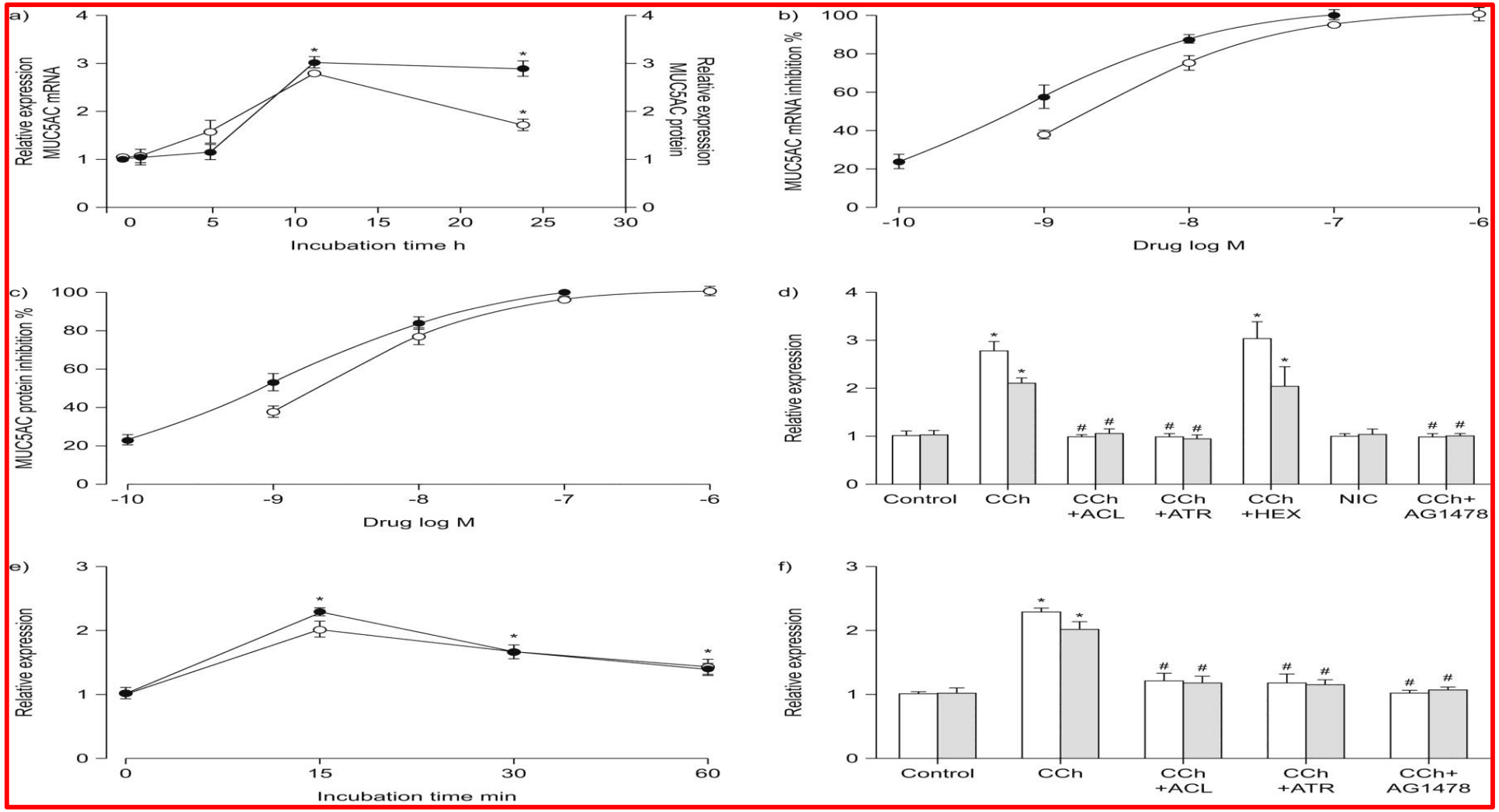
Anderson R et al Med Inflammation 2014

MUC5AC mRNA & protein expression στο βρογχικό επιθήλιο –Η αντιχολινεργική παρέμβαση



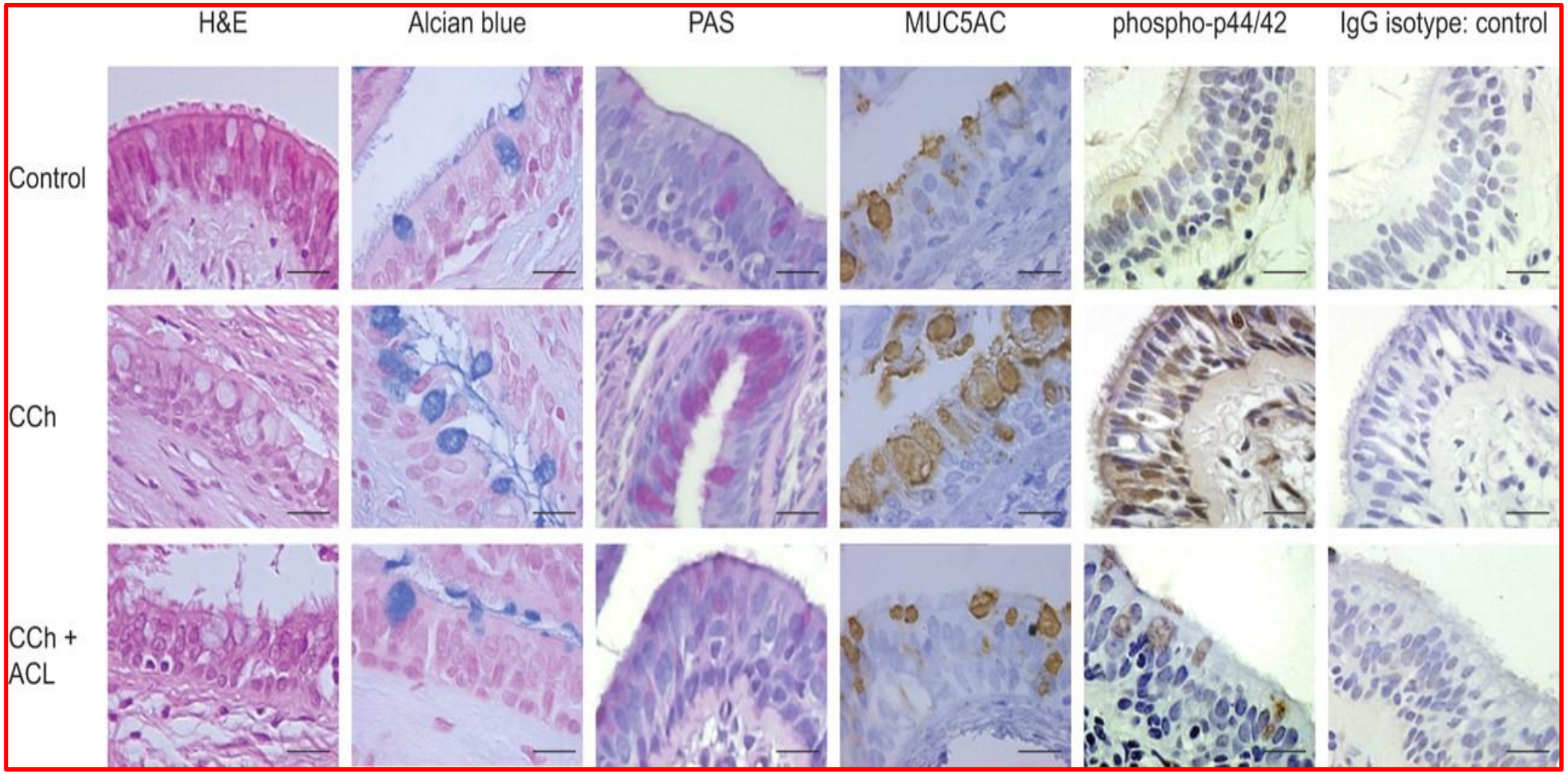
J. Cortijo et al. Eur Respir J 2011;37:244-254

Carbachol (CCh) σχετιζόμενη MUC5AC mRNA & protein expression- Η αντιχολινεργική παρέμβαση



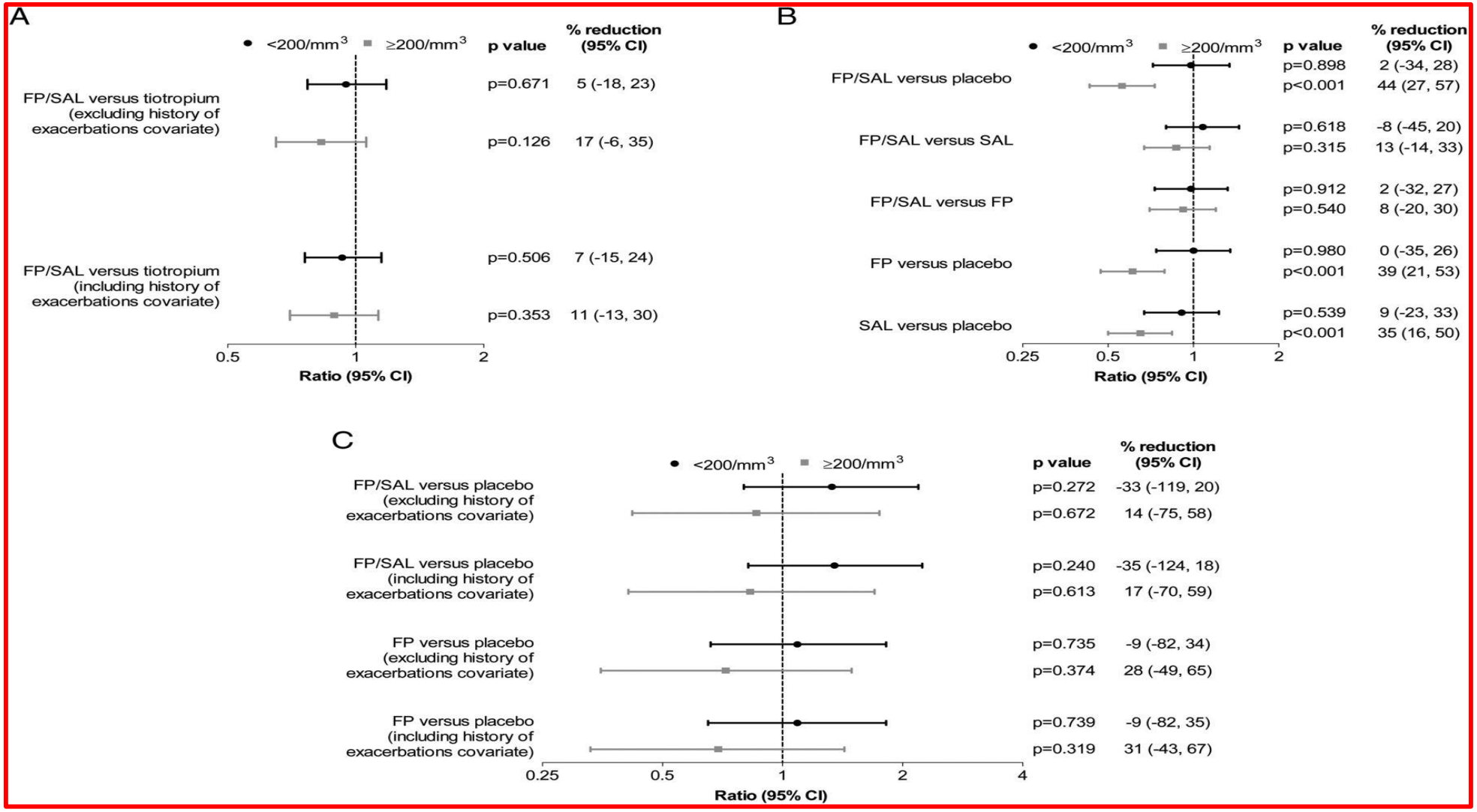
J. Cortijo et al. Eur Respir J 2011;37:244-254

Η ιστολογική απόδειξη



J. Cortijo et al. Eur Respir J 2011;37:244-254

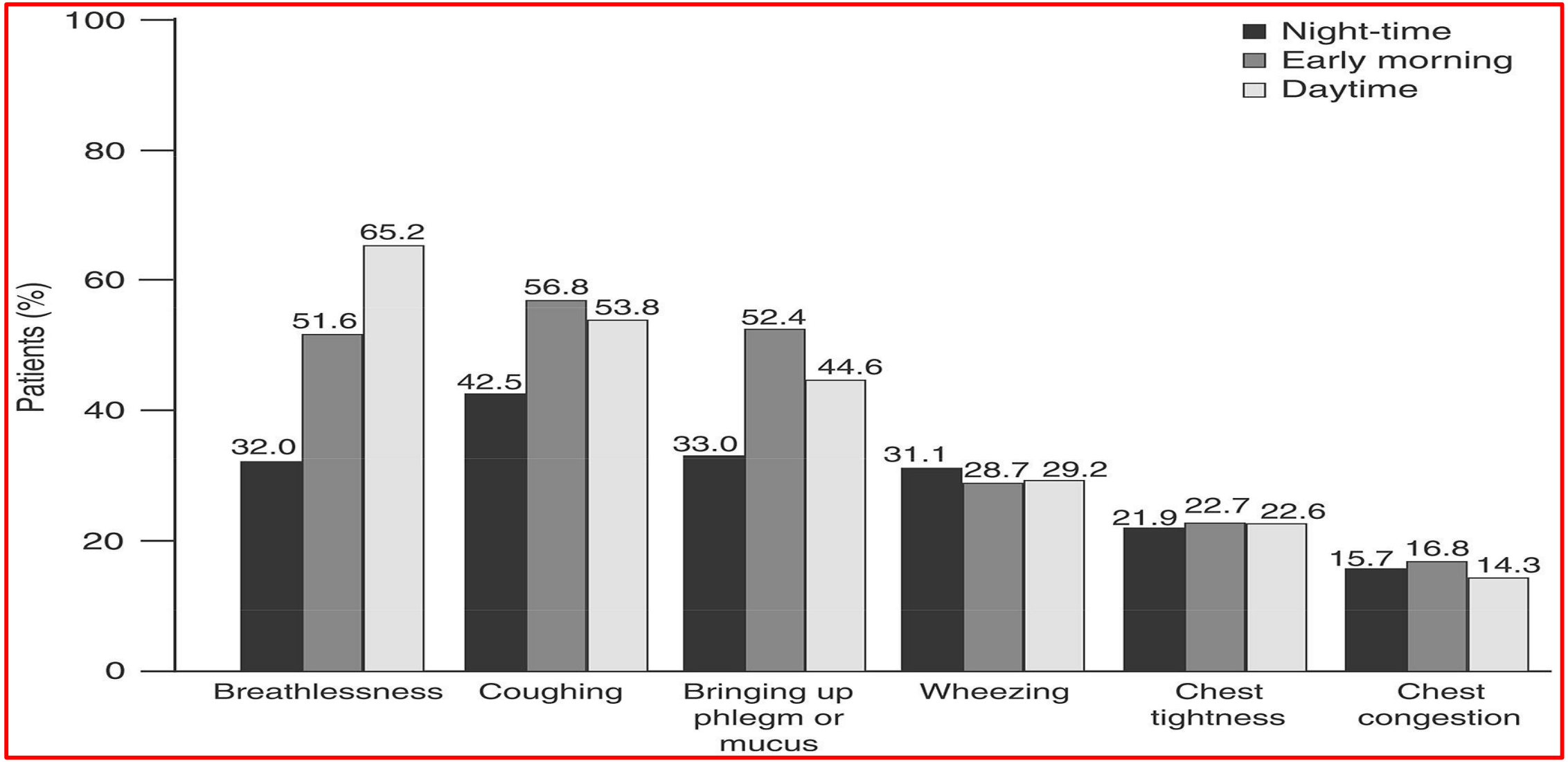
Τιμή ηωσινοφίλων βάσης [AA] και παροξύνσεις : Inspire & Tristan



Ian D Pavord et al. Thorax 2016;71:118-125

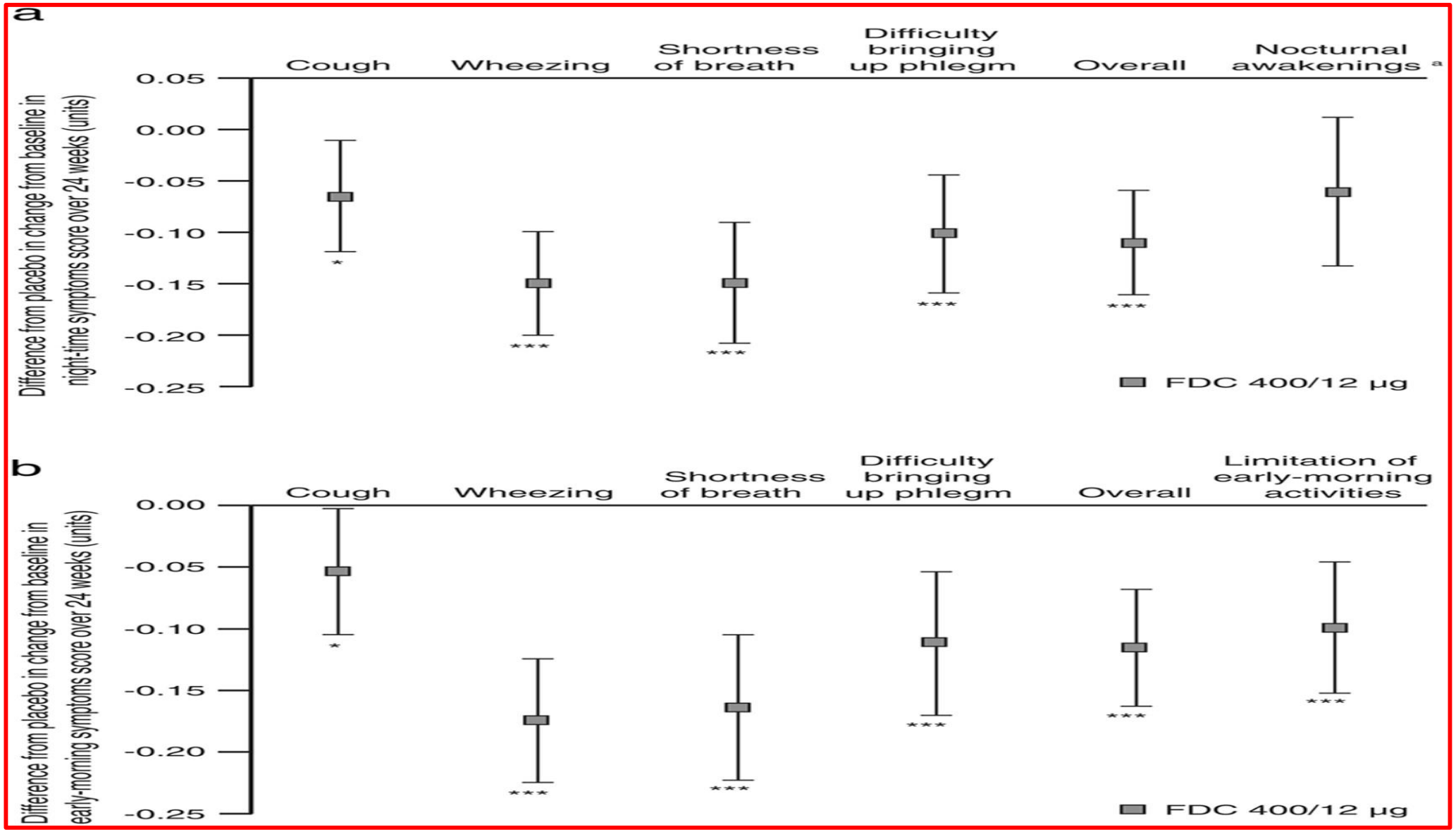
THORAX

Διακύμανση συμπτωμάτων



Miravitlles et al. Respir Res (BioMed Central) 2014,

Παρέμβαση στη διακύμανση συμπτωμάτων



Bateman et al. Respir Res (BioMed Central) 2015

Το σύμπτωμα μετράει?

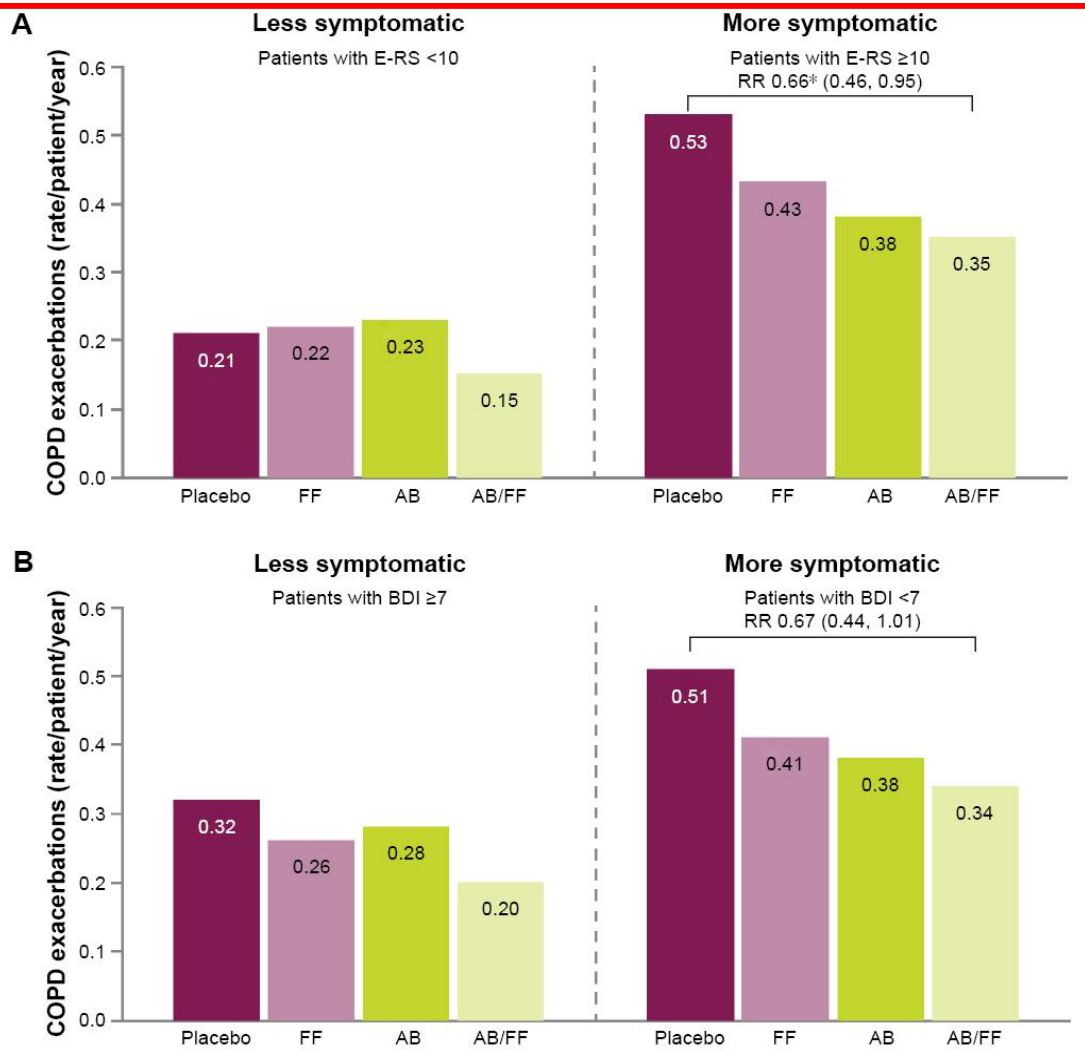
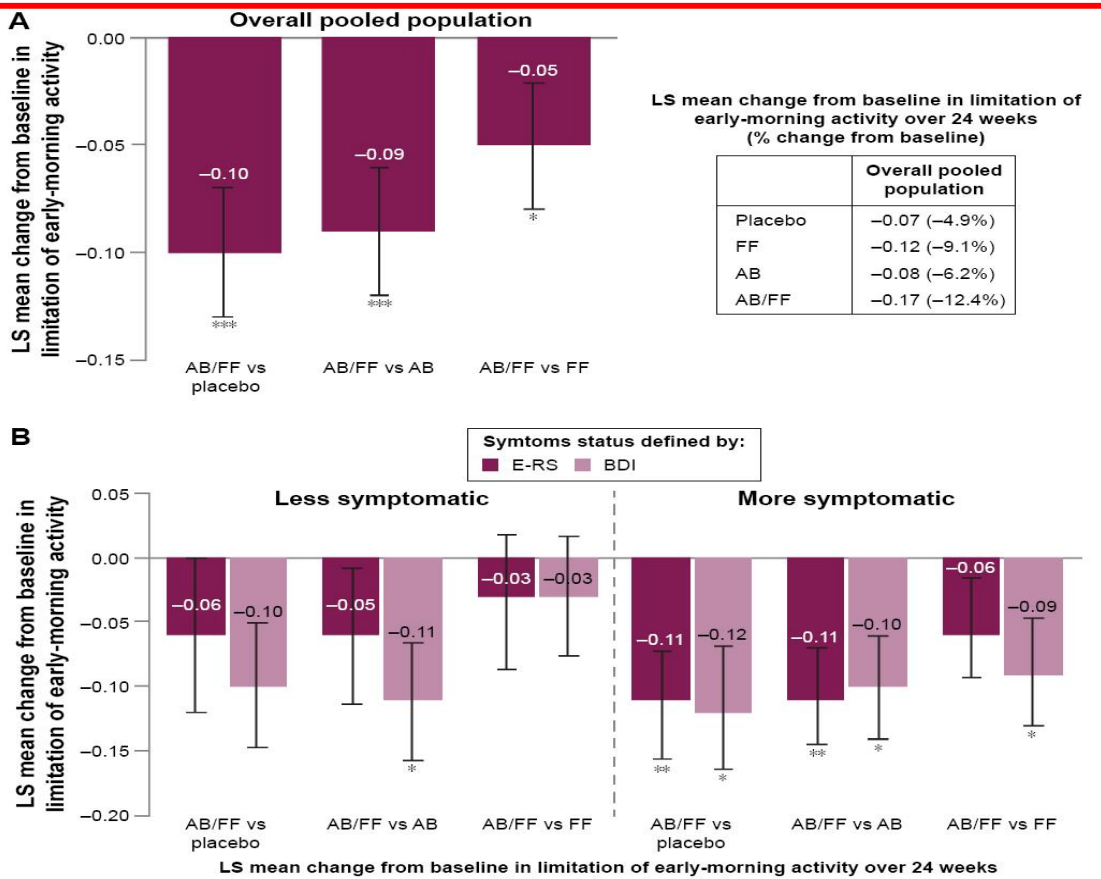


Figure 7 Rate of moderate or severe COPD exacerbations (HCRU criteria) in less symptomatic and more symptomatic patients at Week 24, (**A**) less symptomatic and more symptomatic defined by E-RS score, (**B**) less symptomatic and more symptomatic defined by BDI score.
Note: *$P \leq 0.05$; $P=0.057$ vs placebo in more symptomatic patients with BDI <7; Moderate or severe exacerbations are defined as exacerbations that require treatment with antibiotics or corticosteroids and those which result in hospitalization, respectively; Exacerbations data are RR (95% CI).
Abbreviations: AB, aclidinium bromide 400 µg; BDI, Baseline Dyspnea Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms; FF, formoterol fumarate 12 µg; HCRU, healthcare resource utilization; RR, rate ratio.



LS mean change from baseline in limitation of early-morning activity over 24 weeks (% change from baseline)

	Overall pooled population
Placebo	−0.07 (−4.9%)
FF	−0.12 (−9.1%)
AB	−0.08 (−6.2%)
AB/FF	−0.17 (−12.4%)

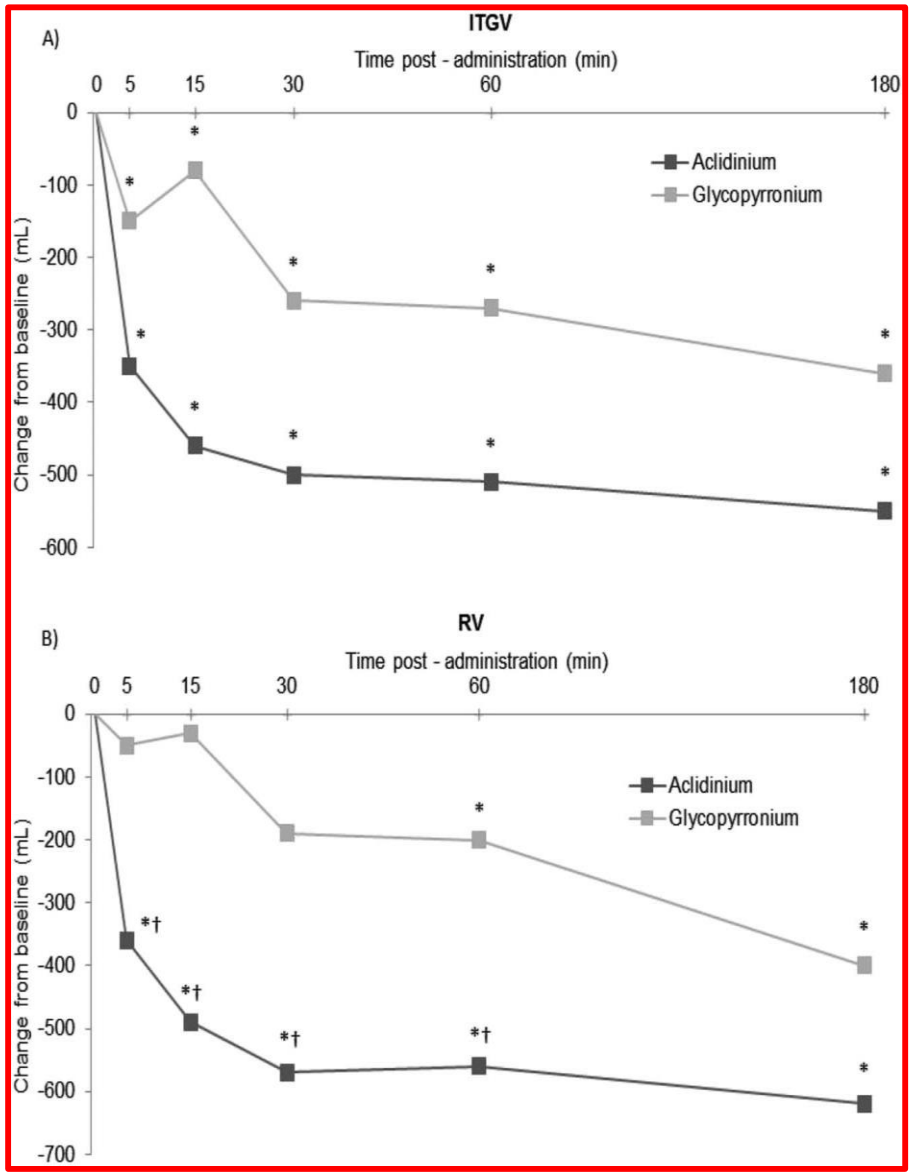
LS mean change from baseline in limitation of early-morning activity over 24 weeks (% change from baseline)

	Less symptomatic		More symptomatic	
	E-RS <10	BDI ≥7	E-RS ≥10	BDI <7
Placebo	−0.09 (−9.8%)	−0.08 (−6.9%)	−0.03 (−2.0%)	−0.03 (−1.8%)
FF	−0.12 (−15.5%)	−0.15 (−14.6%)	−0.09 (−5.8%)	−0.06 (−3.8%)
AB	−0.09 (−11.4%)	−0.06 (−6.7%)	−0.04 (−2.7%)	−0.05 (−3.0%)
AB/FF	−0.15 (−19.6%)	−0.18 (−16.9%)	−0.15 (−9.1%)	−0.15 (−9.2%)

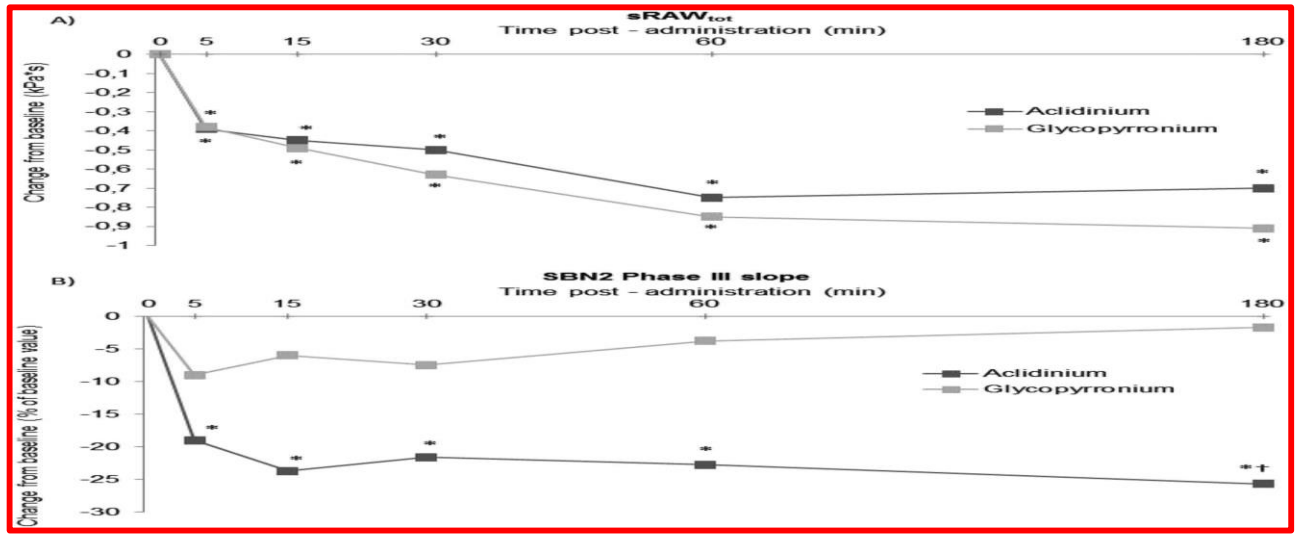
Figure 6 Change from baseline in early-morning limitation of activity in (**A**) the overall pooled population and (**B**) less symptomatic and more symptomatic patients with COPD.
Notes: Data are LS mean ± SE for the pooled ITT population; *$P<0.05$; **$P<0.01$; ***$P<0.001$.
Abbreviations: AB, aclidinium bromide 400 µg; BDI, Baseline Dyspnea Index; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms; FF, formoterol fumarate 12 µg; ITT, intent-to-treat; LS, least squares; SE, standard error.

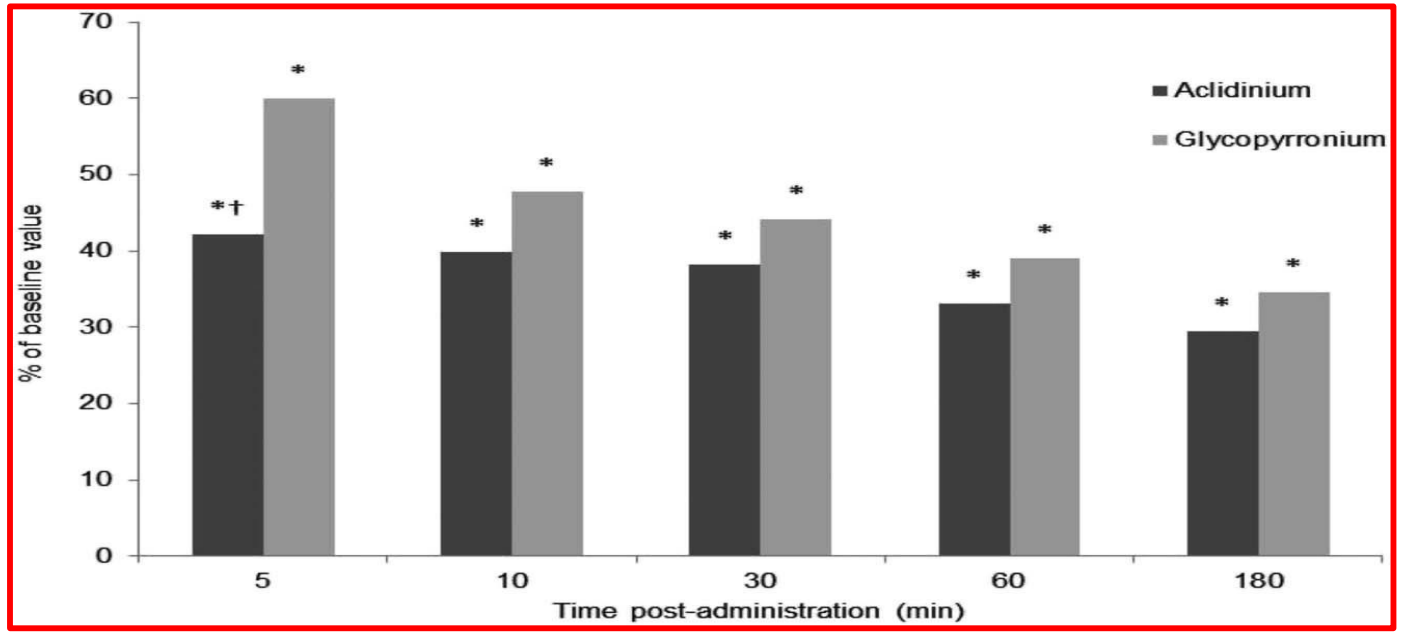
Miravitlles M et al IJCOPD 2016

Παρέμβαση στην υπερδιάταση-ανομοιογένεια αερισμού

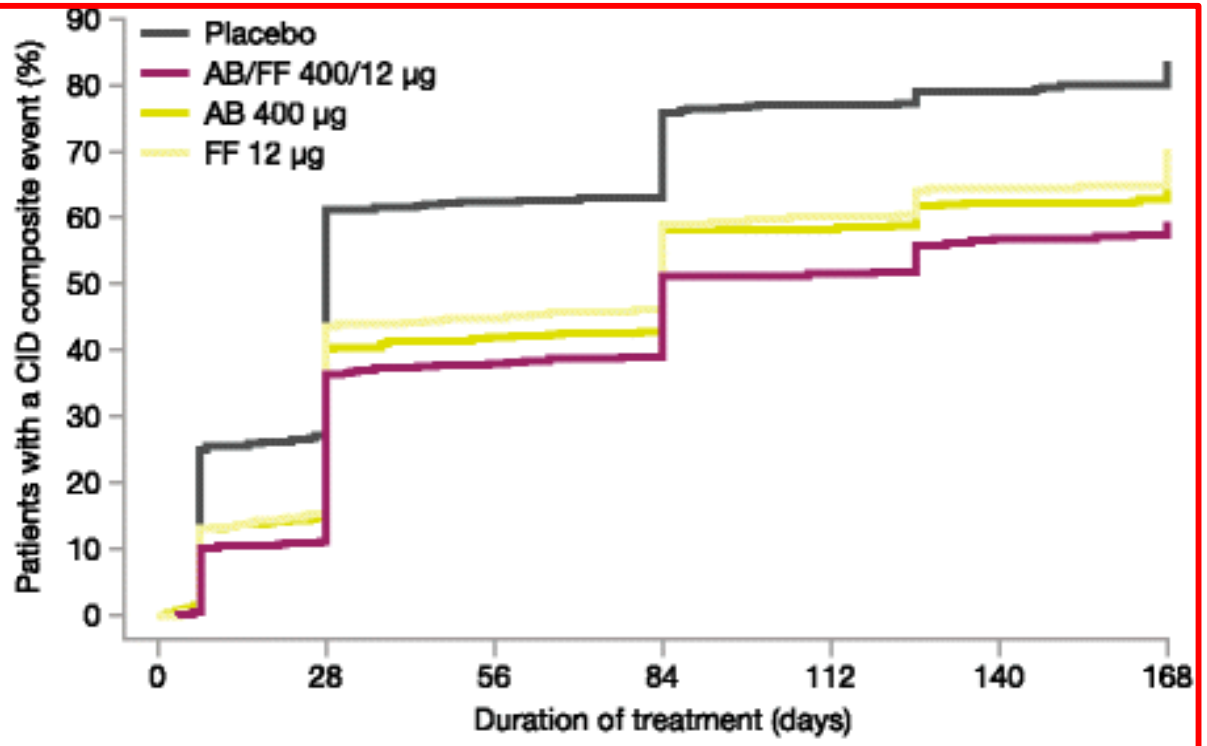


Santus P et al Pulm Pharm Ther 2015

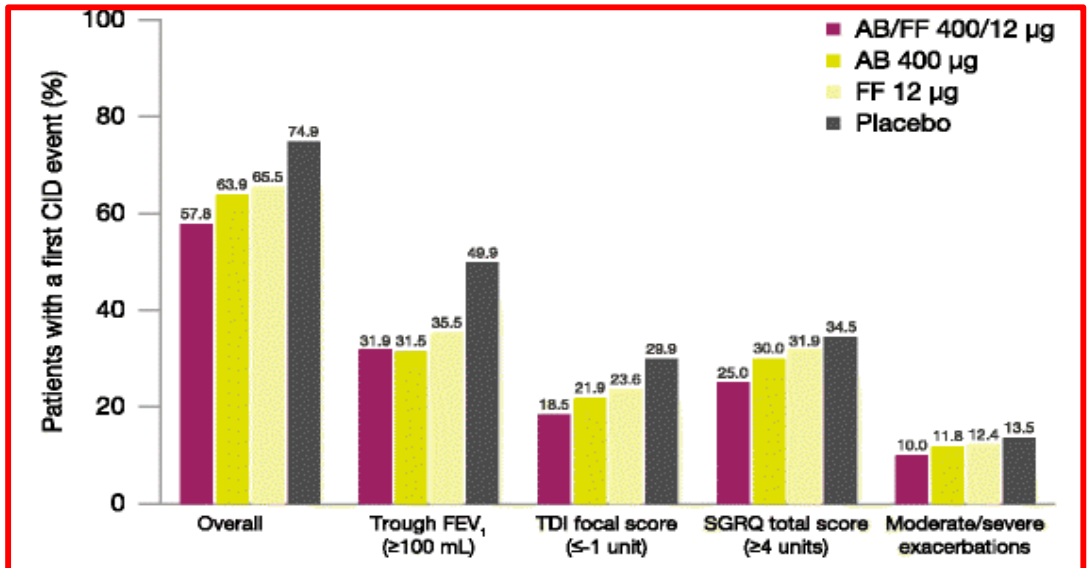




CID μία νέα προσέγγιση



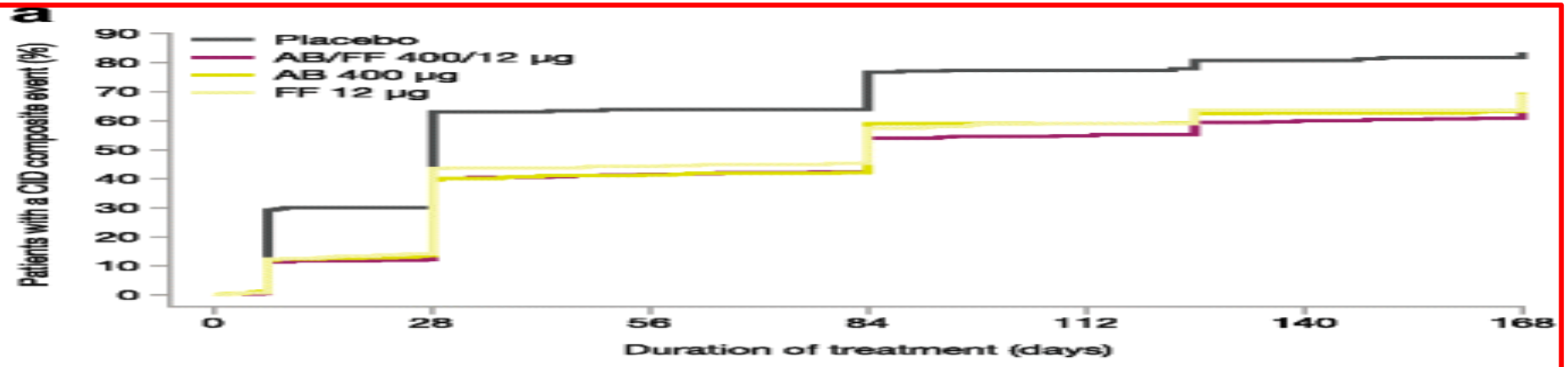
	AB/FF 400/12 μg (n = 720)	AB 400 μg (n = 720)	FF 12 μg (n = 715)	Placebo (n = 525)
HR vs placebo	0.55***	0.65***	0.67***	-
HR vs AB 400 μg	0.85*	-	-	-
HR vs FF 12 μg	0.82**	0.96	-	-



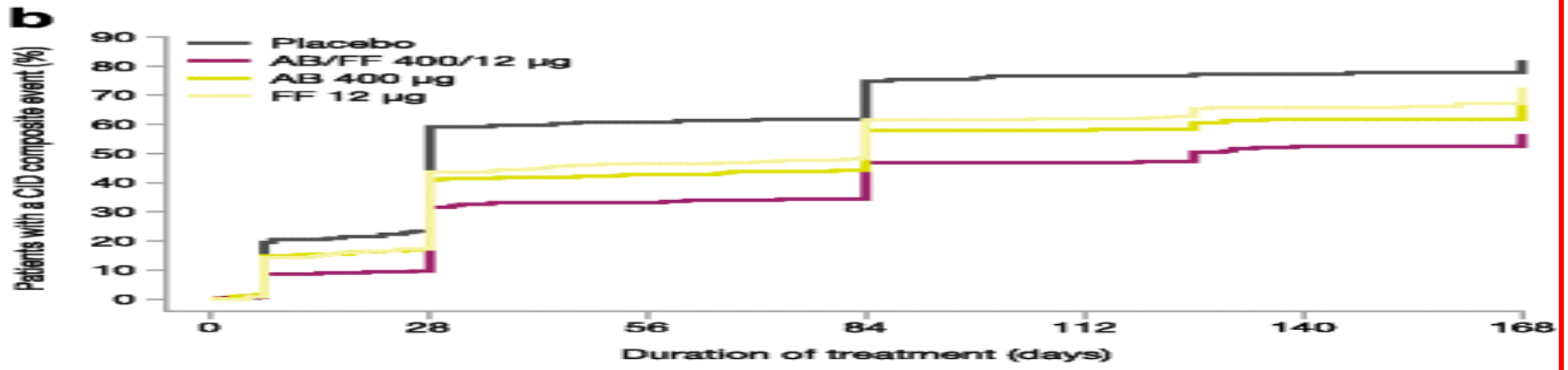
		AB/FF 400/12 μg (n = 720)	AB 400 μg (n = 720)	FF 12 μg (n = 715)
Trough FEV_1 HR (≥100 mL)	vs placebo	0.51***	0.51***	0.59***
	vs AB 400 μg	1.00	-	-
	vs FF 12 μg	0.88	0.87	-
TDI focal score HR (≤-1 unit)	vs placebo	0.54***	0.66***	0.71**
	vs AB 400 μg	0.83	-	-
	vs FF 12 μg	0.76*	0.92	-
SGRQ total score HR (≥4 units)	vs placebo	0.65***	0.80*	0.84
	vs AB 400 μg	0.81*	-	-
	vs FF 12 μg	0.77**	0.95	-
Moderate/severe exacerbations HR	vs placebo	0.67*	0.81	0.85
	vs AB 400 μg	0.82	-	-
	vs FF 12 μg	0.78	0.95	-

Singh D et al Resp Research 2017

Ανεξαρτήτως βαρύτητας?



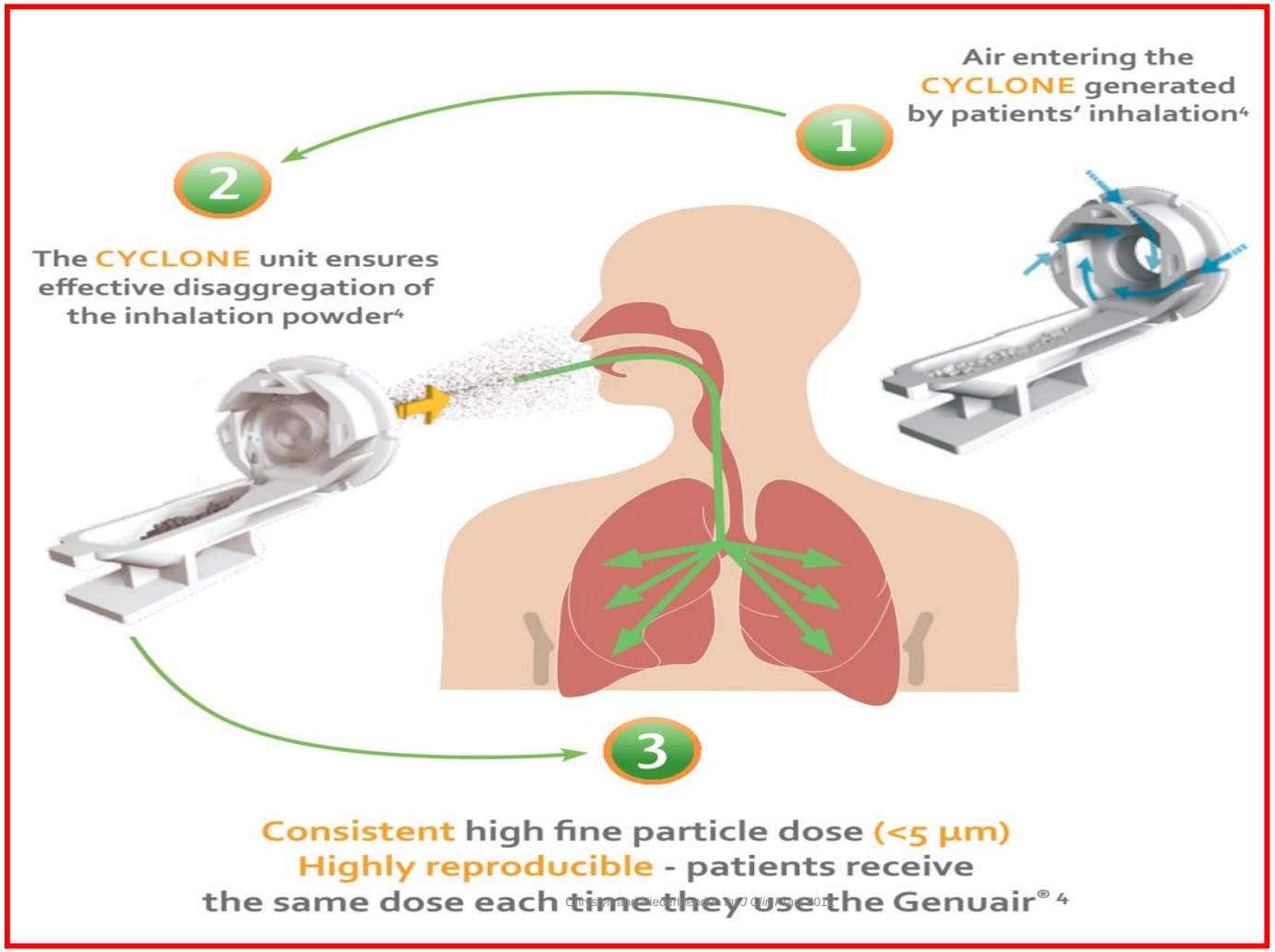
Moderate COPD at baseline[a]	AB/FF 400/12 µg (n = 418)	AB 400 µg (n = 411)	FF 12 µg (n = 436)	Placebo (n = 293)
HR vs placebo	0.58***	0.62***	0.63***	–
HR vs AB 400 µg	0.94	–	–	–
HR vs FF 12 µg	0.93	0.99	–	–



Severe COPD at baseline[b]	AB/FF 400/12 µg (n = 301)	AB 400 µg (n = 306)	FF 12 µg (n = 278)	Placebo (n = 231)
HR vs placebo	0.50***	0.68***	0.75**	–
HR vs AB 400 µg	0.74**	–	–	–
HR vs FF 12 µg	0.67***	0.91	–	–

Singh D et al Resp Research 2017

Τα οφέλη της συσκευής Genuair: Σύστημα cyclone



Chrystyn and Niederlaender. *Int J Clin Pract* 2012

Τα οφέλη της συσκευής Genuair: Εύκολη στη χρήση συσκευή και από τους ηλικιωμένους και από τους ασθενείς με αρθριτικά προβλήματα

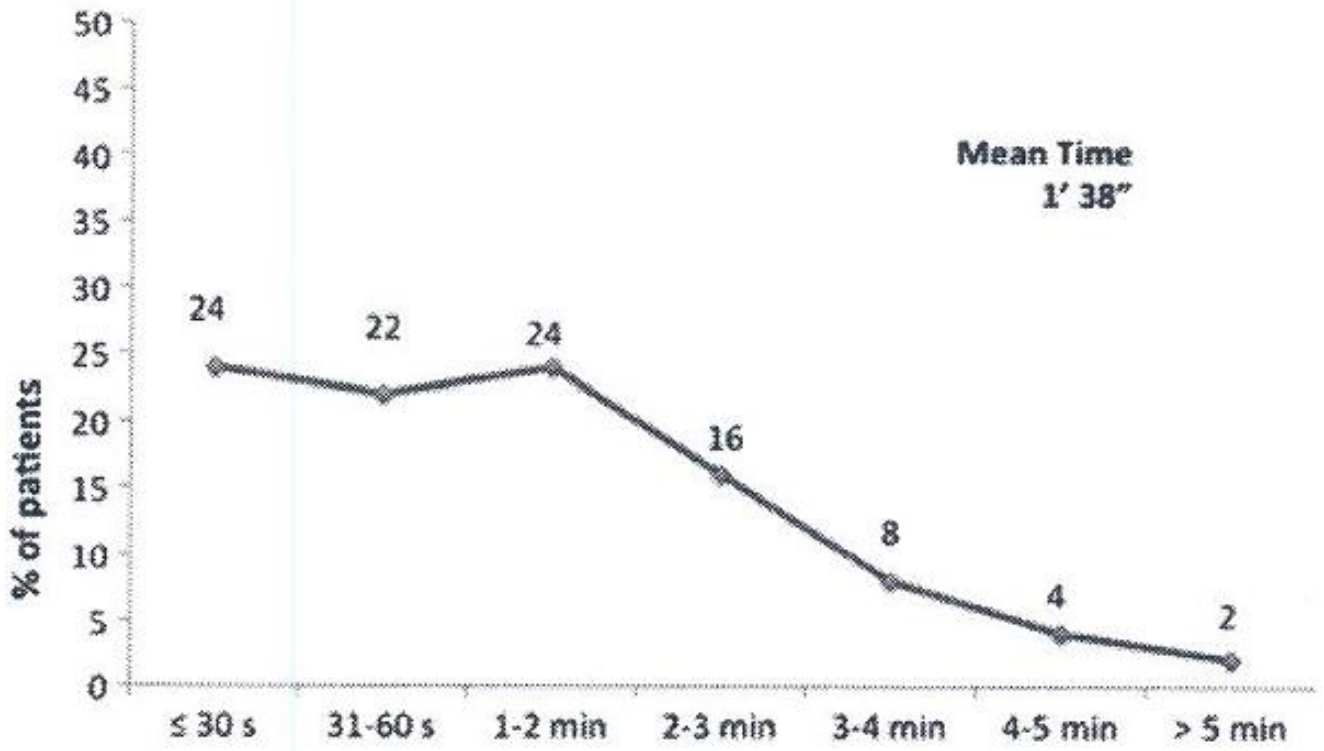


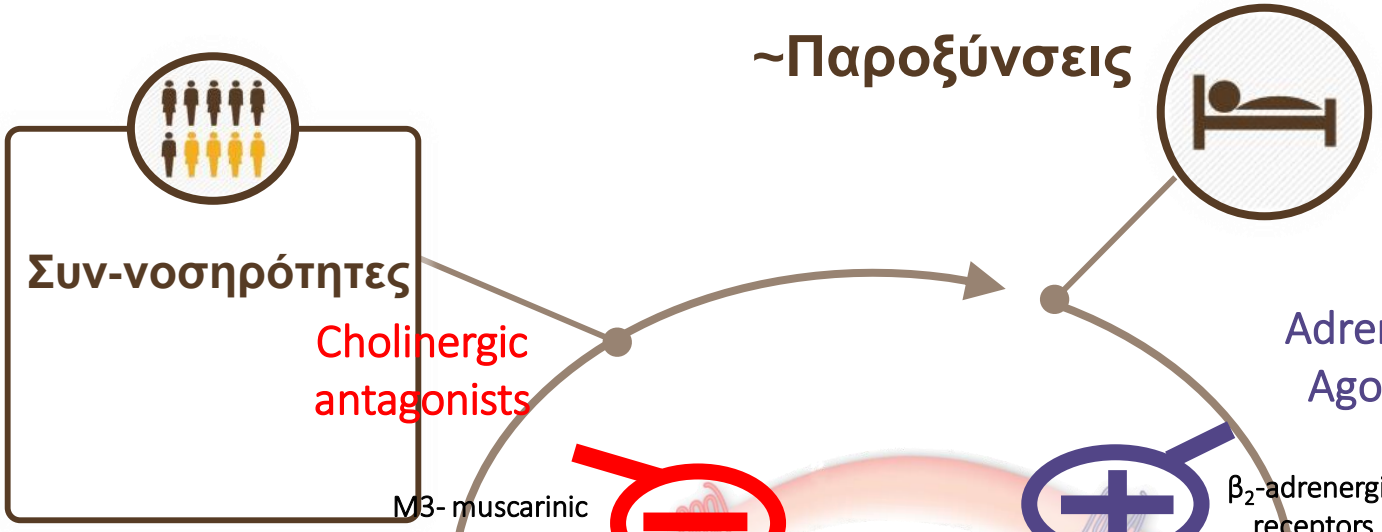
Figure 1. Time necessary to explain the inhaler technique and to perform a correct inhalation.

Blasi F. et al . COPD 2016

Σχεδιασμός

- Μερικά ενδιαφέροντα στοιχεία για να κτίσουμε την υπόθεση
- Έχει η υπόθεση μας θέση για τα LABA LAMA?
- Παρεμβάσεις και τροποποιήσεις
- Ο επίλογος

ΧΑΠ : Σκέψεις σε μια πολυπαραγοντική νόσο



Συν-νοσηρότητες

Cholinergic antagonists

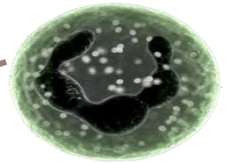
M3- muscarinic receptors

~Παροξύνσεις

Adrenergic Agonists

β_2-adrenergic receptors

Φλεγμονή



SMC contraction

SMC relaxation

SMC, smooth muscle cell

Χαμηλή δυνατότητα για άσκηση

Υπερδιάταση

Συμπτώματα –Βλέννα