Τι νεότερο στη φαρμακοθεραπεία της ΧΑΠ αναμένεται εντός της 10ετίας

Στέλιος Θ. Λουκίδης MD FCCP

ERS secretary group 5.2

Ιατρική σχολή ΕΚΠΑ

Θεραπεία σταθερής ΧΑΠ

I	II	III	IV
Ήπια	**Μέτρια**	**Σοβαρή**	**Πολύ σοβαρή**
FEV_1/FVC<70%	**FEV_1/FVC<70%**	**FEV_1/FVC<70%**	**FEV_1/FVC<70%**
$FEV_1 \geq 80\%$	**FEV_1 50-80%**	**FEV_1 30-50%**	**FEV_1 <30% *ή***
± συμπτώματα	**± συμπτώματα**	**± συμπτώματα**	**FEV_1 <50%**
			+ ΧΑΑ (ή ΧΠΚ)

Διακοπή καπνίσματος, αντιγριππικός εμβολιασμός
Βρογχοδιασταλτικά βραχείας δράσης κατ' επίκληση

ΚΑΙ **Τιοτρόπιο ± LABA (Σαλμετερόλη ή Φορμοτερόλη)**
Ινδακατερόλη
Αποκατάσταση (Rehabilitation)

ΚΑΙ **ICS (Combos)**
(σε συχνές παροξύνσεις)
Ροφλουμιλάστη

ΚΑΙ **LTOT**
± Χειρουργικές επεμβάσεις

GOLD 2011

Νεότερα Βρογχοδιασταλτικά [LABA]

Drug	Characteristics	Latest developments	Company working on this strategy
Indacaterol	It behaves as a nearly full β_2-agonist. It offers a fast onset of action and true 24-h bronchodilation. Large Phase III trials have demonstrated that indacaterol 150 and/or 300 μg once-daily is more effective than formoterol or salmeterol, and at least as effective as tiotropium. It is well tolerated, with a good overall and cardiovascular safety profile.	Already been launched in several countries	Novartis, Basle, Switzerland
Olodaterol	It behaves as a nearly full β_2-agonist, but preserves the β_2-AR signaling capacity even after long-term preincubation. It offers true 24-h bronchodilation. Initial Phase II studies provided proof of the 24-h bronchodilation following 4 weeks once-daily administration.	Phase III Clinical data have not been disclosed	Boehringer Ingelheim, Ingelheim, Germany
Vilanterol	It has a greater intrinsic efficacy than salmeterol and a greater potency than indacaterol and salbutamol. It offers a fast onset of action and true 24-h bronchodilation.	Phase III Published available data on this compound are limited	GlaxoSmithKline, London, UK/Theravance, South San Francisco, CA, USA
LAS100977	Preclinical studies indicates that it is 10 times more potent than salmeterol and similar to formoterol and indacaterol, its onset of action is faster than salmeterol and indacaterol, but slower than formoterol, and its duration of action is longer than formoterol and salmeterol and comparable to indacaterol.	Phase II Published available data on this compound are limited	Almirall Prodesfarma, Barcelona, Spain
PF610355	It is more effective and longer lasting than salmeterol.	Phase II Published available data on this compound are limited	Pfizer, New York, NY, USA
AZD3199	Pharmacological data have not been disclosed.	Phase II Clinical data have not been disclosed	AstraZeneca, Lund, Sweden

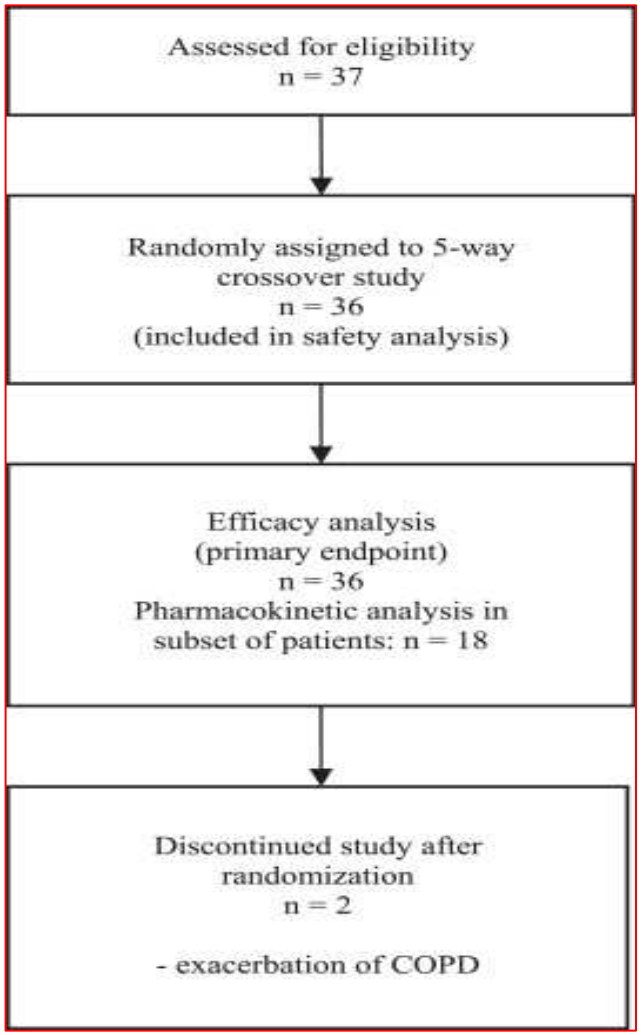
Matera MG et al Trends in Pharmacological Sciences, 2011

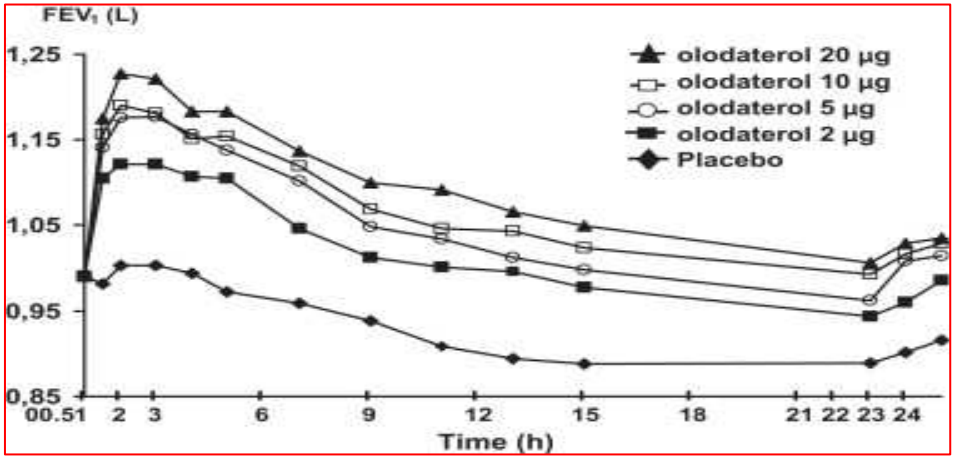
Νεότερα Βρογχοδιασταλτικά [LAMA]

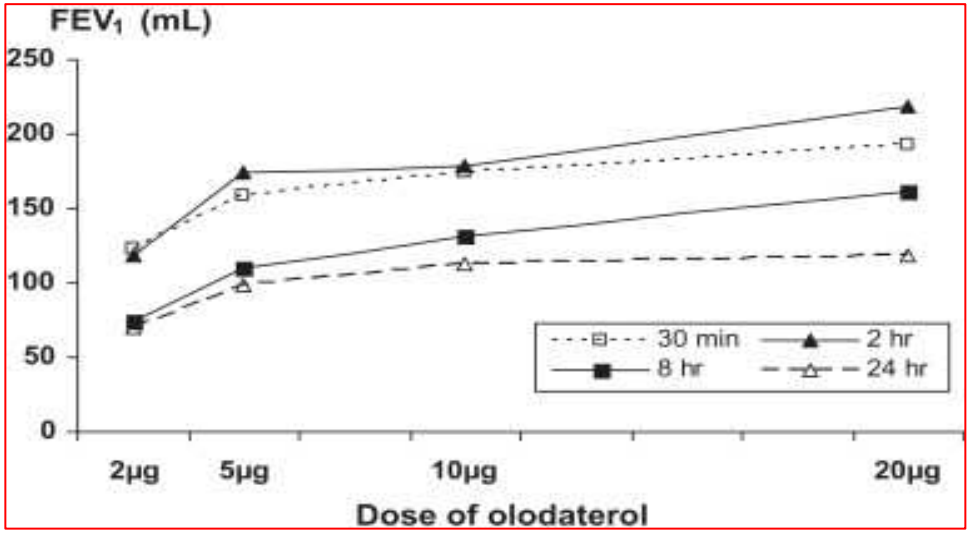
Drug	Characteristics	Latest developments	Company working on this strategy
Glycopyrronium bromide (NVA237)	*In vitro* it shows duration of action intermediate between that produced by tiotropium and that of ipratropium. Glycopyrronium 50 μg once-daily is well tolerated and shows significant and sustained 24-h bronchodilation.	Phase III	Novartis, Basle, Switzerland
Aclidinium bromide	Equivalency to ipratropium for speed of onset and a longer duration of action, but faster onset and shorter duration of action than tiotropium has been documented in human isolated bronchi. The partially disappointing efficacy results of the ACCLAIM/COPD trials question the possibility that aclidinium is at least as effective as tiotropium, but aclidinium 400 μg twice-daily provided bronchodilation over 24 h that was comparable to tiotropium 18 μg once-daily.	Phase III	Almirall Prodesfarma, Barcelona, Spain
GSK573719	Its long duration of action when administered via inhalation in animal models supports the potential for use as a once-daily bronchodilator for COPD.	Phase III Clinical data have not been disclosed	GlaxoSmithKline, London, UK
CHF5407	It is an antagonist as potent and long-acting as tiotropium on human M_3 receptors, but significantly short-acting on M_2 receptors. Its duration of action is similar to that of tiotropium.	Clinical data have not been disclosed	Chiesi Farmaceutici, Parma, Italy
PF4522971	It has an offset profile superior to ipratropium and shorter than tiotropium at the M_3 receptor in ligand binding experiments. It exhibits an equivalent duration of action profile to tiotropium.	Clinical data have not been disclosed	Pfizer, New York, NY, USA
Trospium	Inhaled trospium is able to induce a fast onset of bronchodilation within 15 min after administration with an effect that lasts 24 h.	Phase II Published available data on this compound are limited	Alkermes, Cambridge, MA, USA
RBx343E48F0	It is a novel muscarinic receptor antagonist from a distinct chemical class capable of antagonizing muscarinic receptors with high potency. It exhibits a long duration of action and this effect is supported by its pharmacokinetic property of being retained in the lung. The compound also exhibits a fast onset of action.	Preclinical phase	Ranbaxy Research Laboratories, Gurgaon, India

Matera MG et al Trends in Pharmacological Sciences, 2011

Olodaterol & ХАП

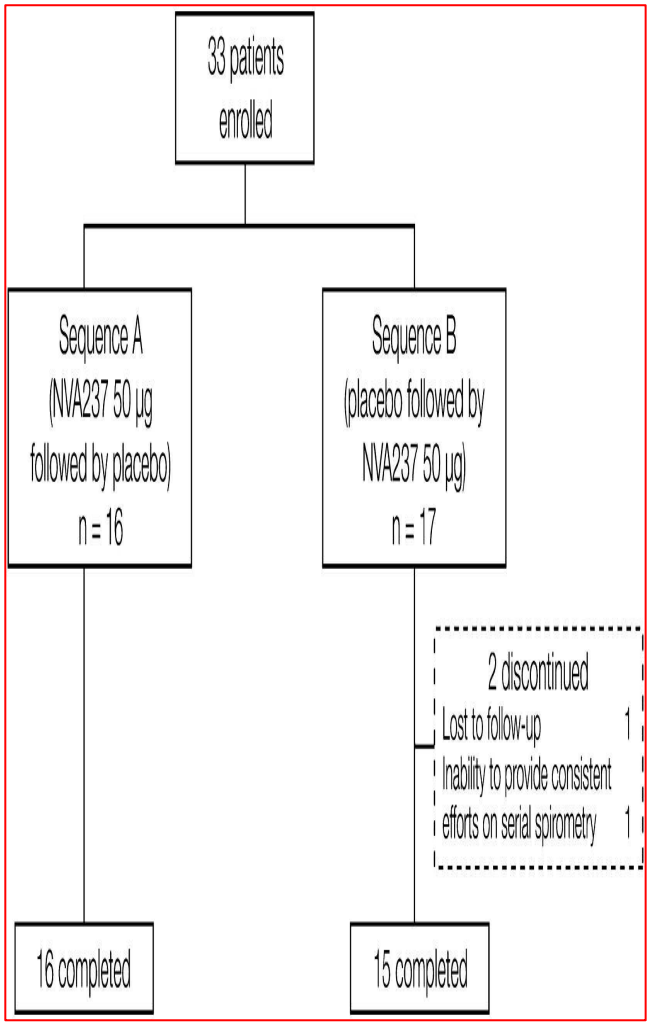


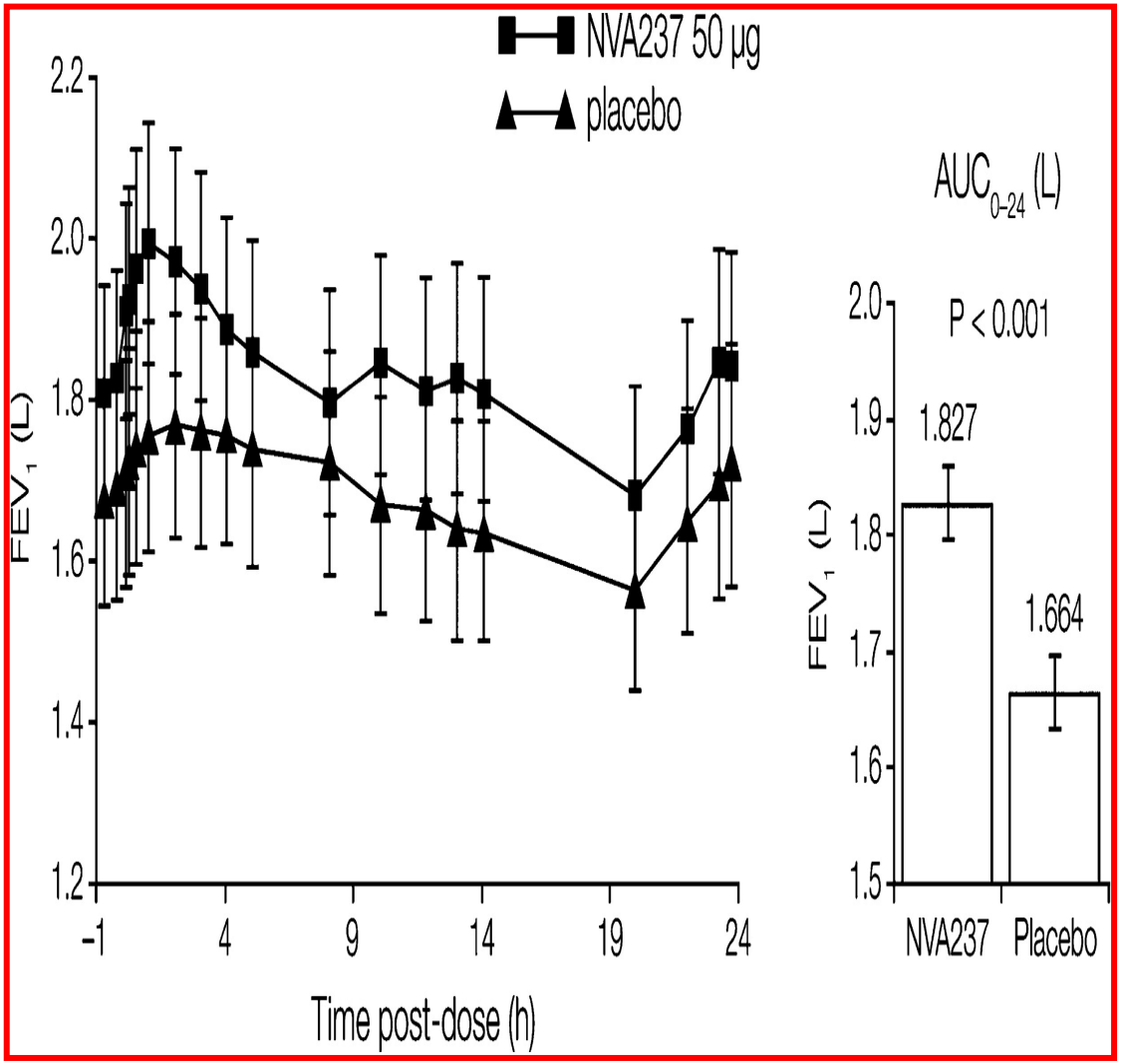




Van Noord JA et al Pulmonary Pharmacology & Therapeutics 2011

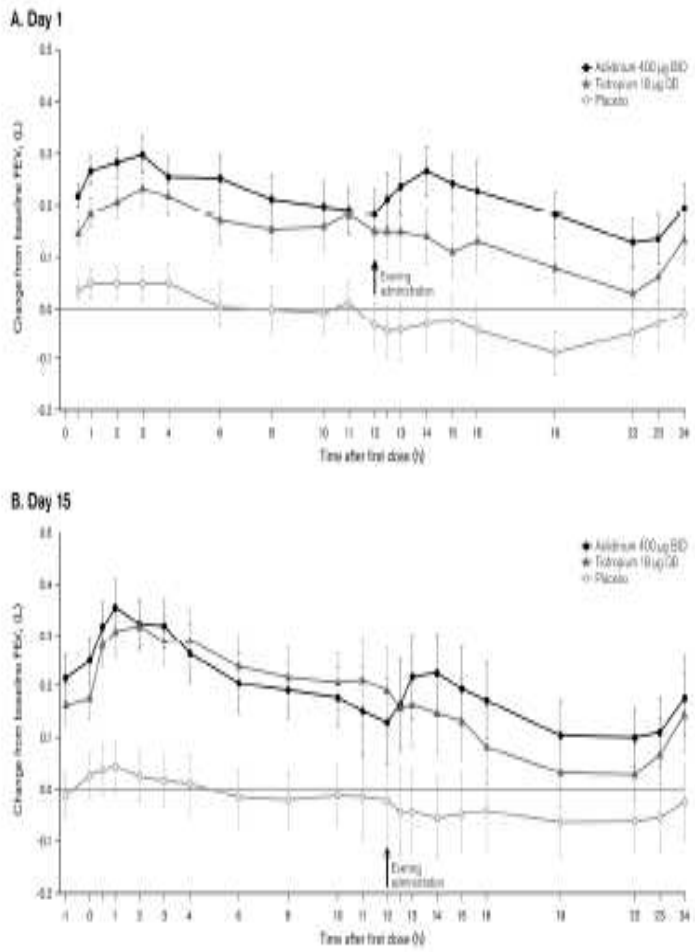
Glycopyrronium bromide (NVA 237) ХАП

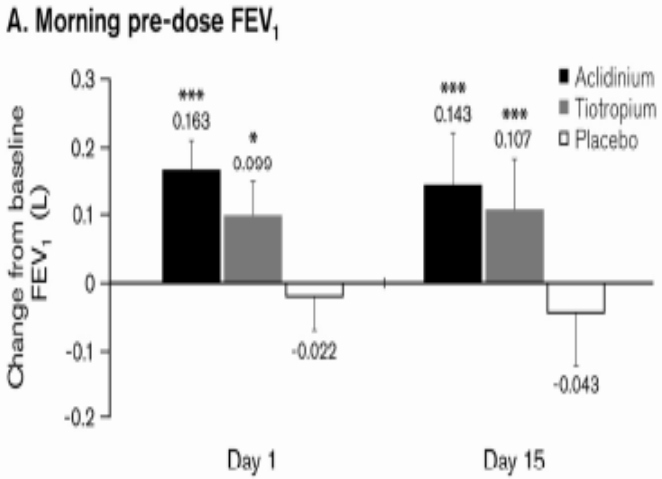


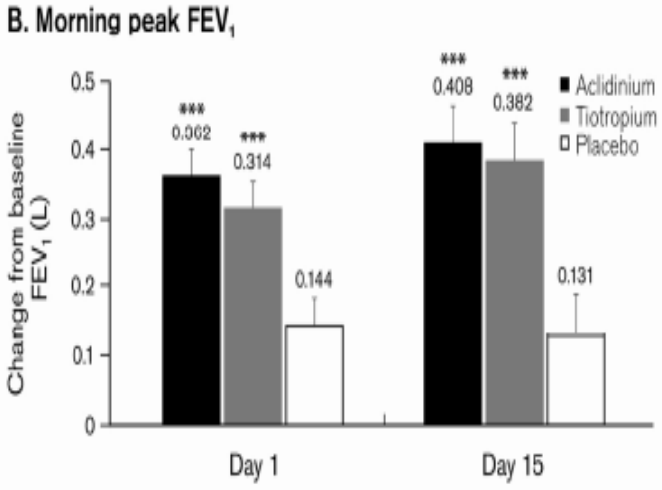


Fogarty C et al Resp Medicine 2011

Aclidinium Bromide 400 μg BID vs Tiotropium σε ΧΑΠ II&III



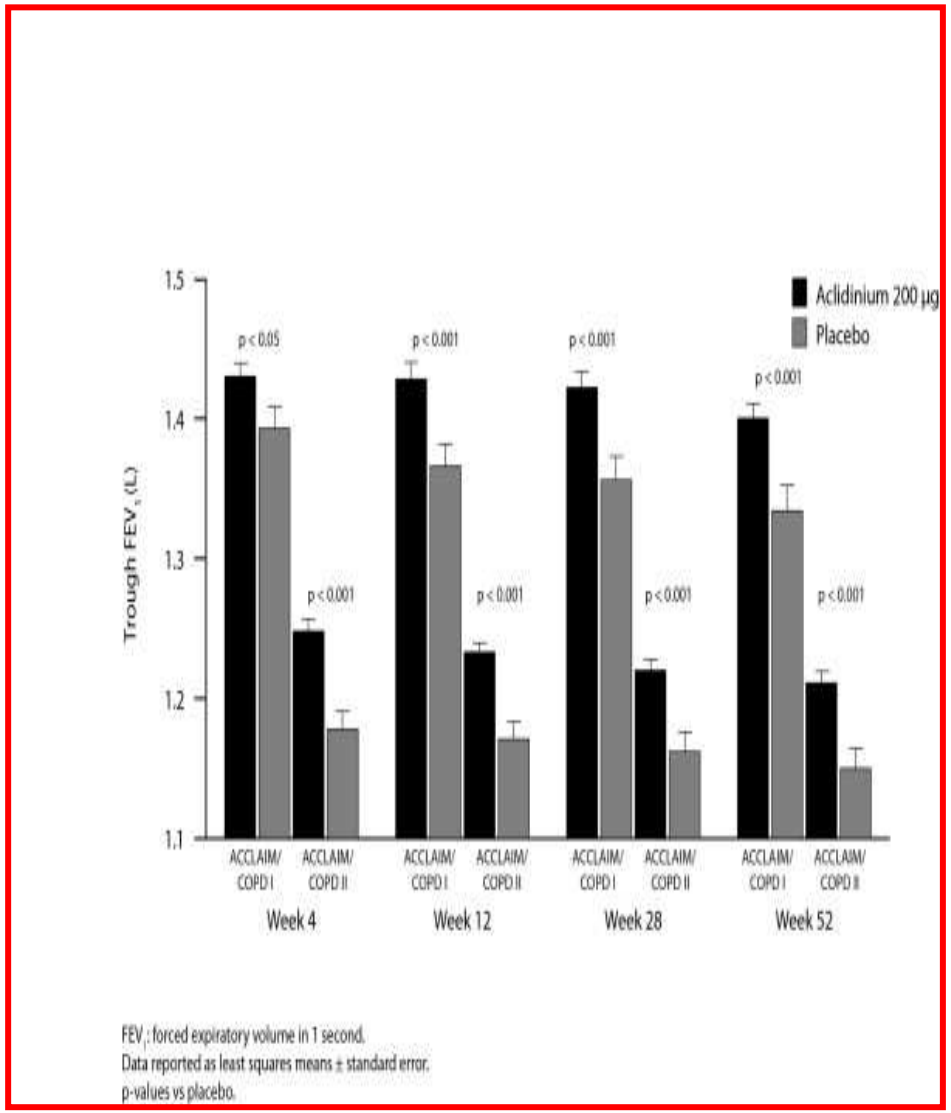


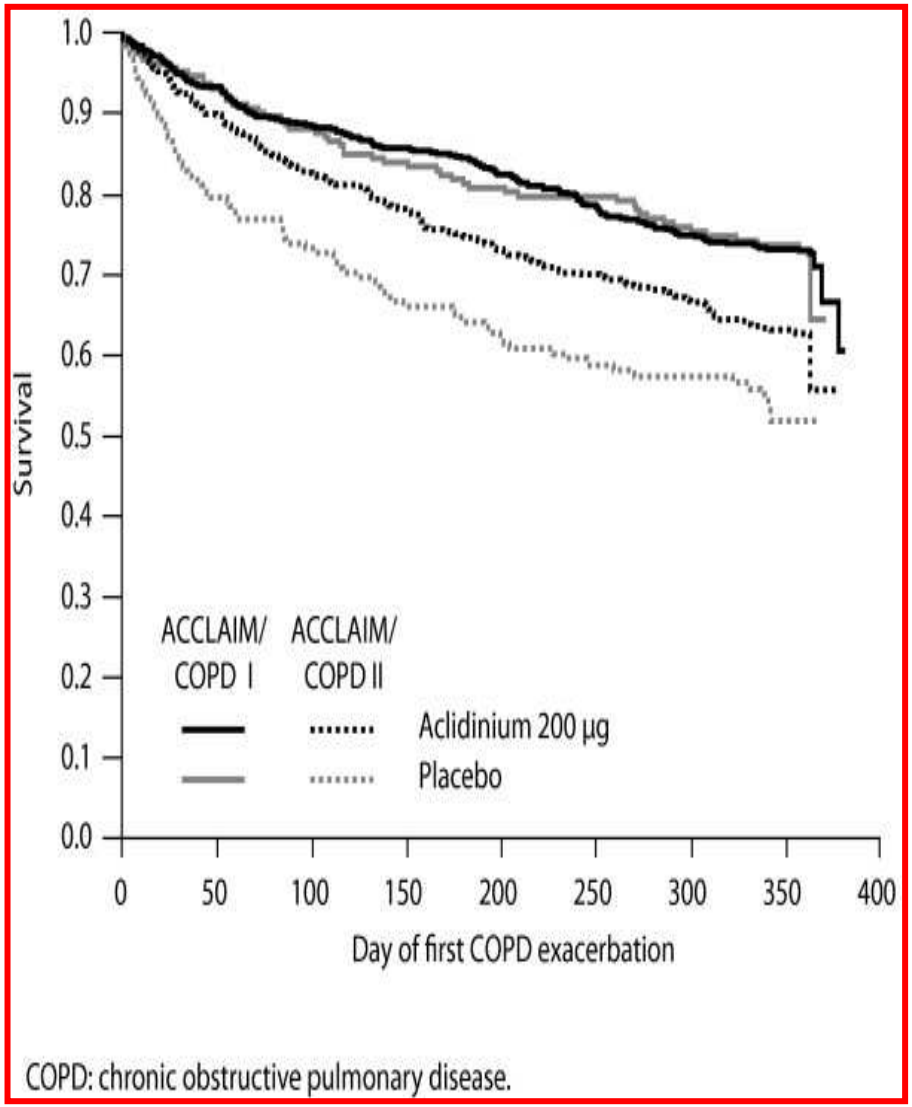


Fuhr R et al Chest 2011 epub ahead

CHEST
The Cardiopulmonary and Critical Care Journal

Aclidinium Bromide 200 μg BID σε ΧΑΠ II&III





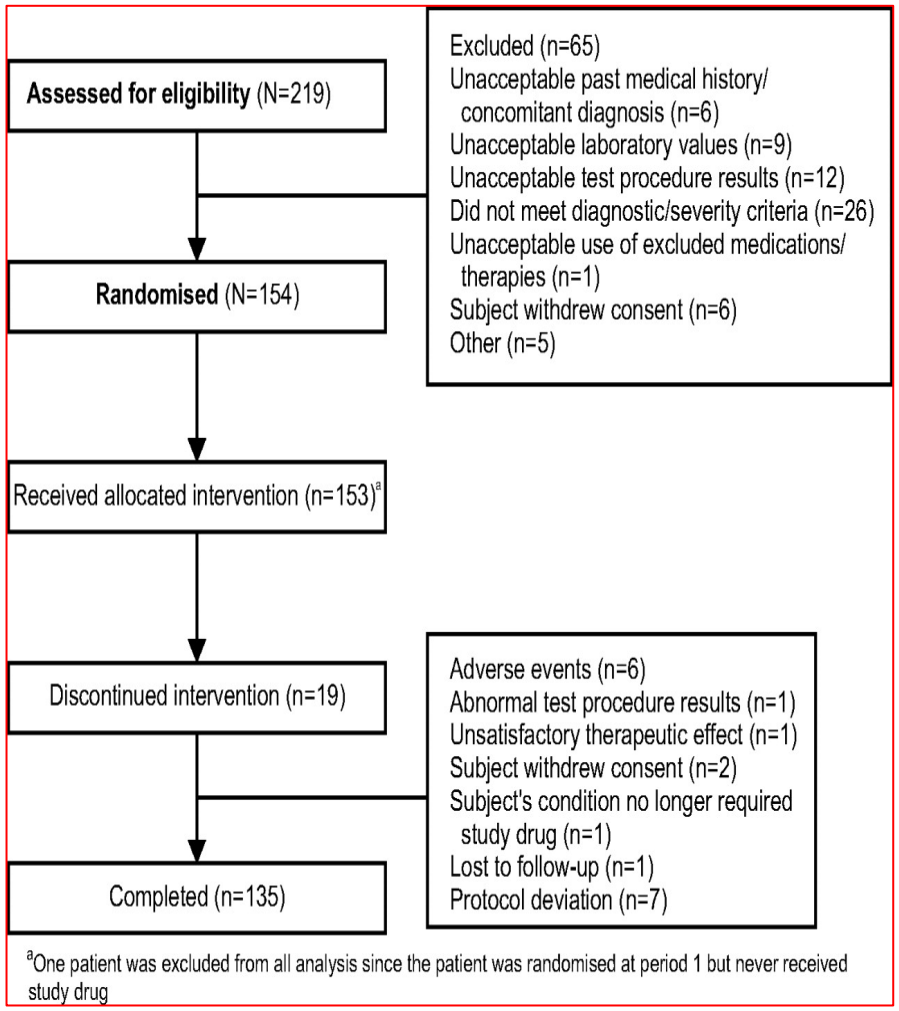
Jones PW et al Resp Res 2011

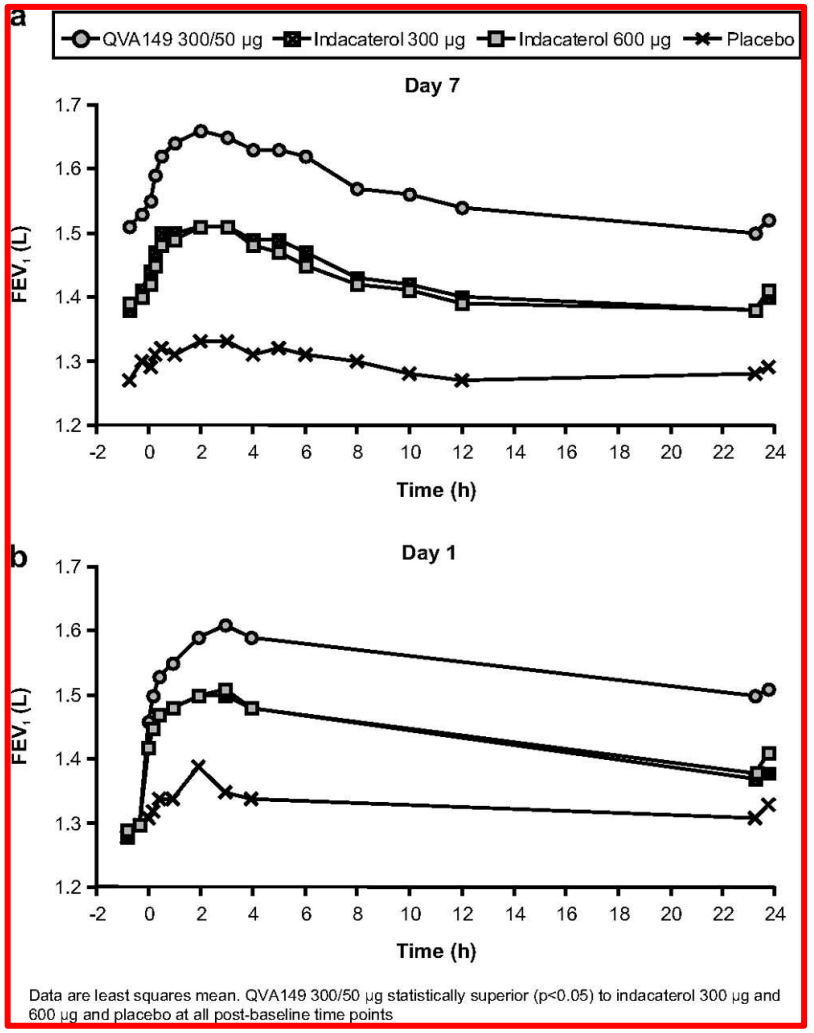
Συνδυασμοί

Drug	Characteristics	Latest developments	Company working on this strategy
β_2-agonist/antimuscarinic agent combinations			
Indacaterol/glycopyrronium bromide (QVA149)	Once-daily combination more active than indacaterol at supramaximal dosage	Phase III	Novartis, Basle, Switzerland
Olodaterol/tiotropium	Once-daily combination more active than tiotropium alone	Phase III Published available data on this combination are limited	Boehringer Ingelheim, Ingelheim, Germany
Vilanterol/GSK573719	Once-daily combination	Phase III Clinical data have not been disclosed	GlaxoSmithKline, London, UK
Formoterol/aclidinium (LAS40464)	Twice-daily combination	Phase II Clinical data have not been disclosed	Almirall Prodesfarma, Barcelona, Spain
Formoterol/glycopyrronium	Twice-daily combination	Phase II Clinical data have not been disclosed	Pearl Therapeutics, Redwood City, CA, USA
GSK961081	It is a single molecule functioning as both an antimuscarinic agent and a β_2-agonist. It is at least equivalent to 50 μg salmeterol b.i.d. plus 18 μg tiotropium u.i.d.	Phase II Clinical data have not been disclosed	GlaxoSmithKline, London, UK/Theravance, South San Francisco, CA, USA
β_2-agonist/inhaled corticosteroid combinations			
Vilanterol/fluticasone furoate	Once-daily combination	Phase III Published available data on this combination are limited	GlaxoSmithKline, London, UK
Indacaterol/mometasone (QMF149)	Once-daily combination	Clinical data have not been disclosed	Novartis, Basle, Switzerland
Formoterol/mometasone (MFF258)	Twice-daily combination	Phase III Clinical data have not been disclosed	Merck & Co., Whitehouse Station, NJ, USA
Formoterol/fluticasone propionate	Twice-daily combination	Phase III Published available data on this combination are limited	Mundipharma Research Limited, Cambridge, UK
Formoterol/ciclesonide	Twice-daily combination	Clinical data have not been disclosed	Nycomed, Zurich, Switzerland
GS424020	Prodrug of desisobutrylciclesonide and salmeterol	Preclinical phase	Gilead Sciences, Foster City, CA, USA

Matera MG et al Trends in Pharmacological Sciences, 2011

Indacaterol &Glycopyrronium bromide (QVA 149) σε ΧΑΠ

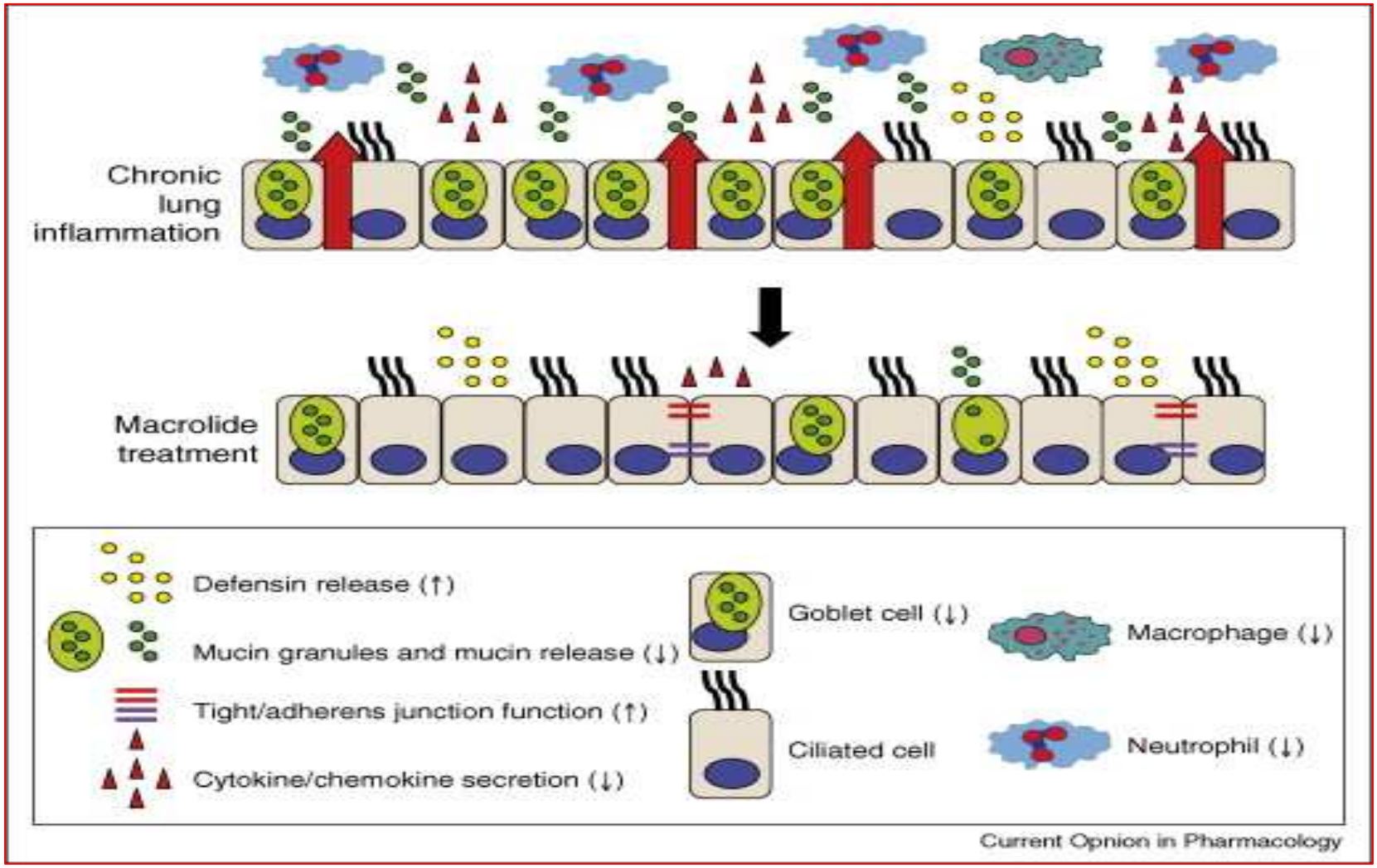




THORAX

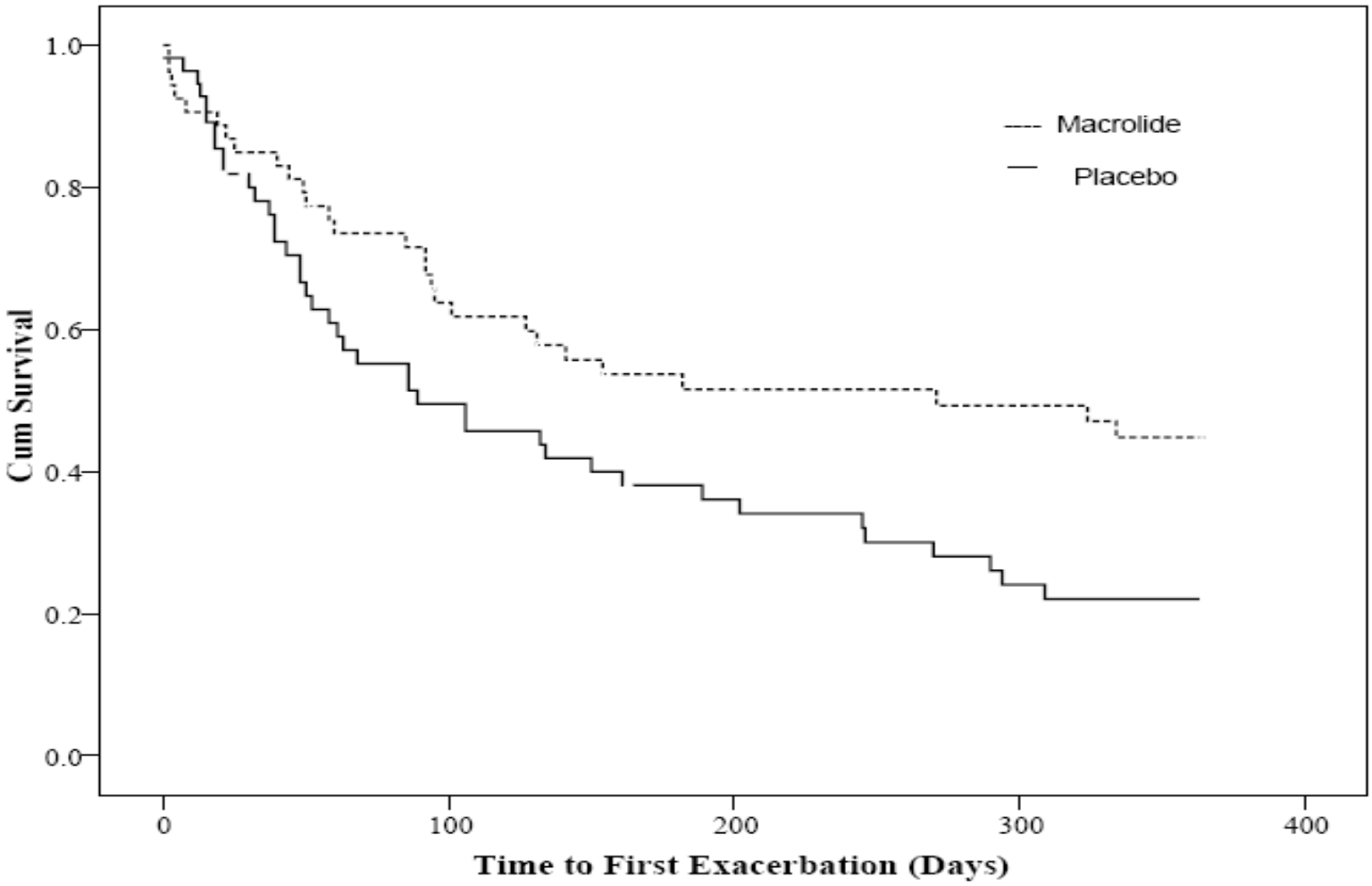
van Noord J A et al. Thorax 2010;65:1086-1091

Μακρολίδες : Πιθανός μηχανισμός δράσης



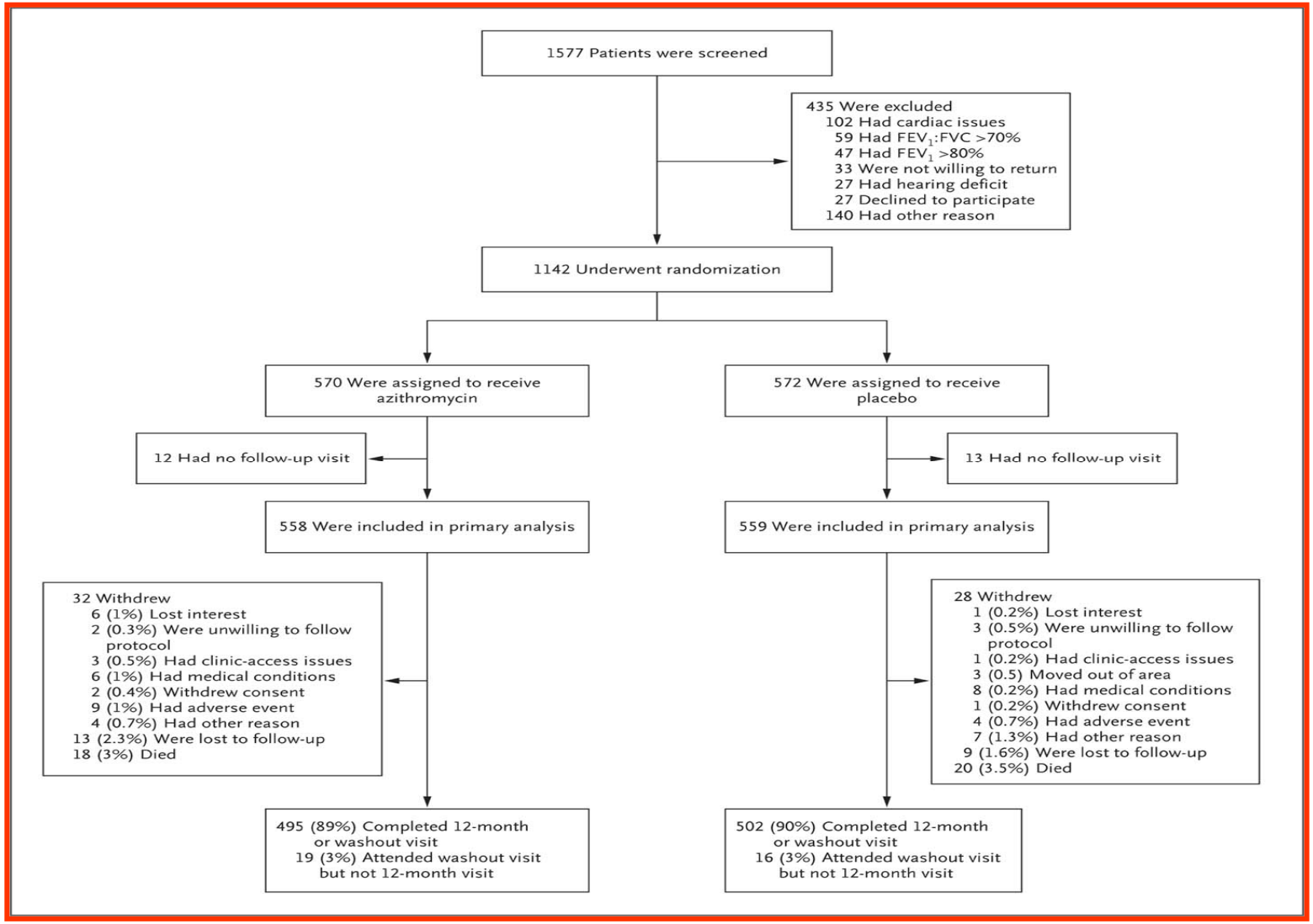
Yolanda S López-Boado et al Current Opinion Pharm 2008

Μακρολίδες : Κλινικά ευρήματα



Seemmungal TER et al AJRCCM 2008

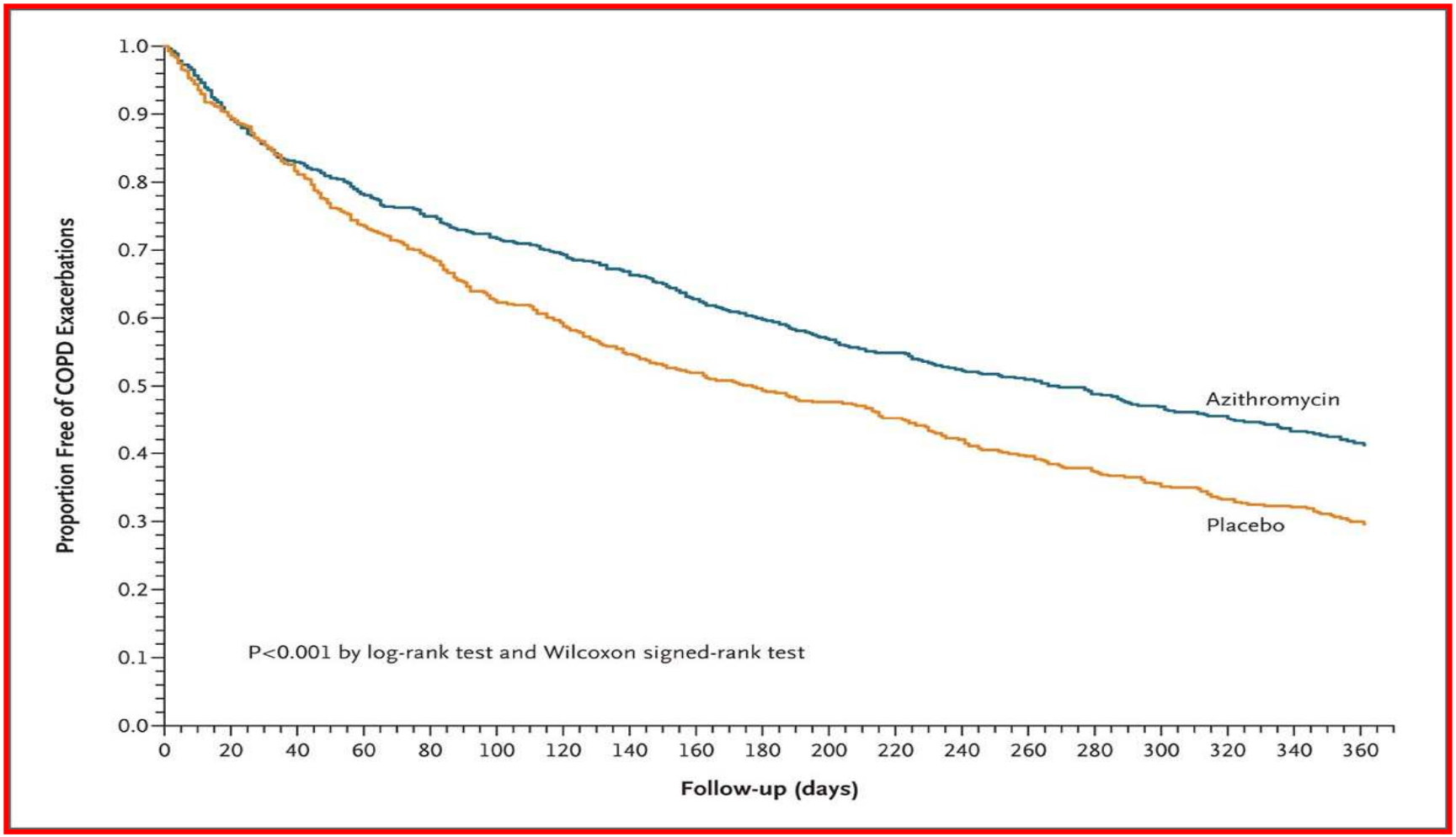
Σχεδιασμός



Albert RK et al. N Engl J Med 2011;365:689-698

The NEW ENGLAND JOURNAL of MEDICINE

Η επίδραση της Αζιθρομυκίνης στις παροξύνσεις της ΧΑΠ.



Albert RK et al. N Engl J Med 2011;365:689-698

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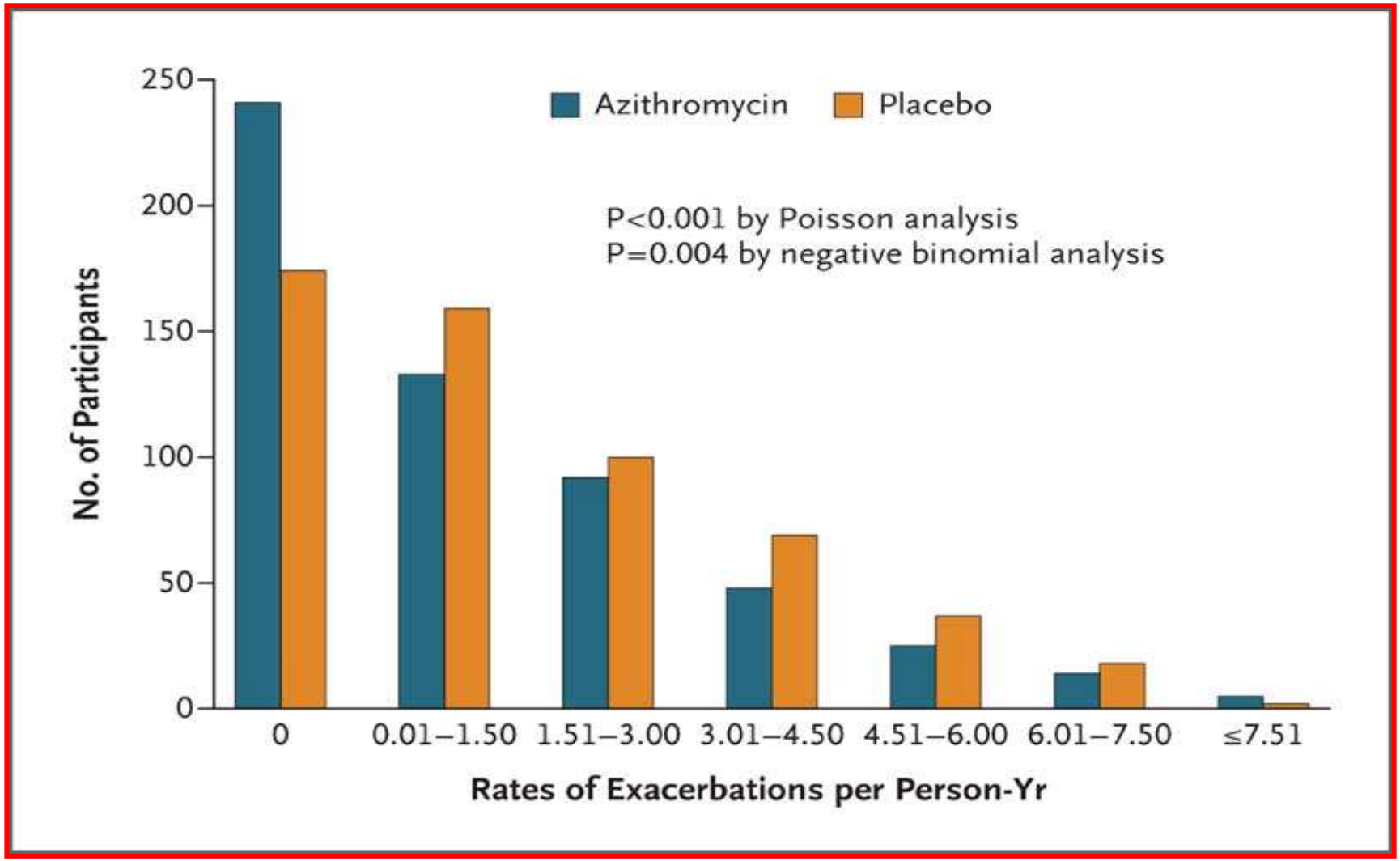
Ανάλυση παροξύνσεων



Albert RK et al. N Engl J Med 2011;365:689-698

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Ανάλυση αποτελέσματος.

Table 2. Effect of Treatment for Chronic Obstructive Pulmonary Disease (COPD) on Hospitalization Rates, Emergency Department or Urgent Care Visits, and Unscheduled Office Visits.

Event	Azithromycin		Placebo		P Value*	Hazard Ratio (95% CI)†	P Value†
	no. of events	*mean events/ patient-yr (95% CI)*	*no. of events*	*mean events/ patient-yr (95% CI)*			
Hospitalization for any cause	323	0.74 (0.60–0.89)	329	0.95 (0.76–1.18)	0.13	0.94 (0.76–1.15)	0.52
Hospitalization related to COPD	156	0.34 (0.26–0.43)	200	0.49 (0.31–0.67)	0.14	0.82 (0.64–1.07)	0.15
Emergency department or urgent care visit	199	0.43 (0.34–0.53)	257	0.48 (0.39–0.57)	0.47	0.81 (0.63–1.04)	0.09
Unscheduled office visit	1202	2.46 (2.08–2.48)	1345	2.57 (2.21–2.60)	0.048	0.85 (0.74–0.98)	0.02
Intubations	11	0.02 (0.01–0.04)	16	0.04 (0.01–0.06)	0.23	0.79 (0.04–1.75)	0.56

* The P value is for the rate of events per patient-year.
† The hazard ratio and P value are for the time to the first event in the azithromycin group as compared with the placebo group.

Albert RK et al. N Engl J Med 2011;365:689-698

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Ποιότητα ζωής

Section C. St. George Respiratory Questionnaire Scores

SGRQ Score*	Azithromycin		Placebo		P value
	N	Mean ± SD	N	Mean ± SD	
Enrollment	556	50.9 ± 16.4	555	50.1 ± 16.4	0.381
Six months	484	47.7 ± 16.3	483	48.1 ± 16.4	0.657
Twelve months	444	46.8 ± 16.7	453	48.0 ± 17.8	0.289
Δ enrollment - six months	484	-2.5 ± 11.6	483	-1.2 ± 10.5	0.076
Δ enrollment - twelve months	444	-2.8 ± 12.1	453	-0.6 ± 11.4	0.006

Albert RK et al. N Engl J Med 2011;365:689-698

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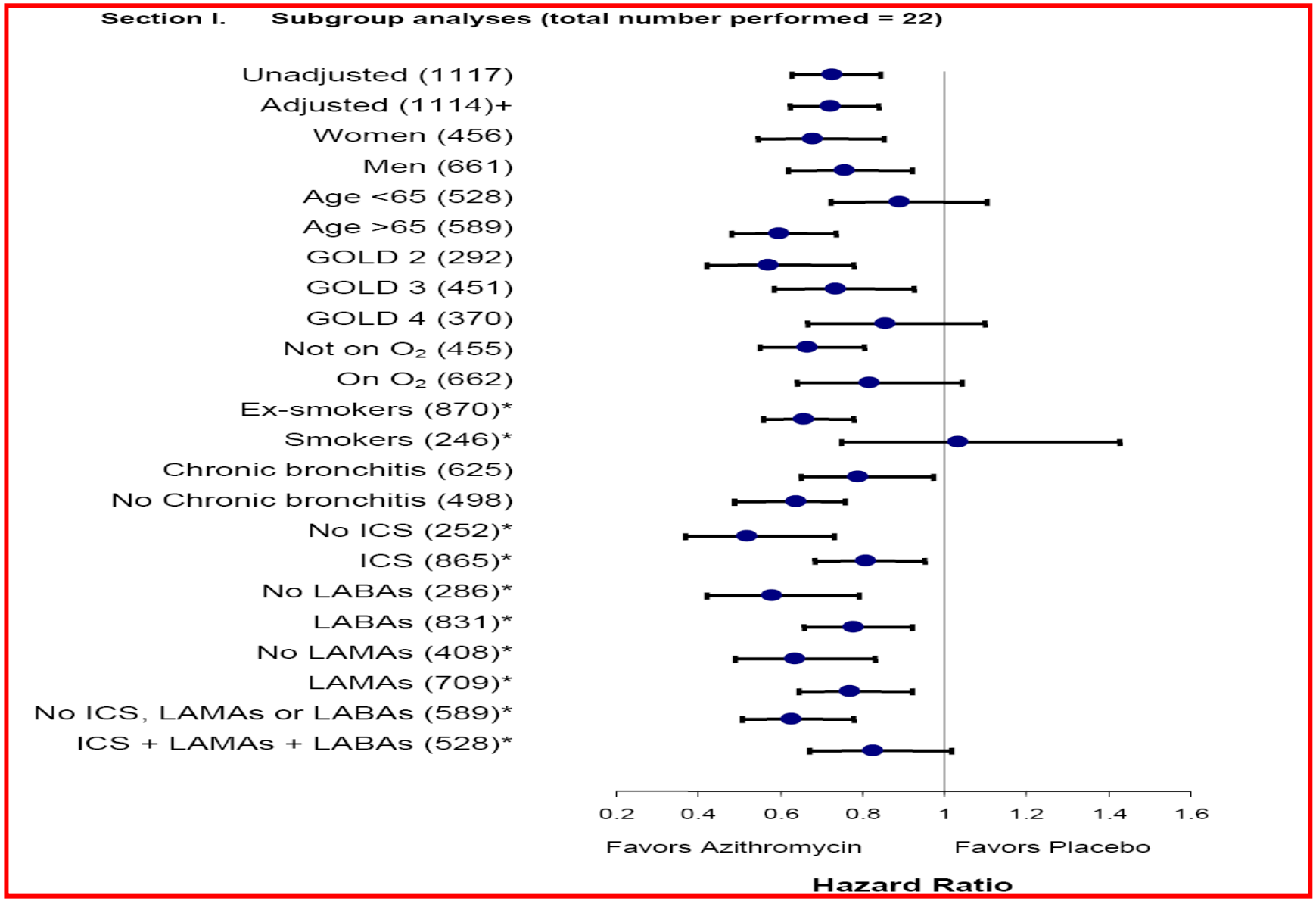
Περαιτέρω αναλύσεις



Albert RK et al. N Engl J Med 2011;365:689-698

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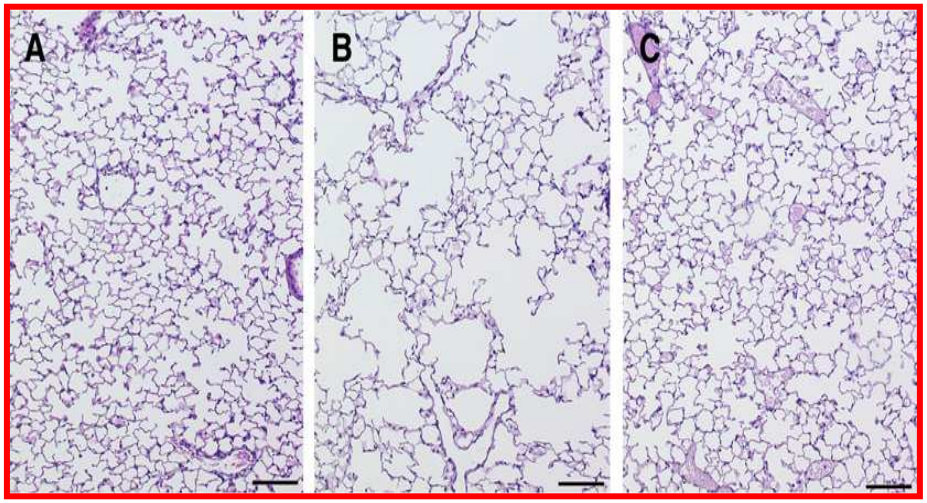
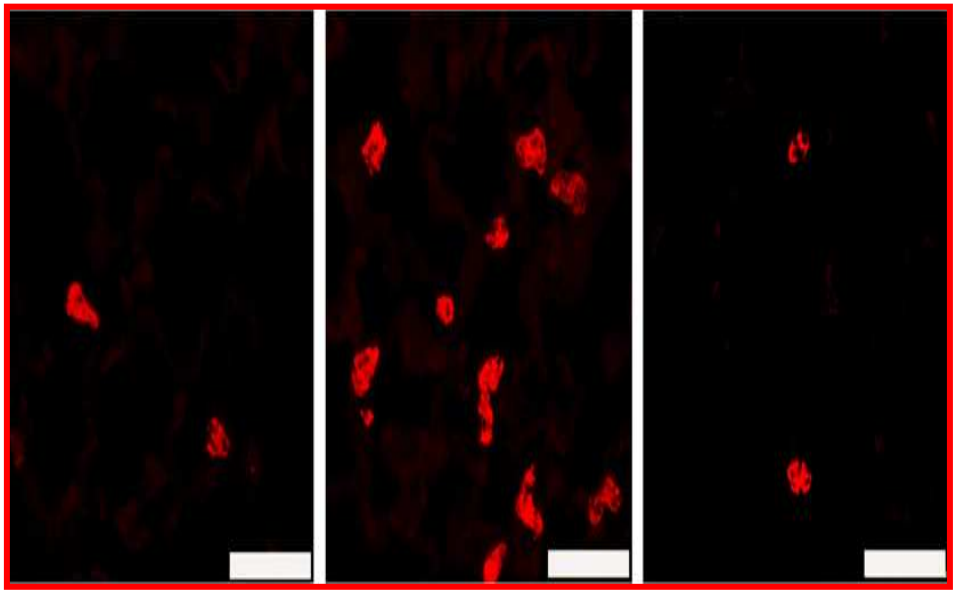
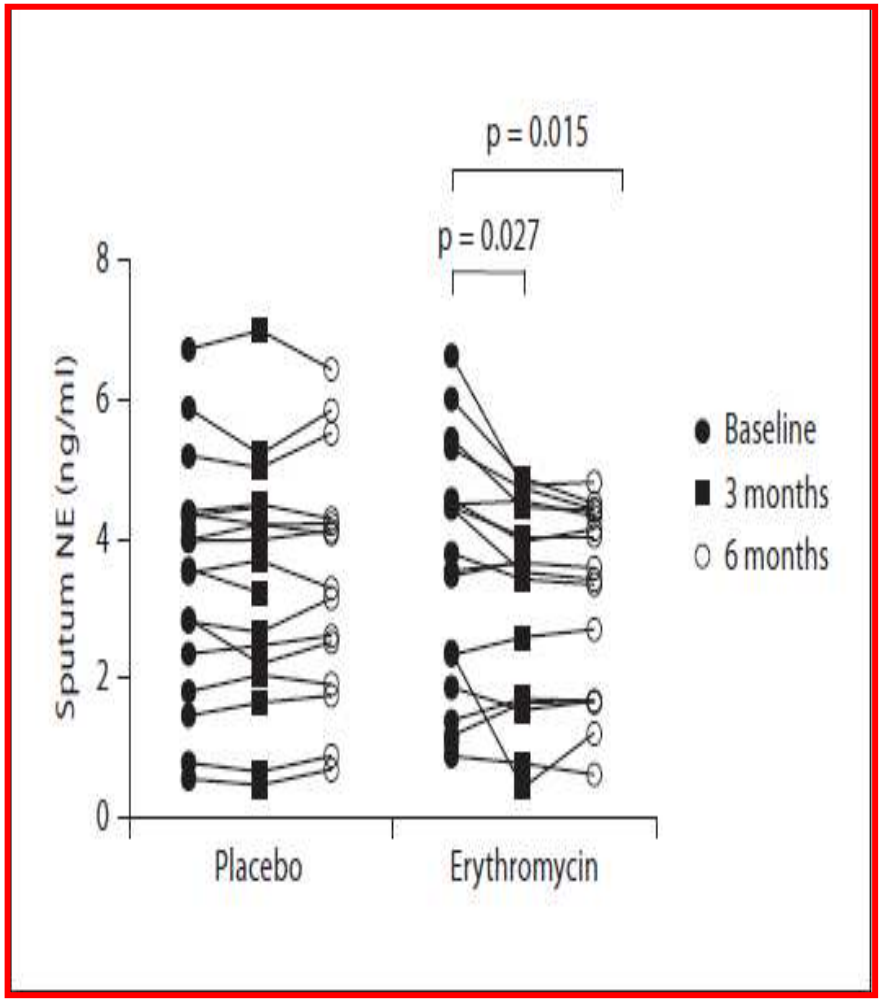
Μακρολίδες και επίπτωση στη φλεγμονή

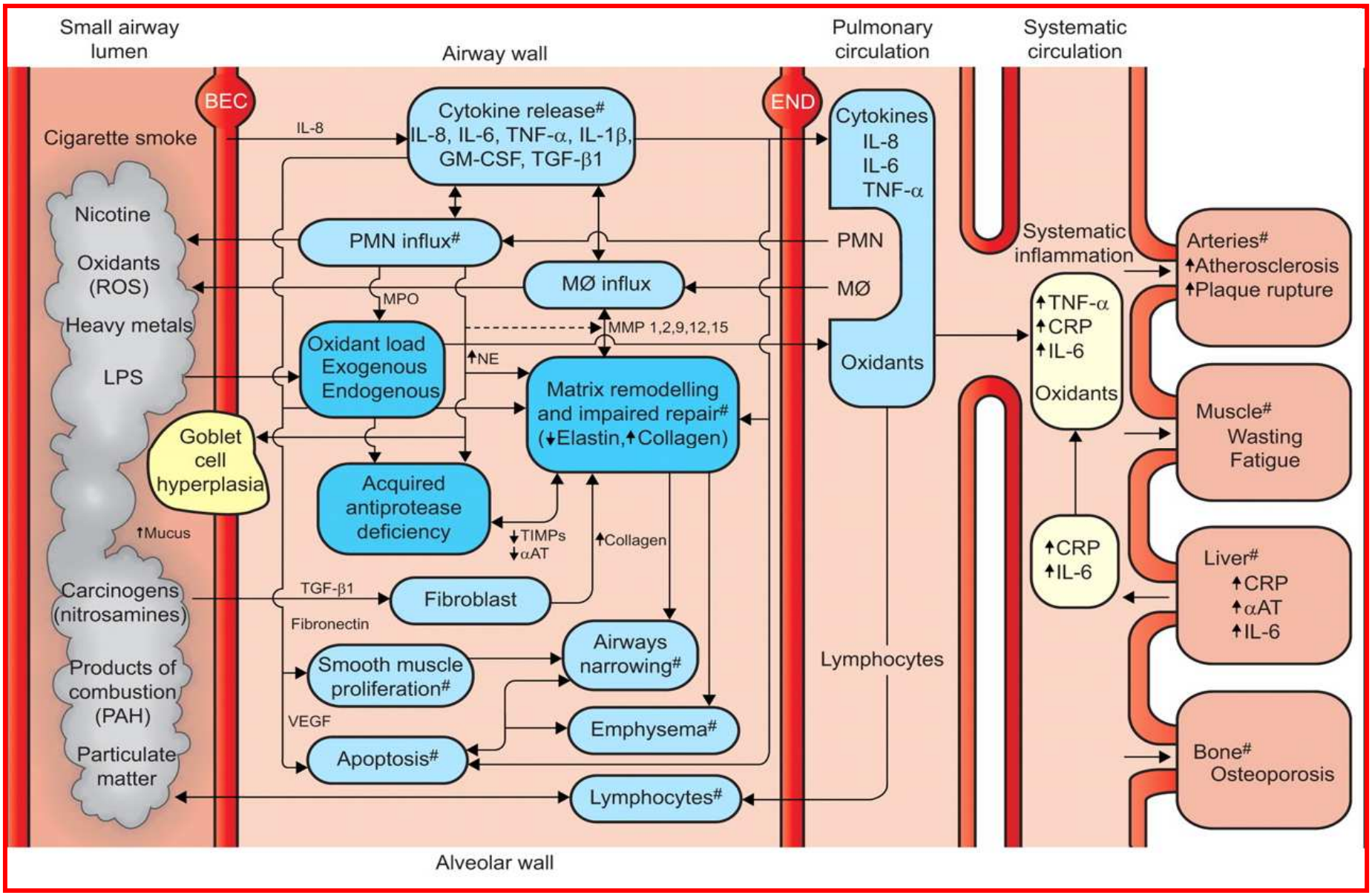






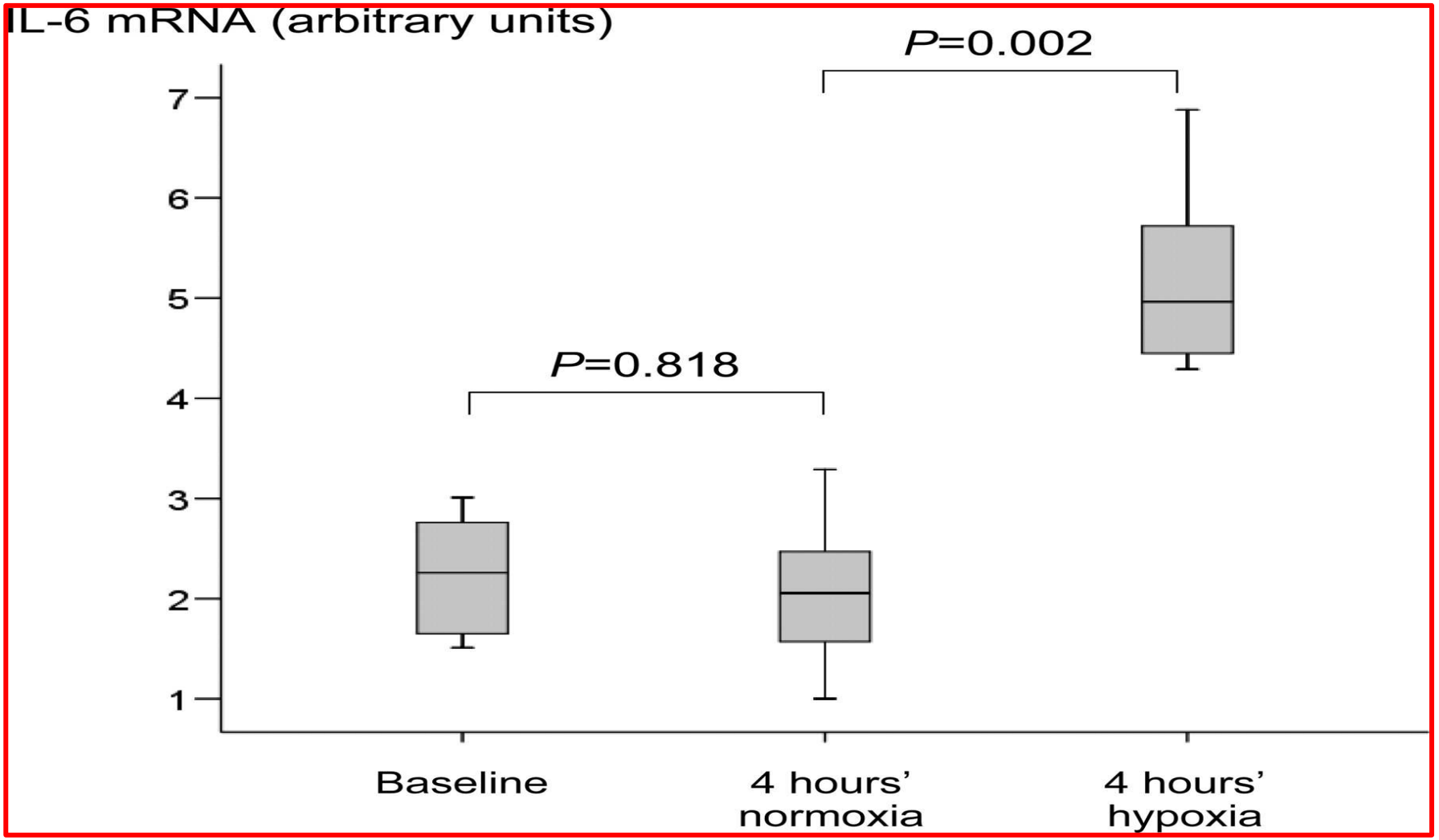
Nakanshi Y et al Blue 2009, Zhi-Yi He et al Respiration 2010

Φλεγμονή στη ΧΑΠ-Στατίνες?



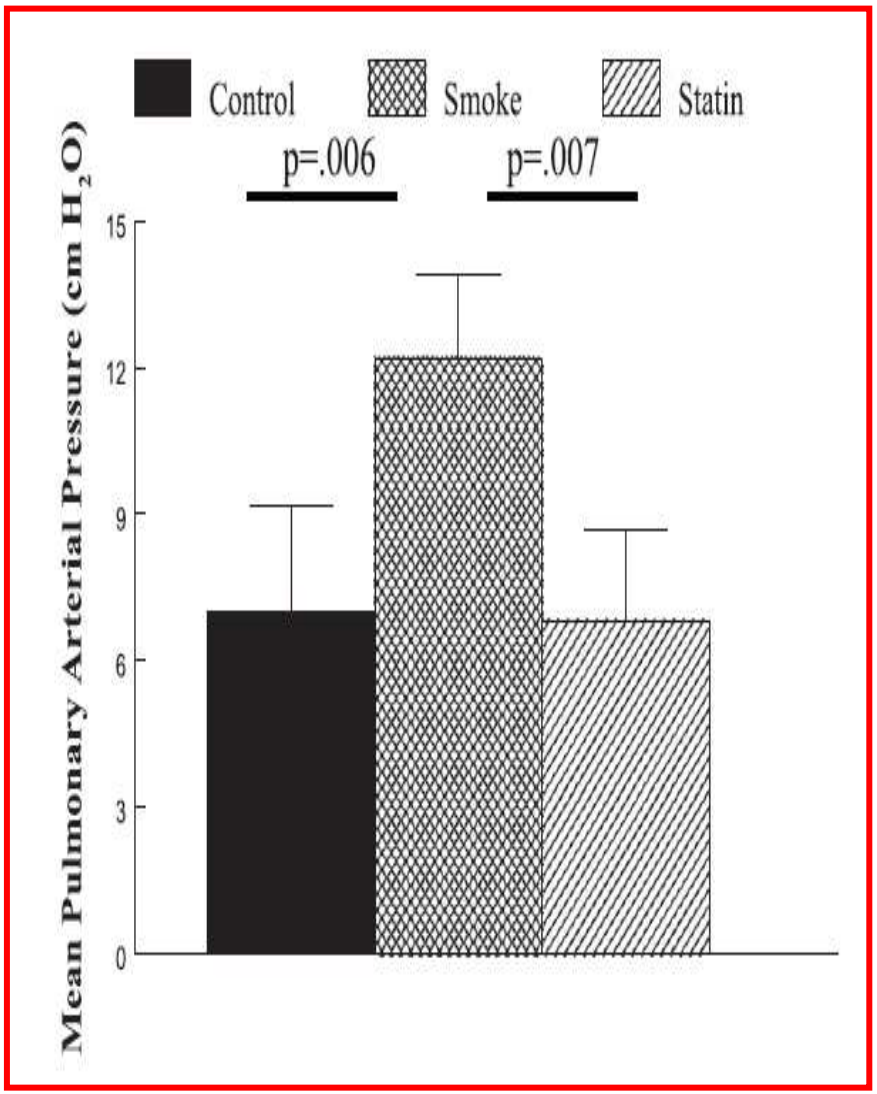
Young RP et al Eur Respir Rev 2011

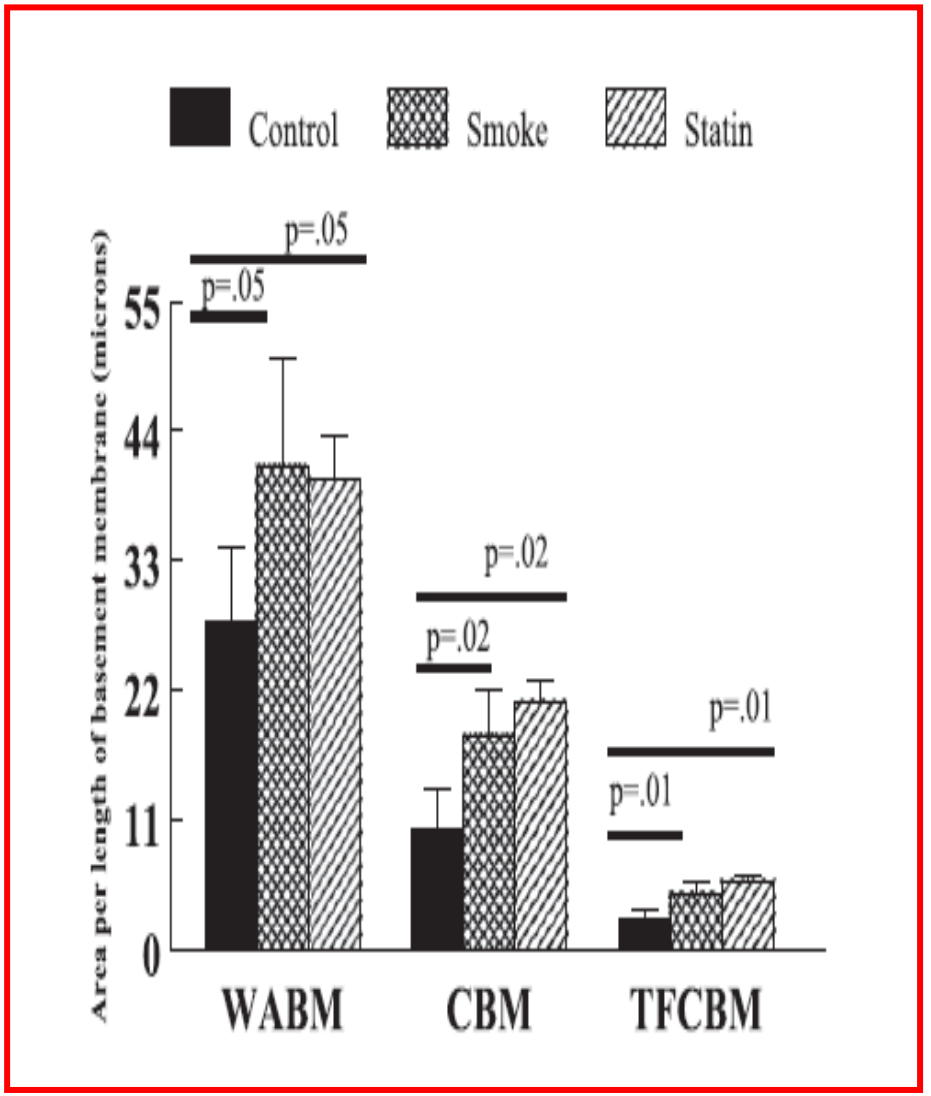
IL-6 mRNA -σύνδεση με Πνευμονική υπέρταση



Chaouat A et al. Chest 2009;136:678-687

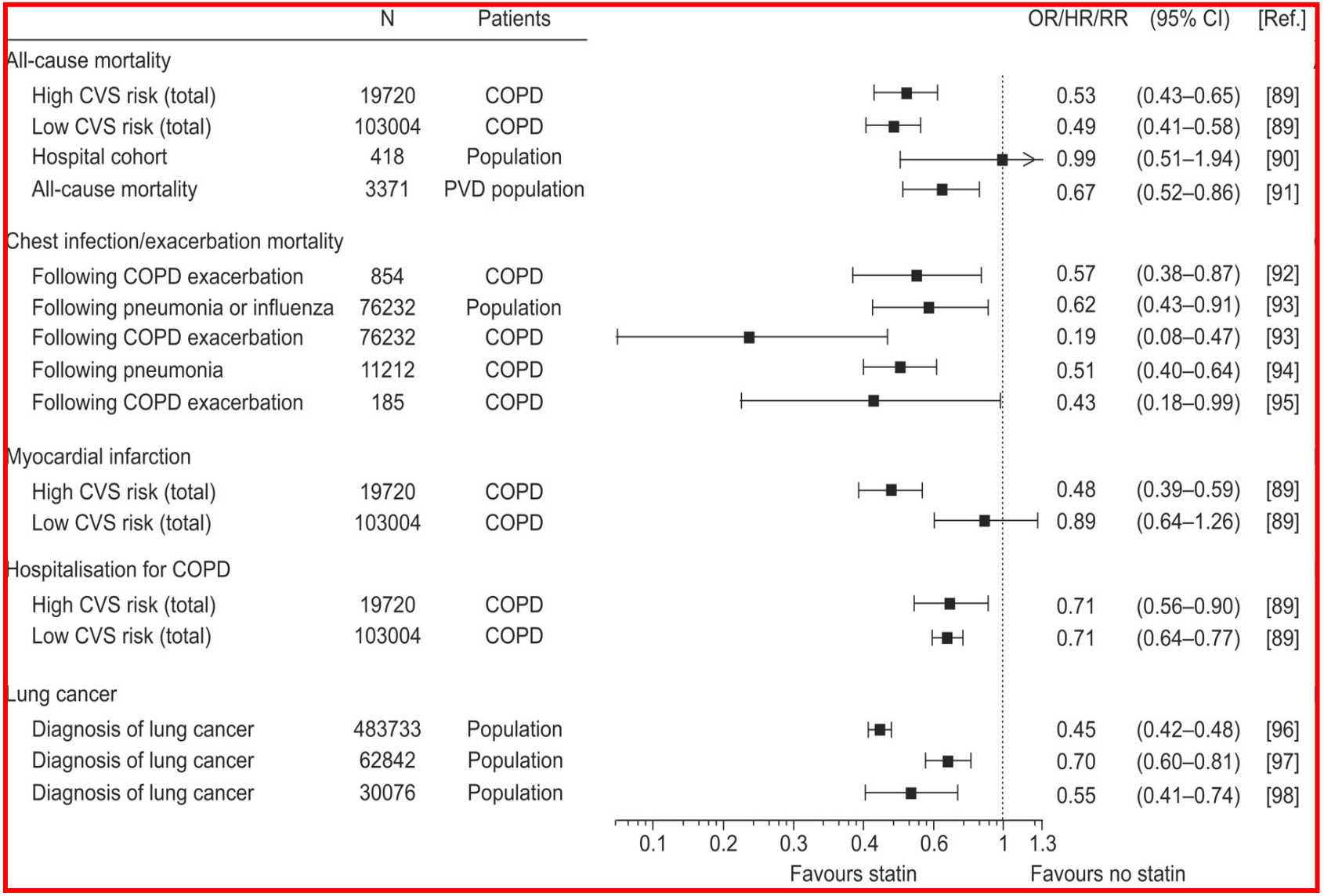
Στατίνες –ΠΥ-αναδιαμόρφωση





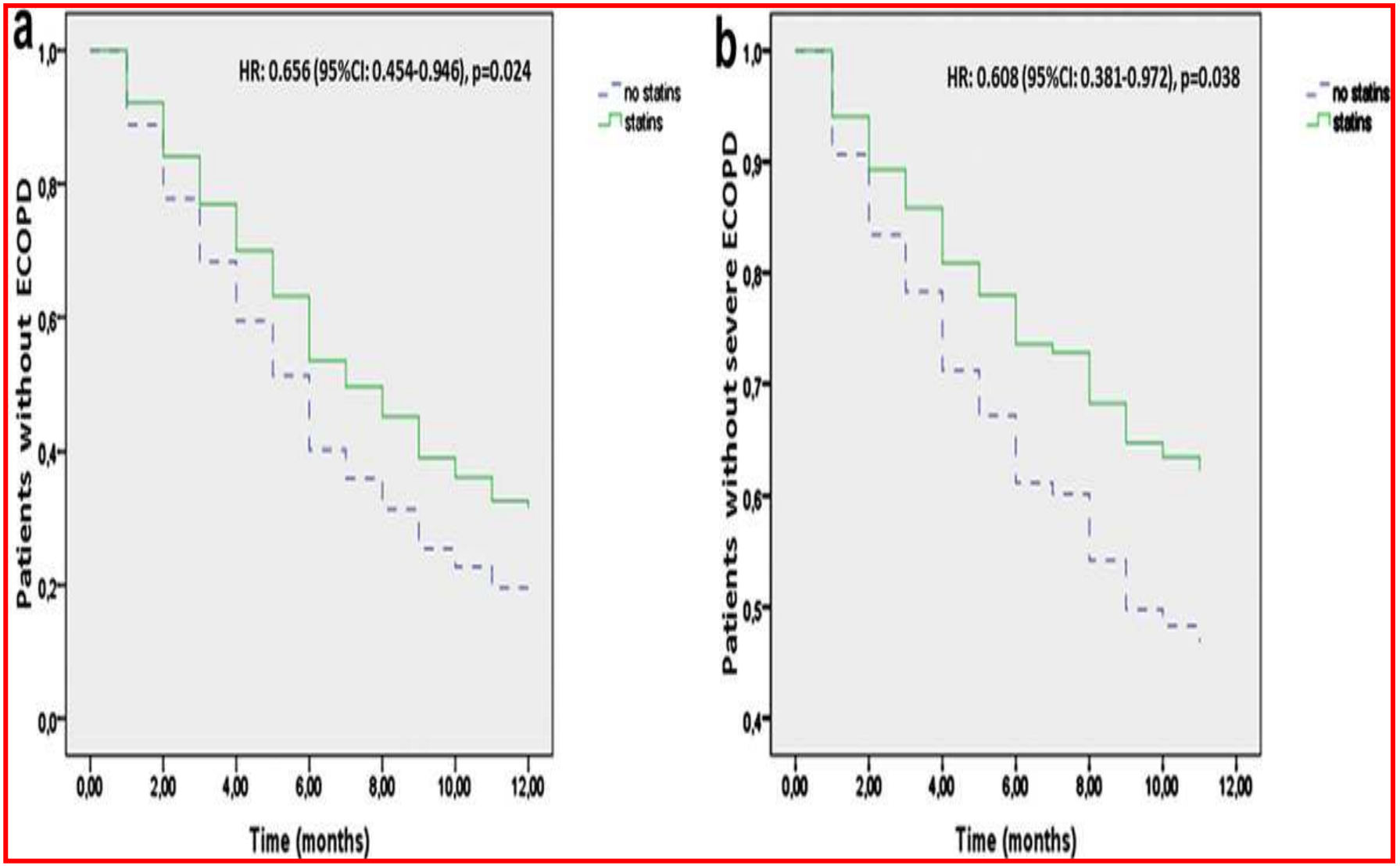
Wright J et al Blue 2011

Στατίνες : Θέση ισχύος σε αναδρομικά μοντέλα



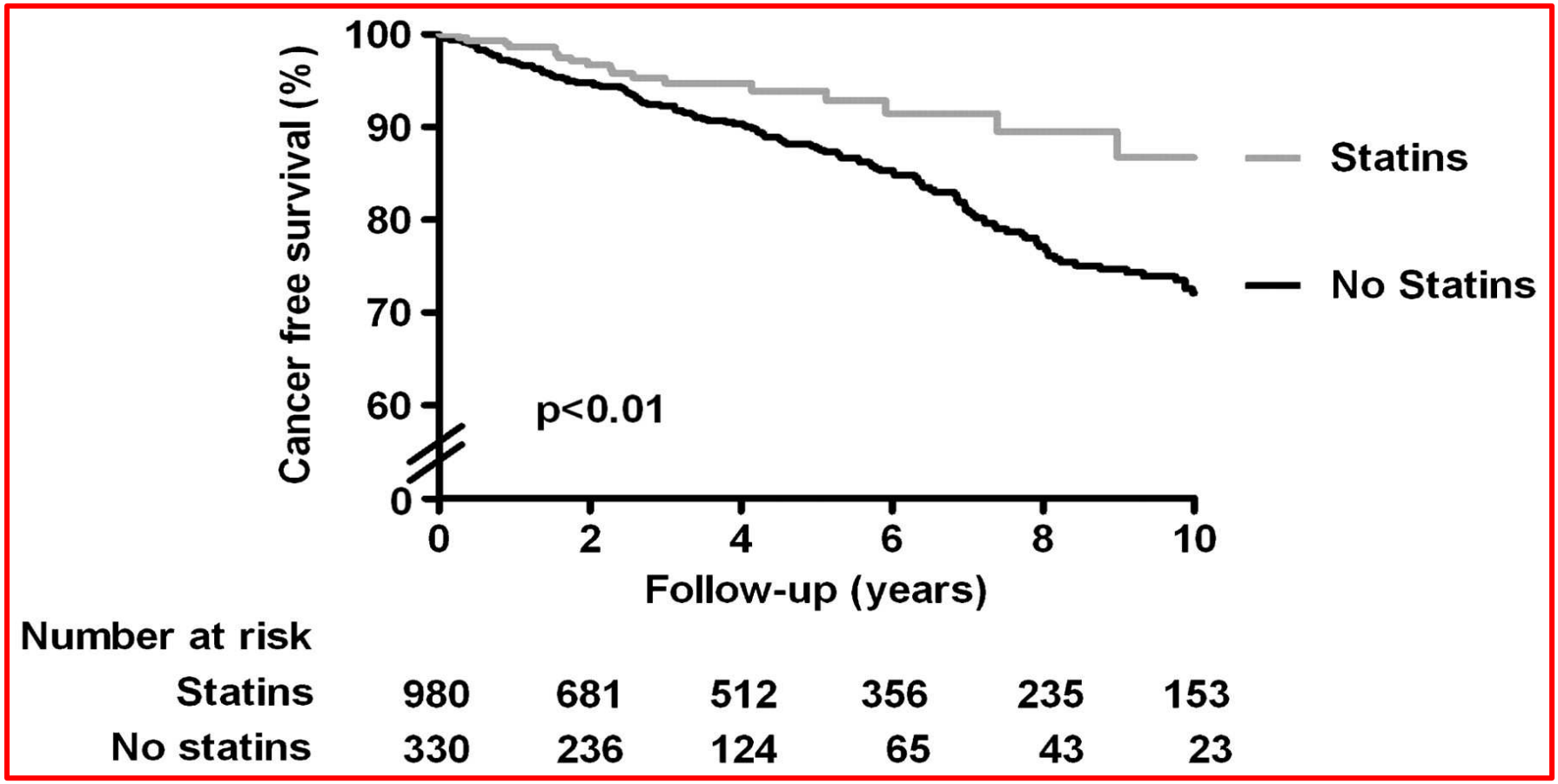
Young RP et al Eur Respir Rev 2011

Η Ελληνική εμπειρία



Bartziokas K et al Pulmonary Pharmacology & Therapeutics 2011

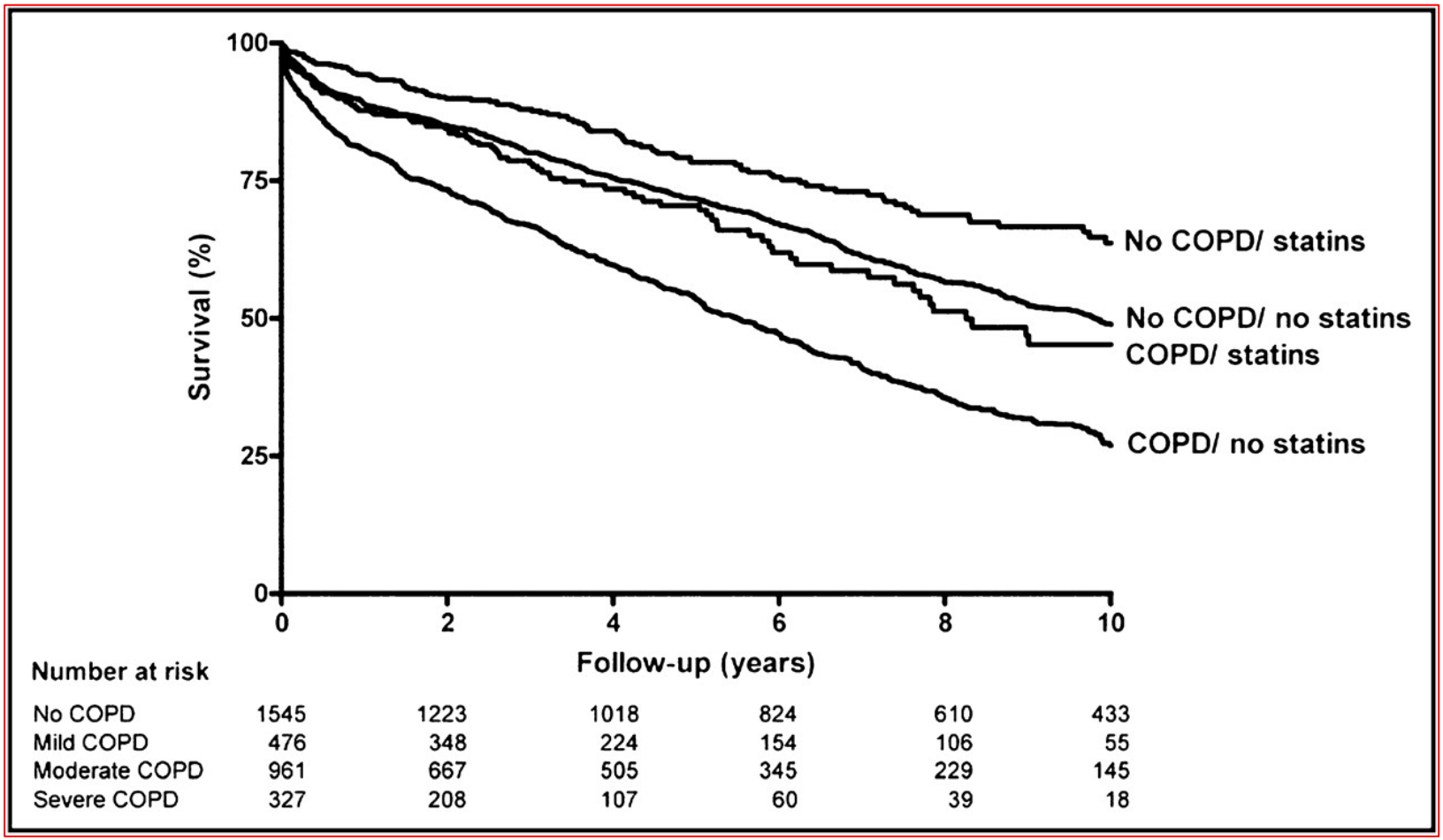
Στατίνες και θνησιμότητα από νεόπλασμα σε ασθενείς με ΧΑΠ



van Gestel Y R B M et al. Thorax 2009;64:963-967

THORAX

Θνησιμότητα από περιφερική αγγειακή νόσο: ΧΑΠ & στατίνες

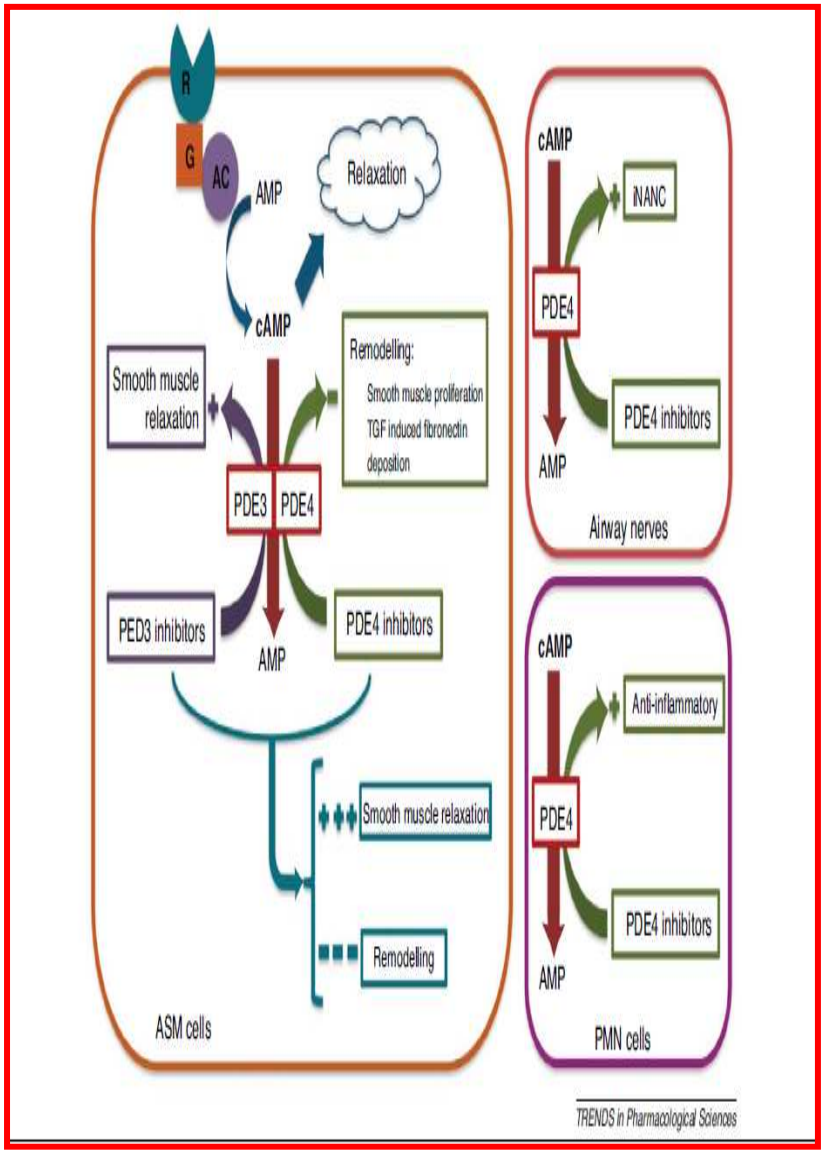


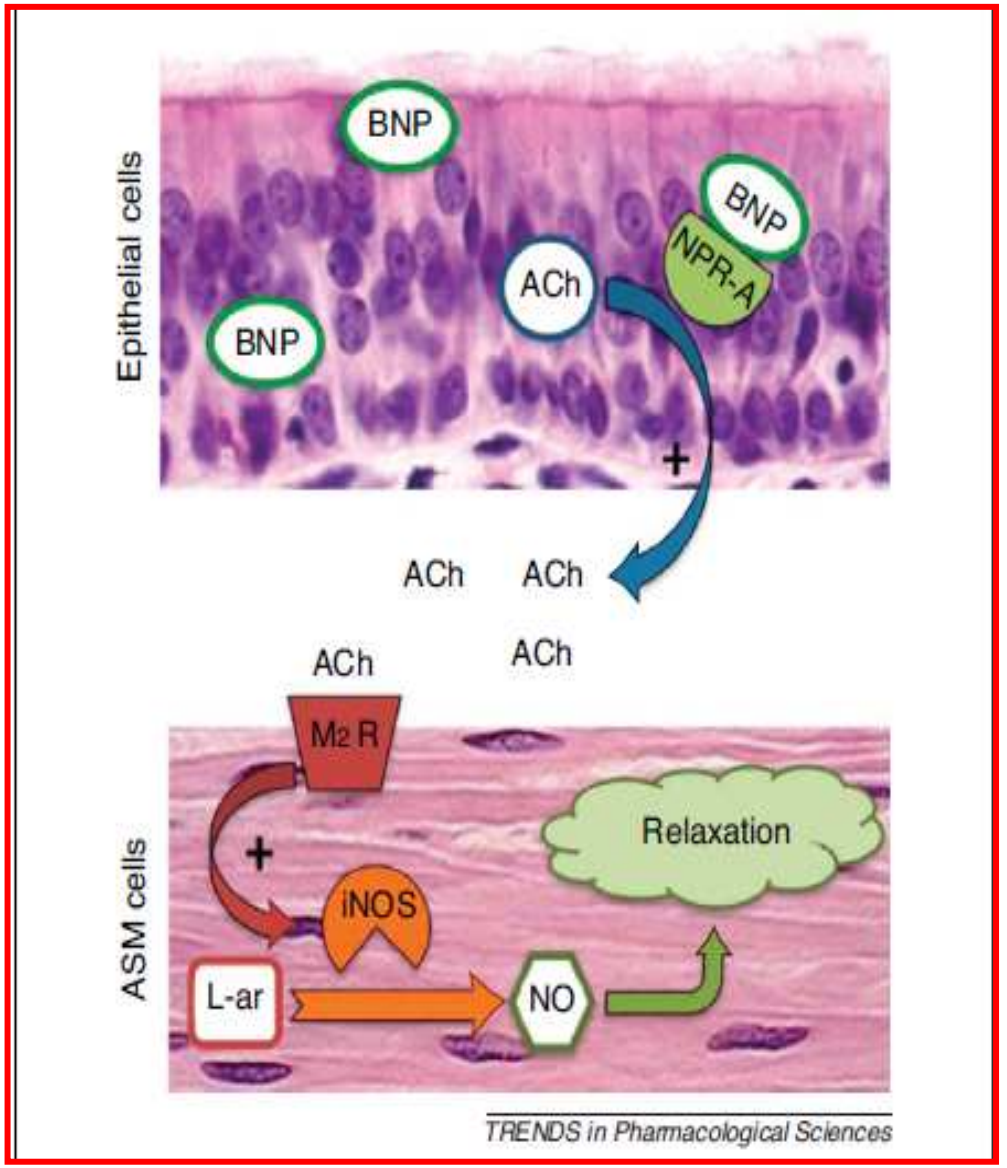
Number at risk

No COPD	1545	1223	1018	824	610	433
Mild COPD	476	348	224	154	106	55
Moderate COPD	961	667	505	345	229	145
Severe COPD	327	208	107	60	39	18

Nussbaumer-Ochsner Y , Rabe K F Chest 2011;139:165-173

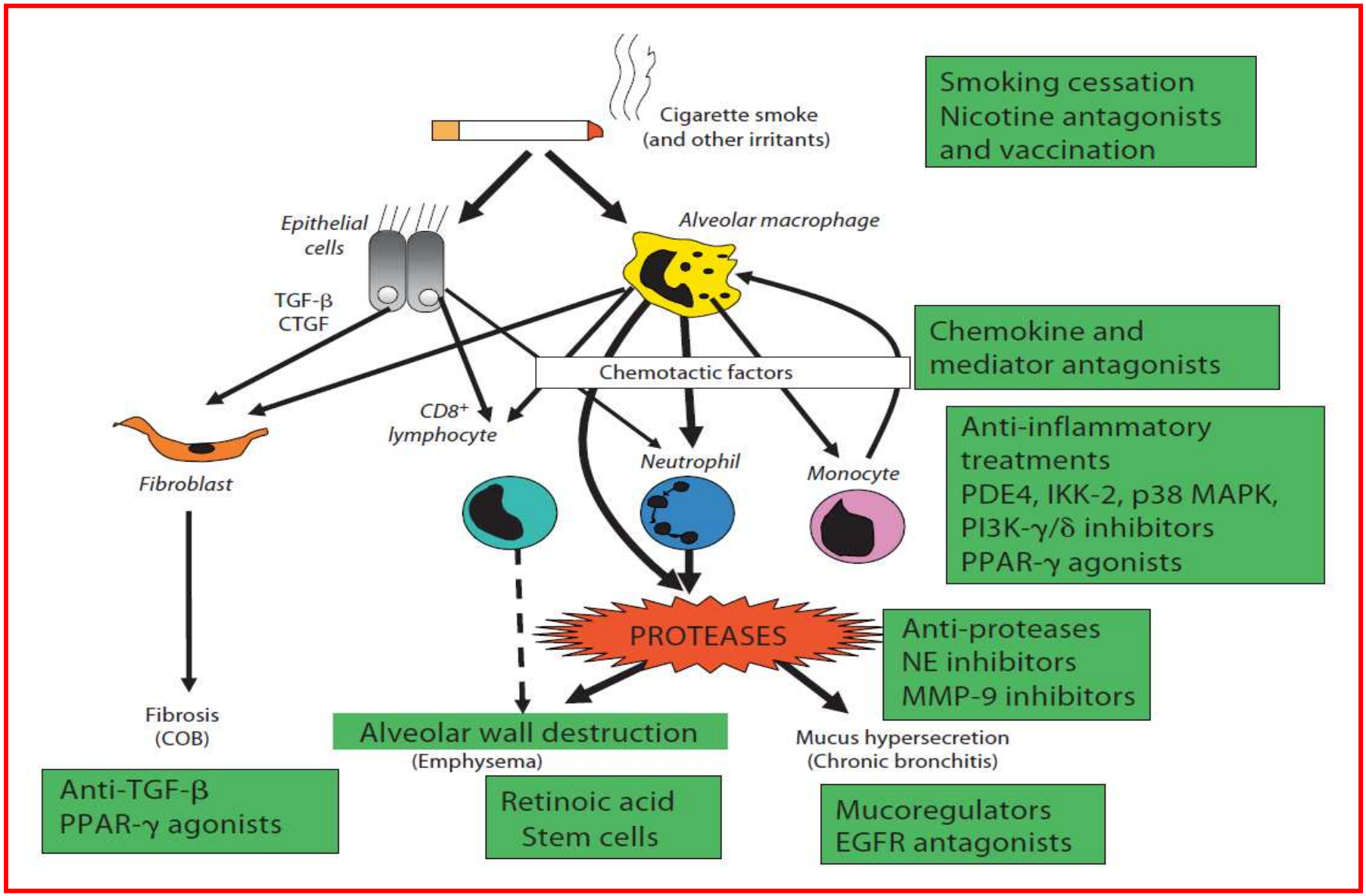
Στόχοι: Βρογχοδιαστολή





Matera MG et al Trends in Pharmacological Sciences, 2011

Στόχοι: Φλεγμονή



PJ Barnes , 2011

Μηνύματα για το σπίτι

- Η φαρμακευτική πρόοδος στο τομέα της ΧΑΠ είναι ένα σημαντικό βήμα στον έλεγχο της νόσου.

- Φαίνεται ότι στην επόμενη 10ετία θα κυριαρχήσουν οι LAMA & ultra LABA και οι πιθανοί συνδυασμοί τους.

- Μακρολίδες και στατίνες : Έτοιμες?

- Η φαινοτυπική στόχευση αποτελεί βασικό χαρακτηριστικό των νέων θεραπειών με κατεύθυνση την φλεγμονή.