ACTUALIZACION TERAPEUTICA EN ENFERMEDADES PREVALENTES. EPOC.

P.ALMAGRO
UGA HOSPITAL UNIVERSITARIO MUTUA DE TERRASSA
COORDINADOR GRUPO EPOC DE LA SEMI
PALMA DE MALLORCA 2011

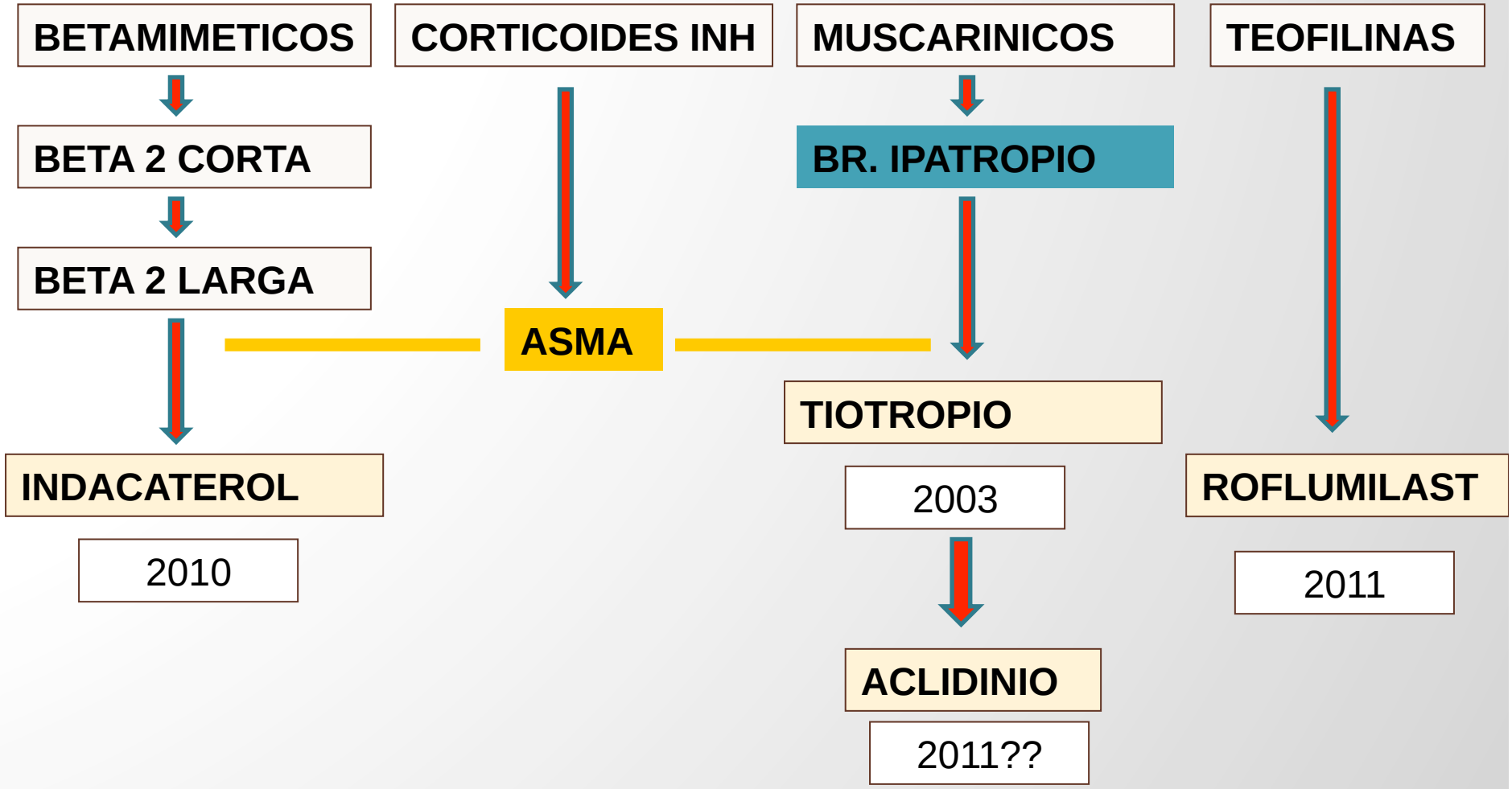
Grupo de EPOC
Enfermedad Pulmonar Obstructiva Crónica

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

REFLEXION

"De hecho la EPOC puede considerarse en muchos aspectos como una enfermedad huérfana,todos los tratamientos para la EPOC en fase estable fueron diseñados para el asma."

Miravitlles M. Eur Respir J 2004; 24: 896

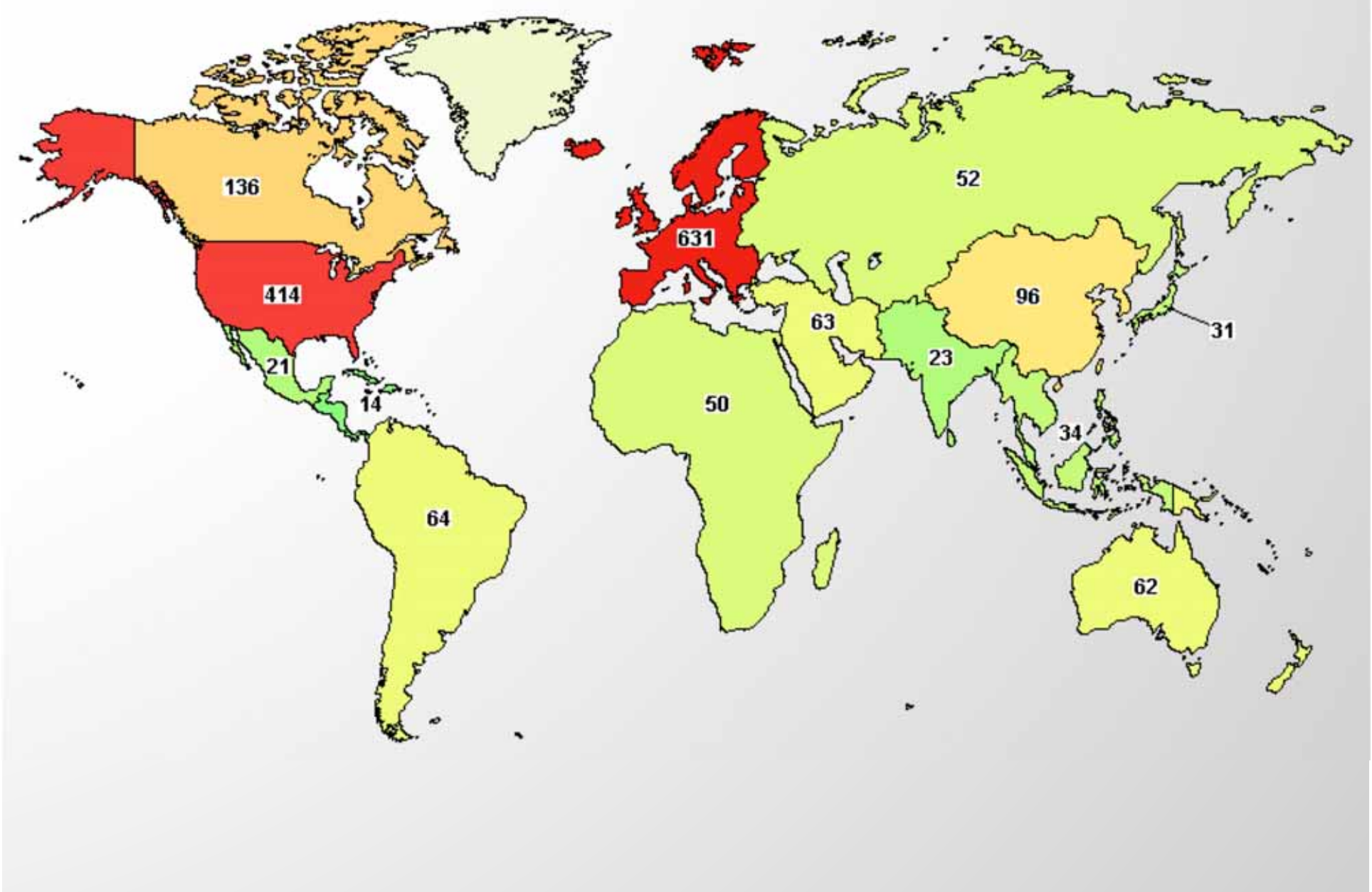


COMBINACIONES

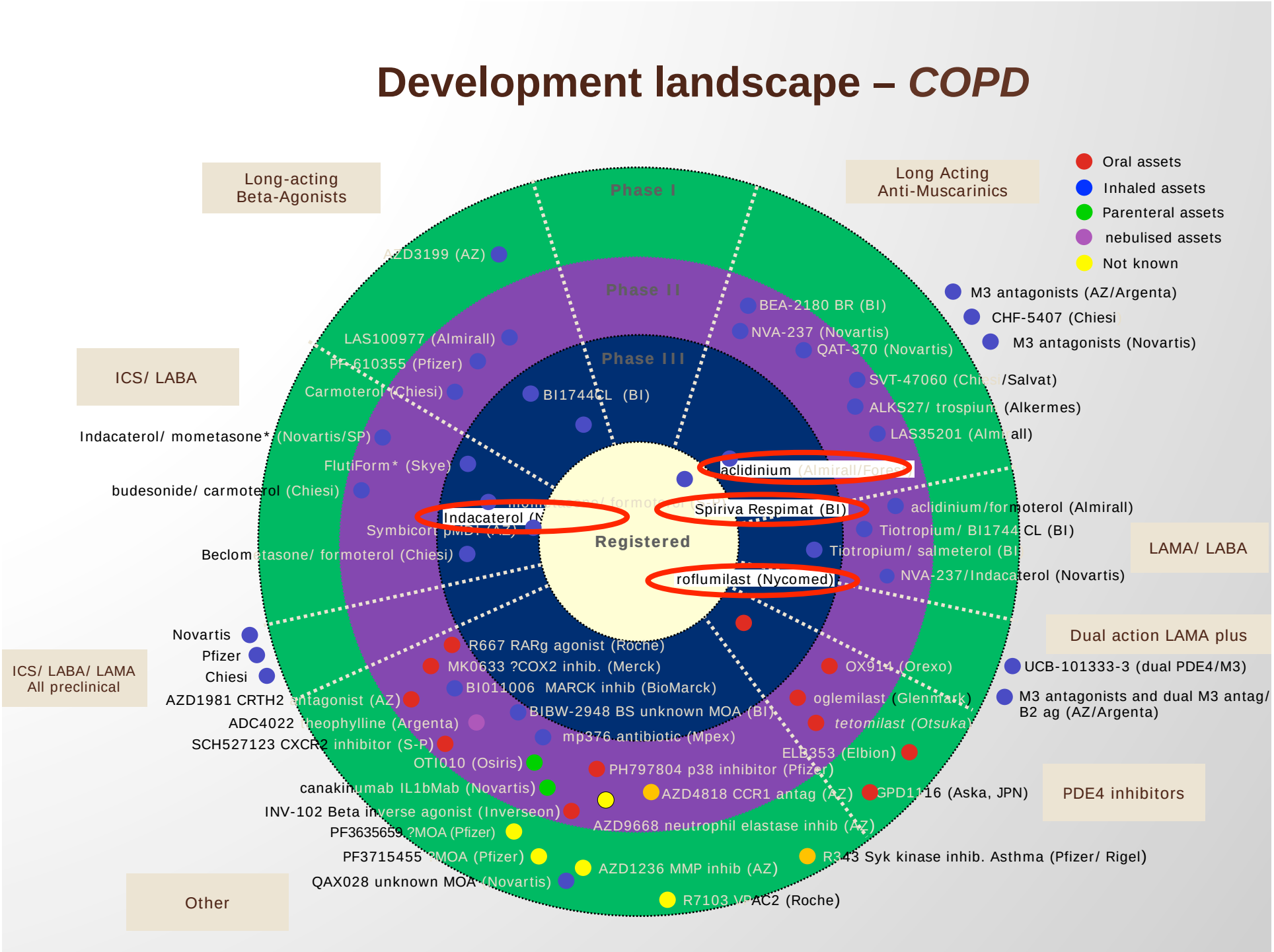
//RESISTENCIA CI
INH.PROTEASAS
BIOLOGICOS
ANTIOXIDANTES…..

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

1258 estudios
154 en fase IV



Development landscape – *COPD*



OBJETIVOS DEL TRATAMIENTO DE LOS PACIENTES CON EPOC

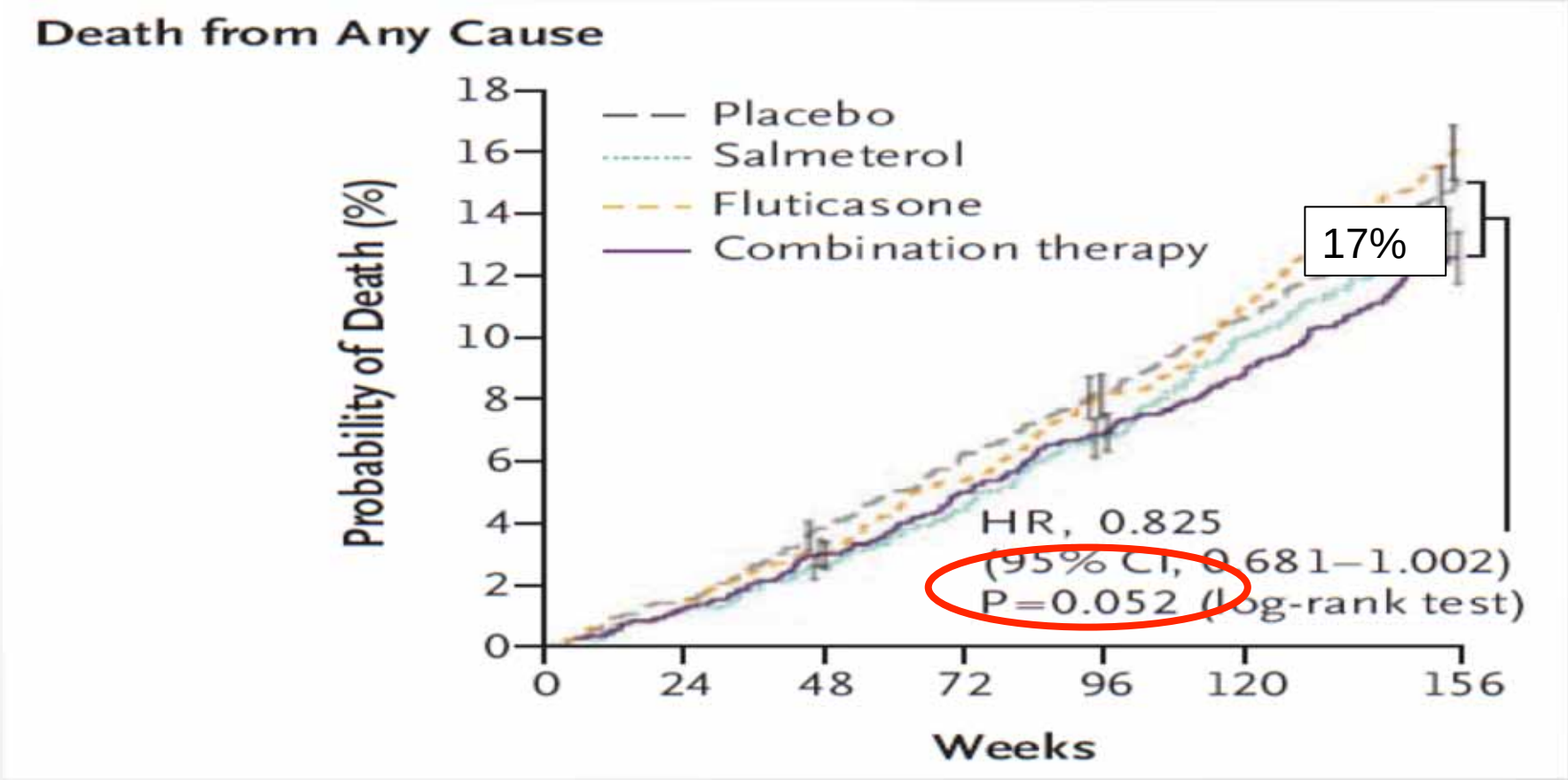
- Alivio de síntomas
- Prevenir la progresión de la enfermedad
- Mejorar la tolerancia al ejercicio
- Mejorar la calidad de vida
- Prevenir y tratar las exacerbaciones
- Reducir la mortalidad

GOLD guidelines. www.goldcopd.com

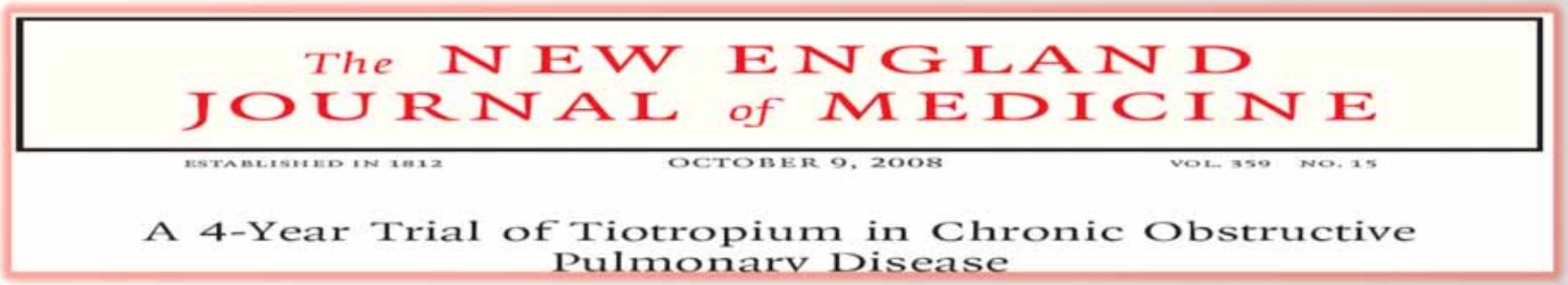
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease



- EPOC POCO REVERSIBLE (PBD <10%)



- NO COMPLETAMENTE REVERSIBLE (FEV1/FVC <70% TRAS PBD)

Eur Respir J 2008; 31: 742–750
DOI: 10.1183/09031936.00129607

Bronchodilator responsiveness in patients with COPD

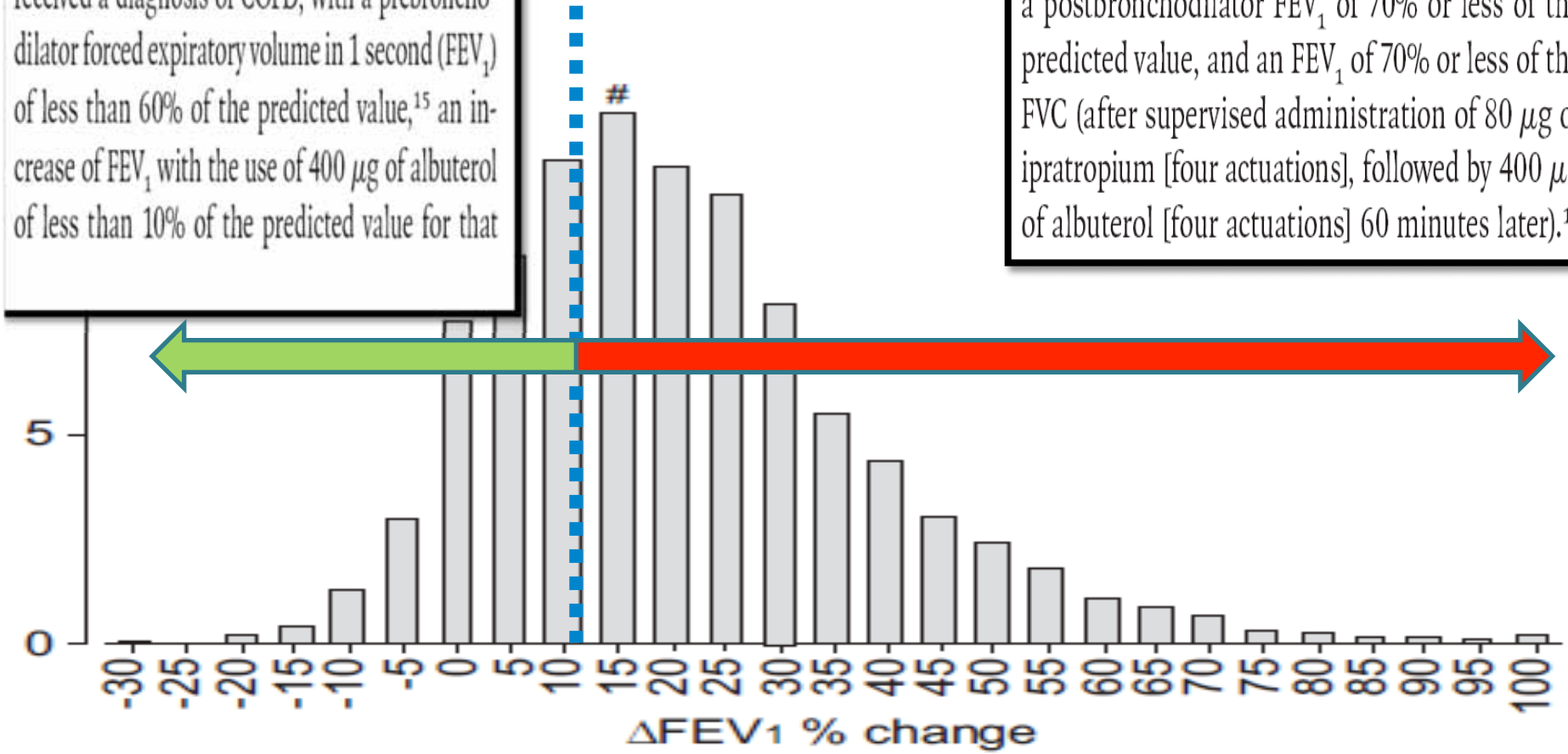
D.P. Tashkin*, B. Celli#, M. Decramer¶, D. Liu+, D. Burkhart+, C. Cassino+ and S. Kesten§

TORCH

received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV_1) of less than 60% of the predicted value,[15] an increase of FEV_1 with the use of 400 μg of albuterol of less than 10% of the predicted value for that

UPLIFT

a postbronchodilator FEV_1 of 70% or less of the predicted value, and an FEV_1 of 70% or less of the FVC (after supervised administration of 80 μg of ipratropium [four actuations], followed by 400 μg of albuterol [four actuations] 60 minutes later).[16]



The NEW ENGLAND JOURNAL of MEDICINE

HOME | SEARCH | CURRENT ISSUE | PAST ISSUES | COLLECTIONS | HELP

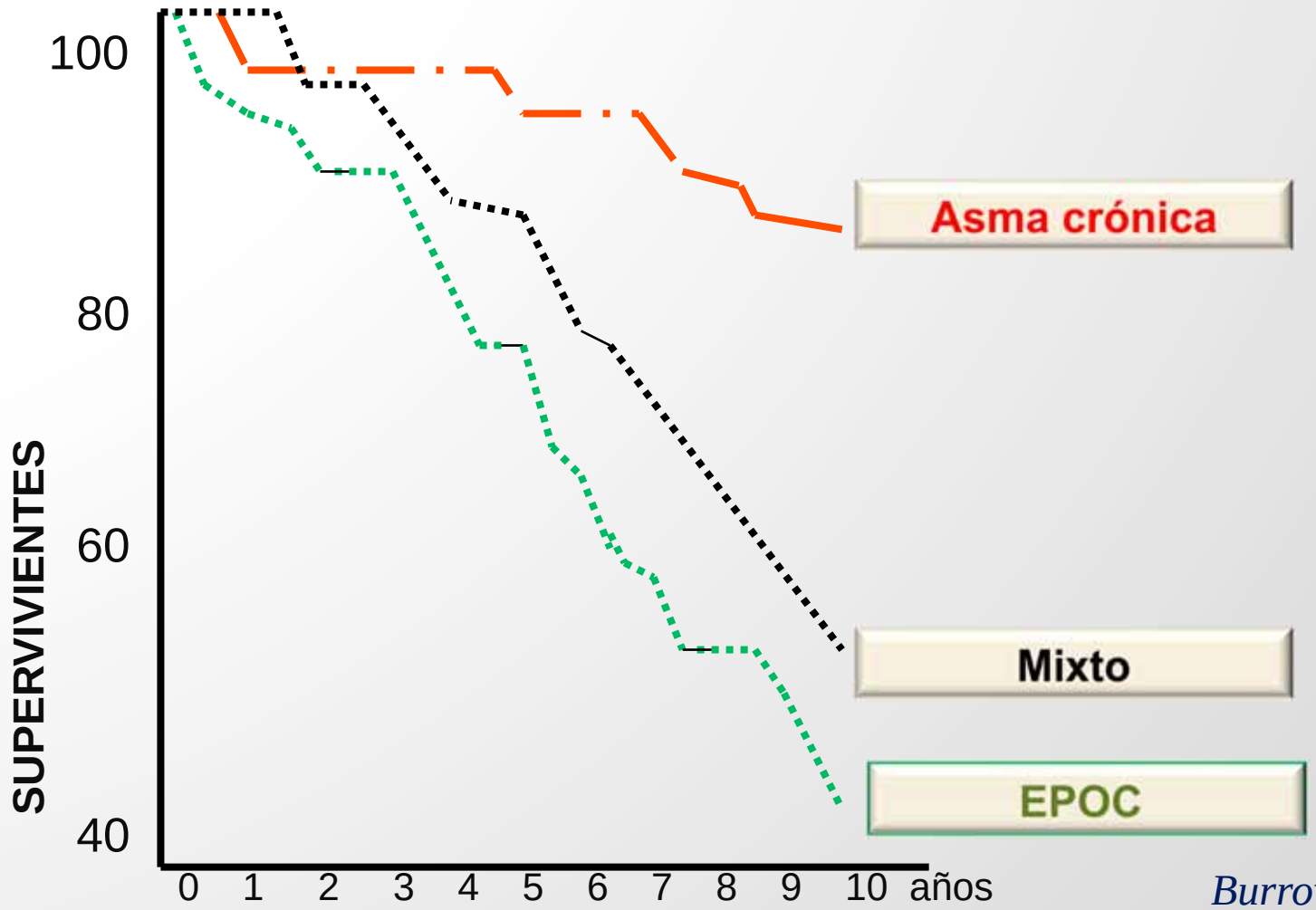
Please sign in for full text and personal services

ORIGINAL ARTICLE

◄ Previous Volume 317:1309-1314 November 19, 1987 Number 21 Next ►

The course and prognosis of different forms of chronic airways obstruction in a sample from the general population

B Burrows, JW Bloom, GA Traver, and MG Cline

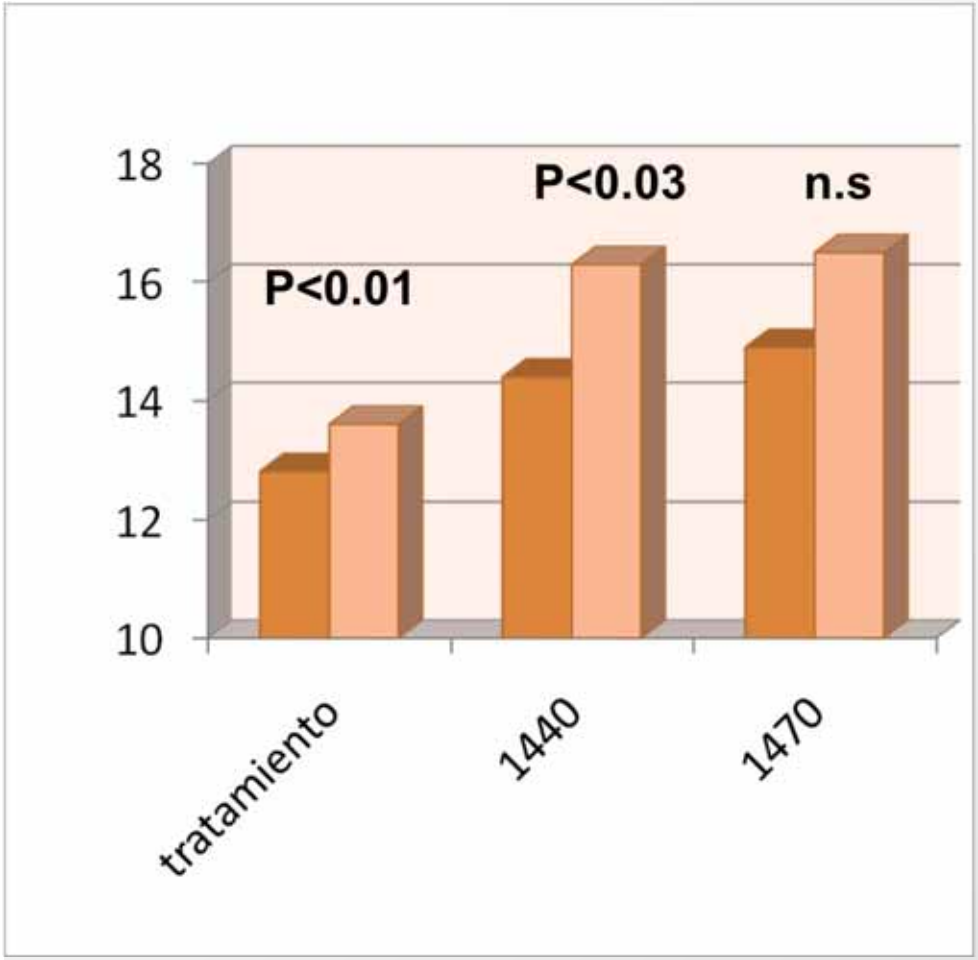


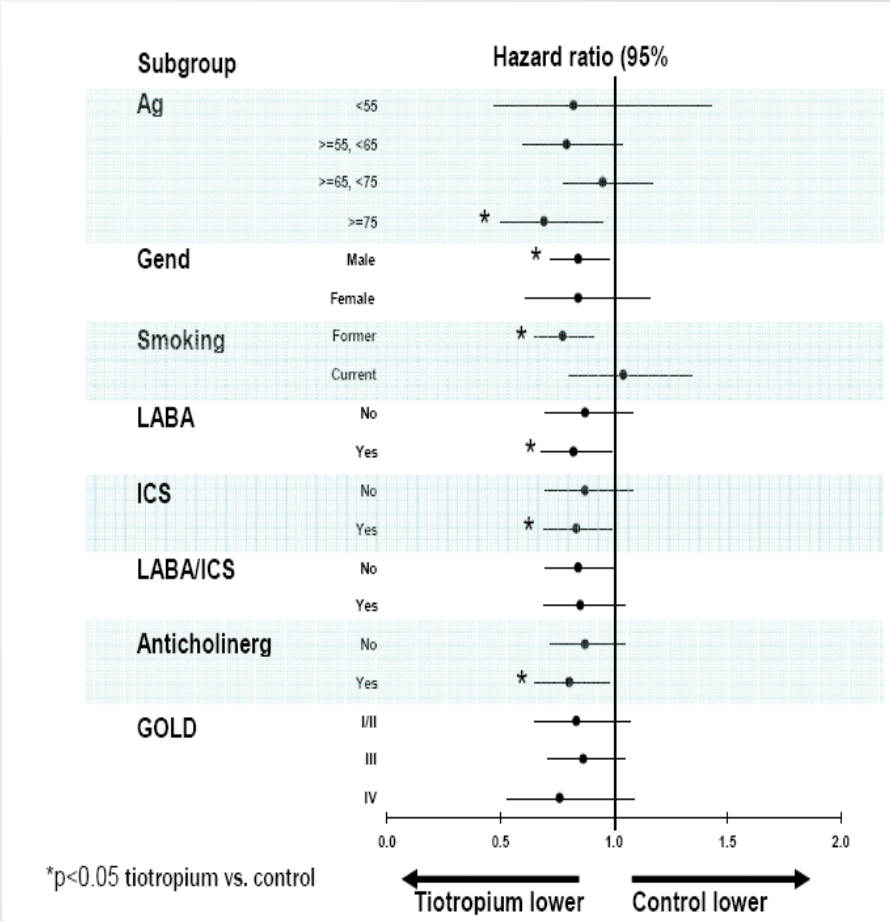
Burrows. NEJM 1987

Mortality in the 4-Year Trial of Tiotropium (UPLIFT) in Patients with Chronic Obstructive Pulmonary Disease

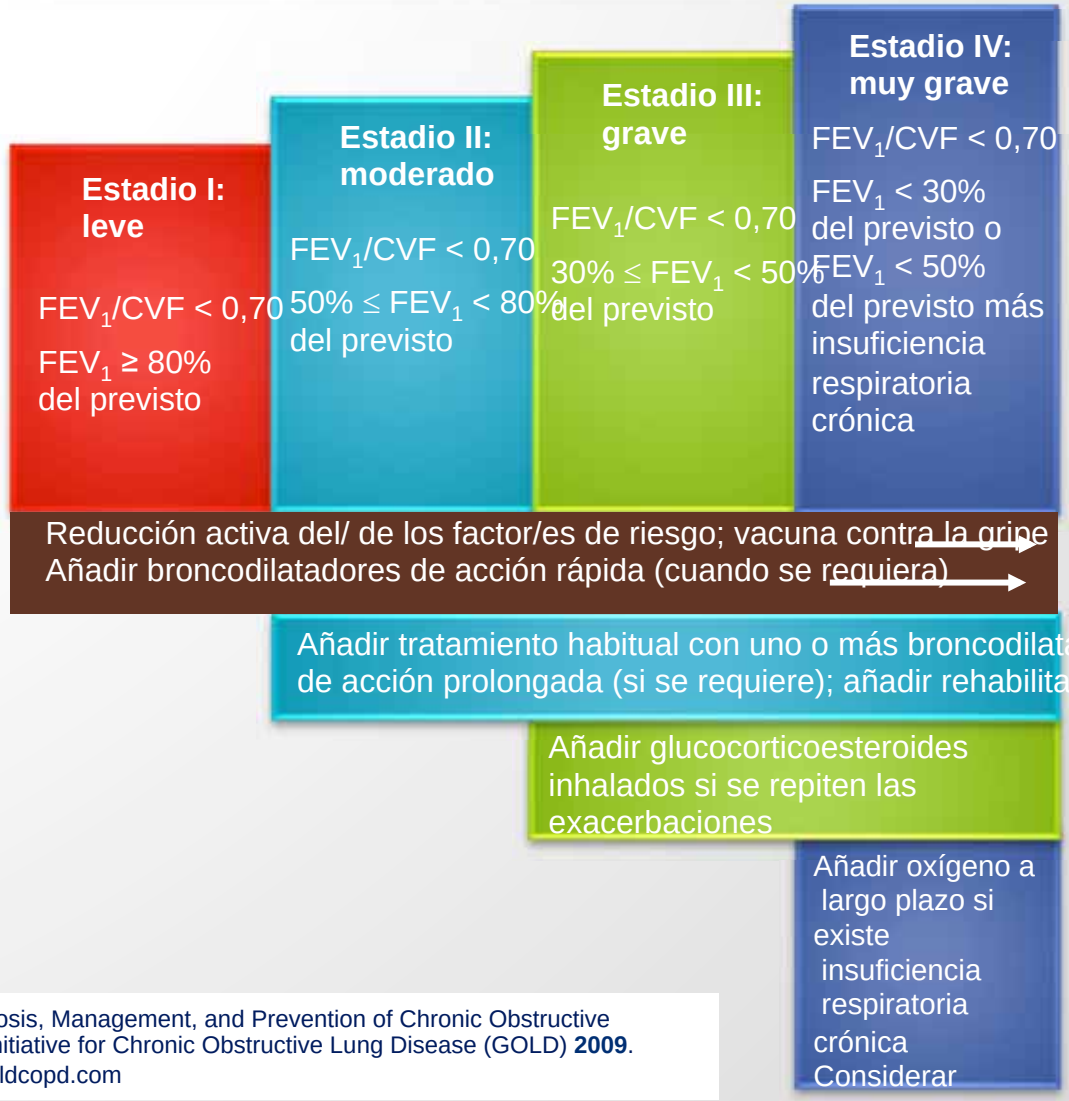
Bartolome Celli[1], Marc Decramer[2], Steven Kesten[3], Dacheng Liu[3], Sunil Mehra[4], and Donald P. Tashkin[5], on behalf of the UPLIFT Study Investigators*

Am J Respir Crit Care Med Vol 180. pp 948–955, 2009





TERAPIA ESCALONADA



Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) **2009**.
Fuente disponible en www.goldcopd.com

TERAPIA ESCALONADA

Beta 2 de corta a demanda

LABA O LAMA

LABA + LAMA

LABA + LAMA+CI y/ o ROFLUMILAST

GRAVEDAD

LABA

SALMETEROL
FORMOTEROL
INDACATEROL

LAMA

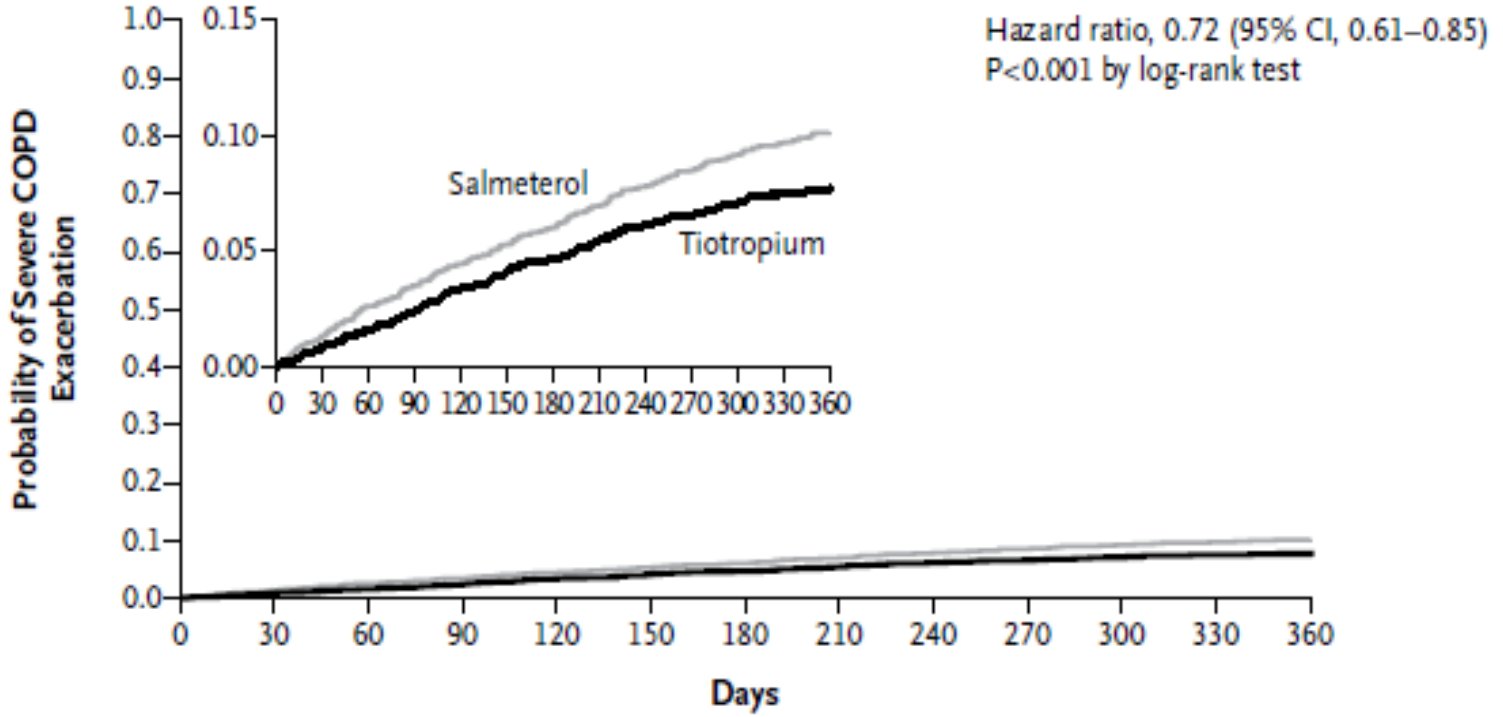
TIOTROPIO

FEV1<50%+EXACERBACIONES

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

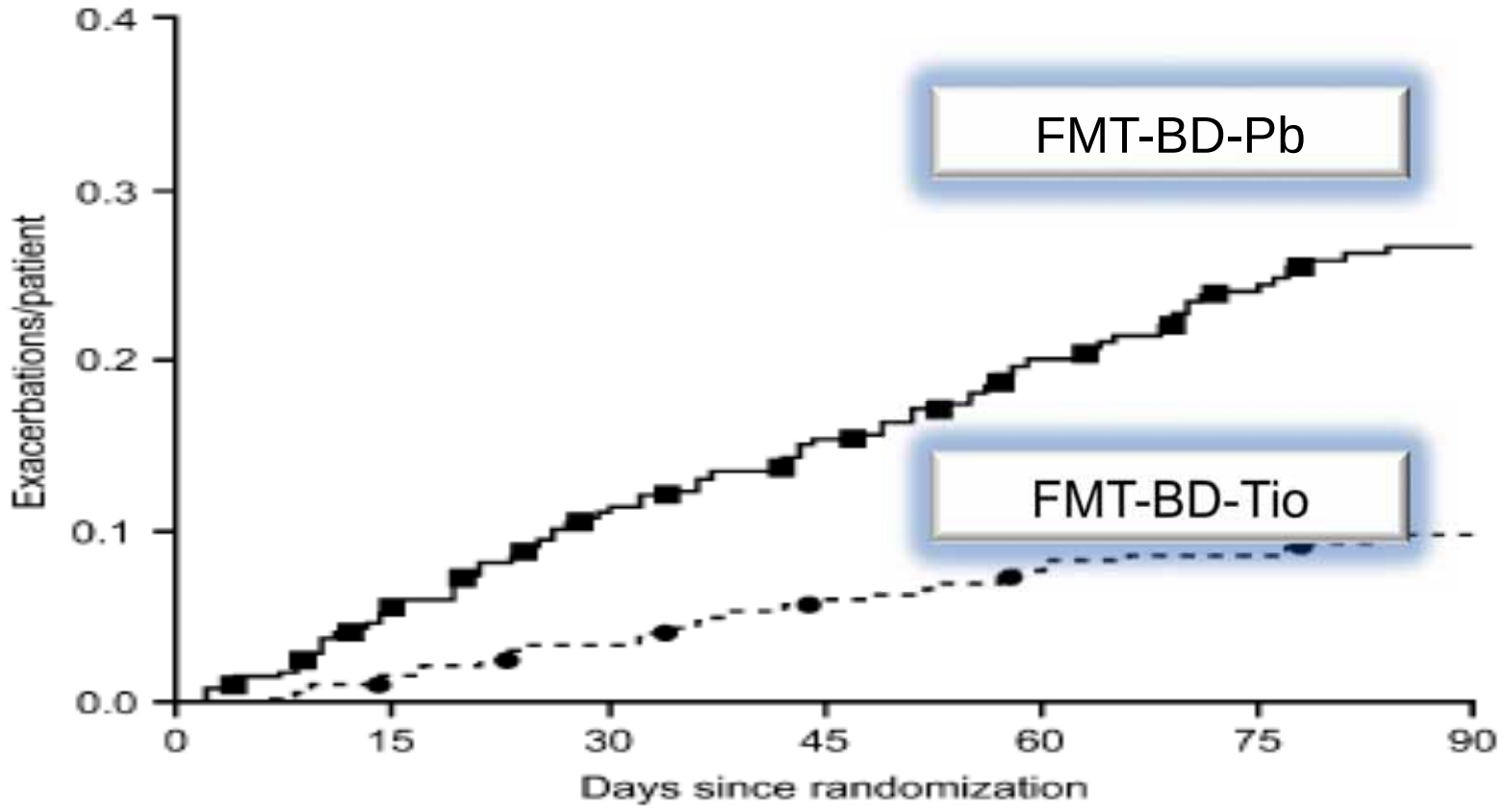
Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD



No. at Risk													
Tiotropium	3707	3564	3453	3359	3285	3217	3177	3125	3066	3017	2977	2948	2663
Salmeterol	3669	3502	3362	3244	3172	3080	3032	2982	2921	2870	2834	2806	2489

Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease

Tobias Welte[1], Marc Miravitlles[2], Paul Hernandez[3], Göran Eriksson[4,5], Stefan Peterson[5], Tomasz Polanowski[5], and Romain Kessler[6]



OPTIMAL Study: Hospitalizations for AECOPD

	Tio + Placebo	Tio + Salmeterol	Tio + Flut./Salm.
Hospitalizations for AECOPD	49	38	26
Rate ratio vs placebo		0.83 (0.54-1.27)	0.53 (0.33-0.86)
p value		0.38	0.01

Aaron S, et al. AIM 2007; 146:545-555.

COPD: Journal of Chronic Obstructive Pulmonary Disease, Early Online:1–38, 2011
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2011.560131

informa
healthcare

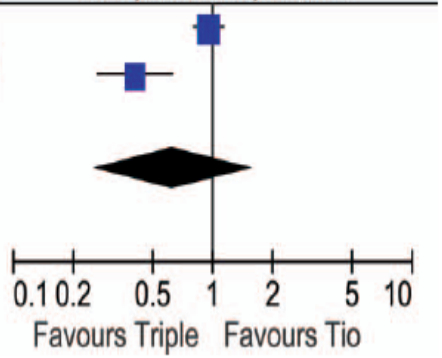
CLINICAL REVIEW

Triple Therapy for the Management of COPD: A Review

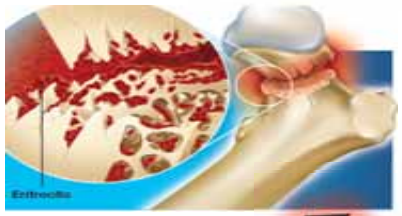
Kathryn Gaebel,[1,2] R. Andrew McIvor,[3,4] Feng Xie,[1,2,5] Gord Blackhouse,[1,5] Diana Robertson,[1,5] Nazila Assasi, Paul Hernandez,[6] and Ron Goeree[1,2,5]

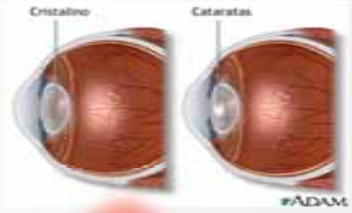
Study or Subgroup	Tio + LABA/ICS Events	Total	Tio Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Aaron 2007	87	145	98	156	52.4%	0.96 [0.80, 1.14]
Welte 2009	25	331	61	329	47.6%	0.41 [0.26, 0.63]
Total (95% CI)		**476**		**485**	**100.0%**	**0.64 [0.26, 1.59]**
Total events	112		159			

Heterogeneity: Tau² = 0.41; Chi² = 14.85, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 0.97 (P = 0.33)



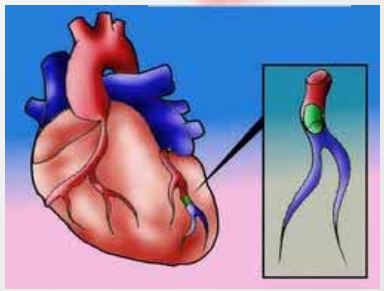
EFECTOS ADVERSOS





CORTICOIDES INHALADOS

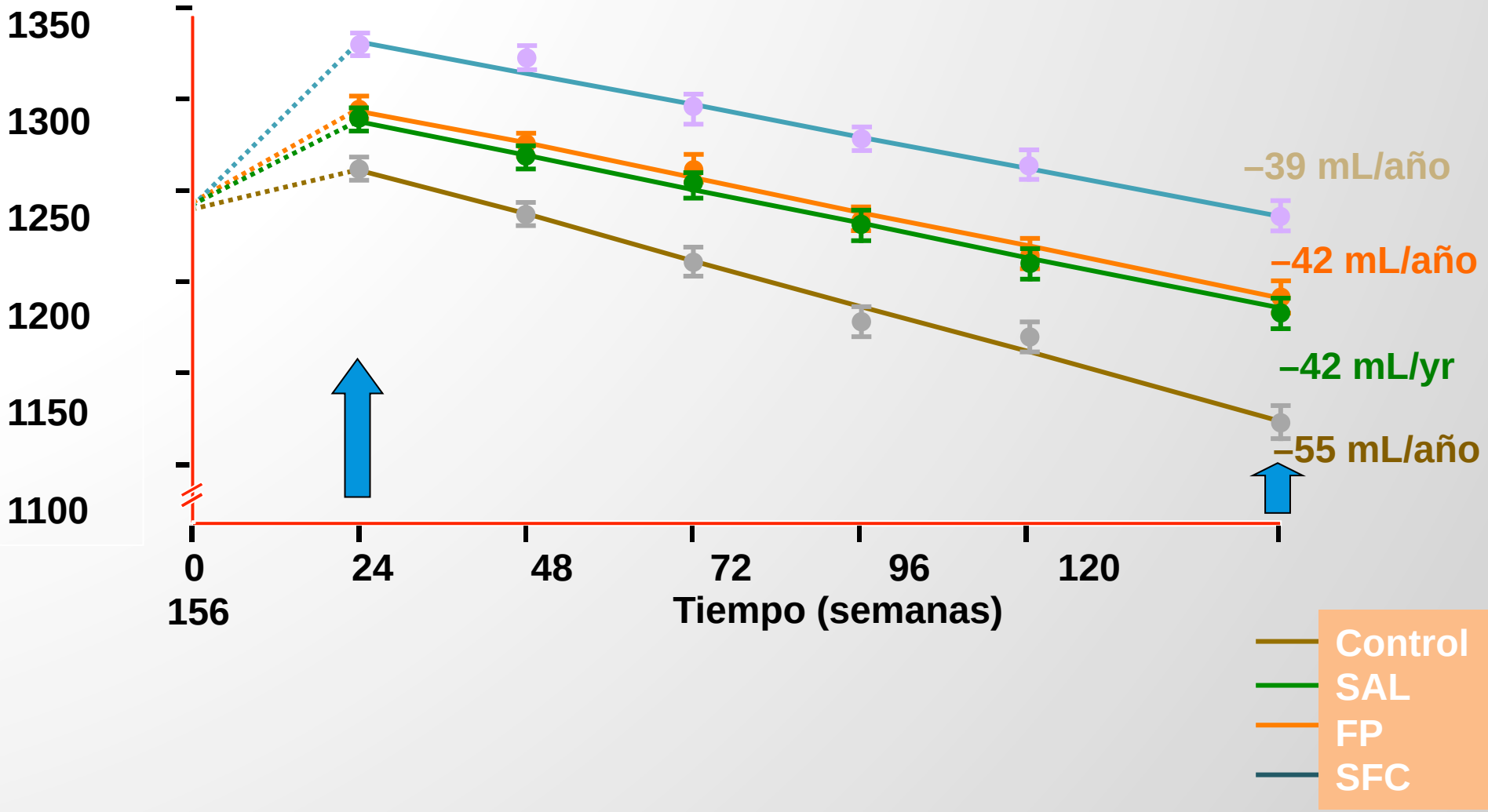
ANTICOLINERGICOS INHALADOS



Effect of Pharmacotherapy on Rate of Decline of Lung Function in Chronic Obstructive Pulmonary Disease

Results from the TORCH Study

Am J Respir Crit Care Med Vol 178. pp 332–338, 2008



Medications to Modify Lung Function Decline in Chronic Obstructive Pulmonary Disease

Some Hopeful Signs

" A pesar de sus limitaciones metodológicas, este estudio demuestra que el no tratamiento (placebo) no es una opción para pacientes con EPOC moderada- severa y que cualquiera de los 3 tratamientos (SM, FC o SM-FC) disminuye la pérdida acelerada de función pulmonar en los pacientes con EPOC".

Suissa S. AJRCCM 2008

Medications to Modify Lung Function Decline in Chronic Obstructive Pulmonary Disease

Some Hopeful Signs

component (6, 8). Moreover, inhaled corticosteroids alone or in combination have been associated with increased risks of glaucoma and possibly osteoporotic fractures (9–11), and have been shown to increase the risk of cataract and pneumonia, particularly with the high doses currently in use (12–16).

On the whole, this study offers two major advances that benefit the patient with COPD. It provides the first possible evidence that lung function decline can be slowed with medications. It also provides further evidence that the use of inhaled corticosteroids, alone or in combination, in COPD is unnecessary and thus inappropriate.

9. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet* 1997;350:979–982.

Inhaled and Nasal Corticosteroid Use and the Risk of Fracture

Am J Respir Crit Care Med Vol 169. pp 83–88, 2004

The implications of our results for the treatment of respiratory disease are important. The fact that long-term use of inhaled

Samy Suissa, Marc Baltzan, Richard Kremer, and Pierre Ernst

high doses, suggests that the doses corresponding to the current treatment guidelines are safe.

CORTICOIDES INHALADOS Y NEUMONÍA

Q J Med 2010; **103**:379–385
doi:10.1093/qjmed/hcq023 Advance Access Publication 15 March 2010

Review

QJM

Inhaled corticosteroids and risk of pneumonia: evidence for and against the proposed association

A. SINGANAYAGAM, J.D. CHALMERS and A.T. HILL

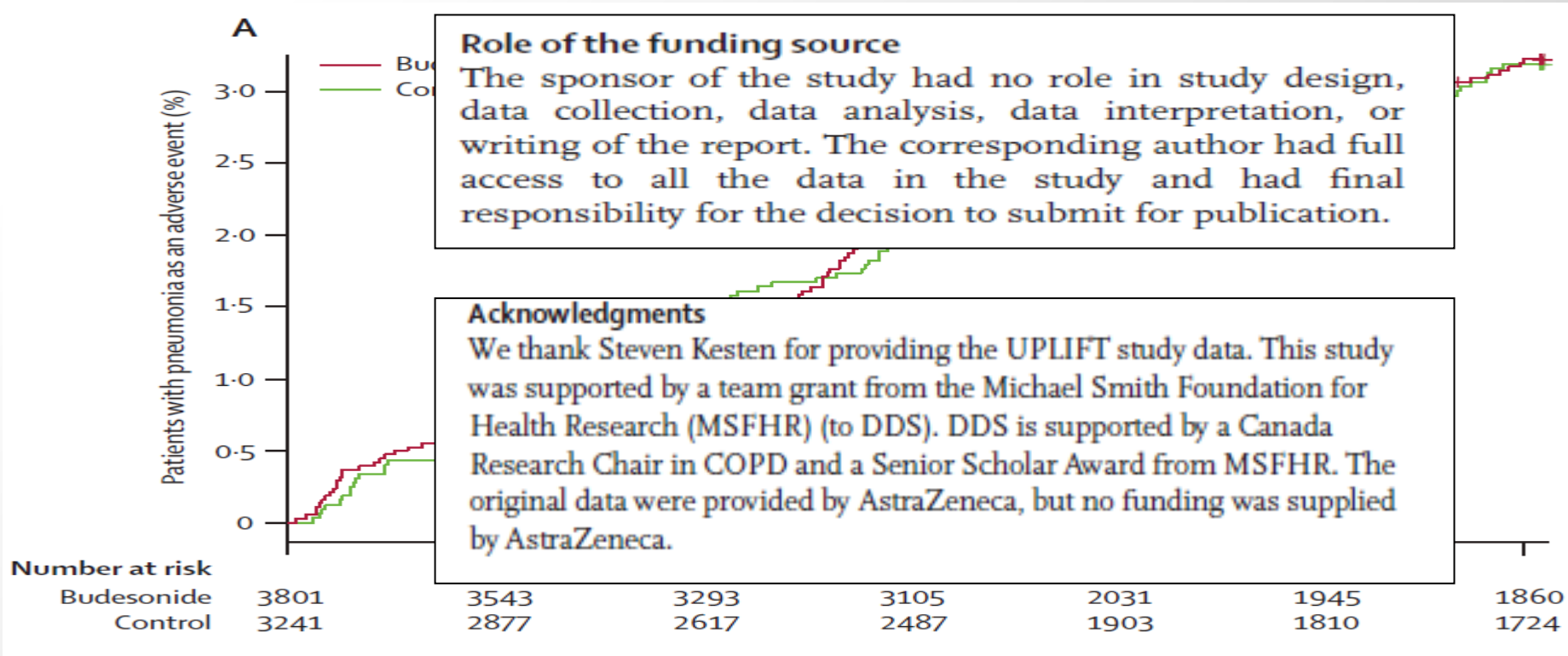
Table 3 Evidence for and against association of ICS and pneumonia from experimental and clinical studies

Evidence supporting association of ICS with pneumonia	Evidence against association of ICS with pneumonia
Biologically plausible link—through inhibition of NF-κB by ICS.	*In vitro* and *in vivo* studies using ICS show reduced bacterial invasion.[32–34]
Several large prospective trials report increased pneumonia associated with ICS use.[5–7]	Clinical trials not designed to assess pneumonia risk and no radiographic confirmation of pneumonia.
Case–control study showing increased risk of pneumonia hospitalization with ICS use.[31]	ICS not identified as an independent risk factor for pneumonia in a population based study.[47]
Two separate meta-analyses showing increased risk of pneumonia associated with ICS use in pooled analysis.[29,30]	Meta-analysis restricted to budesonide trials did not find a link with pneumonia.[44]
	Failure of trials and meta-analyses to control for antibiotic usage in treatment and control groups.

Budesonide and the risk of pneumonia: a meta-analysis of individual patient data

Lancet 2009; 374: 712–19

Don D Sin, Donald Tashkin, Xuekui Zhang, Finn Radner, Ulf Sjöbring, Anders Thorén, Peter M A Calverley, Stephen I Rennard



Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

We thank Steven Kesten for providing the UPLIFT study data. This study was supported by a team grant from the Michael Smith Foundation for Health Research (MSFHR) (to DDS). DDS is supported by a Canada Research Chair in COPD and a Senior Scholar Award from MSFHR. The original data were provided by AstraZeneca, but no funding was supplied by AstraZeneca.

Eur Respir J 2010; 36: 751–757
DOI: 10.1183/09031936.00077509

Inhaled corticosteroid use is associated with lower mortality for subjects with COPD and hospitalised with pneumonia

R. Malo de Molina*,#, E.M. Mortensen*,¶, M.I. Restrepo*,#, L.A. Copeland*,+, M.J.V. Pugh*,§ and A. Anzueto*,#

AJRCCM Articles in Press. Published on April 21, 2011 as doi:10.1164/rccm.201012-2070OC

Observational Study of Inhaled Corticosteroids on Outcomes for COPD Patients with Pneumonia

Dennis Chen, BS[1]
Marcos I. Restrepo, MD, MSc[1,3]
Michael J. Fine, MD, MSc[6,7]
Mary Jo V. Pugh, PhD[1,4]
Antonio Anzueto, MD[1,3]
Mark L. Metersky, MD[8]
Brandy Nakashima, MA[1]
Chester Good, MD[6,7]
Eric M. Mortensen, MD, MSc[1,2]

REVIEW

CLINICIAN'S CORNER

JAMA, September 24, 2008—Vol 300, No. 12

Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease

A Systematic Review and Meta-analysis

The NEW ENGLAND JOURNAL of MEDICINE

The Safety of Tiotropium — The FDA's Conclusions

Theresa M. Michele, M.D., Simone Pinheiro, Sc.D., and Solomon Iyasu, M.D., M.P.H.

BJP British Journal of Pharmacology

British Journal of Pharmacology (2011) **163** 4–17

Themed Issue: Respiratory Pharmacology

REVIEW

β_2-adrenoceptor agonists: current and future direction

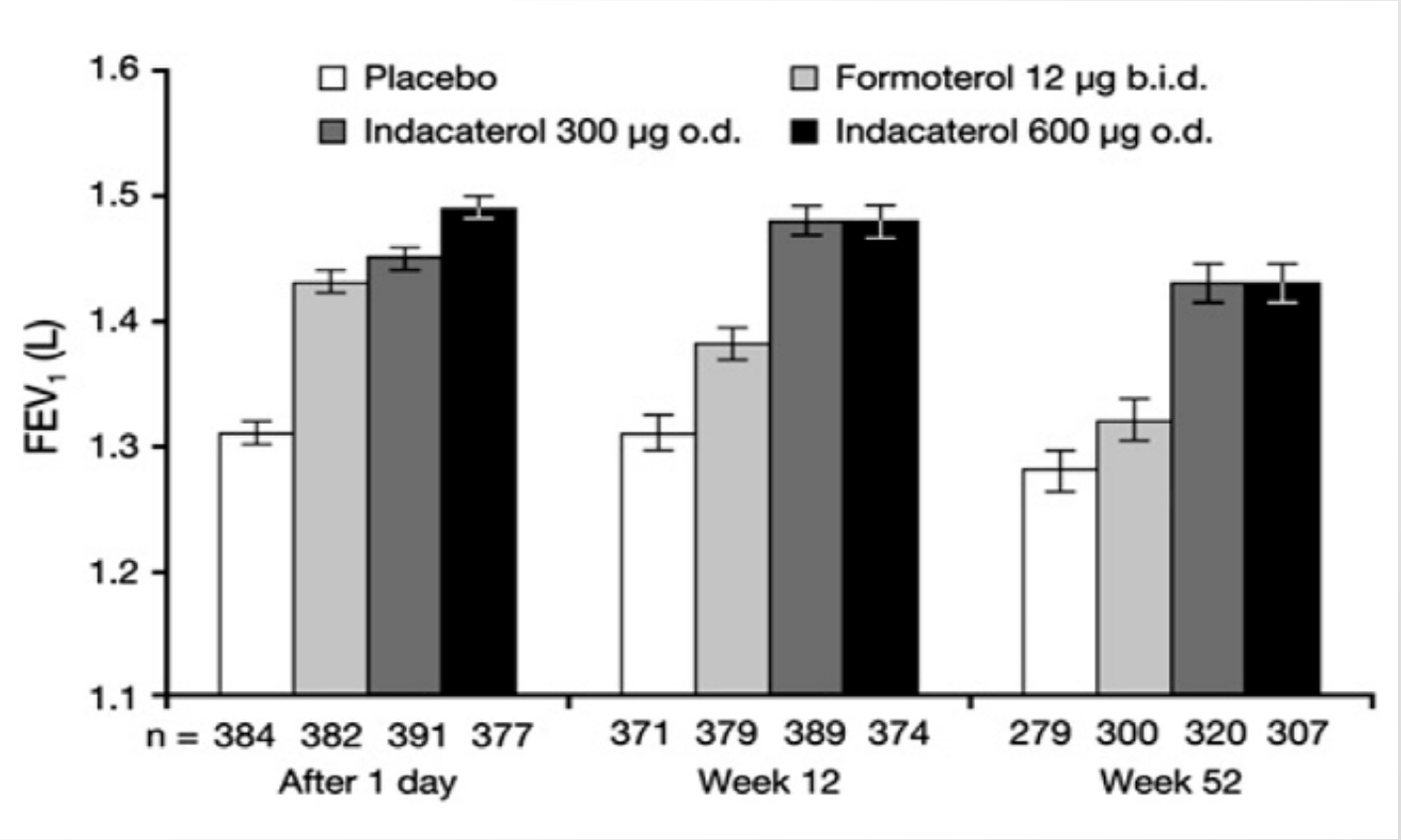
Mario Cazzola[1], Luigino Calzetta[2] and Maria Gabriella Matera[3]

[1]*Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy,* [2]*IRCCS SanRaffaele Pisana, Rome, Italy, and* [3]*Unit of Pharmacology, Department of Experimental Medicine, Second University of Naples, Naples, Italy*

SUPERBRONCODILATADORES

FARMACO	FABRICANTE	COMBINACIONES
INDACATEROL	NOVARTIS	GLICOPIRROLATO/ MOMETASONA
OLODATEROL	BOEHRINGER	TIOTROPIUM
VILANTEROL	GSK	FLUTICASONA
CARMOTEROL	CHIESI	BUDESONIDA
ACLIDINIO	ALMIRALL	FORMOTEROL

Eficacia del indacaterol: comparación con formoterol

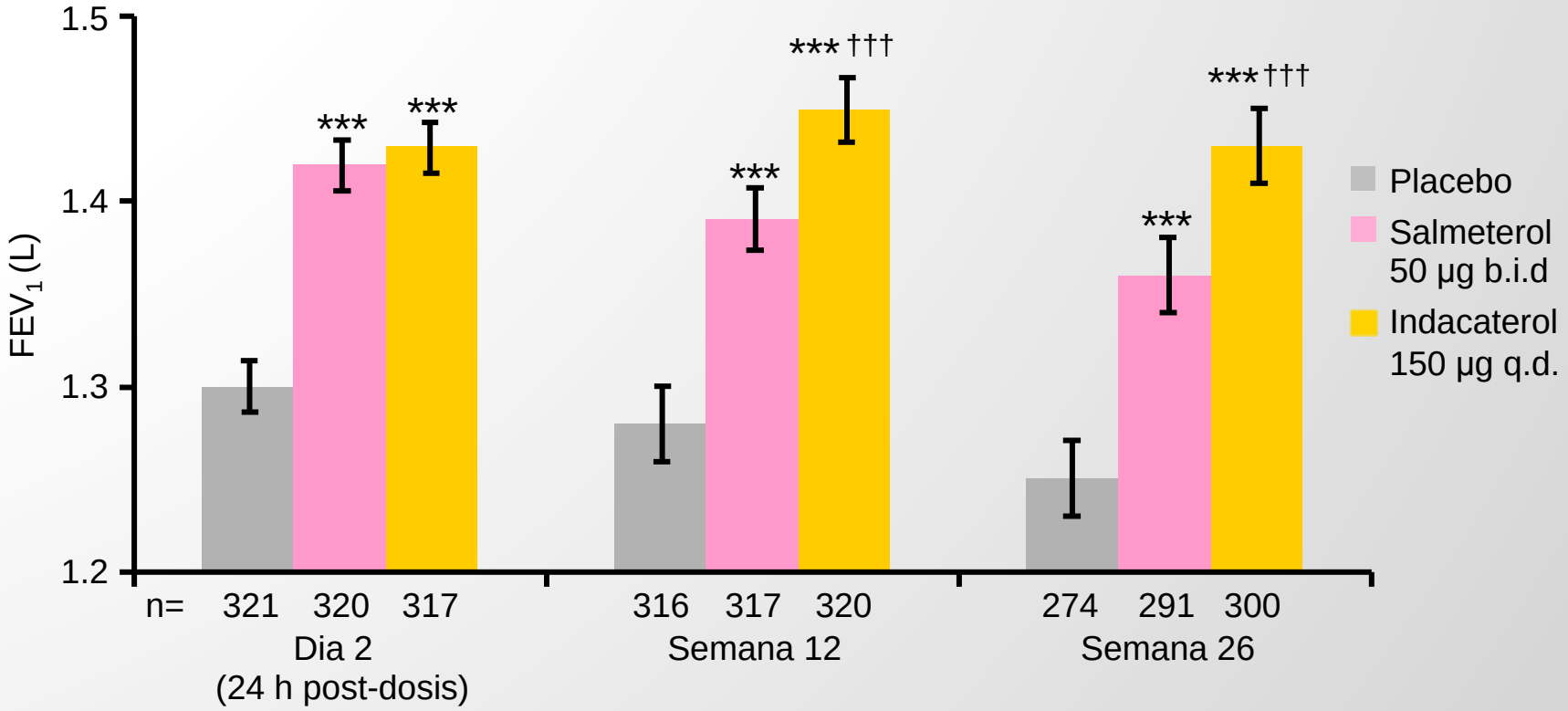


	Placebo (least squares mean, SE)	Difference vs placebo (least squares mean, 95% CI)		
		Indacaterol 300 µg	Indacaterol 600 µg	Formoterol
Trough FEV_1, l§				
After 1 day	1.31 (0.009)	+0.14 (0.11 to 0.16)***†	+0.17 (0.15 to 0.20)***†††	+0.11 (0.09 to 0.13)***
At week 12	1.31 (0.013)	+0.17 (0.13 to 0.20)***†††	+0.17 (0.13 to 0.20)***†††	+0.07 (0.04 to 0.10)***
At week 52	1.28 (0.017)	+0.16 (0.12 to 0.20)***†††	+0.15 (0.11 to 0.19)***†††	+0.05 (0.01 to 0.09)*

Dahl et al 2010. Thorax 2010 65:473-479.

INDACATEROL MEJORA DE FORMA MANTENIDA EL FEV_1 EN 26 SEMANAS COMPARADO CON PLACEBO Y SALMETEROL

- En la semana 12, la diferencia de FEV_1 con indacaterol fue 170 mL sobre placebo (p<0.001)
- En la semana 12, la diferencia de FEV_1 con indacaterol fue 60 mL mayor que salmeterol (p<0.001)
- La superioridad se mantiene en la semana 26 (p<0.001) (70 mL mayor que salmeterol)

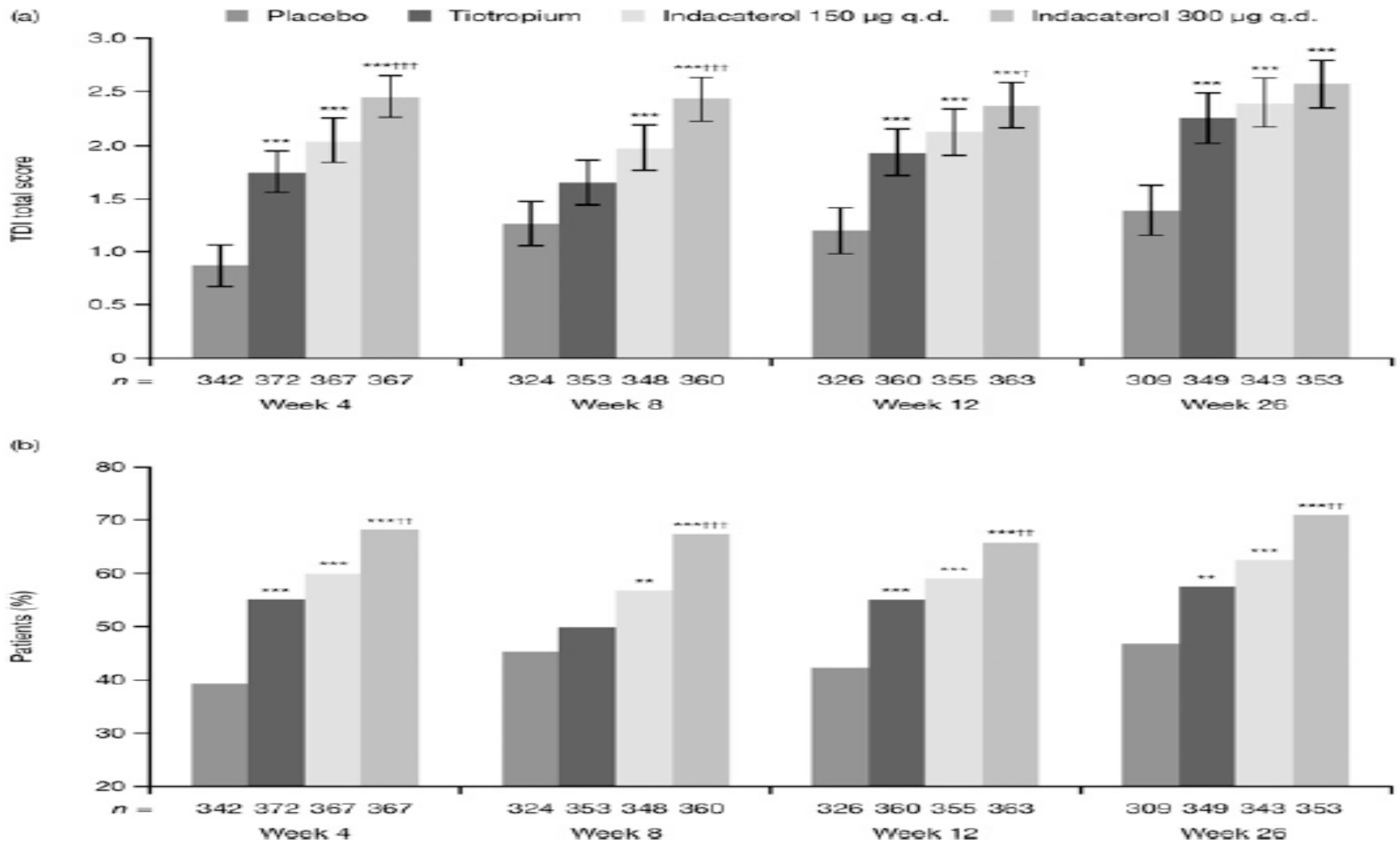


Datos estan en MMS +/– standard error
*****p<0.001 vs placebo; †††p<0.001 vs salmeterol**

Once-Daily Bronchodilators for Chronic Obstructive Pulmonary Disease

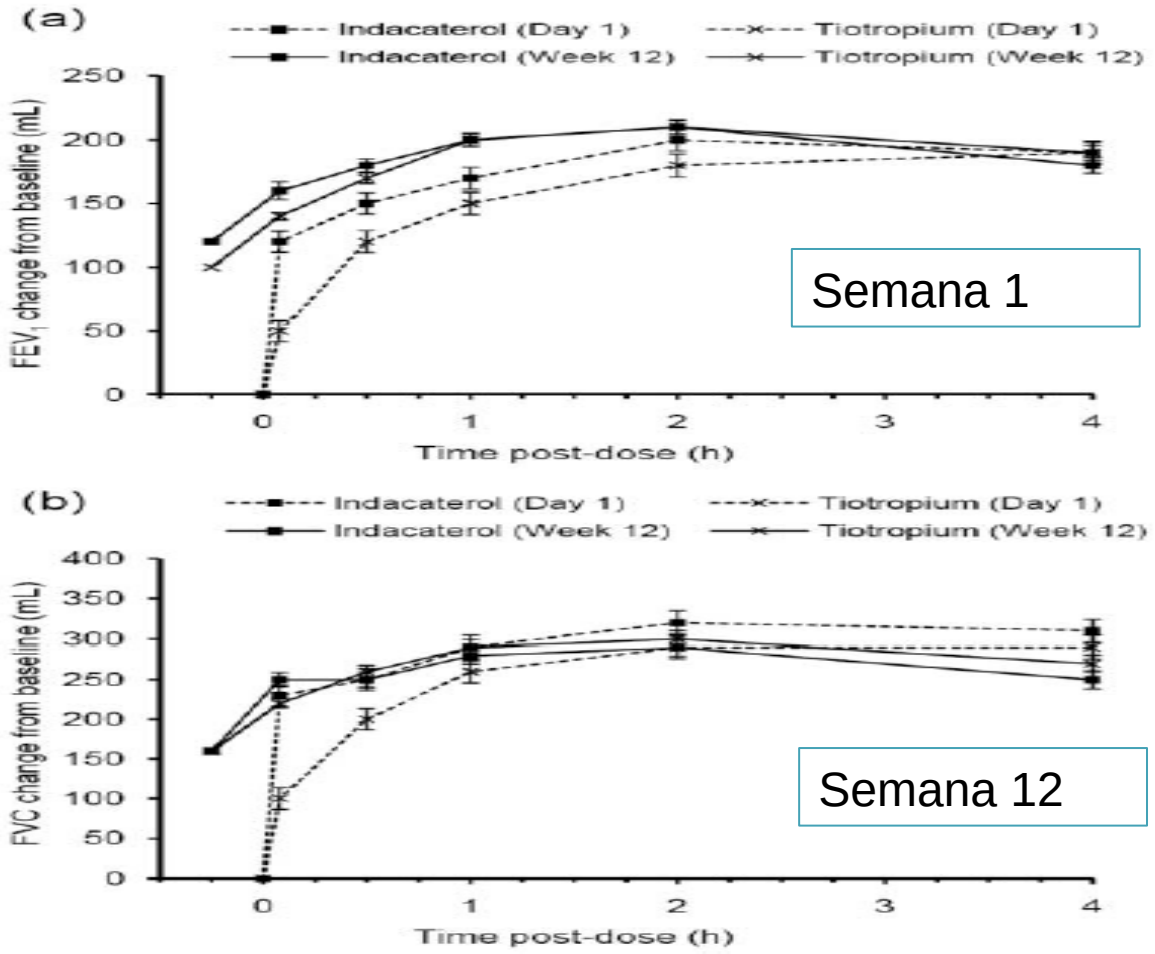
Indacaterol Versus Tiotropium

Am J Respir Crit Care Med Vol 182. pp 155–162, 2010

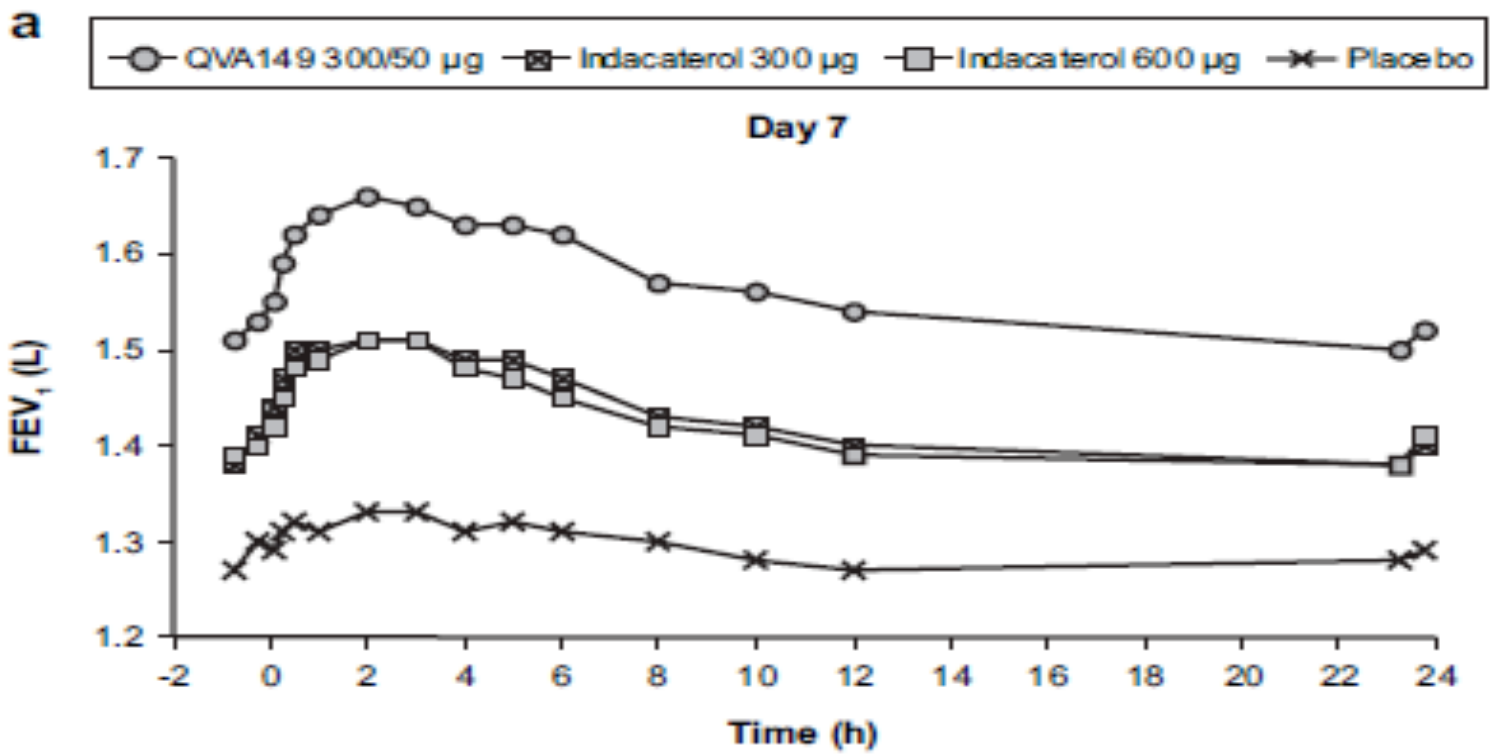


ERJ Express. Published on May 26, 2011 as doi: 10.1183/09031936.00191810

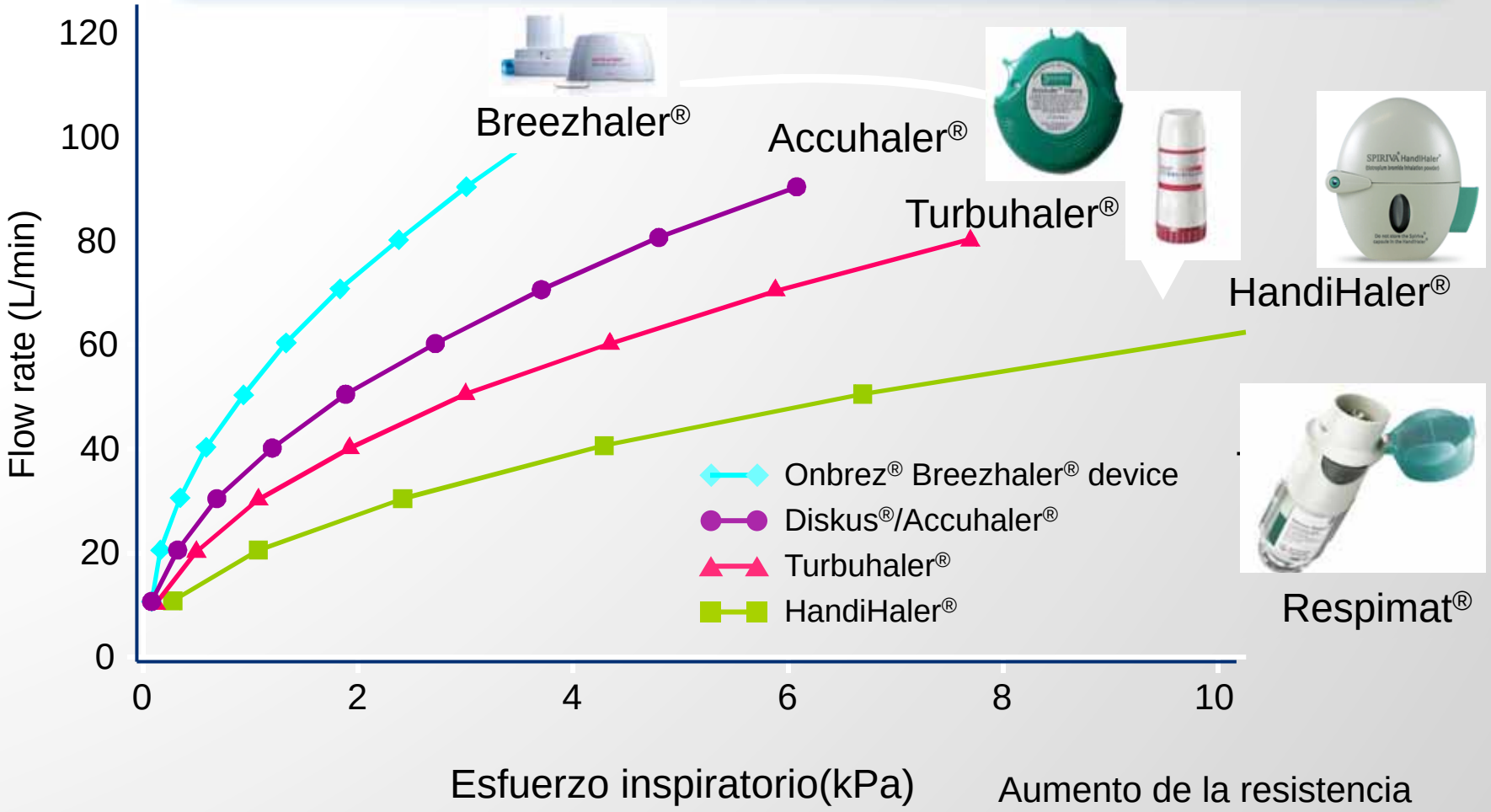
Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD



QVA149 demonstrates superior bronchodilation compared with indacaterol or placebo in patients with chronic obstructive pulmonary disease



RESISTENCIA AL FLUJO AÉREO



Singh D, et al. Dose delivery characterization of indacaterol following inhalation by COPD patients. American Thoracic Society (ATS) 2010 (poster).

- **Tratamiento de los efectos sistémicos de la EPOC: nuevos antiinflamatorios**.

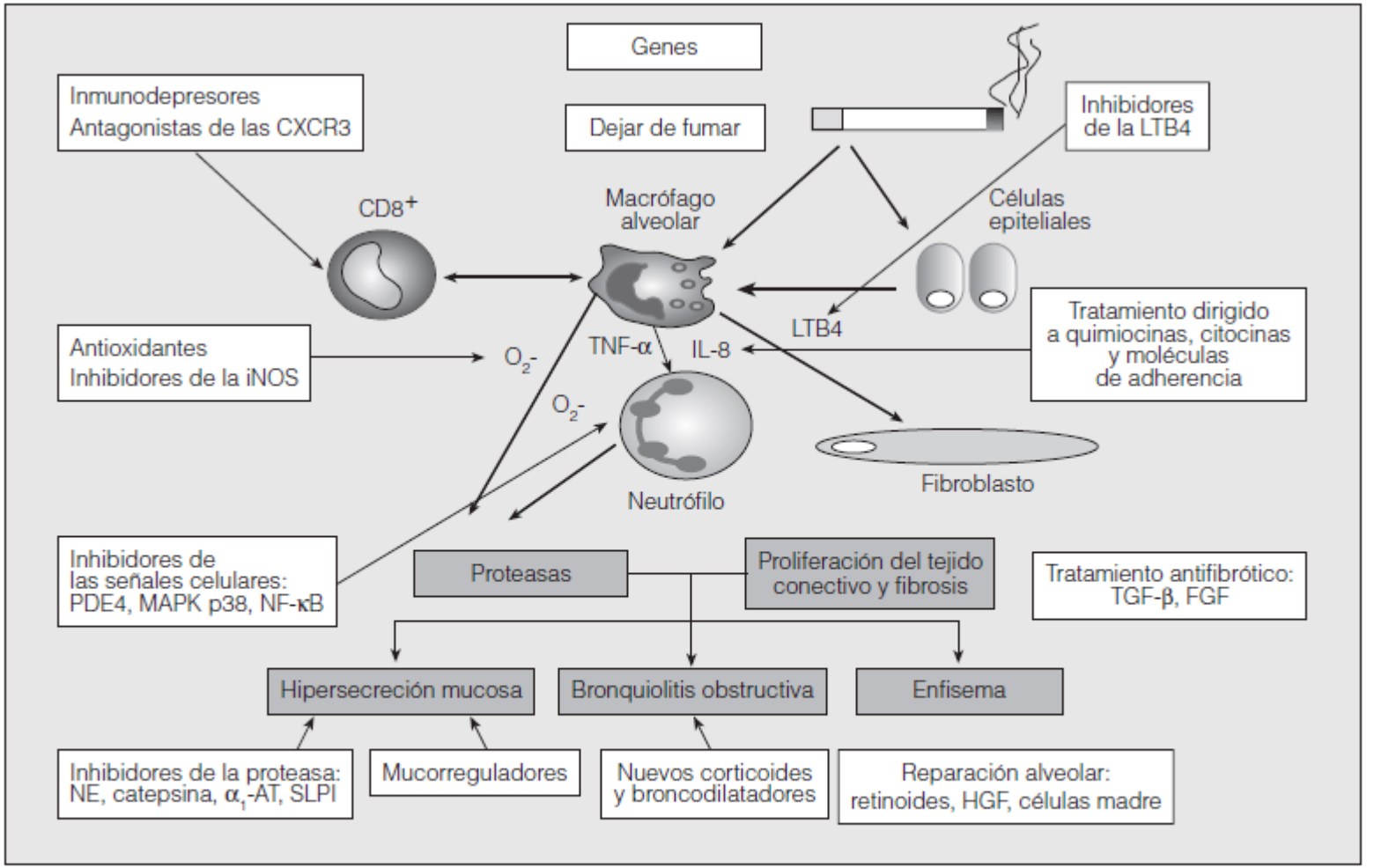
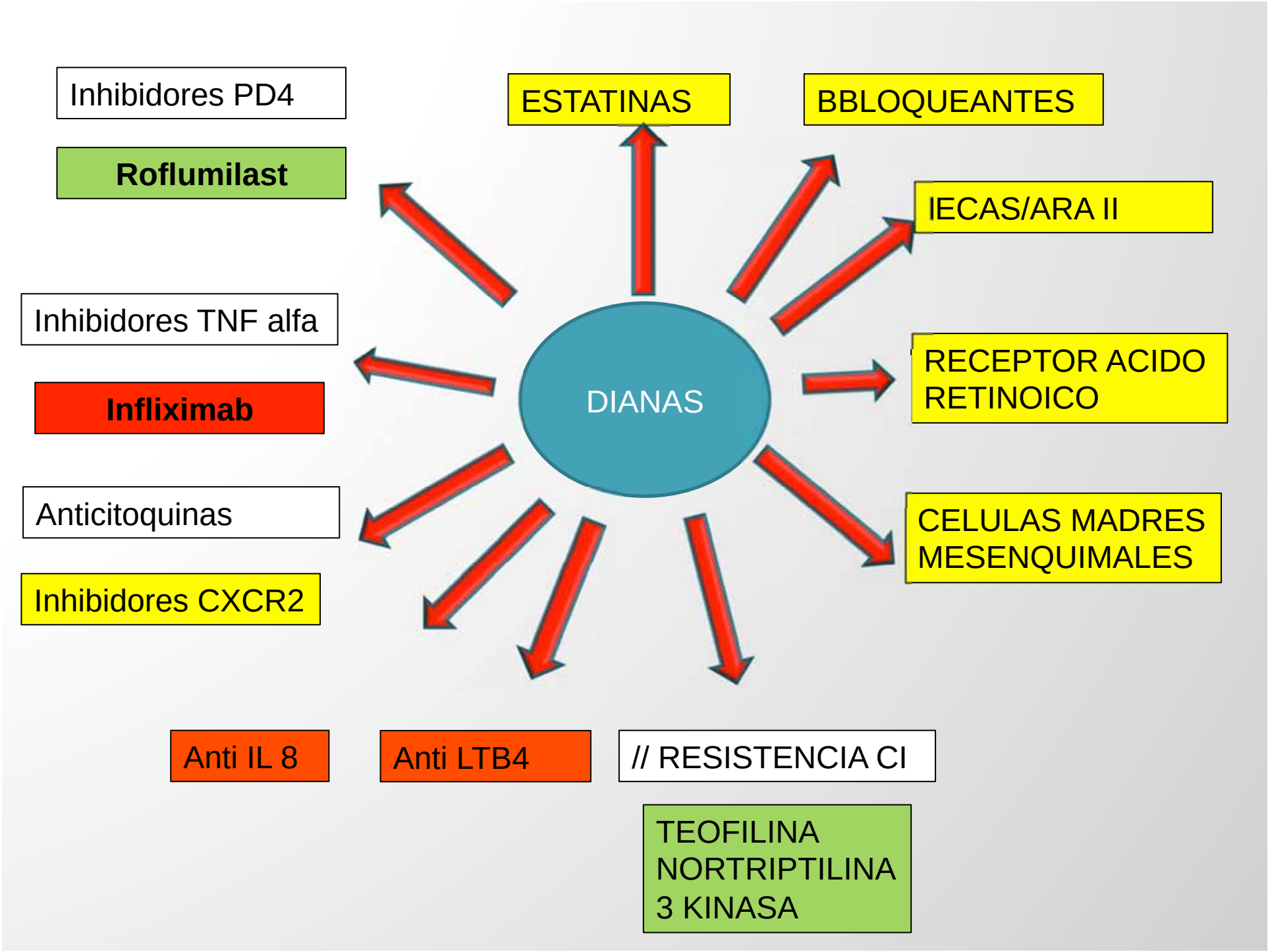
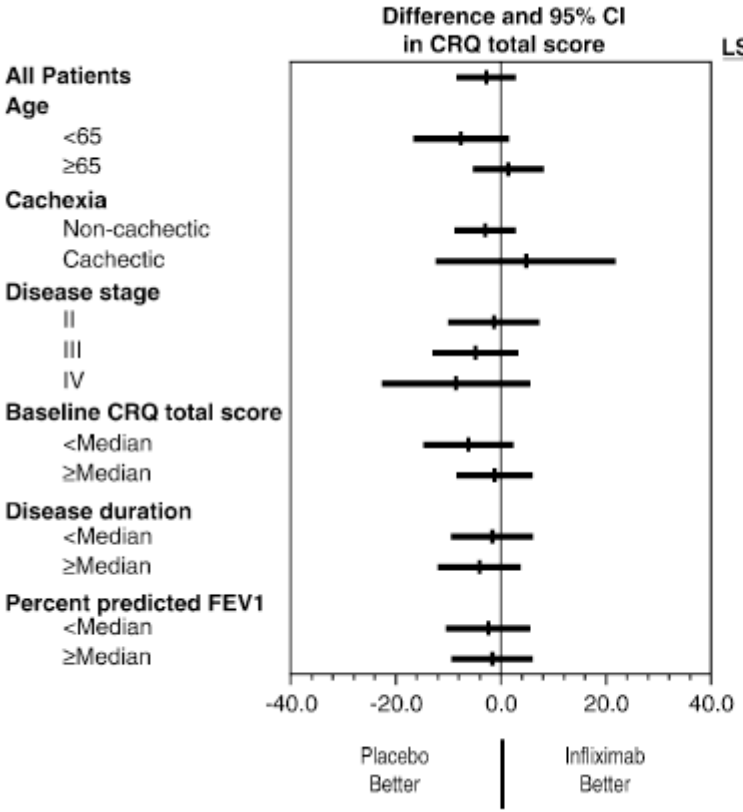


Fig. 1. Tratamiento farmacológico dirigido a la patogenia de la EPOC. α_1-AT: alfa-1-antitripsina; EGF: factor de crecimiento epidérmico; FGF: factor de crecimiento fibroblástico; HGF: factor de crecimiento de los hepatocitos; IL-8: interleucina-8; iNOS: sintetasa inducible del ácido nítrico; LTB4: leucotrieno B4; MAPK: proteincinasa activada por mitógeno; NE: elastasa de neutrófilos; NF-κB: factor nuclear-κB; PDE4: fosfodiesterasa-4; SLPI: inhibidor de la leucoproteasa sérica; TGF-β: factor transformador del crecimiento tipo beta; TNF-α: factor de necrosis tumoral alfa. (Modificado de Hansel TT, Barnes PJ. Atlas de la EPOC. Pathenon Publishing Group; 2005.)

Cosío BG. Arch Bronconeumol 200/; 43 Supp 4:27-35.

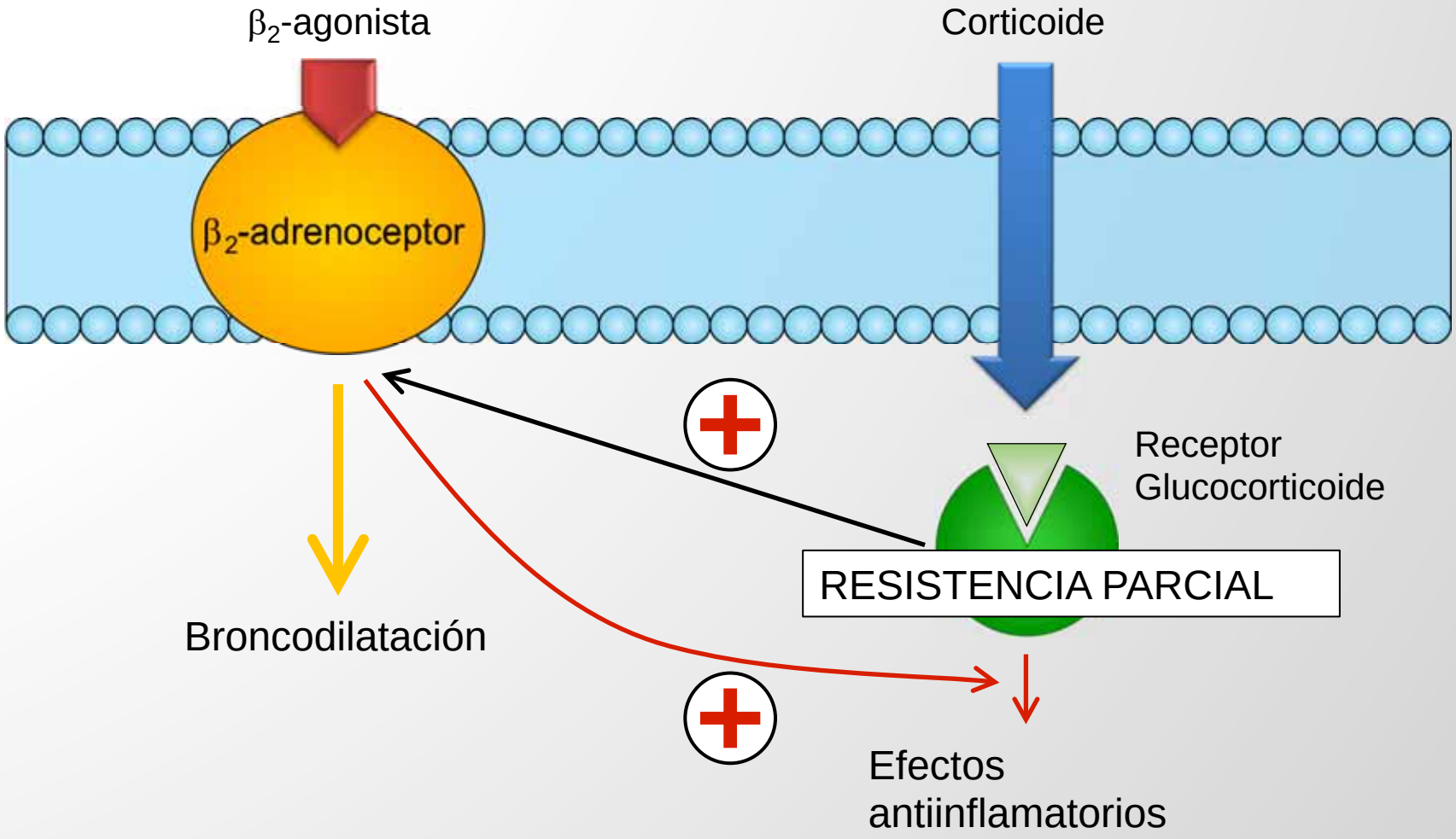

Inhibidores PD4
Roflumilast
Inhibidores TNF alfa
Infliximab
Anticitoquinas
Inhibidores CXCR2
ESTATINAS
BBLOQUEANTES
IECAS/ARA II
RECEPTOR ACIDO RETINOICO
CELULAS MADRES MESENQUIMALES
DIANAS
Anti IL 8
Anti LTB4
// RESISTENCIA CI
TEOFILINA
NORTRIPTILINA
3 KINASA

The Safety and Efficacy of Infliximab in Moderate to Severe Chronic Obstructive Pulmonary Disease



	Placebo		Combined Infliximab		
	LS Mean	n	LS Mean	n	p-value
All Patients	12.6	74	9.8	148	0.2679
Age					
<65	18.1	32	10.6	72	0.0778
≥65	8.2	42	9.6	76	0.6496
Cachexia					
Non-cachectic	12.8	66	9.8	132	0.2580
Cachectic	12.6	7	17.4	14	0.5477
Disease stage					
II	12.1	37	10.8	55	0.7417
III	14.1	28	9.2	60	0.2015
IV	15.8	8	7.3	27	0.1980
Baseline CRQ total score					
<Median	21.9	31	15.7	80	0.1253
≥Median	4.0	43	2.8	68	0.7194
Disease duration					
<Median	13.4	40	11.7	72	0.6458
≥Median	11.9	34	7.8	76	0.2628
Percent predicted FEV1					
<Median	9.9	29	7.5	80	0.5181
≥Median	14.2	45	12.5	68	0.6404

Esteroides y β_2-agonistas



Barnes PJ, et al. Eur Respir J 2002; 19:182–191

Targeting Phosphoinositide-3-Kinase-δ with Theophylline Reverses Corticosteroid Insensitivity in Chronic Obstructive Pulmonary Disease

Yasuo To[1*], Kazuhiro Ito[1*], Yasuo Kizawa[1,2], Marco Failla[1], Misako Ito[1], Tadashi Kusama[2], W. Mark Elliott[3], James C. Hogg[3], Ian M. Adcock[1], and Peter J. Barnes[1]

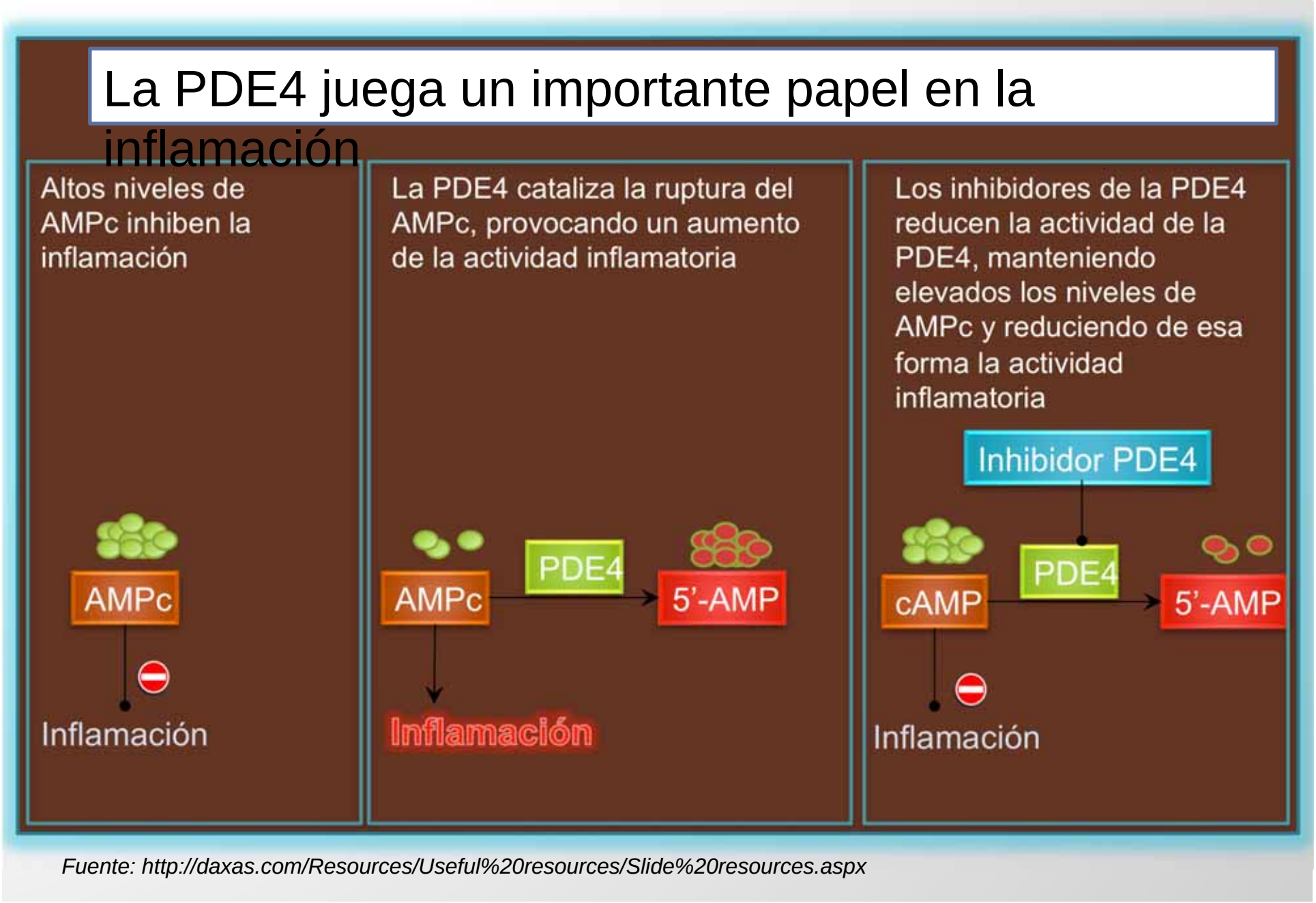
Am J Respir Crit Care Med Vol 182. pp 897–904, 2010

Treatment Effects of Low-Dose Theophylline Combined With an Inhaled Corticosteroid in COPD

Paul A. Ford, PhD; Andrew L. Durham, PhD; Richard E. K. Russell, PhD; Fabiana Gordon, PhD; Ian M. Adcock, PhD; and Peter J. Barnes, DM, FCCP

CHEST 2010; 137(6):1338–1344

INHIBIDORES DE LA FOSFODIESTERASA 4 (PDE4)



Fuente: http://daxas.com/Resources/Useful%20resources/Slide%20resources.aspx

INHIBIDORES FOSFODIESTERASA (PD)

- EXISTEN 11 ISOENZIMAS DE LA PD
- PD5 (SILDENAFILO)-D.ERECTIL. HTPP
- PD2-PD9 DEMENCIA *INVESTIGACIÓN*
- PD2 -SEPSIS,SDRA *INVESTIGACIÓN*
- PD4-PD10 ESQUIZOFRENIA *INVESTIGACIÓN*
- VARIOS-CANCER *INVESTIGACIÓN*

Table 1. Classification and expression of phosphodiesterases (PDEs).

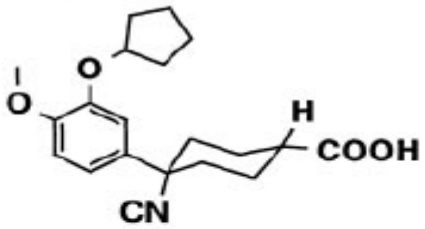
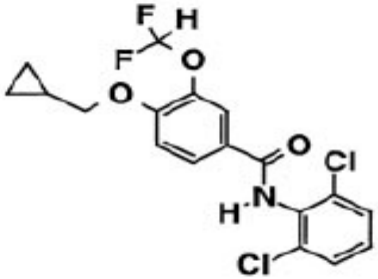
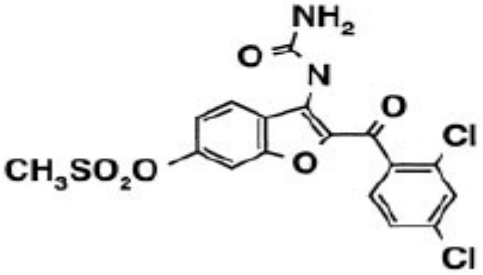
Family	Members	Substrate	Regulation	Tissue/cellular expression	Commonly used inhibitors
PDE1	A, B, C	cAMP/cGMP	$Ca2^{+}$/calmodulin	Lung, smooth muscle, heart, brain, testis, sperm, lymphocytes, macrophages	Vinpocetine, IC224, SCH51866, 8-MeoM-IBMX
PDE2	A	cAMP/cGMP	cGMP stimulated	Adrenal gland, lung, liver, platelets, heart, brain, macrophages, endothelial cells	EHNA, BAY60-7550, PDP, IC933
PDE3	A, B	cAMP/cGMP	Phosphorylation/ cGMP inhibited	Lung, heart, immune cells, adipose tissue, liver, platelets, smooth muscle, adipocytes, hepatocytes, kidney	Milrinone, Tolafentrine, Cilostazol, Cilostamide, Trequinsin, OPC-33540, Dihydropyridazinone, Lixazinone
PDE4	A, B, C, D	cAMP	Phosphorylation/ cAMP-specific UCR1/UCR2 regions	Ubiquitous	Cilomilast, Rolipram, Ro20-1724, Roflumilast, AWD12281, V11294A,SCH35159, Denbufylline, Arofylline
PDE5	A	cGMP	Phosphorylation/ cGMP-specific	Lung, smooth muscle, platelets, cerebellum, skeletal muscle, heart, brain, kidney	Sildenafil, Tadalafil, DA8159, E402, Vardenafil, Zaprinast, DMPPO, Dipyridamole
PDE6	A, B, C, D, G	cGMP	Phosphorylation/ cGMP-specific	Photoreceptors	Zaprinast
PDE7	A, B	cAMP	Rolipram-insensitive	Immune cells, skeletal muscle, heart, liver, kidney, brain, pancreas, testis	BRL 50481, IC242, Dipyridamole, BMS-586353, Thiadiazoles
PDE8	A, B	cAMP	cAMP-specific	Testes, liver, skeletal muscle, heart, kidney, brain, immune cells, testis, thyroid, spleen, ovary, colon	Dipyridamole
PDE9	A	cGMP	cGMP-specific	Kidney, liver, lung, brain, spleen, prostate	BAY 73-669, SCH 51866, Zaprinast
PDE10	A	cAMP/cGMP	Unknown	Testis, brain, heart, thyroid	Papaverine, Dipyridamole, PQ-10
PDE11	A	cAMP/cGMP	Unknown	Skeletal muscle, kidney, liver, pituitary glands, prostate, testis, thyroid	Dipyridamole

Savai R. Targeting cancer with phosphodiesterase inhibitors.Expert Opin Investig Drugs 2010

Phosphodiesterase 4 Inhibitors for the Treatment of COPD*

Graham Sturton and Mary Fitzgerald

Chest 2002;121;192S-196S

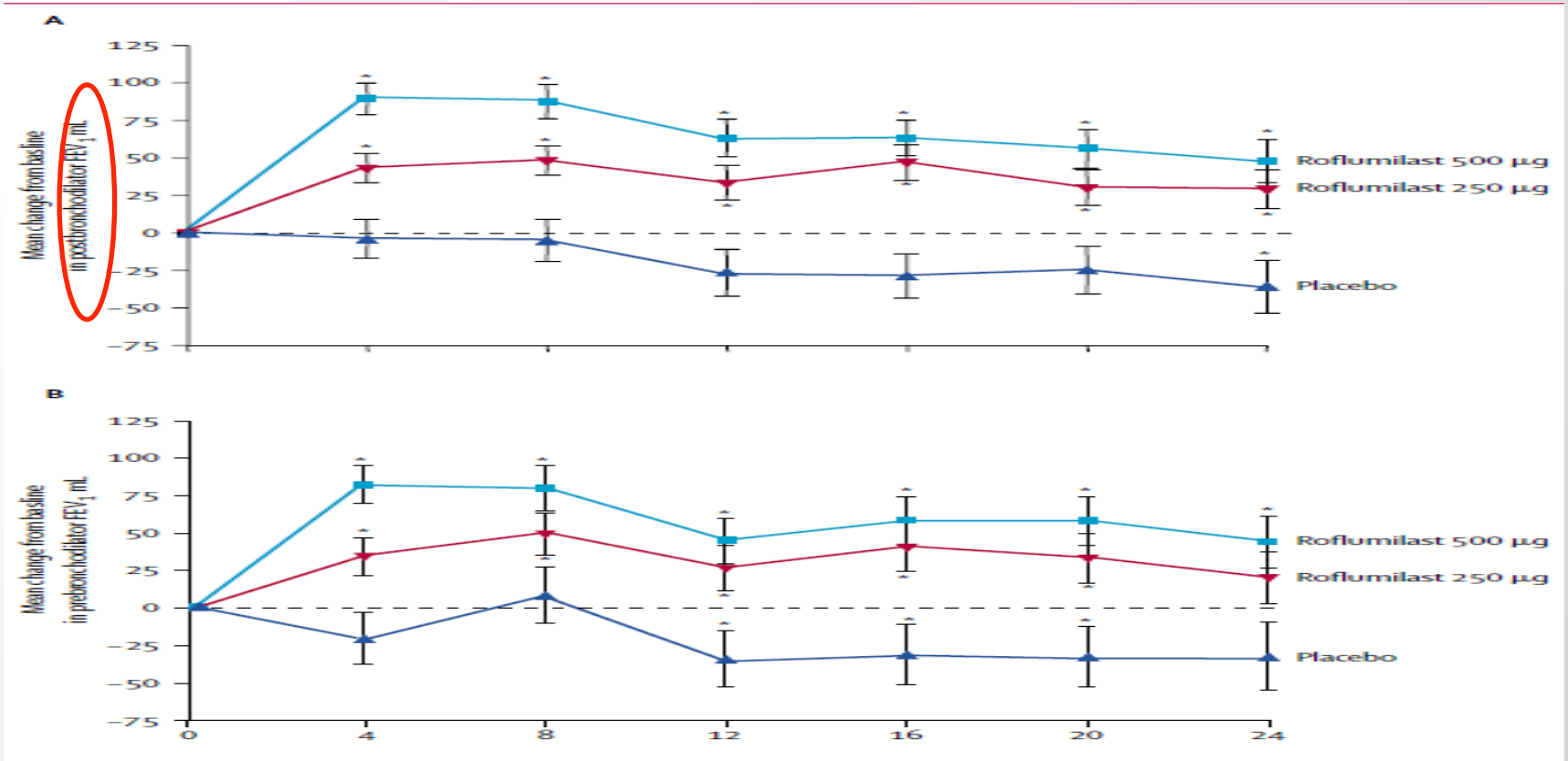
Ariflo™ (Glaxo Smith-Kline) Cilomilast		15 mg b.i.d. orally	**Phase III**
Roflumilast (Byk Gulden)		0.5 mg o.d. orally	**Phase II**
BAY 19-8004 (Bayer) Liromilast		5 mg o.d. orally	**Phase II**

Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial

Lancet 2005; 366: 563–71

Klaus F Rabe, Eric D Bateman, Denis O'Donnell, Stephan Witte, Dirk Bredenbröker, Thomas D Bethke

ESTUDIO EN FASE III. 1400 EPOC. 24 SEMANAS.R 250/500/Pb



Chronic Obstructive Pulmonary Disease Phenotypes

The Future of COPD

MeiLan K. Han[1], Alvar Agusti[3], Peter M. Calverley[4], Bartolome R. Celli[5], Gerard Criner[6], Jeffrey L. Curtis[1,7], Leonardo M. Fabbri[8], Jonathan G. Goldin[9], Paul W. Jones[10], William MacNee[11], Barry J. Make[12], Klaus F. Rabe[13], Stephen I. Rennard[14], Frank C. Sciurba[15], Edwin K. Silverman[5,16], Jørgen Vestbo[17], George R. Washko[5], Emiel F. M. Wouters[18], and Fernando J. Martinez[2]

POTENTIAL PHENOTYPES

COPD Exacerbations

patients with COPD with recurrent AECOPDs may reflect a distinct phenotypic group. This subgroup may be particularly relevant in consideration as a phenotype because it appears to be responsive to therapy with inhaled bronchodilators either alone or in combination with inhaled corticosteroids (39). Furthermore, a chronic bronchitic subgroup with sputum production and prior exacerbation history has recently identified a COPD cohort who experience improvement with the novel phosphodiesterase 4 inhibitor roflumilast (40). Here we have an example of targeting a drug for a specific COPD subpopulation that was identified by *post hoc* analysis of prospectively collected data from well-conducted clinical trials. This methodology may have value when considering variables not defined by therapeutic responses and is analogous to the widely adopted approach of identifying and then confirming genotypic information in replicate data sets. *Post hoc* analysis of well-done, prospective, placebo-controlled clinical trials conducted in patients with COPD with a range of disease severity and symptoms may be a fertile area in which to conduct responder analyses. This method of retrospective analysis may help to

Am J Respir Crit Care Med Vol 182. pp 598–604, 2010
Originally Published in Press as DOI: 10.1164/rccm.200912-1843CC on June 3, 2010
Internet address: www.atsjournals.org

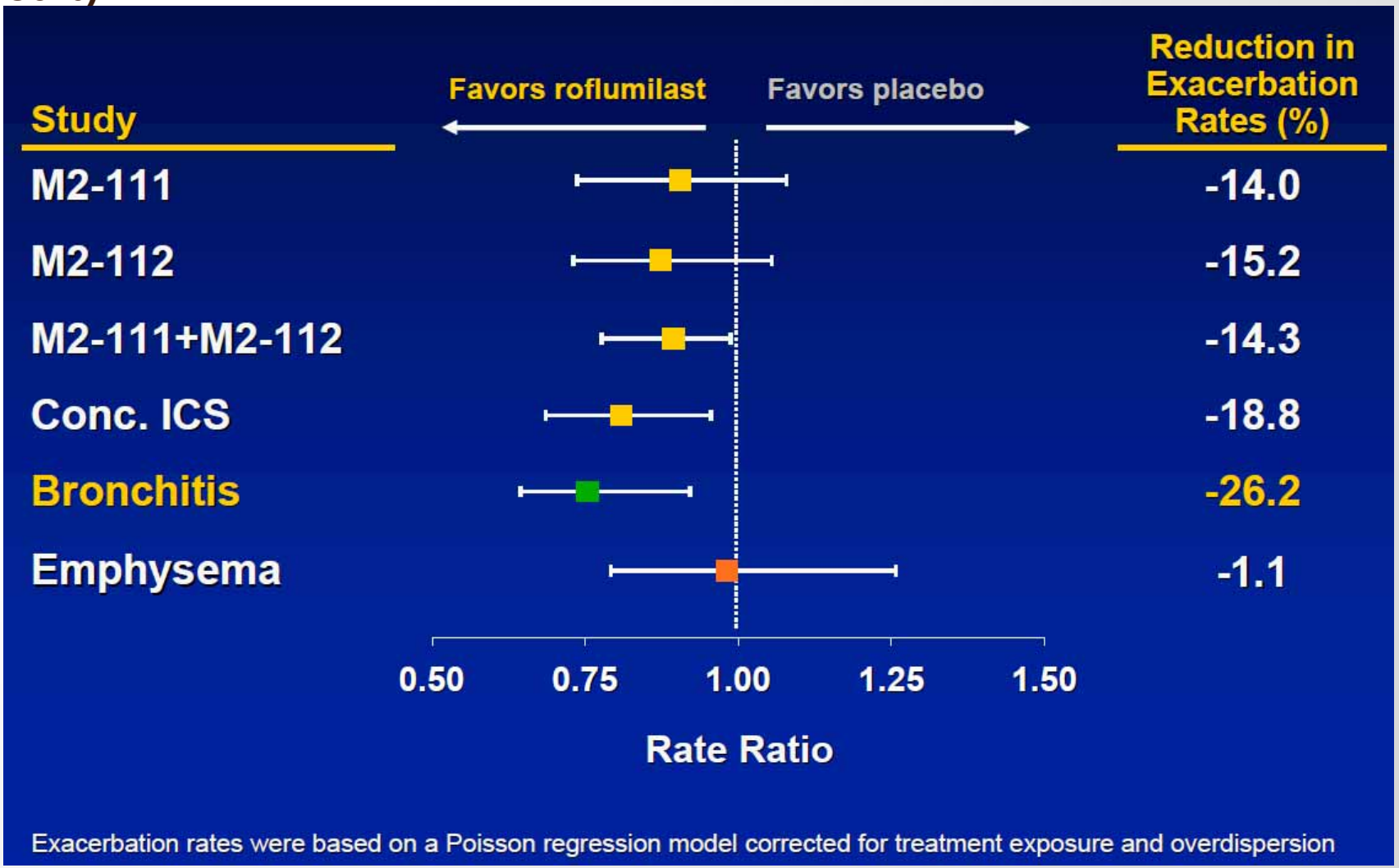
WHERE DO WE GO FROM HERE?

(59). In COPD, roflumilast was initially studied in a general COPD population, but it was ultimately determined that it is a subpopulation of patients ($FEV_1 < 50\%$ predicted, chronic cough, and sputum production) who demonstrate the greatest clinical response. Mechanistic studies, however, will be needed to understand the biologic basis for response in this subgroup.

En el desarrollo de Roflumilast se ha identificado un subgrupo (bronquítico crónico) que ha mostrado una mayor respuesta clínica

INHIBIDORES DE LA FOSFODIESTERASA 4 (PDE4)

Estudios M2-111/112: 52 semanas de seguimiento. EPOC grave (FEV1 ≤ 50%)



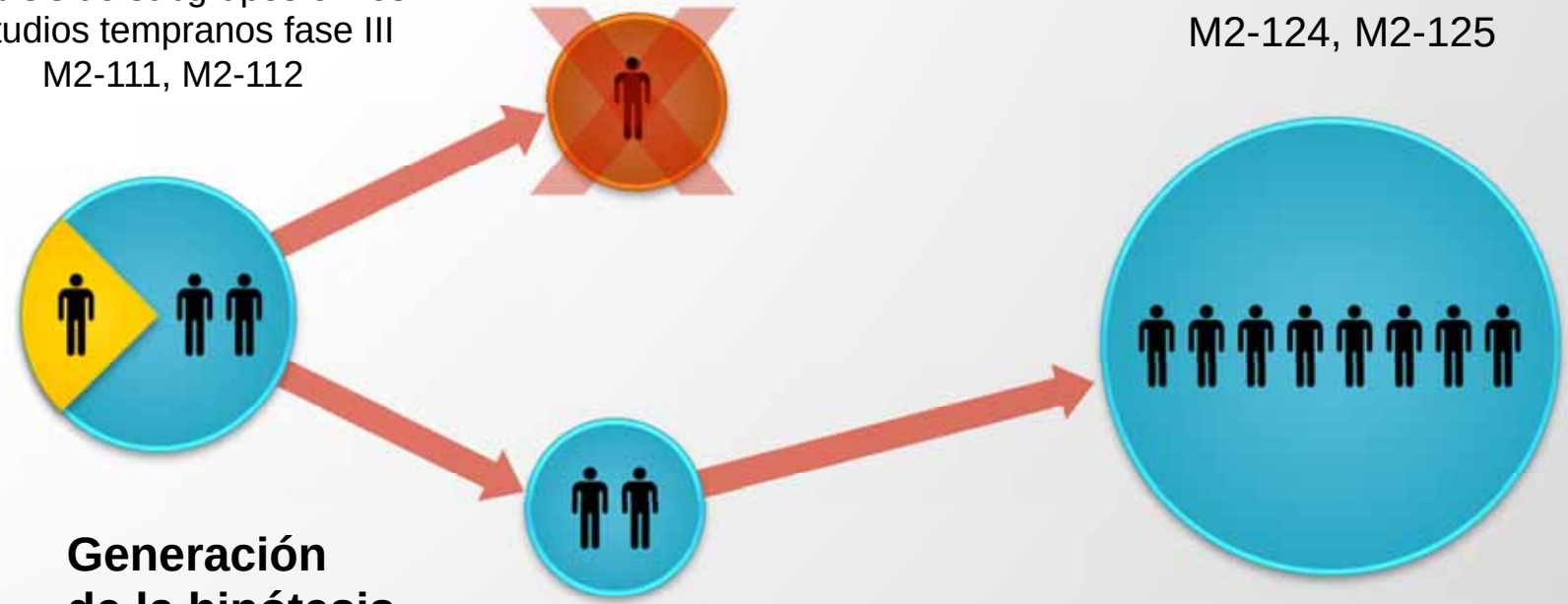
Fuente: Daxas ® 22-(roflumilast) Tablets NDA 22 522 Pulmonary- Allergy Drugs Advisory Committee Meeting April 7, 2010
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM208711.pdf

EVOLUCIÓN DEL PROGRAMA CLÍNICO DE ROFLUMILAST

IDENTIFICACIÓN DE LA POBLACIÓN OBJETIVO DE PACIENTES

Análisis de subgrupos en los estudios tempranos fase III
M2-111, M2-112

Estudios pivotales confirmatorios de 1 año de duración
M2-124, M2-125



Generación de la hipótesis

- **Pacientes con enfermedad grave/ muy grave**
- **Antecedentes de tos crónica y expectoriación**
- **Antecedentes de exacerbaciones**

Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Peter M A Calverley, Klaus F Rabe*, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri†, Fernando J Martinez†, for the M2-124 and M2-125 study groups‡*

ROFLUMILAST vs PLACEBO
EPOC GRAVE
EXACERBADORES
BRONQUITIS CRONICA

Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials

Leonardo M Fabbri, Peter M A Calverley*, José Luis Izquierdo-Alonso, Daniela S Bundschuh, Manja Brose, Fernando J Martinez†, Klaus F Rabe†, for the M2-127 and M2-128 study groups‡*

M2-127 SALMETEROL + ROFLUMILAST o Pb
M2-128 TIOTROPIO + ROFLUMILAST o Pb

Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Lancet 2009; 374: 685–94

Peter M A Calverley*, Klaus F Rabe*, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri†, Fernando J Martinez†, for the M2-124 and M2-125 study groups‡

- EL CAMBIO EN EL FEV1 FUE INDEPENDIENTE DEL USO DE LABAS

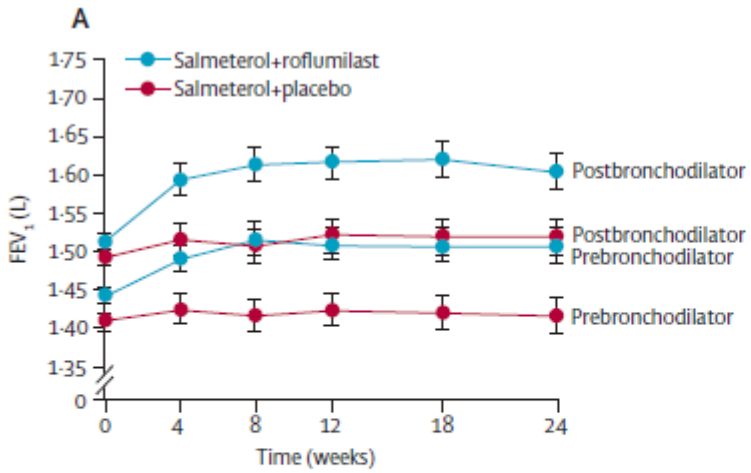
- REDUCCION DE EXACERBACIONES CON ROFLUMILAST EN UN 17 % (OR 83%; IC 95% 0.75-0.92; P<0.0003)

- AUMENTO DEL PERIODO LIBRE DE EXACERBACIONES (P<00.2)

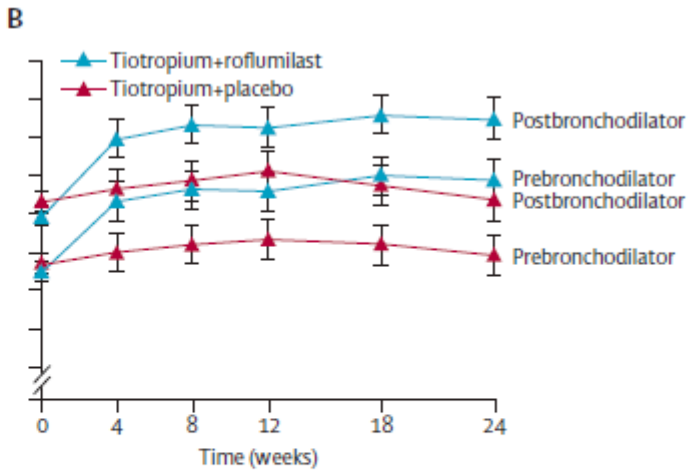
Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials

Lancet 2009; 374: 695–703

Leonardo M Fabbri, Peter M A Calverley*, José Luis Izquierdo-Alonso, Daniela S Bundschuh, Manja Brose, Fernando J Martinez†, Klaus F Rabe†, for the M2-127 and M2-128 study groups‡*



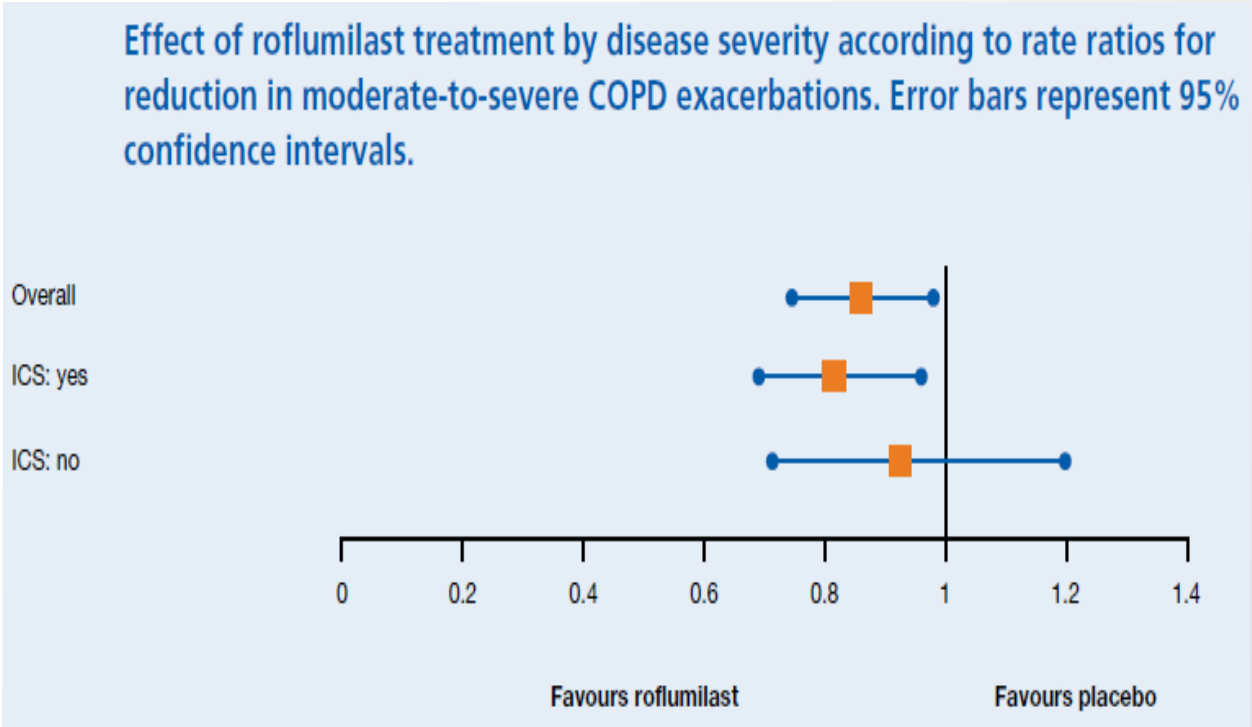
Number at risk*						
Prebronchodilator						
Salmeterol+roflumilast	466	455	410	389	374	359
Salmeterol+placebo	467	463	437	419	403	384
Postbronchodilator						
Salmeterol+roflumilast	466	450	410	387	372	359
Salmeterol+placebo	467	459	435	418	401	383



Number at risk*						
Prebronchodilator						
Tiotropium+roflumilast	371	364	343	325	318	310
Tiotropium+placebo	372	363	352	350	346	333
Postbronchodilator						
Tiotropium+roflumilast	371	363	341	323	316	310
Tiotropium+placebo	370	361	352	349	345	333

ROFLUMILAST REDUJO LA TASA DE EXACERBACIONES SOBRE EL EFECTO DEL CSI

- **Análisis *post-hoc* conjunto de los estudios M2-111 y M2-112**



Reducción en la tasa de exacerbaciones (%)

Población total	Población BC*
-14.3 (p=0.026)	-26.2 (p=0.001)
-18.8 (p=0.014)	-30.2 (p=0.001)
-7.7 (p=0.55)	-15.5 (p=0.31)

* BC: Bronquitis Crónica

Martinez FJ, Calverley PMA, Goehring UM, et al. COPD7 **2010; resumen 12.** Disponible en: www.copdconferences.org

ICS: corticoesteroide inhalado

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

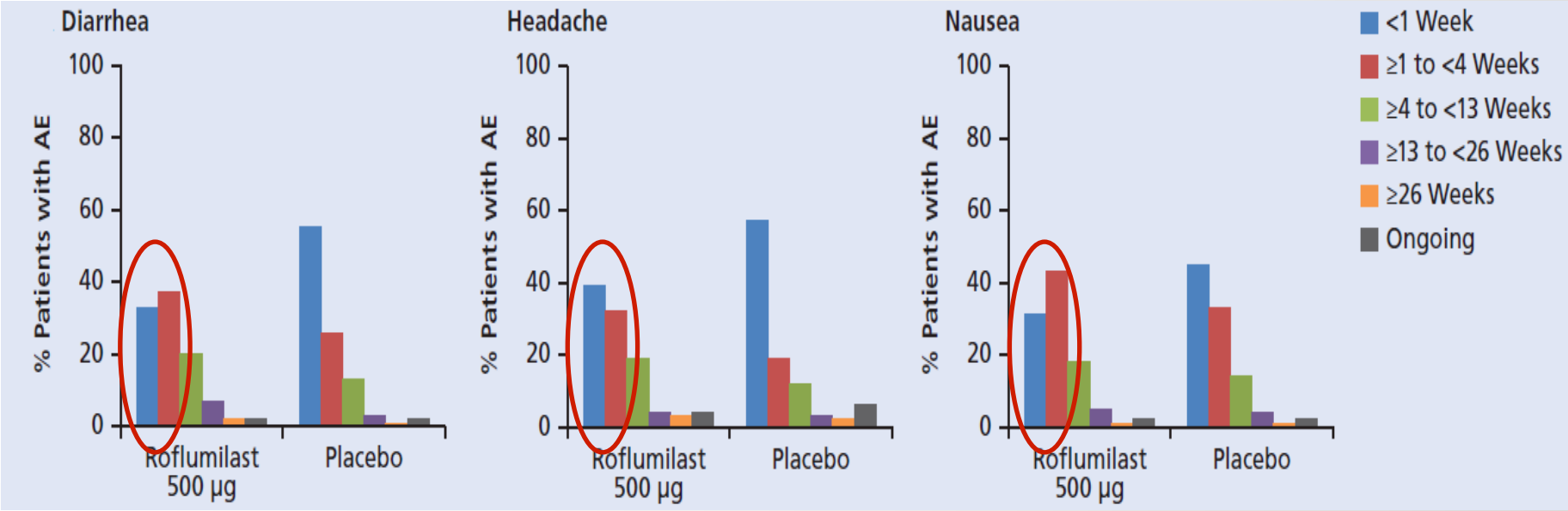
ORIGINAL RESEARCH

Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis

This article was published in the following Dove Press journal:
Clinical Epidemiology
25 March 2011
Number of times this article has been viewed

Treatment	Absolute treatment effect	95% CI
Placebo	1.20	(1.17, 1.23)
Roflumilast	1.01	(0.89, 1.14)
LABA	1.04	(0.96, 1.12)
LAMA	0.89	(0.81, 0.98)
ICS	0.98	(0.91, 1.06)
Roflumilast + LABA	0.87	(0.75, 1.01)
Roflumilast + LAMA	0.75	(0.64, 0.87)
Roflumilast + ICS	0.82	(0.71, 0.95)
LABA + LAMA	0.77	(0.67, 0.87)
LABA + ICS	0.85	(0.77, 0.94)
LAMA + ICS	0.73	(0.64, 0.82)
Roflumilast + LABA + LAMA	0.65	(0.54, 0.77)
Roflumilast + LABA + ICS	0.71	(0.61, 0.83)
LAMA + LABA + ICS	0.63	(0.54, 0.73)
Roflumilast + LABA + LAMA + ICS	0.53	(0.43, 0.64)

ROFLUMILAST: DURACIÓN DE LOS ACONTECIMIENTOS ADVERSOS MÁS FRECUENTES



- **Pefil de efectos secundarios diferente al de otros fármacos utilizados para el tratamiento de la EPOC (i.e. broncodilatadores)**
- **Habitualmente transitorios: aprox. 80% remitieron en 4 semanas de tratamiento**

Gross N et al. Chest 2010; 138:466A

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

Chong J, Poole P, Leung B, Black PN

THE COCHRANE COLLABORATION®

Authors' conclusions

In people with COPD, PDE_4 inhibitors offered benefit over placebo in improving lung function and reducing likelihood of exacerbations, however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common. The optimum place of PDE_4 inhibitors in COPD management remains to be defined. Longer-term trials are needed to determine whether or not PDE_4 inhibitors modify FEV_1 decline, healthcare utilisation or mortality in COPD.

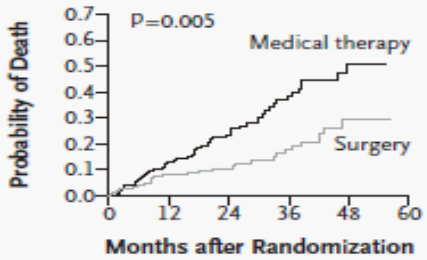
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 22, 2003 VOL. 348 NO. 21

A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

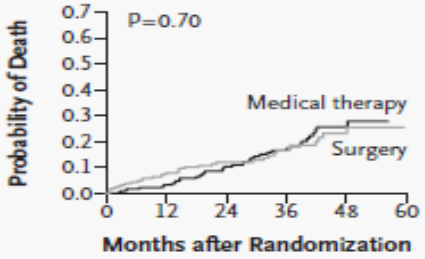
National Emphysema Treatment Trial Research Group*

D Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)



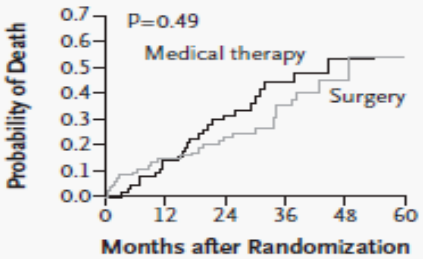
No. at Risk					
Surgery	139	121	93	61	17
Medical therapy	151	120	85	43	13

E Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=419)



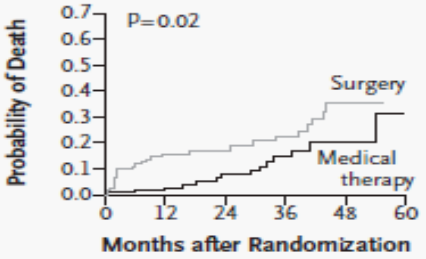
No. at Risk					
Surgery	206	176	124	82	35
Medical therapy	213	192	149	104	35

F Non–Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=149)



No. at Risk					
Surgery	84	67	52	28	6
Medical therapy	65	55	36	17	5

G Non–Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=220)



No. at Risk					
Surgery	109	83	71	43	12
Medical therapy	111	96	69	40	17

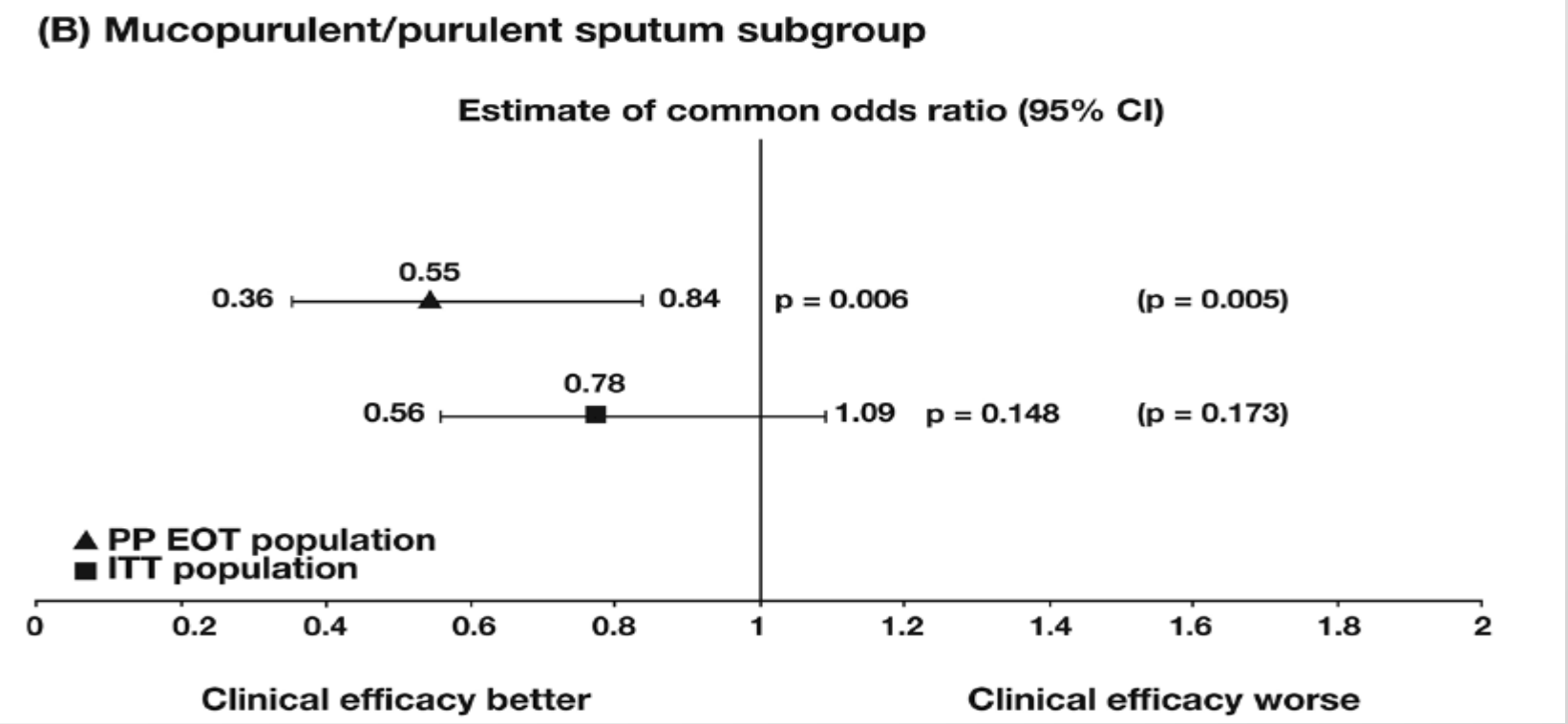
Sethi *et al. Respiratory Research* 2010, **11**:10
http://respiratory-research.com/content/11/1/10

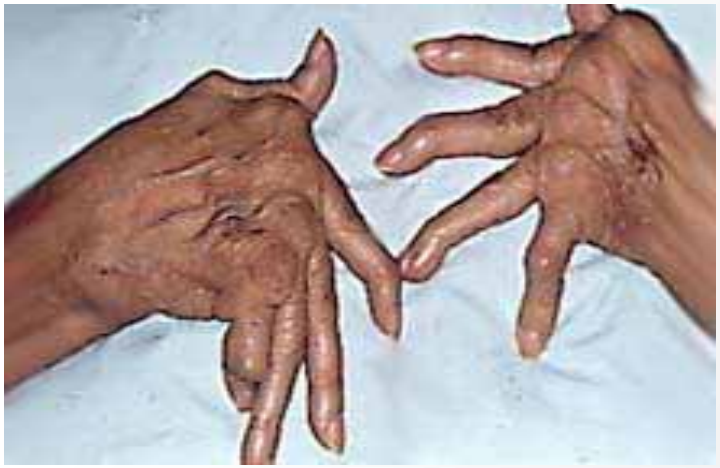
RESPIRATORY RESEARCH

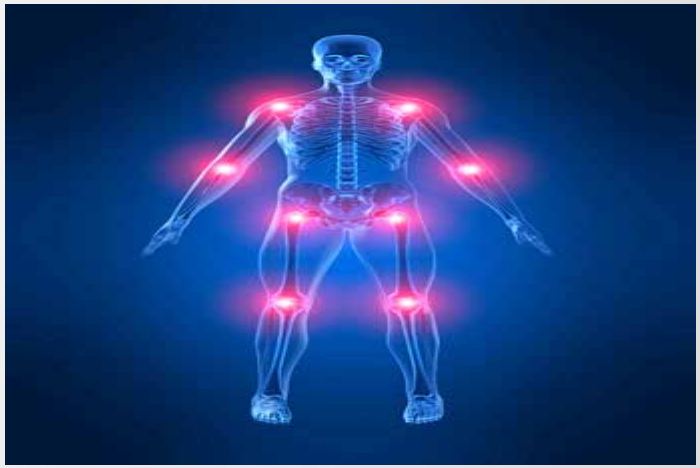
RESEARCH Open Access

Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial

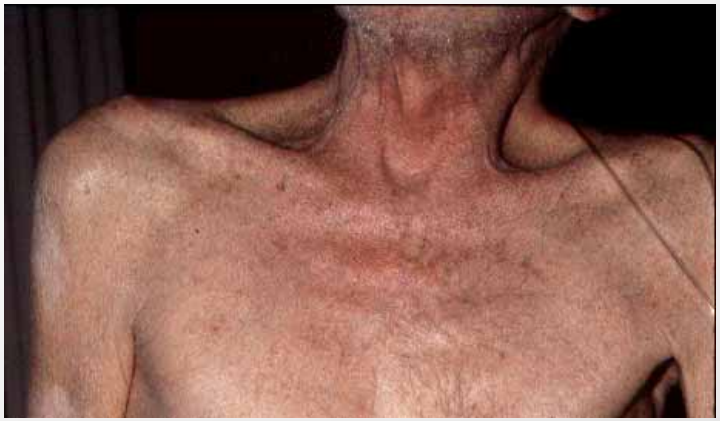
Sanjay Sethi[1*], Paul W Jones[2], Marlize Schmitt Theron[3], Marc Miravitlles[4], Ethan Rubinstein[5], Jadwiga A Wedzicha[6], Robert Wilson[7], the PULSE Study group

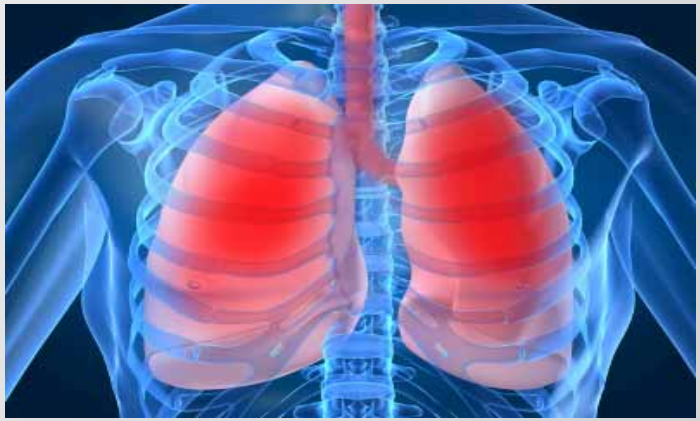






GRAVEDAD ≠ ACTIVIDAD

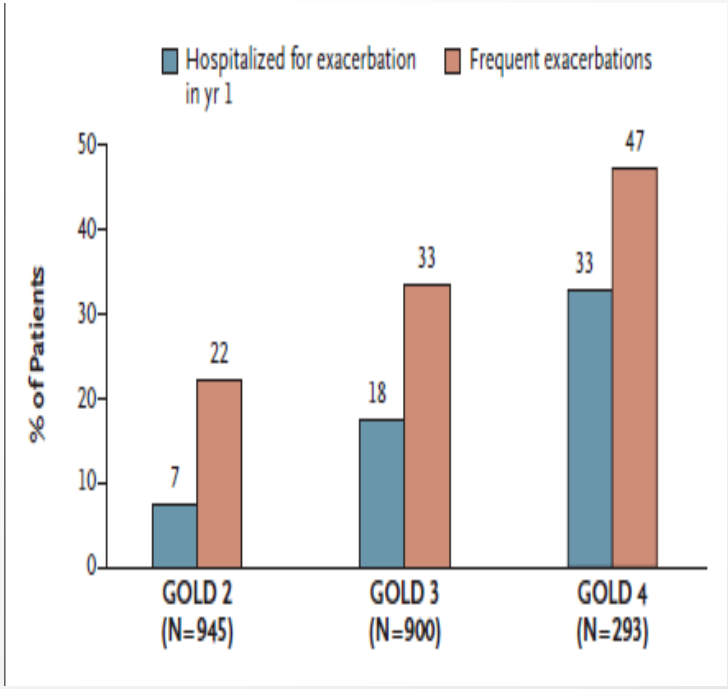


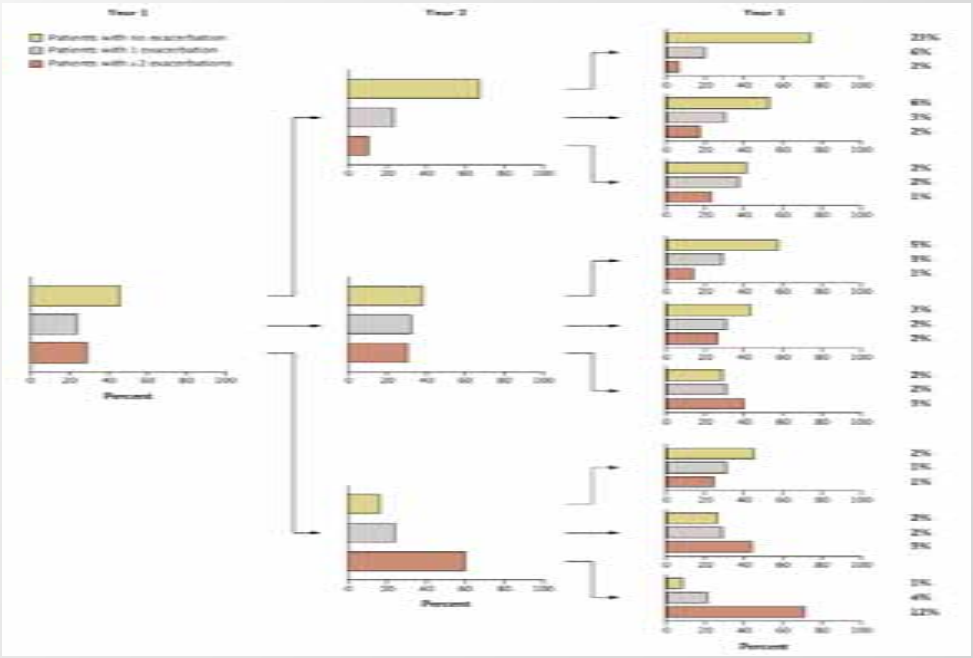


The NEW ENGLAND JOURNAL of MEDICINE

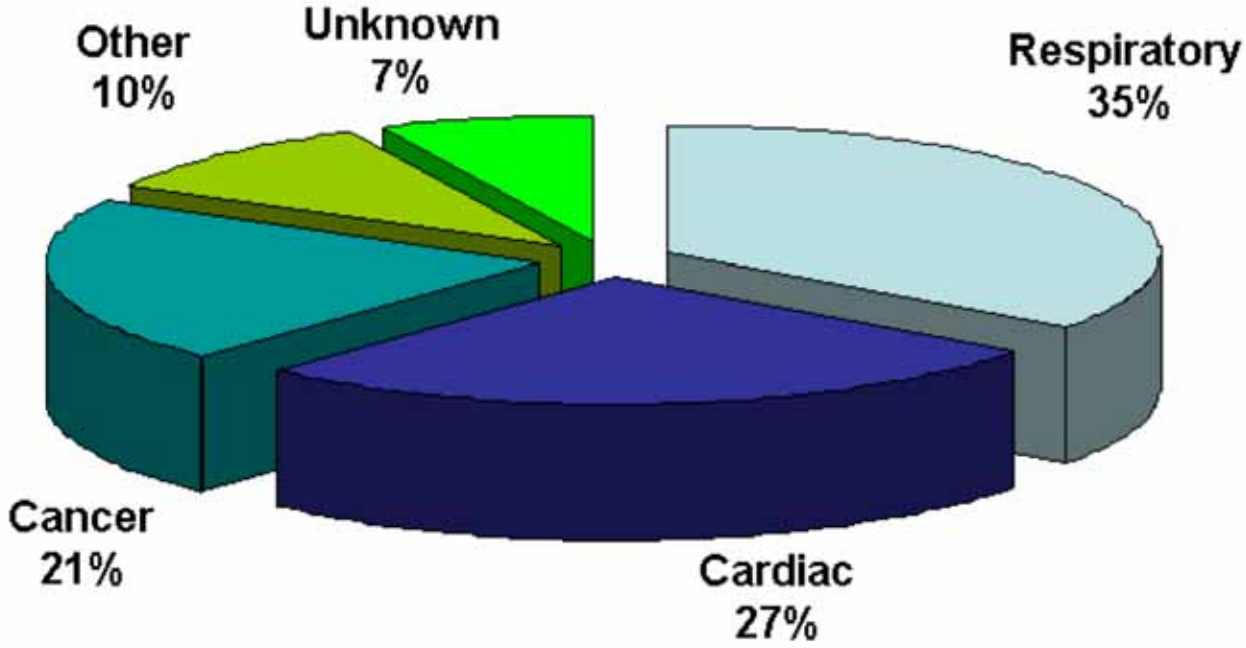
ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease





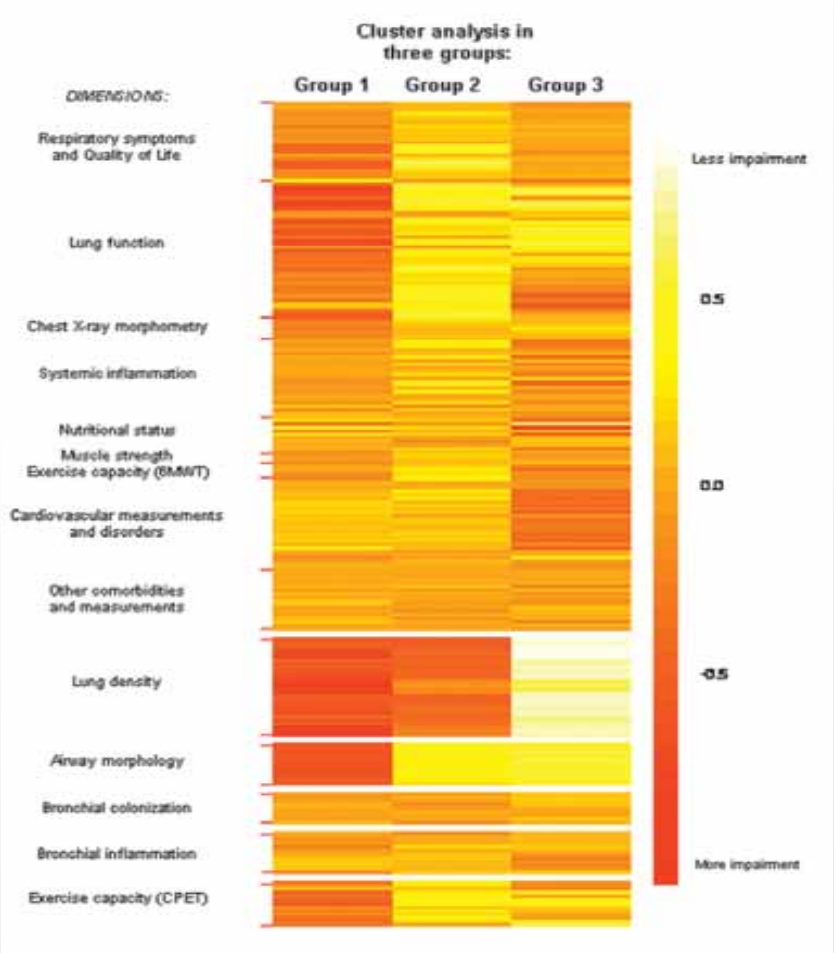
Overall Causes of Death in COPD Patients*



*as adjudicated by the TORCH Clinical Endpoint Committee

Calverley et al. NEJM 2007; 356:775-89.

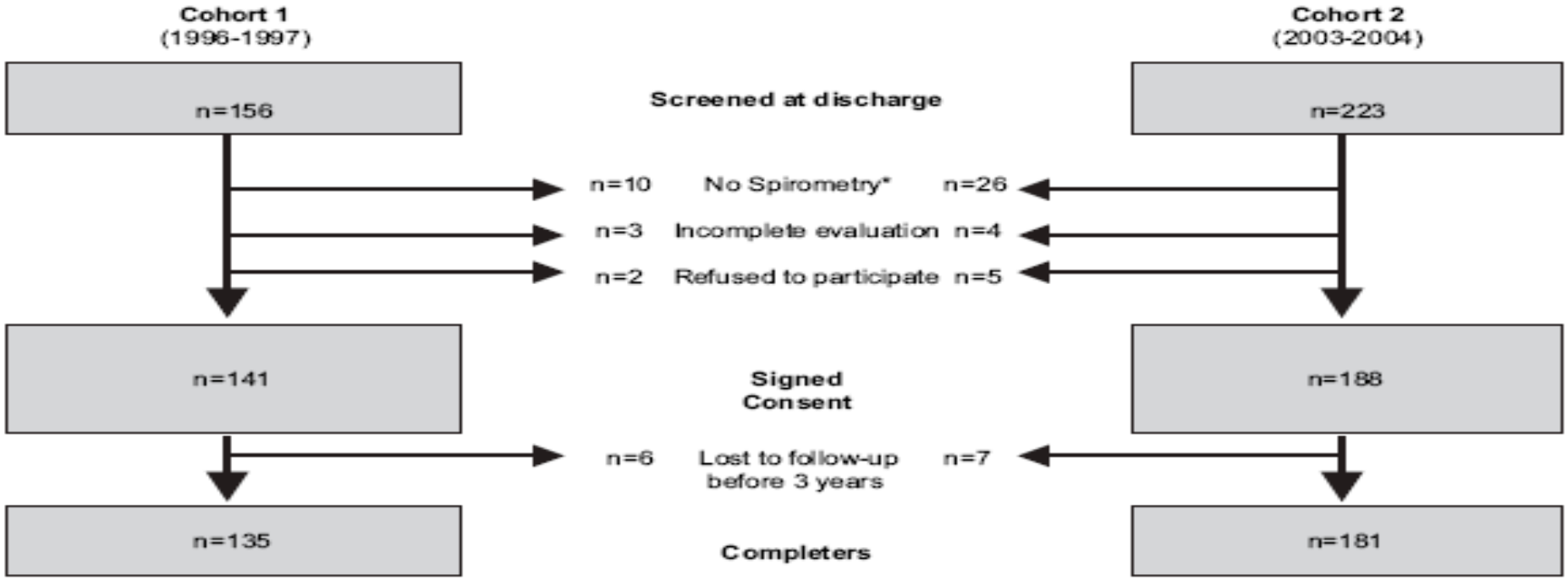
Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes



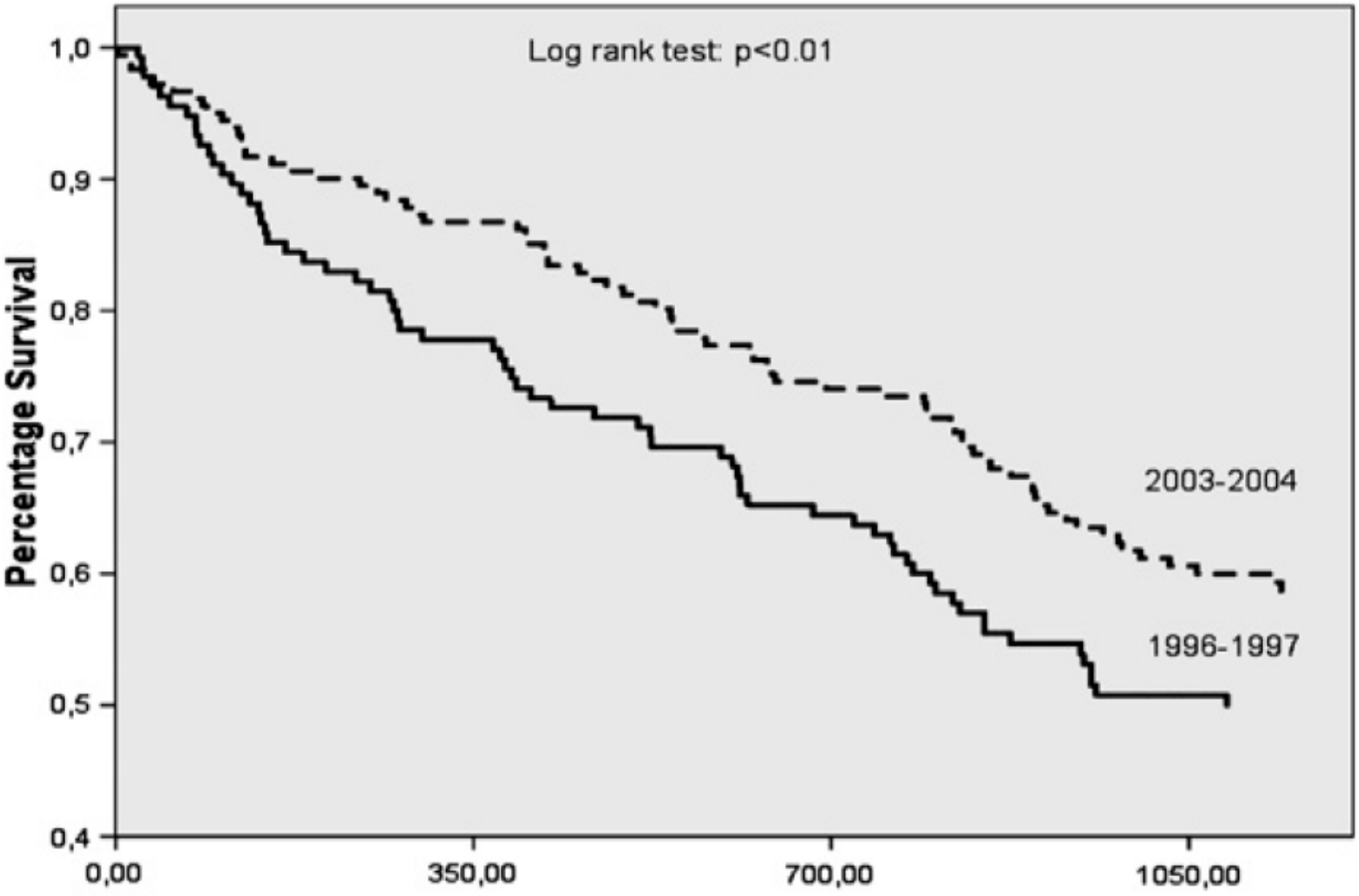
In conclusion, in patients with COPD recruited at their first hospitalisation, three different COPD subtypes have been identified and prospectively validated, which we propose to label as 'severe respiratory COPD', 'moderate respiratory COPD', and 'systemic COPD'.

Recent improvement in long-term survival after a COPD hospitalisation

Pere Almagro,[1] M Salvadó,[1] C Garcia-Vidal,[1] M Rodriguez-Carballeira,[1] M Delgado,[1] B Barreiro,[2] J L Heredia,[2] Joan B Soriano[3]



Almagro P, et al. Thorax 2010



Almagro P, et al. Thorax 2010

Table 3 Distribution of selected co-morbidities, by cohort

	1996–7 n (%)	2003–4 n (%)	p Value
Ischaemic heart disease	20 (15)	33 (18)	0.4
Heart failure	43 (32)	46 (26)	0.3
Stroke	11 (8.3)	9 (5.1)	0.4
Diabetes mellitus	18 (13.5)	29 (16.4)	0.5
Kidney failure	6 (4.5)	8 (4.5)	1
Cancer	6 (4.5)	15 (8.5)	0.1
Liver cirrhosis	4 (3)	9 (5)	0.3
Charlson index±SD	2.22±1.06	2.19±1.34	0.84

ables by cohort

	996—7	2003—04	p Value
	2.3±9.2	72.0±9.8	0.8
	24 (92%)	172 (95%)	0.5
			0.02
	8 (17%)	41 (23%)	
	6 (73%)	132 (75%)	
	4 (10%)	3 (2%)	
	02 (76%)	120 (75.5%)	1
			0.6
	4	19	
	0.4%)	(12.0%)	
	18	135	
	(88.1%)	(84.9%)	

Institutionalised
BMI±SD
Charlson index±SD
Yesavage index±SD
Functional status (Katz) ±SD
COPD in the previous 12 month
No. of hospitalisations*
ER visits*
Days of stay±SD
COPD hospitalisations in the ne
12 months*

*Median (IQR; 25—75%).
BMI, body mass index; COPD, cl

Table 4 Treatment at discharge, by cohort

	1996–7 %	2003–4 %	p Value
Short-acting β_2 agonists	97.6	78.5	0.0001
Long-acting β_2 agonists	1.2	77.9	0.0001
Ipratropium bromide	89	58.1	0.0001
Tiotropium	0	33.1	0.0001
Inhaled corticosteroids	87.4	84.9	0.3
Chronic systemic corticosteroids	2.4	2.3	0.6
Statins	1.6	16.9	0.001
ACE inhibitors	27.6	27.3	0.5
Angiotensin II receptor antagonists	0	7.6	0.001
β-Blockers	1.6	5.8	0.057
Antiplatelet drugs	16.5	30.2	0.004

Respiratory Research

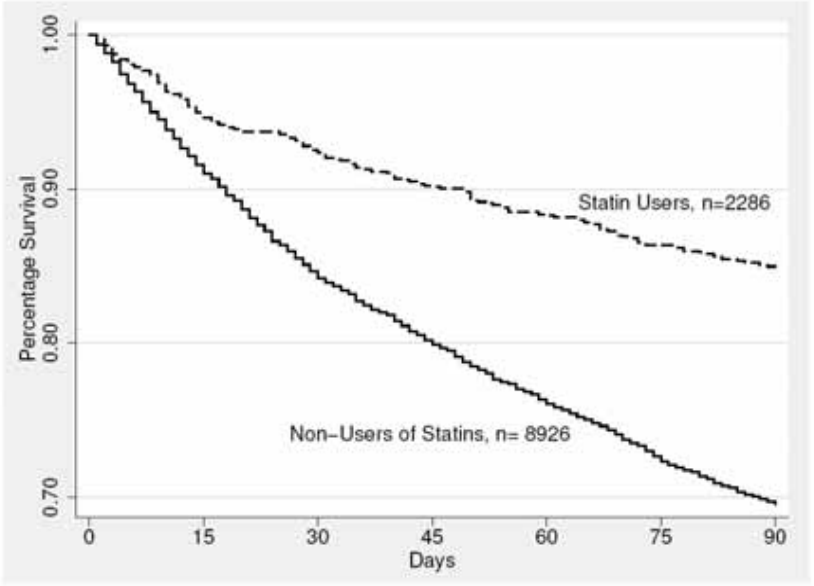
BioMed Central

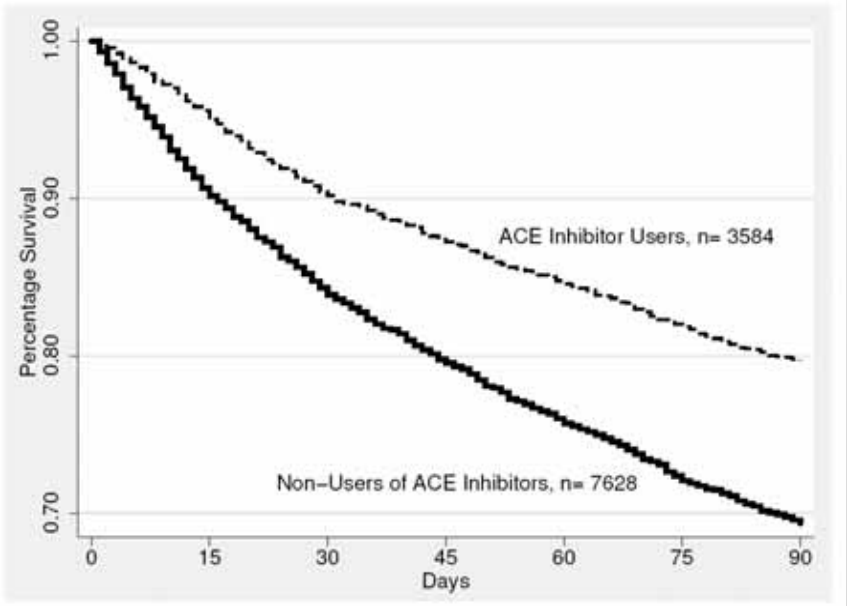
Research

Open Access

Impact of statins and ACE inhibitors on mortality after COPD exacerbations

Eric M Mortensen*[1,2], Laurel A Copeland[1,3], Mary Jo V Pugh[1,4], Marcos I Restrepo[1,5], Rosa Malo de Molina[1,5], Brandy Nakashima[1] and Antonio Anzueto[1,5]





	O.R.	95 % C.I.
IECA /ARAII	0.62	0.53-0.73
ESTATINAS	0.49	0.39-0.61
AMBOS	0.40	0.32-0.52


Gracias