

Investigación en terapéutica de la EPOC

JB Soriano

**Programa de Epidemiología e Investigación Clínica,
CIMERA, Bunyola, Islas Baleares**



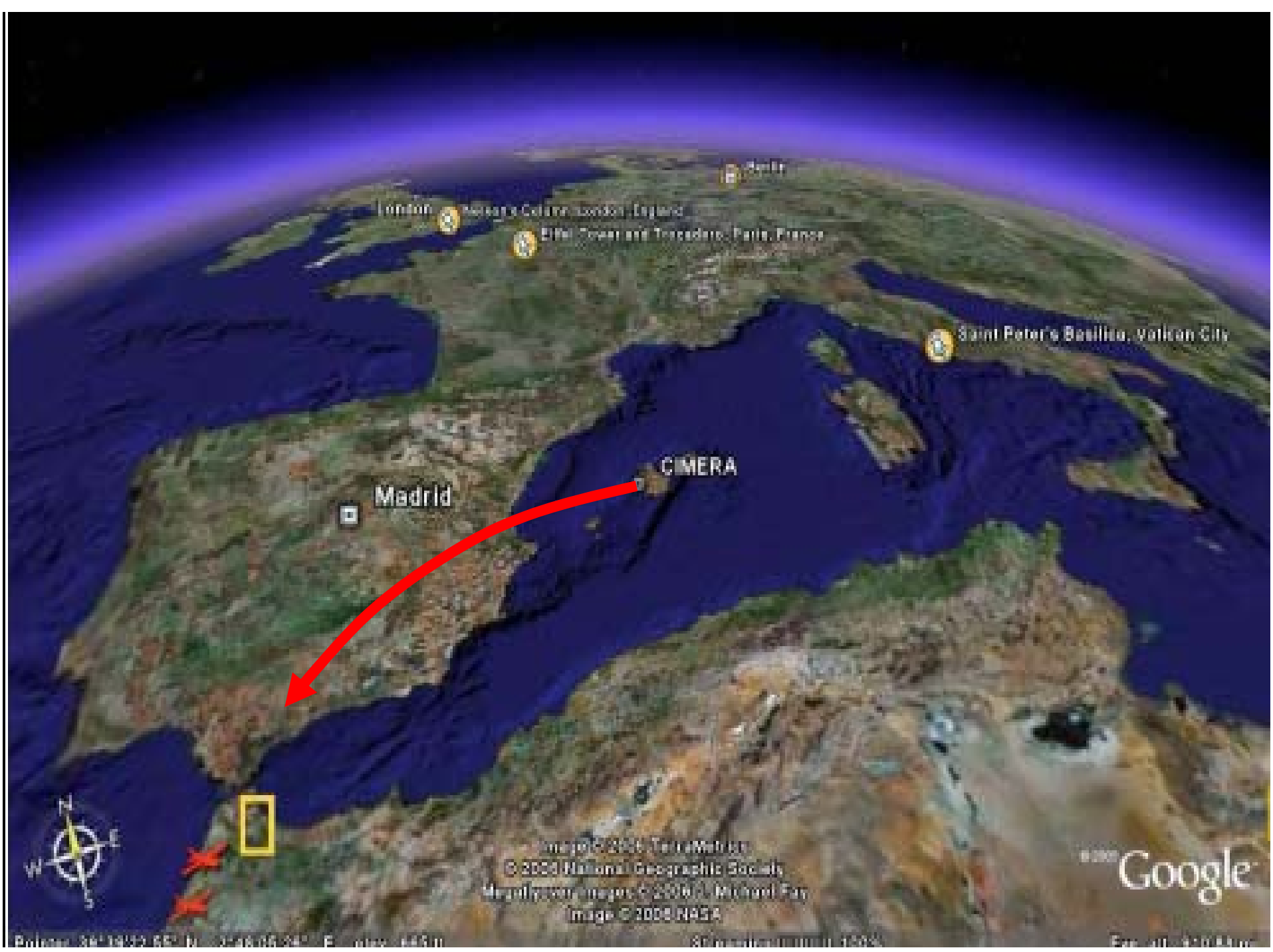
**SEMI**
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

**Grupo de EPOC**
Instituto de Diagnóstico y Referencia Epidemiológica

**HcA**
Hospital Comarcal de la Axarquía

**IV Reunión
de EPOC**

12-14 Marzo de 2009
Hotel Husa Mainake
Torre del Mar (Málaga)



London

Big Ben, London, England

Eiffel Tower and Trocadero, Paris, France

Saint Peter's Basilica, Vatican City

Madrid

CIMERA



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Hoy

- **Semiología: 40 años de ensayos terapéuticos en EPOC**
- **La pregunta: ¿Mejoran los tratamientos la vida de los pacientes con EPOC?**

Artículos más referenciados en la EPOC (1998 - 2008)

1999 - 2003

- 827** **Burge PS, et al** Randomised double blinde, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE study. (BMJ, 2000)
- 605** **Plant PK, et al** Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a randomised controlled trial (Lancet, 2000)
- 495** **Vestbo, et al** Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randmised controlled trial (Lancet, 1999)
- 461** **Casaburi, et al** A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease (ERJ, 2002)
- 460** **Calverley, et al** Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. (Lancet, 2003)

CSI

VNI

CSI

Tiotropio

LABA / CSI

2004 - 2008

- 579** **Celli BR, et al** The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease (NEJM, 2004)
- 506** **Hogg JC, et al** The nature of small-airway obstruction in chronic obstructive pulmonary disease (NEJM , 2004)
- 205** **Anthonisen, et al** The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial (Ann Int Med, 2005)
- 182** **Calverley, et al** Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. (NEJM, 2007)
- 144** **Ito, et al** Decreased histone deacetylase activity in chronic obstructive pulmonary disease (NEJM, 2005)

BODE

A. Patológ.

Tabaquismo

LABA/ CSI

Histonas



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

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D.,
Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

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OCTOBER 9, 2008

VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive
Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D.,
Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

Annals of Internal Medicine

ARTICLE

**Tiotropium in Combination with Placebo, Salmeterol, or
Fluticasone–Salmeterol for Treatment of Chronic Obstructive
Pulmonary Disease**

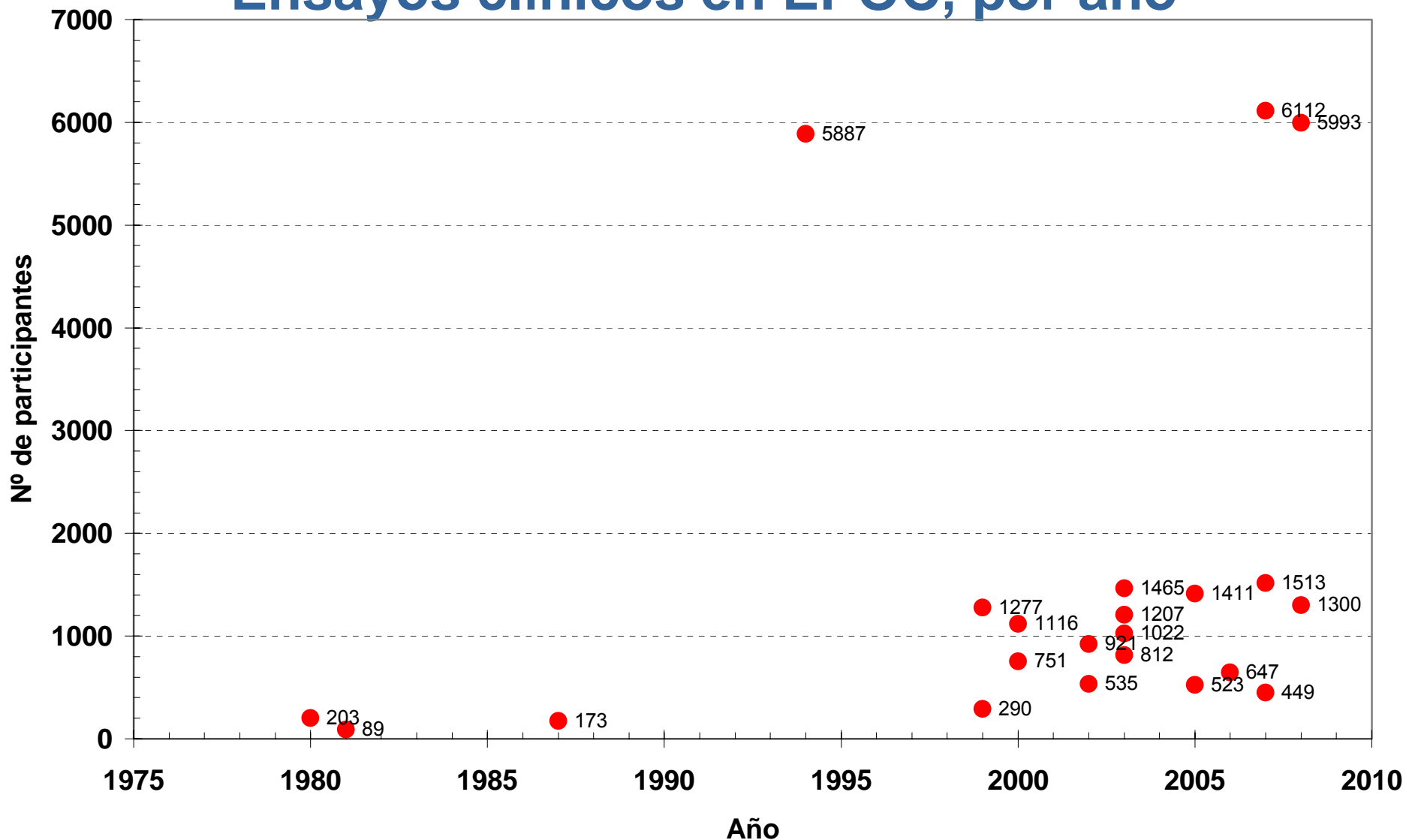
A Randomized Trial

**The Prevention of Chronic Obstructive Pulmonary
Disease Exacerbations by Salmeterol/Fluticasone
Propionate or Tiotropium Bromide**

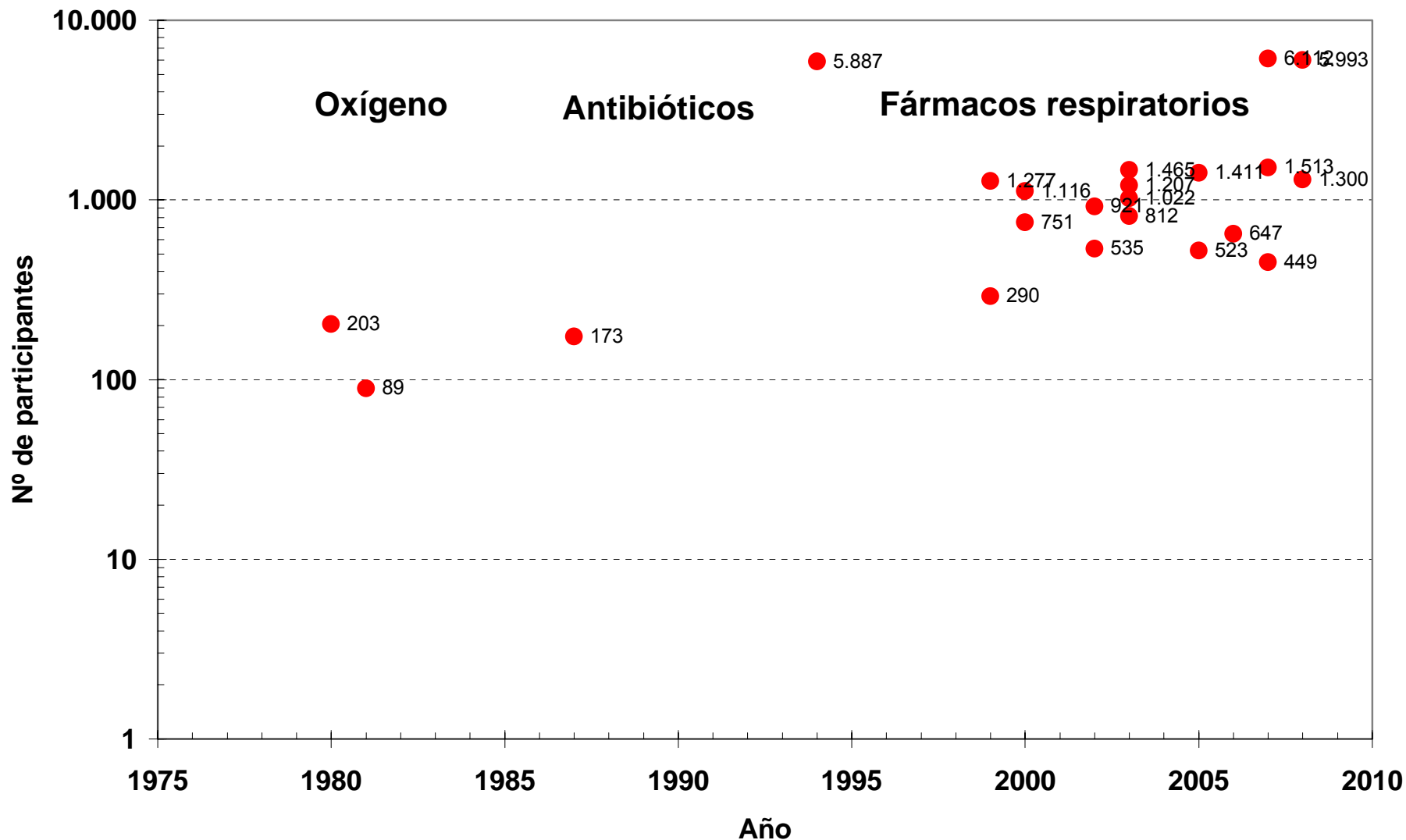
Jadwiga A. Wedzicha¹, Peter M. A. Calverley², Terence A. Seemungal³, Gerry Hagan⁴, Zainab Ansari⁴, and
Robert A. Stockley⁵, for the INSPIRE Investigators

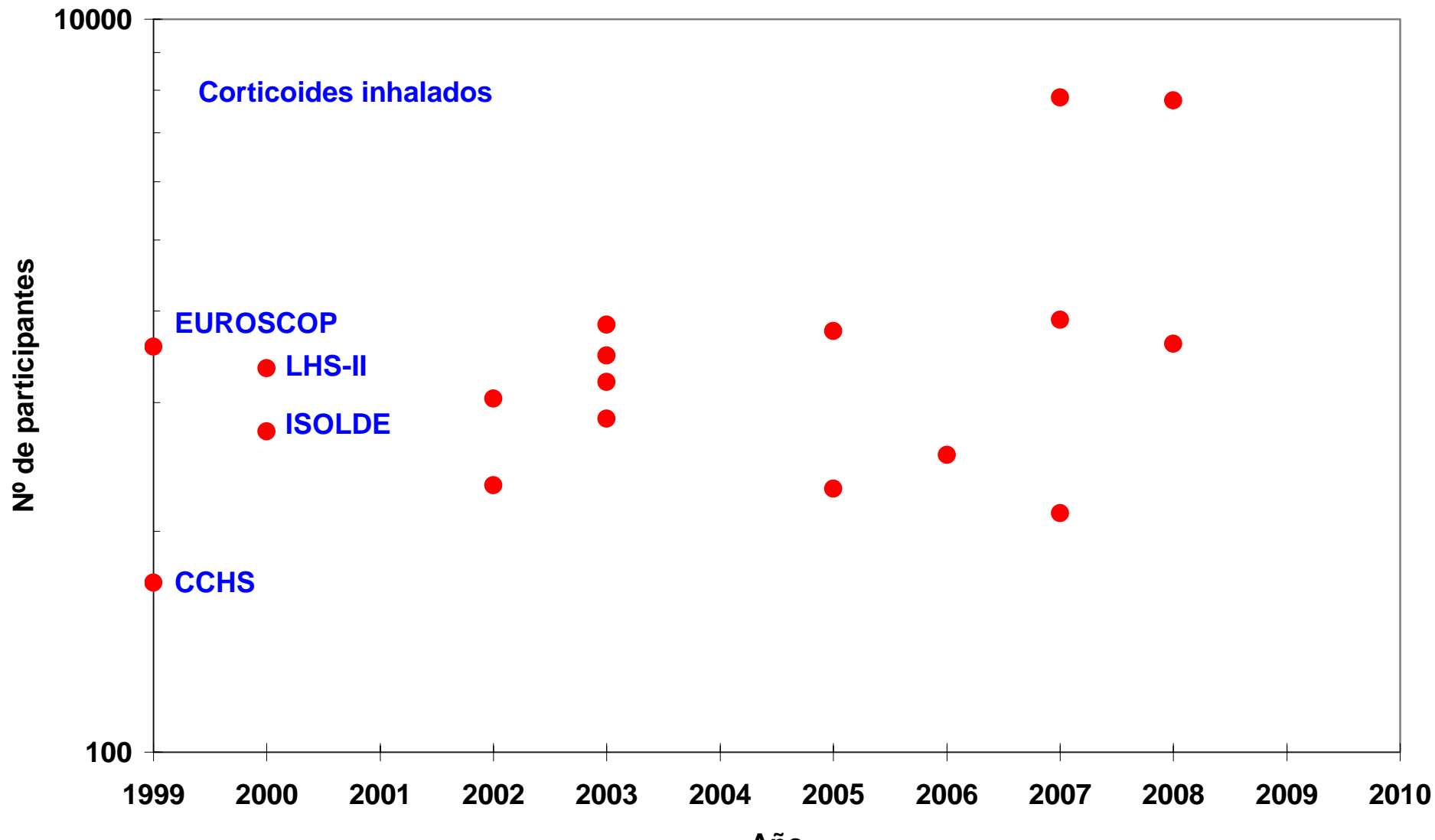
Am J Respir Crit Care Med 2008; 177: 19-26

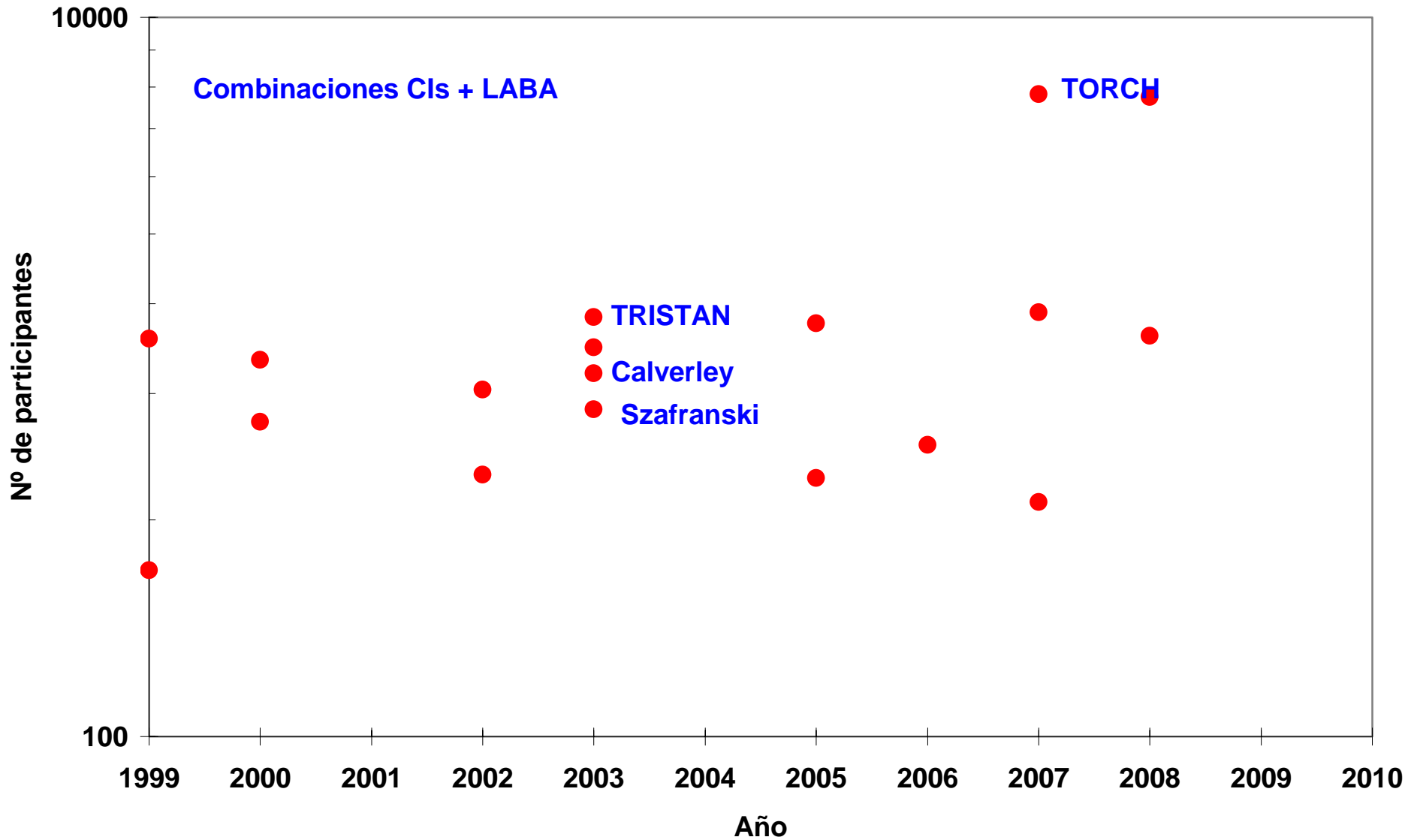
Ensayos clínicos en EPOC, por año

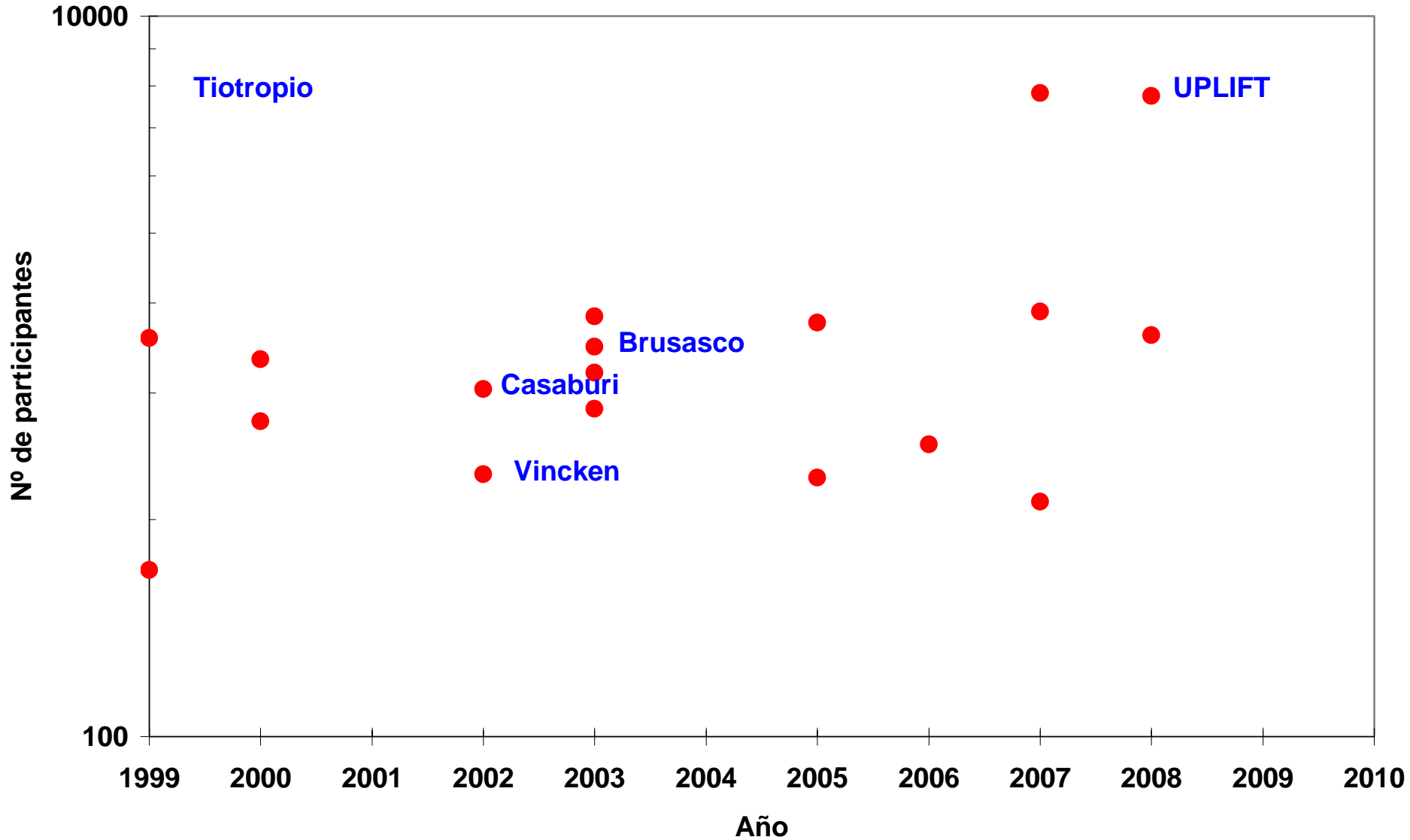


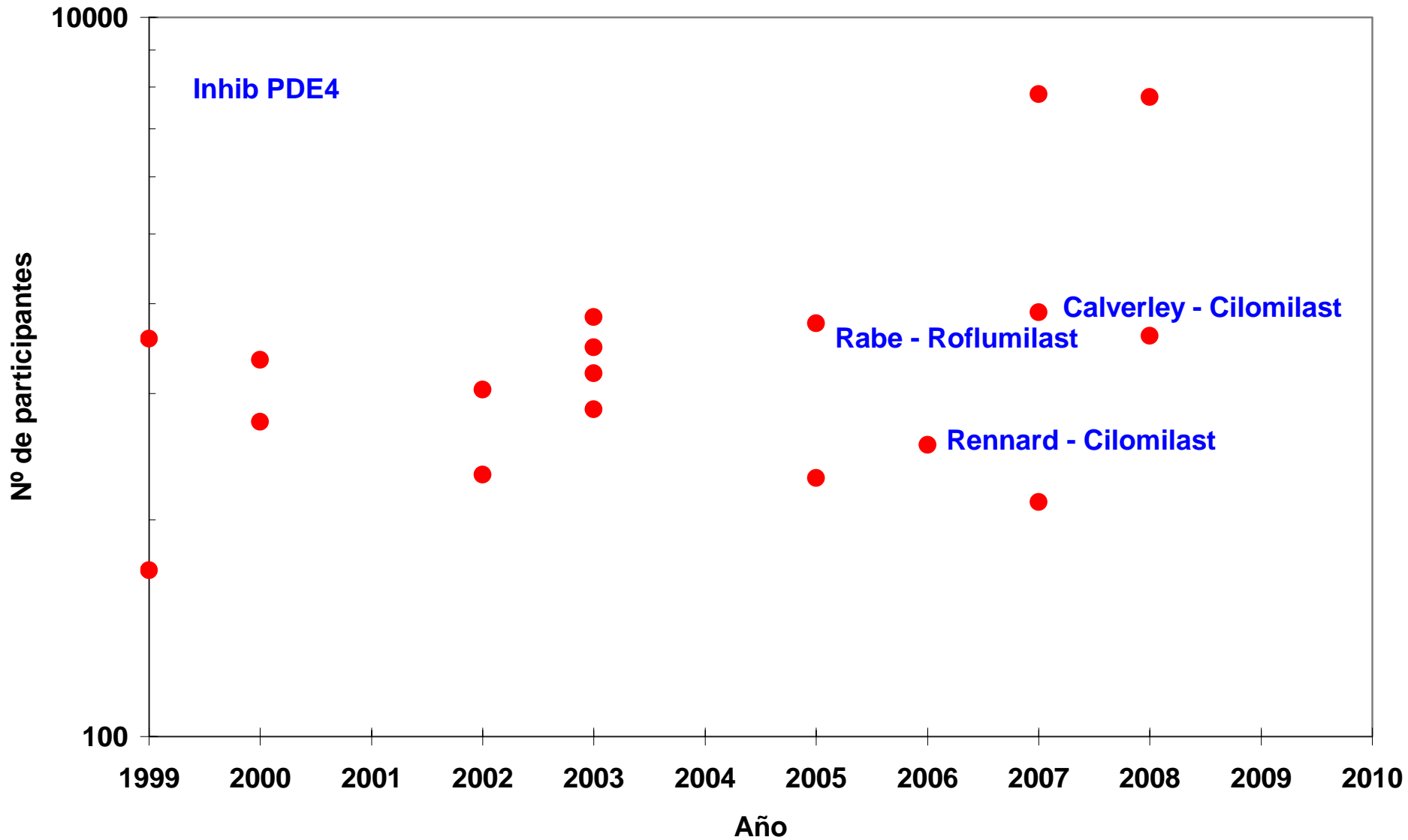
Ensayos clínicos en EPOC, por año

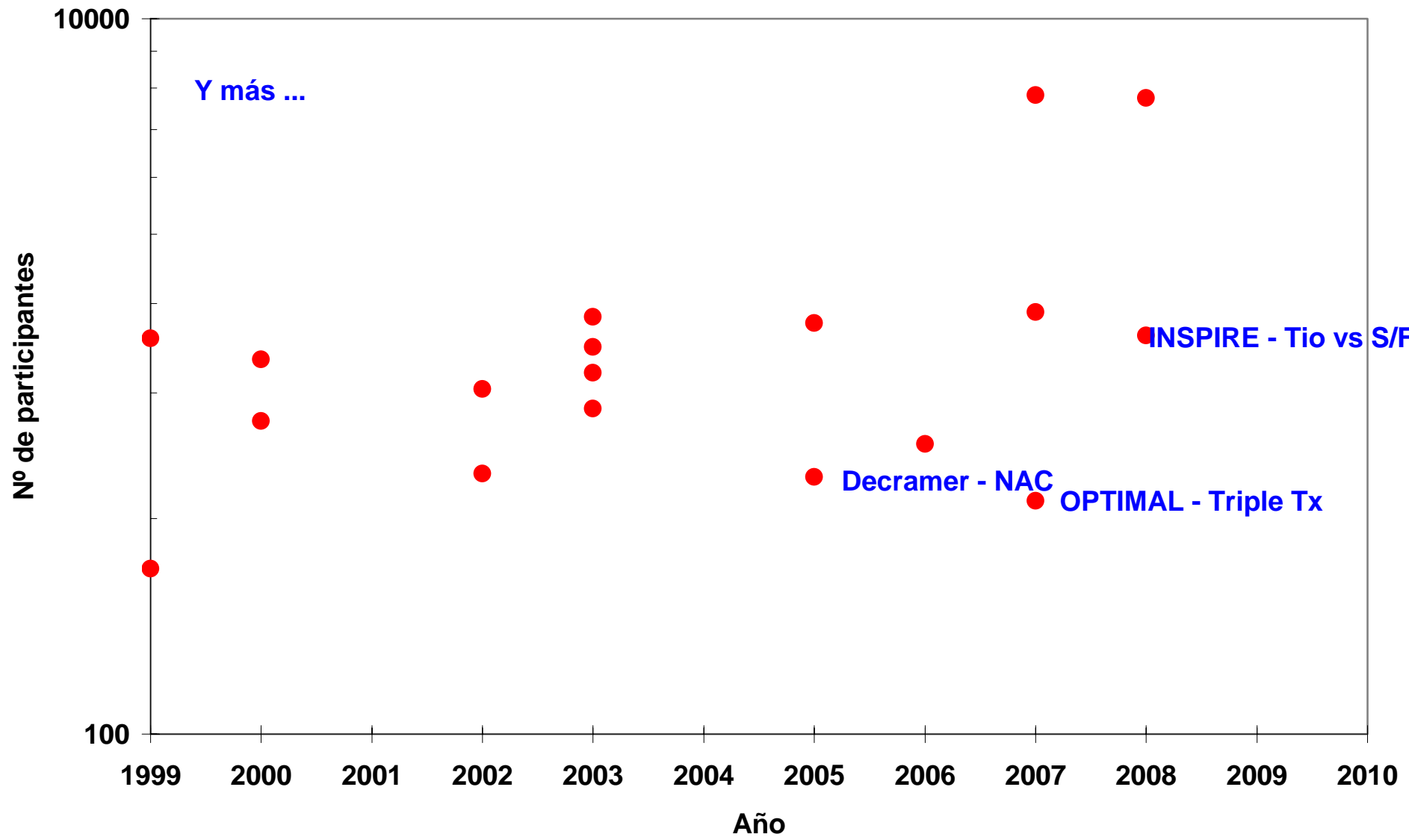












What have we learned from large drug treatment trials in COPD?

Peter M A Calverley, Stephen I Rennard

Lancet 2007; 370:774-85

Division of Infection and Immunity, Clinical Sciences Centre, University Hospital Aintree, Liverpool, UK (P M A Calverley MD); and University of Nebraska Medical Centre, Omaha, NE, USA (Prof S I Rennard MD)

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Although the development of effective treatments for patients with chronic obstructive pulmonary disease (COPD) has not been seen as a high priority, the past decade has seen a substantial increase in the number of clinical studies examining different treatments for this disease. Large studies are needed to adequately assess the effectiveness of treatment because of the chronic nature of the disease and the intermittent occurrence of some key outcomes such as exacerbations. Data from randomised controlled trials show that treatment improves exercise performance by increasing lung volume rather than changing expiratory flow. Although assessment of lung function remains the cornerstone of drug assessment, improvements in health status, the number of exacerbations and admissions to hospital are now recognised as important treatment outcomes. Randomised controlled trial data provide the best evidence for treatment efficacy, but results of these studies can be affected by differences in inclusion criteria and patient dropout during the study. Bronchodilator reversibility testing does not reliably define subgroups that will respond to a particular treatment. Carefully done and adequately powered clinical trials continue to inform, not only our views about treatment, but also our understanding of COPD and how it is best assessed and managed. Ensuring that these expensive studies are done objectively to the highest standard is an important goal for the next decade.

Calverley PMA, Rennard SI. Lancet 2007.

Mejora del diseño e interpretación de los ensayos en EPOC...

- Reversibilidad broncodilatadora
- Abandono de participantes en los ensayos
- Evitar los períodos de lavado y aleatorización a placebo
- Evaluación de otros resultados (“endpoints”) más allá del FEV₁, como calidad de vida, exacerbaciones y otros
- Validez interna y externa: comorbilidades
- Análisis estadístico

Dos lecciones:

- La mayoría de los ensayos eran de escaso tamaño y duración
- Diferentes diseños generan diferentes respuestas

GENERAL PRINCIPLES EMEA - FDA PARALLEL SCIENTIFIC ADVICE MEETINGS PILOT PROGRAM



*Table 1. American College of Physicians' Clinical Practice Guidelines Grading System**

Quality of Evidence	Strength of Recommendation	
	Benefits Do or Do Not Clearly Outweigh Risks	Benefits, Risks, and Burdens Are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms	I recommendation	

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

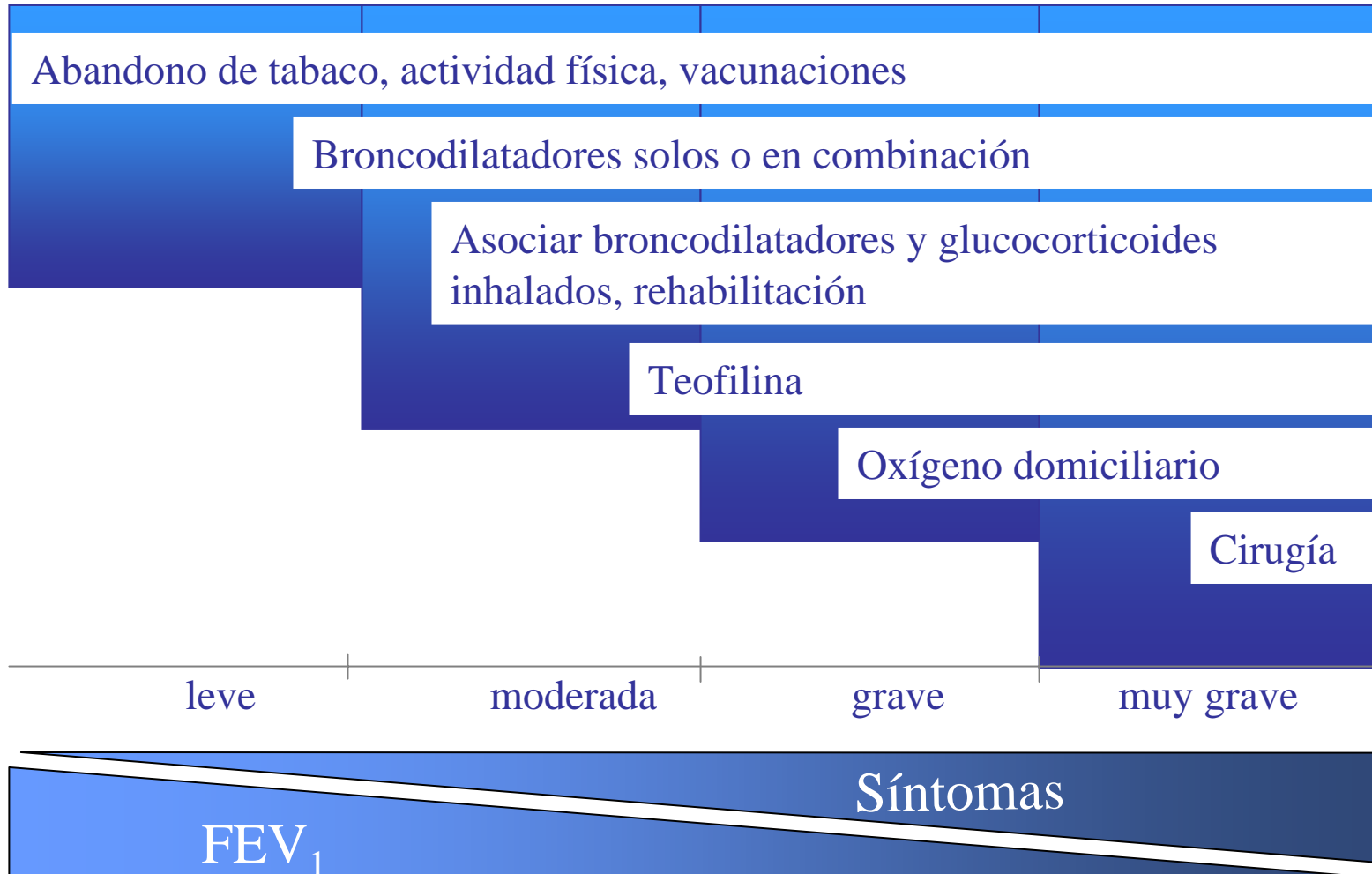
ERS/ATS COPD Guidelines:

Pharmacological Therapy (6): Effects on commonly used medications on important clinical outcomes in COPD

Medication	FEV1	Lung volume	Dyspnoea	HRQoL
Short-acting β -agonist	Yes (A)	Yes (B)	Yes (A)	NA
Ipratropium bromide	Yes (A)	Yes (B)	Yes (A)	No (B)
Long acting β -agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)
Theophylline	Yes (A)	Yes (B)	Yes (A)	Yes (B)

Medication	AE	Exercise endurance	Disease modifier by FEV1	Mortality	Side-effects
Short-acting β -agonist	NA	Yes (B)	NA	Na	Some
Ipratropium bromide	Yes (B)	Yes (B)	No	NA	Some
Long acting β -agonists	Yes (A)	Yes (B)	No	NA	Minimal
Tiotropium	Yes (A)	Yes (B)	NA	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	No	NA	Some
Theophylline	NA	Yes (B)	NA	NA	Important

SEPAR-ALAT 2007



Treatment of Chronic Obstructive Pulmonary Disease and Its Comorbidities

Fabrizio Luppi¹, Francesca Franco², Bianca Beghé¹, and Leonardo M. Fabbri¹

¹Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy; and ²Department of Internal Medicine, C. Magati Hospital, Scandiano, Reggio Emilia, Italy

Luppi F, et al. PATS 2008.

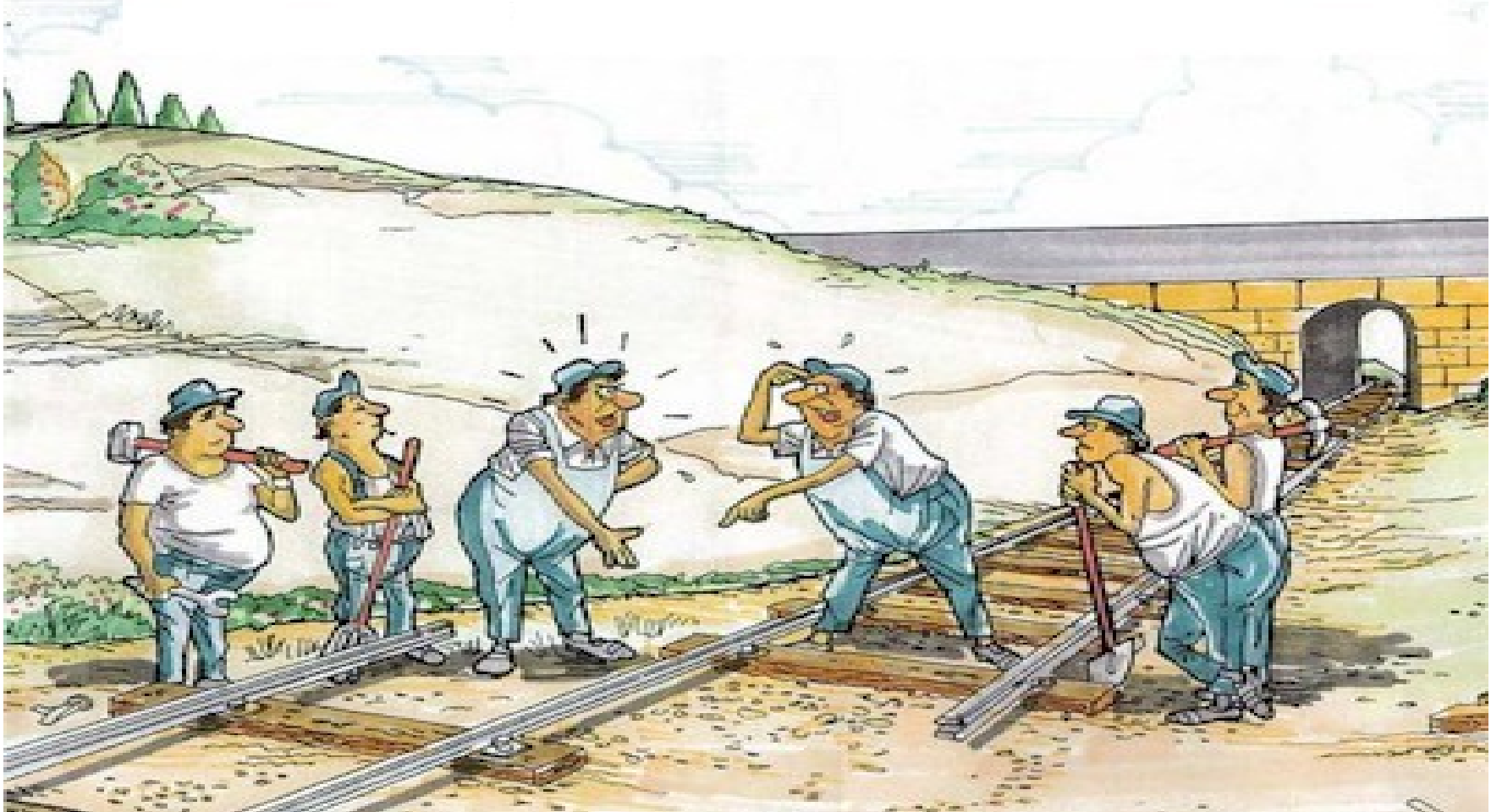
Lessons from Multidisciplinary Cross-Fertilization Chronic Obstructive Pulmonary Disease, Lung Cancer, and Heart Disease

Stephen I. Rennard¹

¹Pulmonary and Critical Care Medicine, Nebraska Medical Center, Omaha, Nebraska

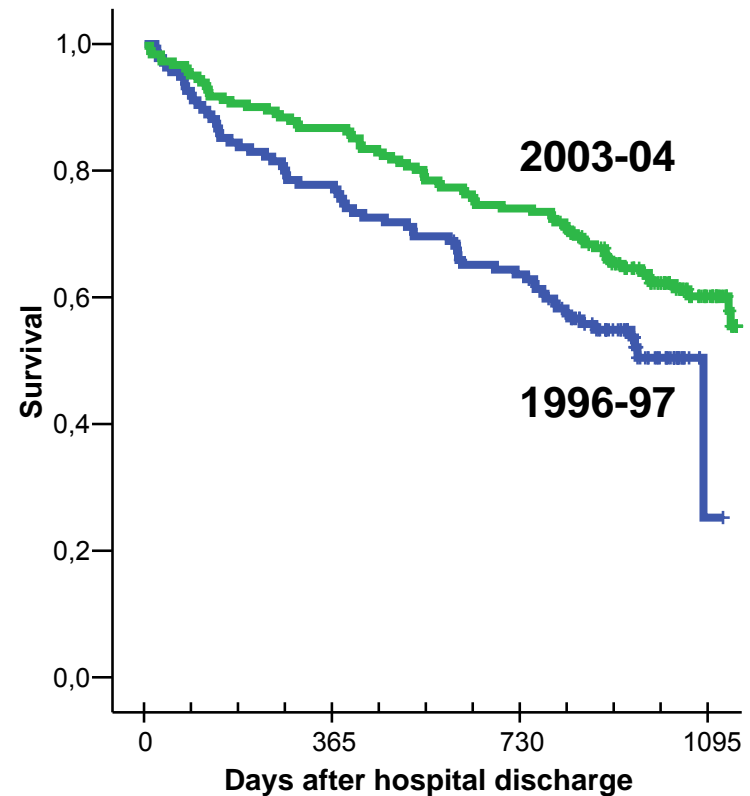
Rennard SI. PATS 2008.

Colaboración/coherencia/consistencia!!



Is there a recent improvement in long-term survival after a COPD hospitalization?

	1996-1997	2003-2004	p
Age, mean±SD	72.3	72.0	0.8
Men, n (%)	124	172	0.5
Smoking, n (%)			0.02
current	23	41	
ex-smoker	96	132	
never-smoker	14	3	
Married status, n (%)	102	120	1
Residential status, n (%)			0.6
living alone	14	19	
living with family	118	135	
institutionalized	2	5	
BMI, mean±SD	26.3	27.9	0.006
Charlson index, mean±SD	2.2	2.1	0.8
Yesavage index, mean±SD	4.7	5.1	0.3
Functional status (Katz), mean±SD	5.4	5.5	
COPD hospitalisations in the previous 12 months, mean±SD	1.	1.3	0.2
Days hospitalized due to COPD in the previous 12 months, mean±SD	12.8	12.8	1
COPD ER visits in the previous 12 months, mean±SD	0.7	0.8	0.8
Length of stay (days) mean±SD	13.5	10	0.0001
COPD hospitalisations in the next 12 months, mean±SD	1.2	1.2	0.9



Almagro P, et al. SEMI 2009.

CONCLUSIONES

- Existe un interés creciente en investigar y tratar la EPOC
- Probablemente, el tratamiento integral de la EPOC repercute en múltiples mejorías globales de los pacientes con EPOC
- Quedan muchas preguntas pendientes:
 - ¿Se benefician todos los pacientes?
 - ¿Cuáles son los mecanismos de mejoría de la supervivencia?
 - ¿Cuál es la influencia del Tto. sobre comorbilidad?
 - ¿Y la historia natural?