EPOC, comorbilidades e inflamación sistémica

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COPD is *a disease state characterized by* ***airflow limitation*** *that is not fully reversible. The airflow limitation is usually both progressive and associated with an* ***abnormal inflammatory response of the lungs*** *to noxious particles or gases.*

2001

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant ***extrapulmonary effects*** *that may contribute to the severity in individual patients. Its pulmonary component is characterized by* ***airflow limitation*** *that is not fully reversible. The airflow limitation is usually progressive and associated with an* ***abnormal inflammatory response of the lung*** *to noxious particles or gases.*

2011

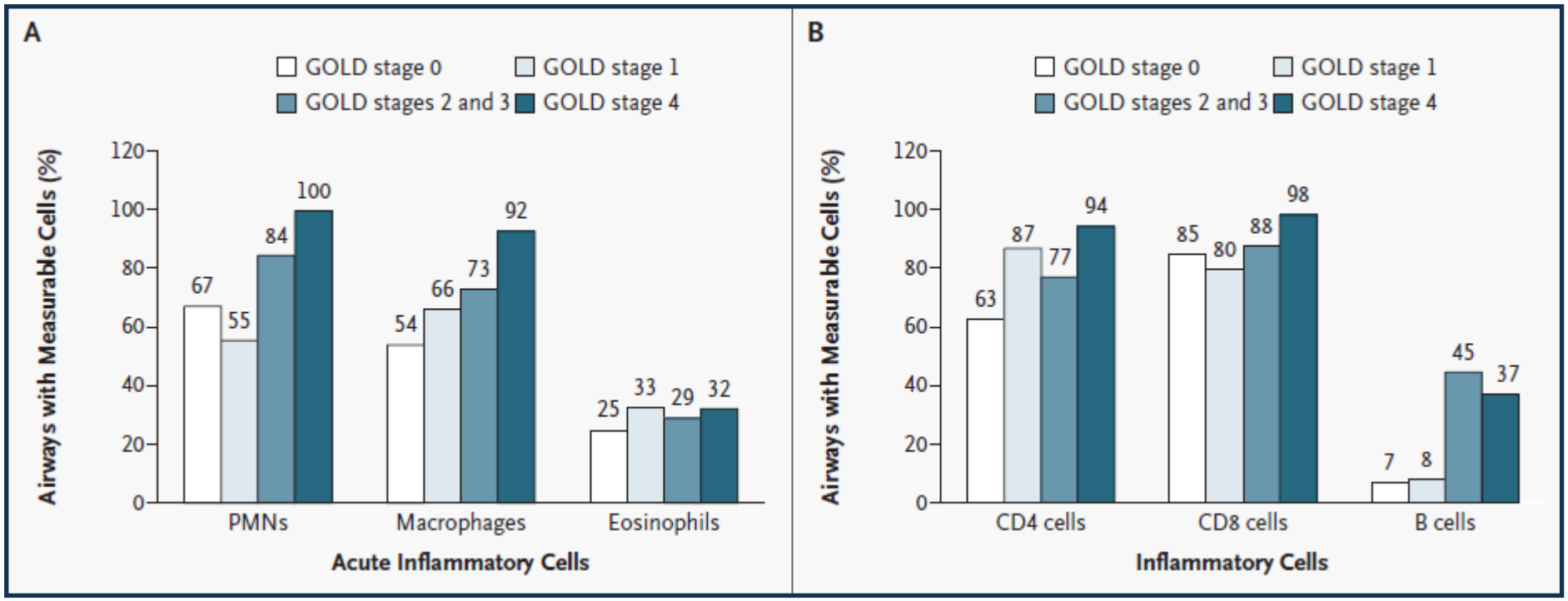
COPD is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extrapulmonary effects, and ***important comorbidities*** wich may contribute to the severity of the disease in individual patients.

- EPOC e inflamación
- EPOC y comorbilidad
- Comorbilidad e inflamación en la EPOC

- EPOC e inflamación

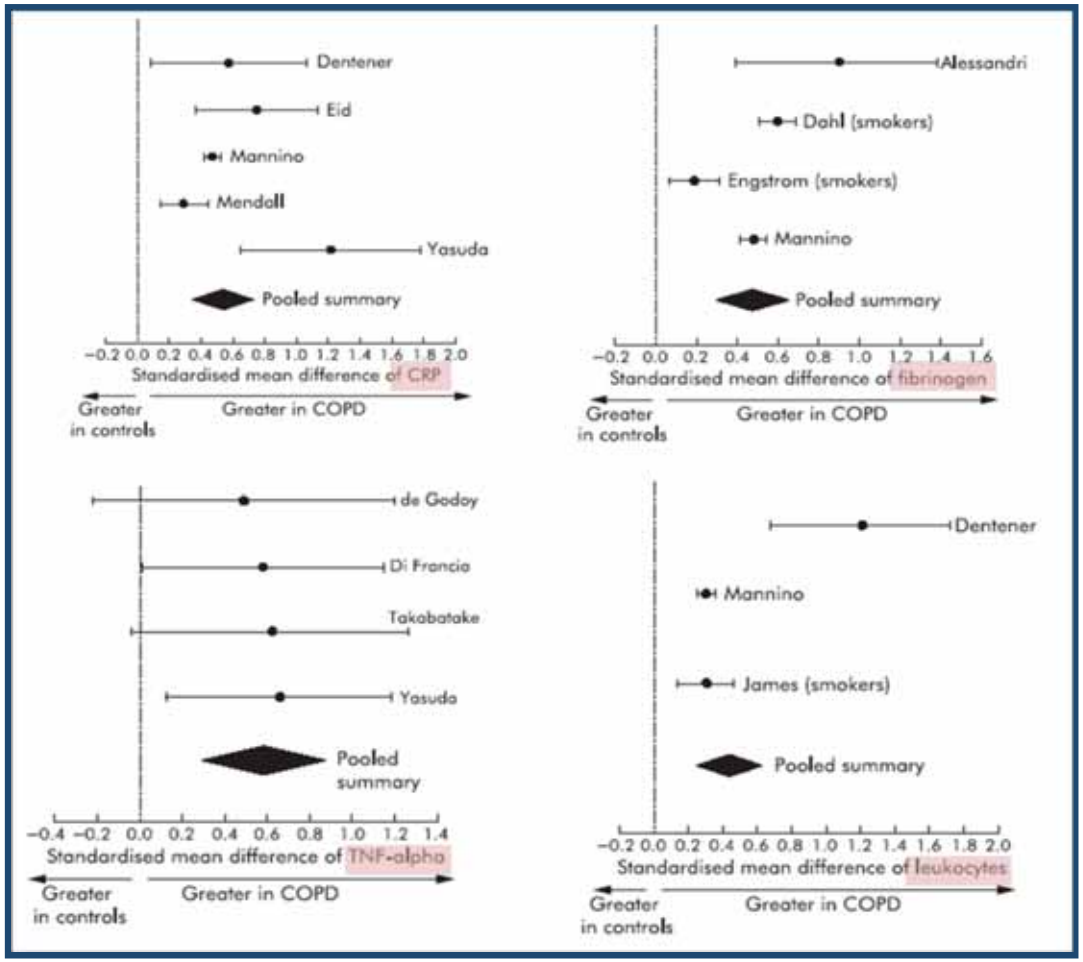
Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant ***extrapulmonary effects*** *that may contribute to the severity in individual patients. Its pulmonary component is characterized by* ***airflow limitation*** *that is not fully reversible. The airflow limitation is usually progressive and associated with an* ***abnormal inflammatory response of the lung*** *to noxious particles or gases.*

EPOC e inflamación



Hogg JC, et al. N Engl J Med. 2004;350:2645-2653.

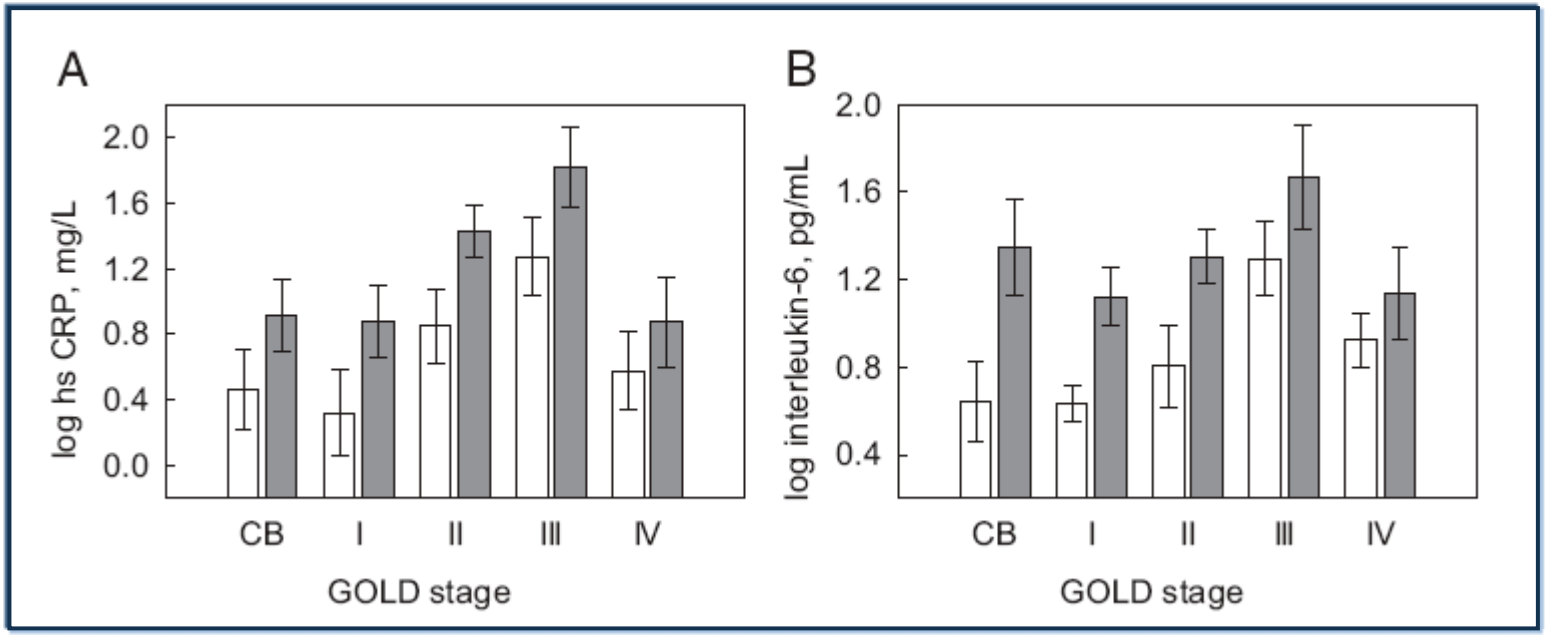
EPOC e inflamación



Gan WQ et al. Thorax 2004; 59: 574.

EPOC e inflamación

p=0,003 P<0,001



Watz H et al. Chest 2009; 136: 1039-46.

Relationship Between Inflammatory Markers and Symptom Severity

COPD forum

MRC Dyspnoea Grade	N	Neopterin (n/mol/l)	TNF-α (pg/ml)	CRP (mg/l)	IL6 (pg/ml)
MRC 1 & 2	10	5.1 (7.5)	10.2 (27.9)	2.6 (5.9)**	1.9 (2.3)*
MRC 3 & 4	21	6.3 (8.6)	15.7 (27.1)	6.8 (32.7)	3.6 (28.7)
MRC 5	10	7.1 (11.1)	19.5 (28.1)	7.2 (16.4)**	3.6 (8.2)*

MRC = Medical Research Council

** Difference between groups at $P<0.01$; * Difference between groups at $P<0.04$

Gerrod R, et al. *Prim Care Respir J* 2007;16:236-240. Permission requested.

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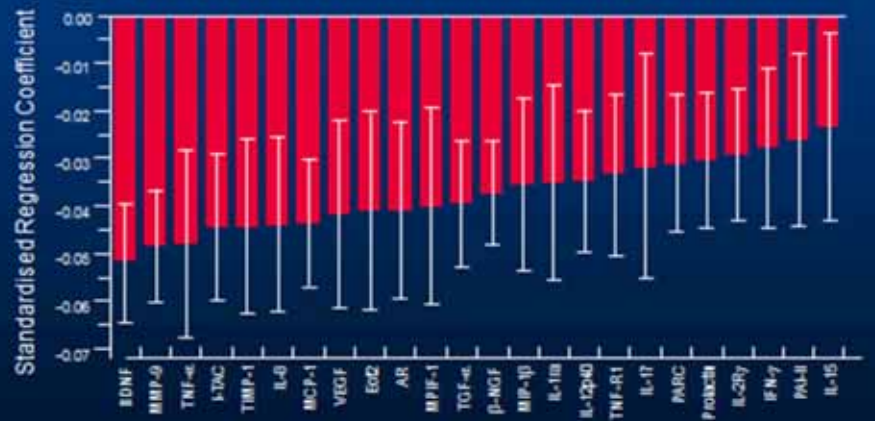
Association of Serum Biomarkers With FEV_1

COPD forum



Pinto-Plata V, et al. *Thorax* 2007;62:595-601. Permission requested.

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Biomarkers Elevated During Exacerbations

COPD forum

Cytokine/marker	Patients with	
	Exacerbated COPD (n=30)	Stable COPD (n=30)
VEGFser (pg/ml)	602 (457-883)**	229 (151-310)
IL-6 (pg/ml)	3.5 (0.8-6.2)*	2.2 (1.7-2.9)
TNF-α (pg/ml)	1.0 (0.7-1.3)	1.3 (0.9-2.3)
CRP (mg/l)	6.0 (1-31)**	4.0 (2-6)
Fibrinogen (mg/dl)	419 (329-470)	424 (358-459)
PBNC count (x10^3 cells/µl)	9.5 (6-12)*	7.0 (5-9)

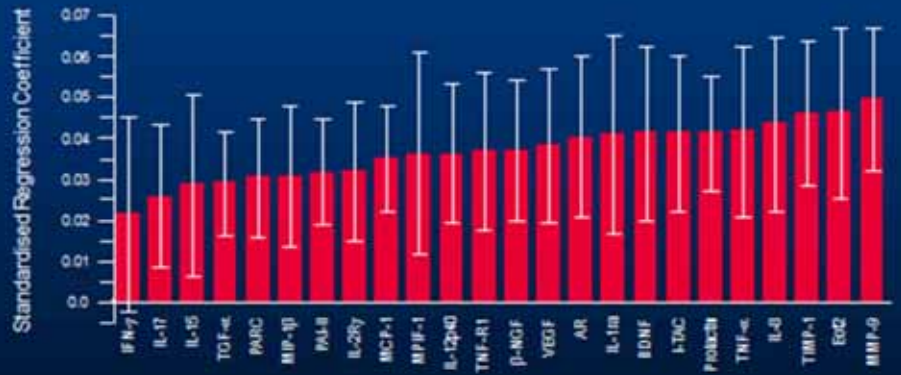
* $P<0.05$, ** $P<0.01$ compared to patients with stable COPD and healthy controls

Adapted from Veljpur A, et al. *Clin Sci* 2008;115:229-232.

13

Association of Serum Biomarkers With Exacerbation Frequency

COPD forum



Pinto-Plata V, et al. *Thorax* 2007;62:595-601. Permission requested.

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Inflammatory Mediators in COPD – Summary

Cell	Selected Mediators
 Neutrophils	Serine proteases, TNF-α, ROS, IL-8, MPO, LTB_4
 Macrophages	IL-8, IL-6, TGF-β1 TGF-α, IP-10, Mig, I-TAC, LTB_4, GRO-α, MCP-1, ROS, MMP-9
 $CD8^+$ T-cell	Granzyme B, perforins, IFN-γ, TNF-α
 Epithelial cell	IL-8, TGF- β1, IP-10, Mig, I-TAC, LTB4, GRO- α, MCP-1, MMP-9

- EPOC y comorbilidad

COPD is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extrapulmonary effects, and ***important comorbidities*** wich may contribute to the severity of the disease in individual patients.

Systemic manifestations and comorbidities of COPD

P.J. Barnes* and B.R. Celli#

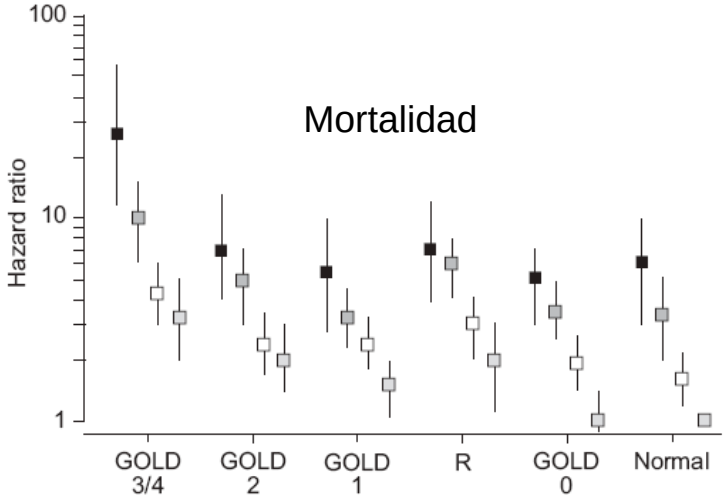
ABSTRACT: Increasing evidence indicates that chronic obstructive pulmonary disease (COPD) is a complex disease involving more than airflow obstruction. Airflow obstruction has profound effects on cardiac function and gas exchange with systemic consequences. In addition, as COPD results from inflammation and/or alterations in repair mechanisms, the "spill-over" of inflammatory mediators into the circulation may result in important systemic manifestations of the disease, such as skeletal muscle wasting and cachexia. Systemic inflammation may also initiate or worsen comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes. Comorbid diseases potentiate the morbidity of COPD, leading to increased hospitalisations, mortality and healthcare costs. Comorbidities complicate the management of COPD and need to be evaluated carefully.

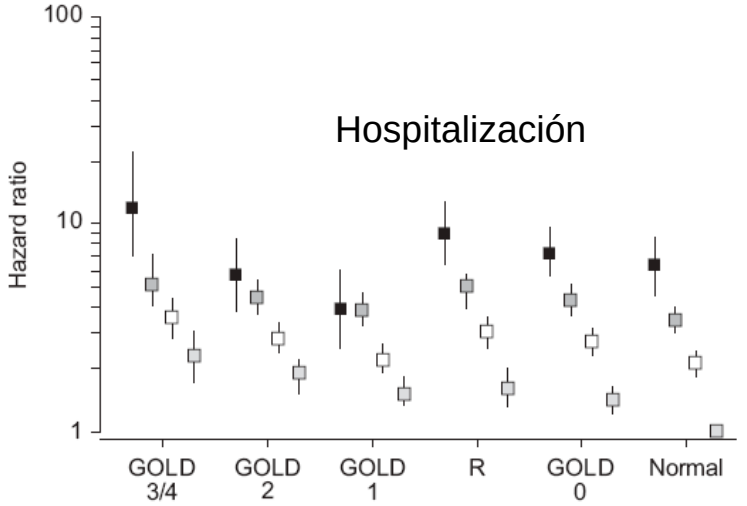
Eur Respir J 2009; 33: 1165–1185

Comorbilidades más frecuentes en los pacientes con EPOC		
	ECCO	ESMI
Comorbilidad	%	%
Hipertensión	55,0	65,6
Anemia	33,0	27,1
Diabetes mellitus	29,5	37,1
Insuficiencia cardiaca	27,0	35,5
Arritmia	27,0	25,8
Obesidad	22,0	29,4
Cardiopatía isquémica	17,0	22,0
Enfermedad arterial periférica	12,6	17,4
Ulcus péptico	12,3	9,5
Neoplasia	9,8	13,1
Accidente cerebrovascular	9,5	12,2
Osteoporosis	9,3	16,1
Hepatopatía crónica	9,6	6,6
Insuficiencia renal	6,5	16,8

EPOC y comorbilidad

Indice de Charlson y mortalidad en EPOC		
	Riesgo	p
Almagro et al Chest 2002; 121: 1441	2,20 (1,26-3,84)	0,005
Sanjaume et al Rev Clin Esp 2009; 209: 364	1,47 (1,03-2,09)	< 0,05
Díez Manglano et al Rev Clin Esp 2011 Epub ahead on print	1,16 (1,06-1,27)	0,002
Almagro et al Estudio ESMI (en revisión)	1,74 (1,09-1,55)	0,003





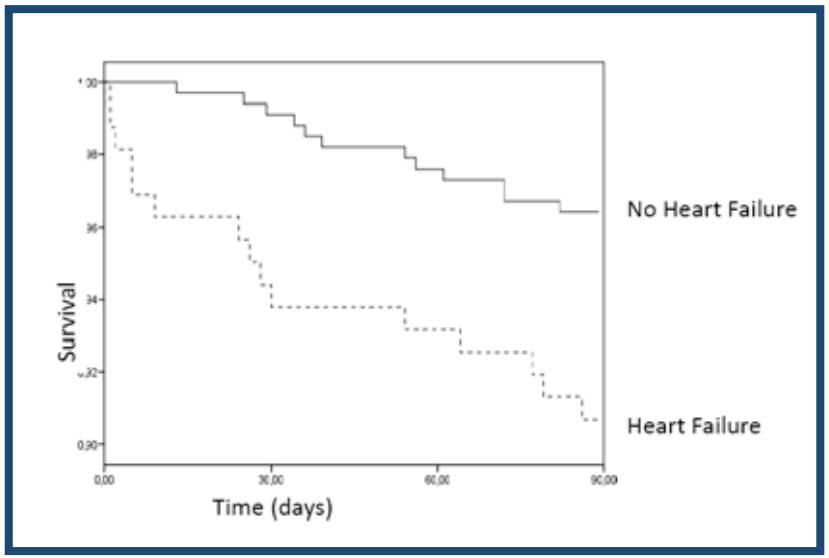
Mannino DM et al. Erur Respir J 2008; 32: 9621

	Número de comorbilidades			
	0	1	2	3-8
Mortalidad hospitalaria	Referencia	1,34 (1,08-1,65) p=0,007	1,36 (1,09-1,68) p=0,006	1,54 (1,23-1,92) p<0,001
Mortalidad 90 días	Referencia	1,42 (1,21-1,68) p<0,001	1,40 (1,18-1,65) p<0,001	1,61 (1,36-1,91) p<0,001
Estancia > 7 días	Referencia	1,19 (1,09-1,29) p<0,001	1,26 (1,15-1,38) p<0,001	1,34 (1,23-1,47) p<0,001
Reingreso 90 días	Referencia	1,12 (1,02-1,23) p=0,02	1,18 (1,08-1,29) p<0,001	1,26 (1,14-1,39) p<0,001

Roberts CM et al. COPD 2011; 8: 354

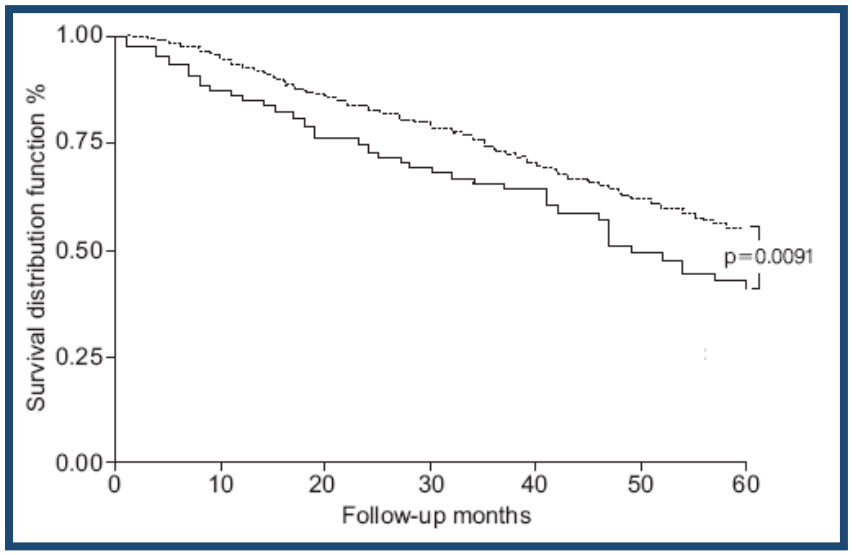
EPOC y comorbilidad

Insuficiencia cardiaca



Almagro P et al. Estudio ESMI (en revisión editorial)

Anemia



Cote C et al. Eur Respir J 2007; 29: 923

- EPOC e inflamación
- EPOC y comorbilidad
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Systemic manifestations and comorbidities of COPD

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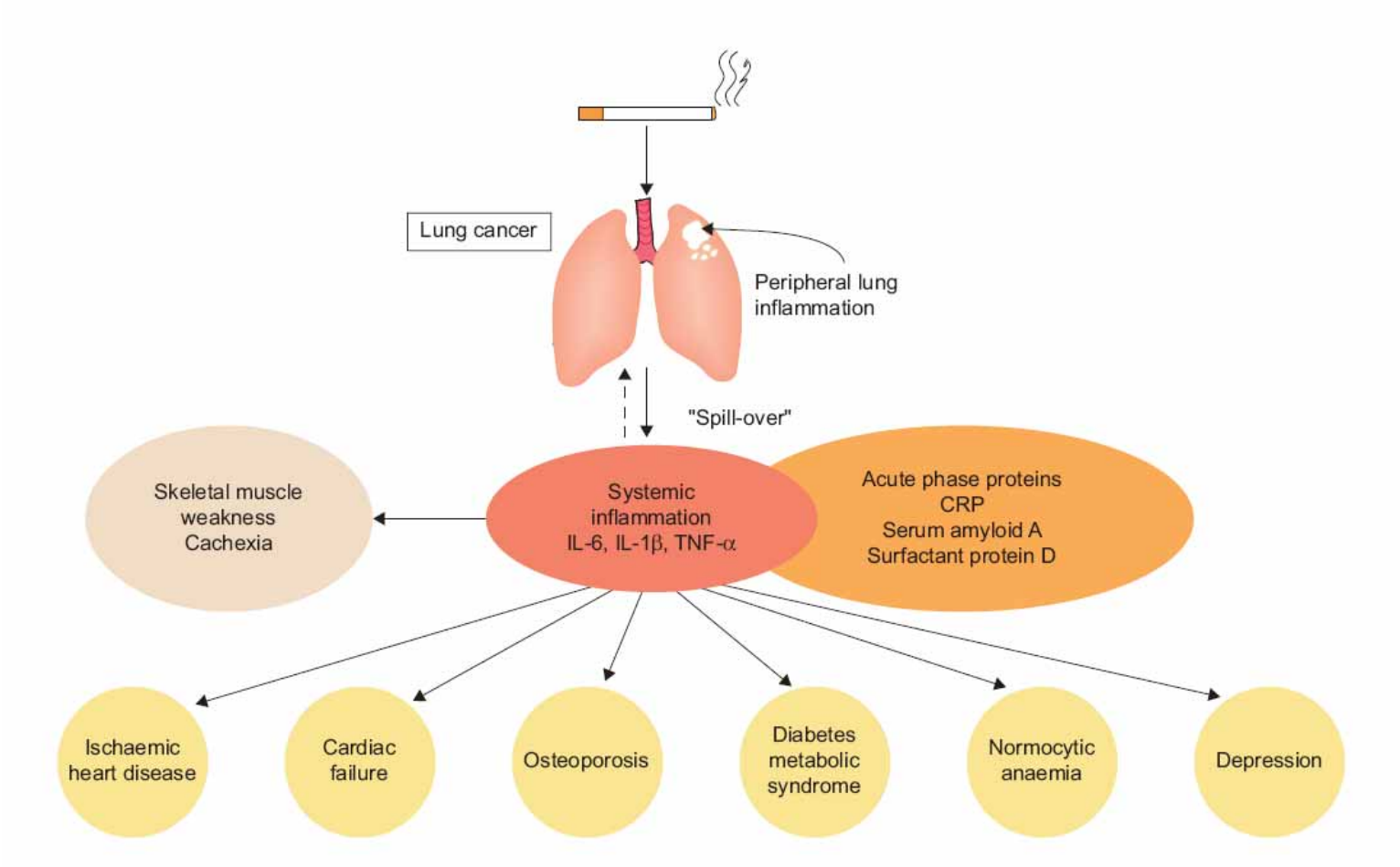
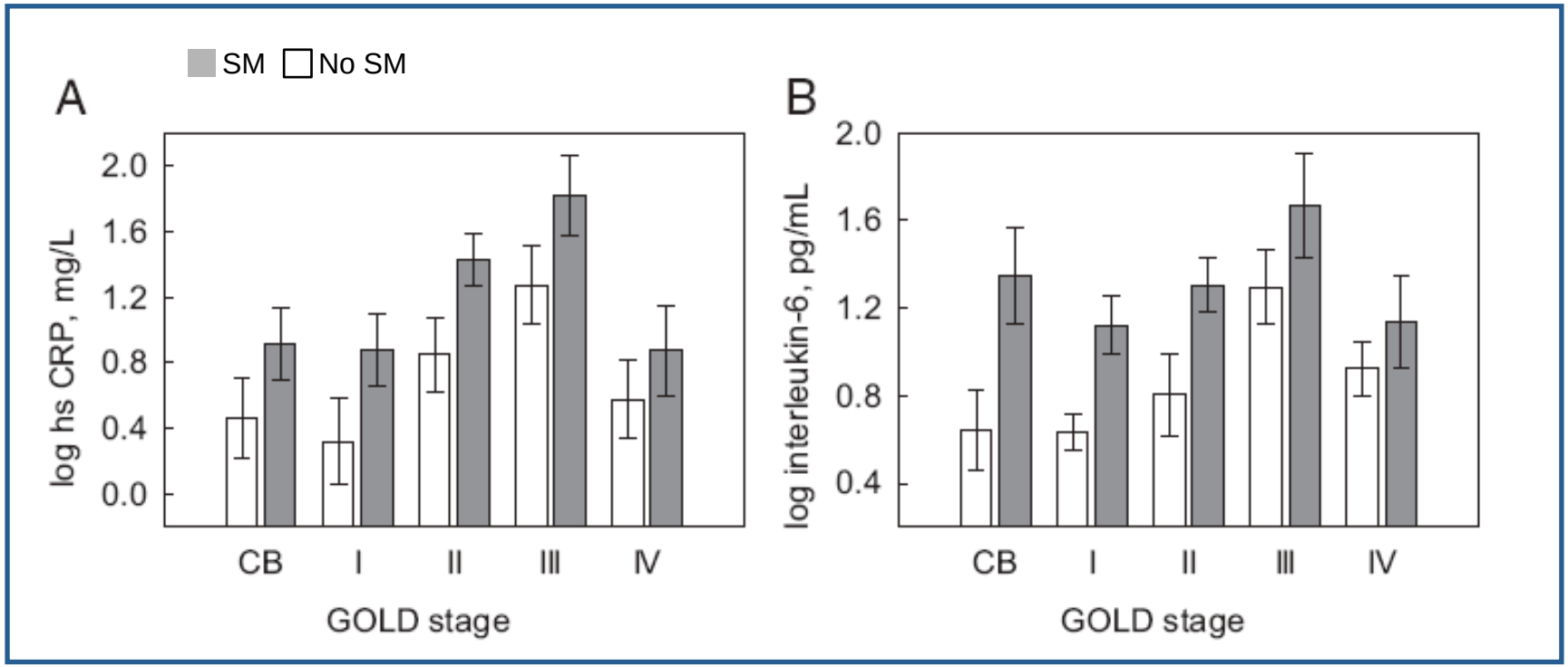
Eur Respir J 2009; 33: 1165–1185

Comorbilidad e inflamación en la EPOC



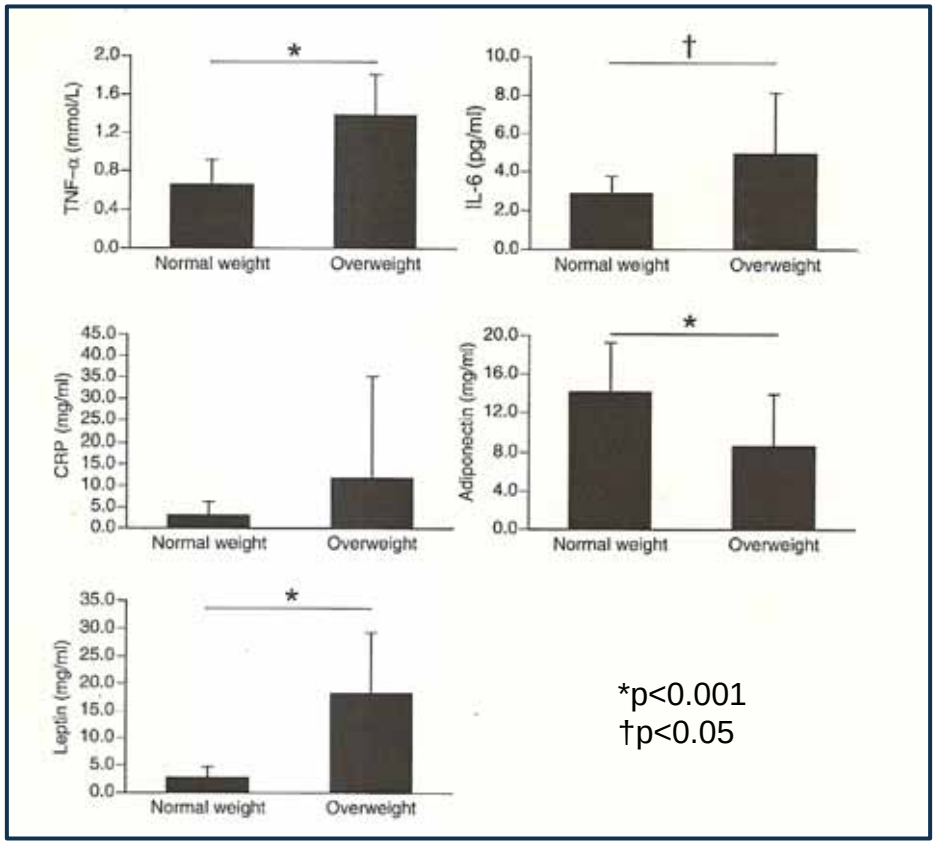
Barnes PJ, Celli BR. Eur Respir J 2009; 33:1165.

Síndrome metabólico e inflamación en la EPOC



Watz H et al. Chest 2009; 136: 1039.

Obesidad e inflamación en la EPOC



Poulain M et al. Chron Respir Dis 2008; 5: 35.

Anemia e inflamación en la EPOC

Variables	Nonanemic COPD Patients (n = 88)	Anemic COPD Patients (n = 13)	p Value, Anemic vs Nonanemic
Hemoglobin, g/dL	14.7 ± 0.2	11.9 ± 0.4	< 0.0001
Hematocrit	0.44 ± 0.01	0.36 ± 0.01	< 0.0001
Erythrocytes/picoliter	4.85 ± 0.05	4.09 ± 0.11	< 0.0001
Erythropoietin, U/L	16.3 ± 2.9 (n = 60)	41.8 ± 25.4 (n = 9)	< 0.05
Log CRP, mg/dL	− 0.199 ± 0.067 (n = 80)	0.465 ± 0.228 (n = 11)	< 0.001
Median; IQR	− 0.154; 0.916	0.398; 1.042	
Log IL-6, pg/mL	0.854 ± 0.041 (n = 66)	1.061 ± 0.215 (n = 8)	0.1
Median; IQR	0.699; 0.255	0.699; 0.764	
IL-8, pg/mL	5.3 ± 0.1 (n = 46)	5.4 ± 0.4 (n = 6)	0.9
IL-10, pg/mL	4.3 ± 0.4 (n = 54)	5.2 ± 1.6 (n = 10)	0.4

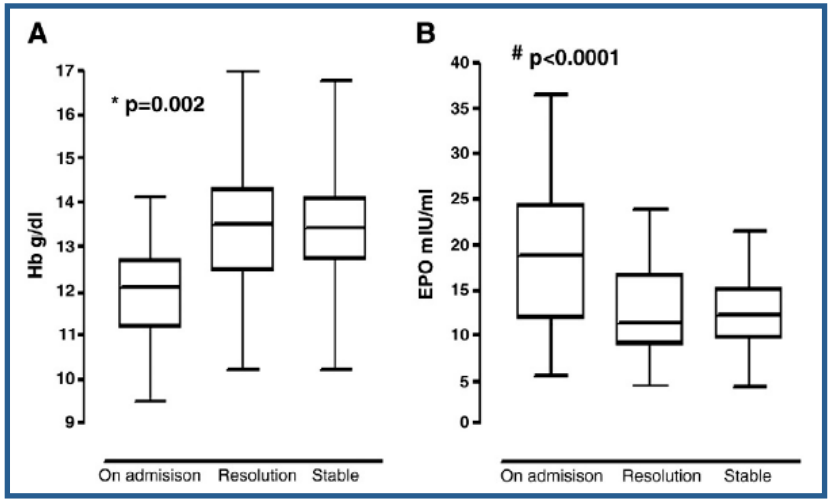
*Data are shown as mean ± SEM.

John M et al. Chest 2005; 127: 825.

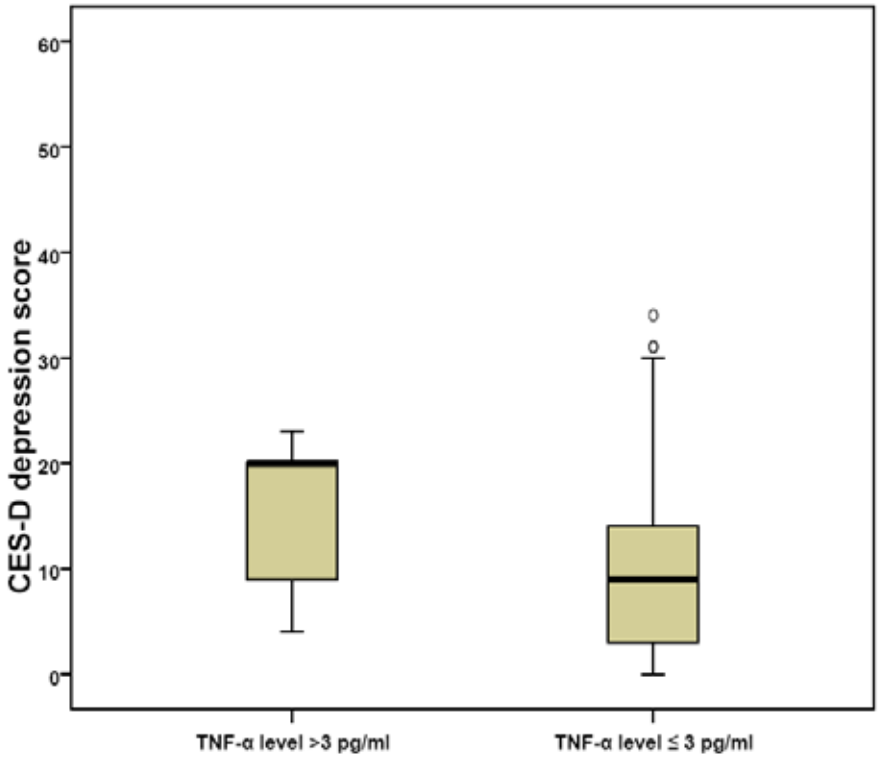
Time-course of the levels of Hb, EPO and inflammatory biomarkers.

Parameter	Admission	Resolution	12 weeks
Hb [g/dl]	12.1 (11.2–12.7)	13.5 (12.4–14.3)*	13.4 (12.7–14.08)
EPO [mIU/ml]	18.9 (11.8–24.3)	11.3 (8.9–16.7)**	12.2 (9.7–15.2)
Fibrinogen [mg/dl; mean ± SD]	475 ± 103	364 ± 64**	387 ± 79
CRP [g/dl]	4.9 (2.7–8.3)	1.2. (0.6–1.7)**	0.9 (0.5–1.2)
IL-6 [pg/ml]	15 (9–18)	8.7 (6–12.5)**	8.5 (6–11.5)
TNF-α [pg/ml]	2.7 (1.7–3.7)	1.6 (1–2)**	1.6 (1.2–1.7)

Markoulaki D et al. Eur J Intern Med 2001; 22: 103



Depresión e inflamación en la EPOC



Al-Shair K et al. Respir Res 2011; 12:3

Arch Bronconeumol. 2009;45(Supl 4):14-17

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www.archbronconeumol.org

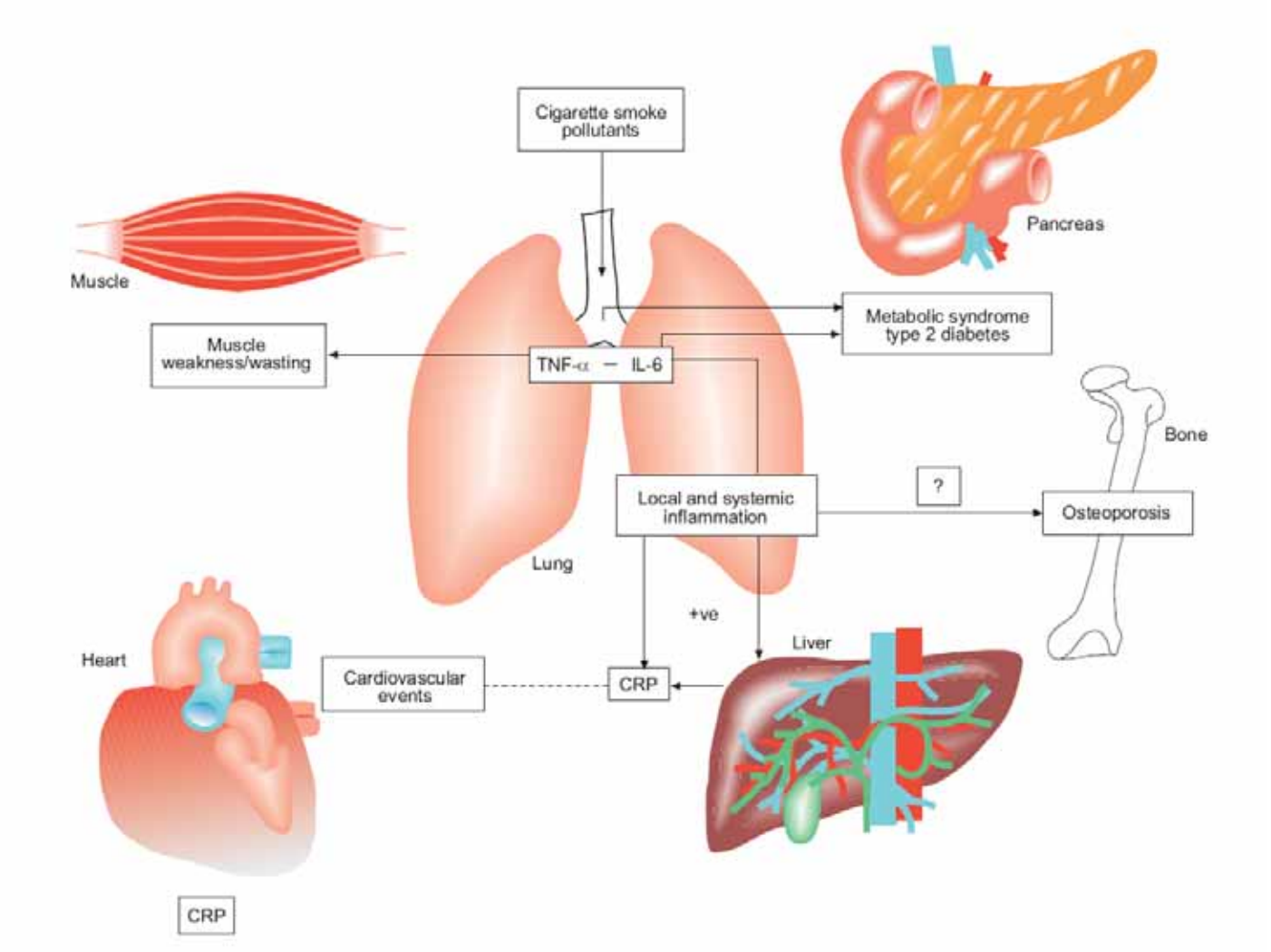
EPOC e inflamación sistémica. Una vía de enlace para la comorbilidad

Alvar Agustí

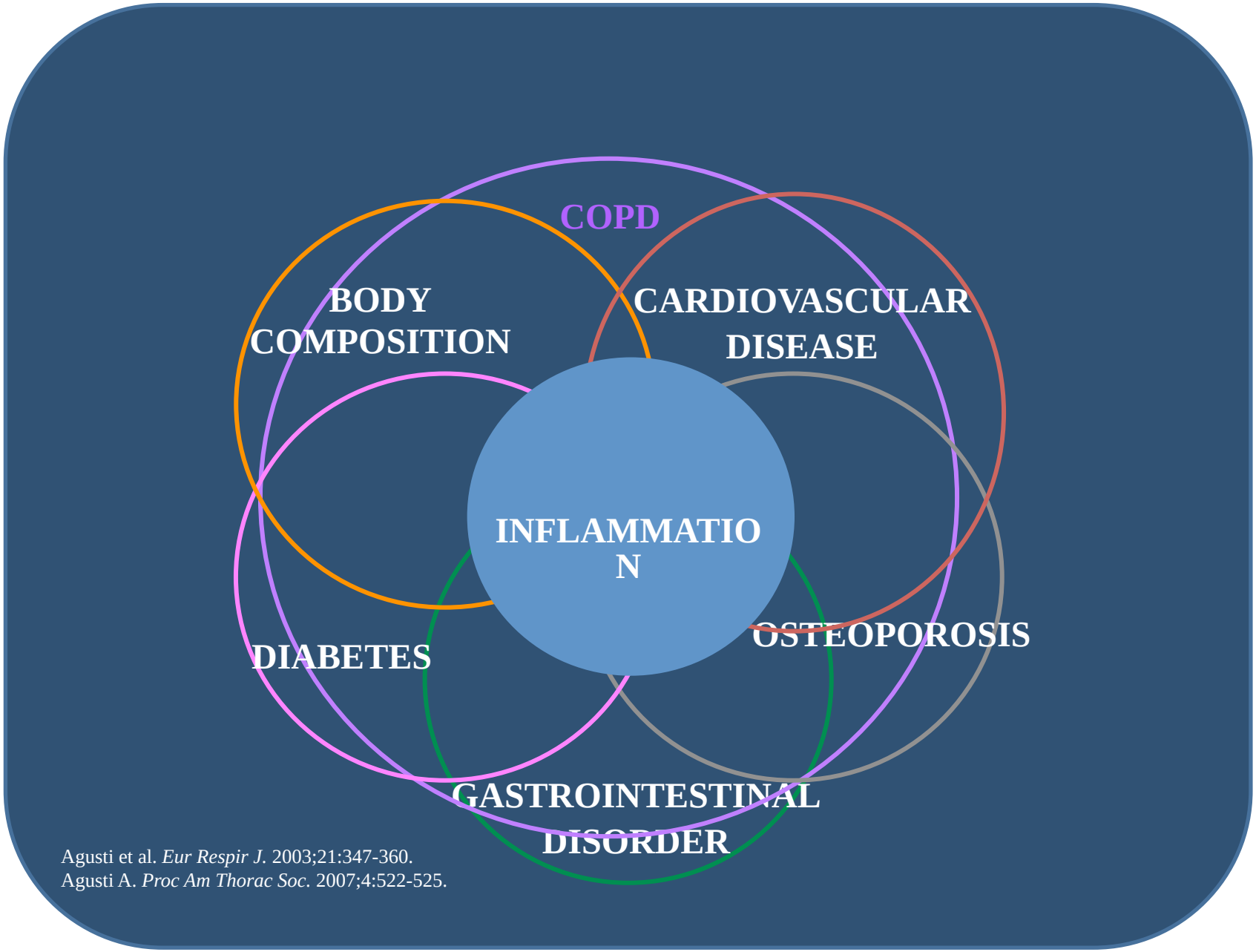
Institut del Tòrax, Hospital Clínic, Universitat de Barcelona, CIBER Enfermedades Respiratorias, Fundación Caubet-Cimera, Illes Balears, España

Conclusiones

Muchos pacientes con EPOC presentan diversas enfermedades comórbidas concomitantes. Hay evidencia firme que muchos (pero no todos) de los pacientes con EPOC presentan valores elevados en plasma de diversos marcadores inflamatorios ("inflamación sistémica"). La asociación entre ambas observaciones es tentadora, pero todavía no demostrada.

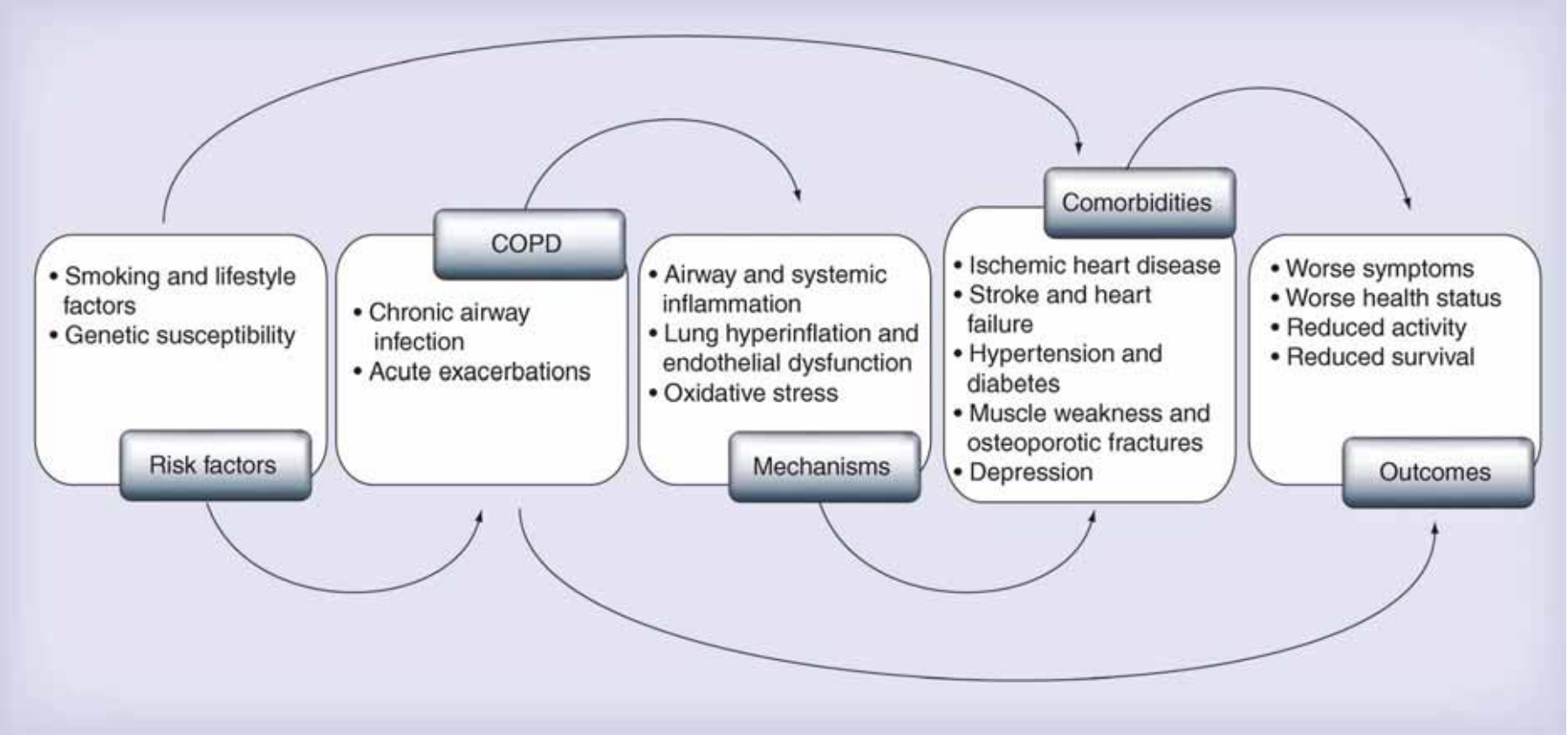


Fabbri LM et al. Eur Respir J 2008; 31: 204.



Agusti et al. *Eur Respir J.* 2003;21:347-360.
Agusti A. *Proc Am Thorac Soc.* 2007;4:522-525.

Comorbilidad e inflamación en la EPOC



Patel ARC, Hurst JR. Expert Rev Respir Med 2011; 5: 647.

EPOC con fenotipo inflamatorio

Respiratory Research

BioMed Central

Commentary

Open Access

Chronic Obstructive Pulmonary Disease, inflammation and co-morbidity – a common inflammatory phenotype?

Martin J Sevenoaks and Robert A Stockley*

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* Corresponding author

Published: 02 May 2006

Respiratory Research 2006, **7**:70 doi:10.1186/1465-9921-7-70

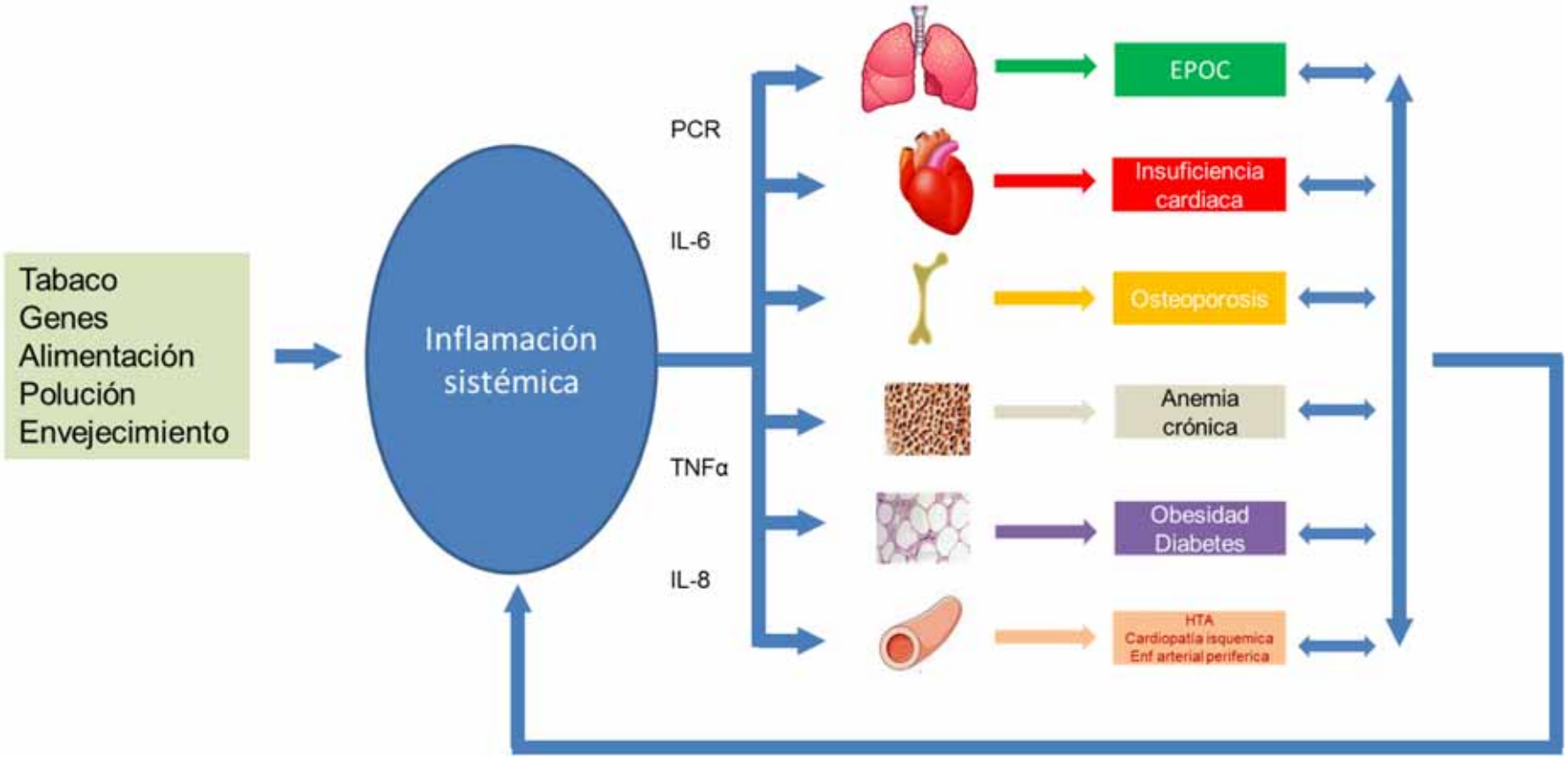
Received: 06 December 2005

Accepted: 02 May 2006

Otras enfermedades con inflamación

Enfermedad	PCR	IL-6	Referencia
ICC	X	X	Heart 2005; 91: 32
Enfermedad arterial periférica	X	X	Am Heart J 2005; 150: 276
Cardiopatía isquémica	X	X	Am J Cardiol 2005; 95: 452
Diabetes	X	X	JAMA 2001; 286: 327
Obesidad	X		JAMA 1999; 282; 13
Hipertensión arterial	X	X	J Clin Endocrinol Metab 2001; 86: 1154
Osteoporosis		X	J Clin Endocrinol Metab 2001; 86: 2032
Anemia de proceso crónico		X	Sem Arthr Rheum 2009; 38: 382

Inflamación sistémica



EPOC, inflamación y comorbilidad. XXXII Congreso Nacional de la SEMI. Maspalomas 26-29 octubre 2011

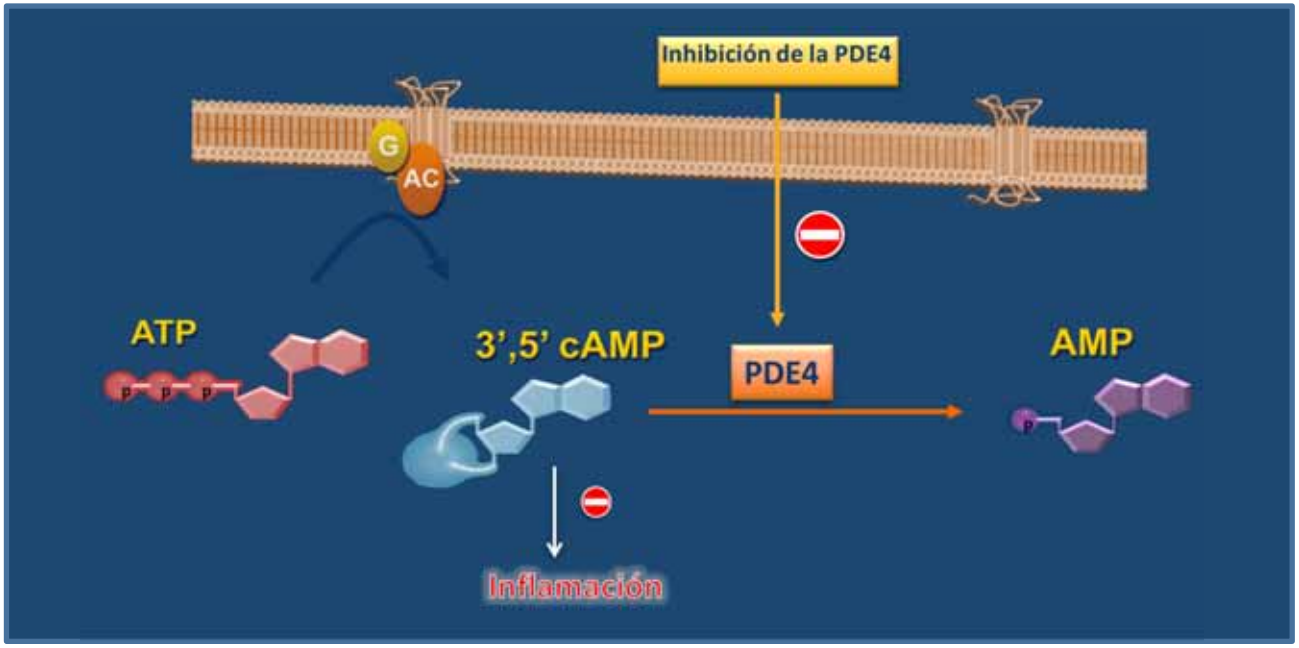
Síndrome inflamatorio sistémico crónico

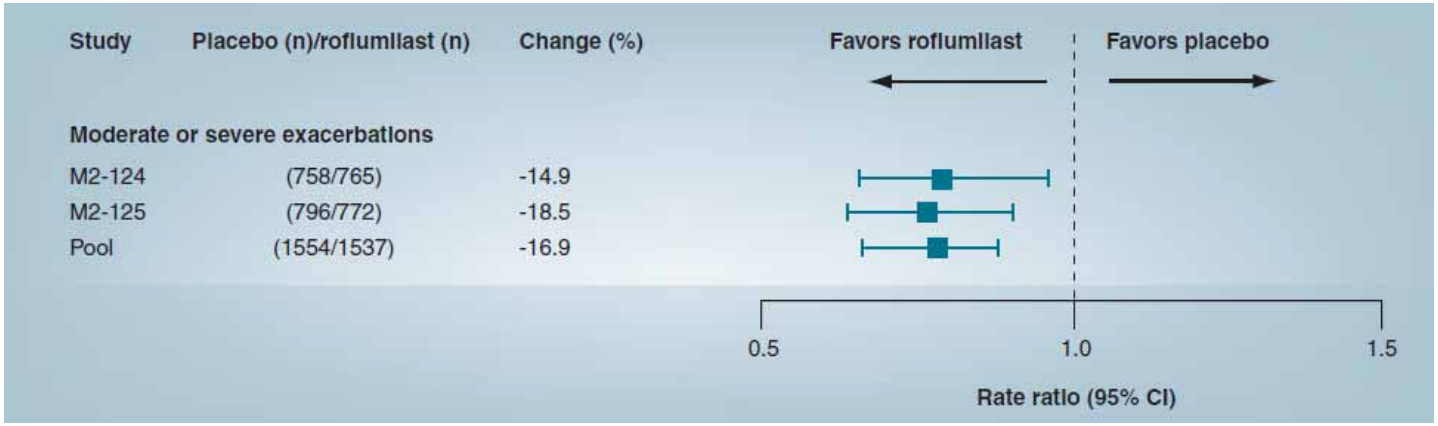
- Edad superior a 40 años.
- Tabaquismo durante más de 10 años-paquete.
- Síntomas y alteración de la función pulmonar compatible con EPOC.
- Insuficiencia cardiaca crónica.
- Síndrome metabólico.
- Aumento de proteína C reactiva.

Son necesarios 3 o más criterios para el diagnóstico.

Fabbri LM, Rabe KF. Lancet 2007; 370: 797.

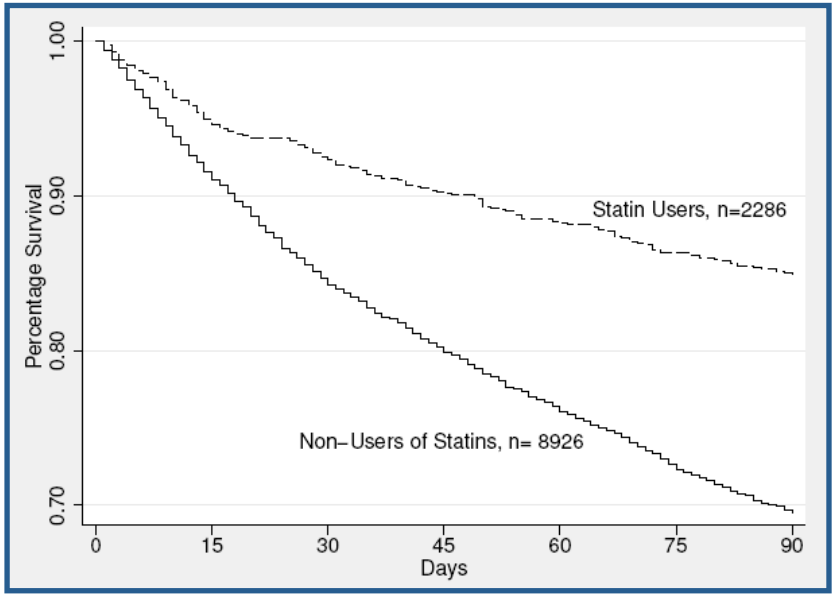
Roflumilast

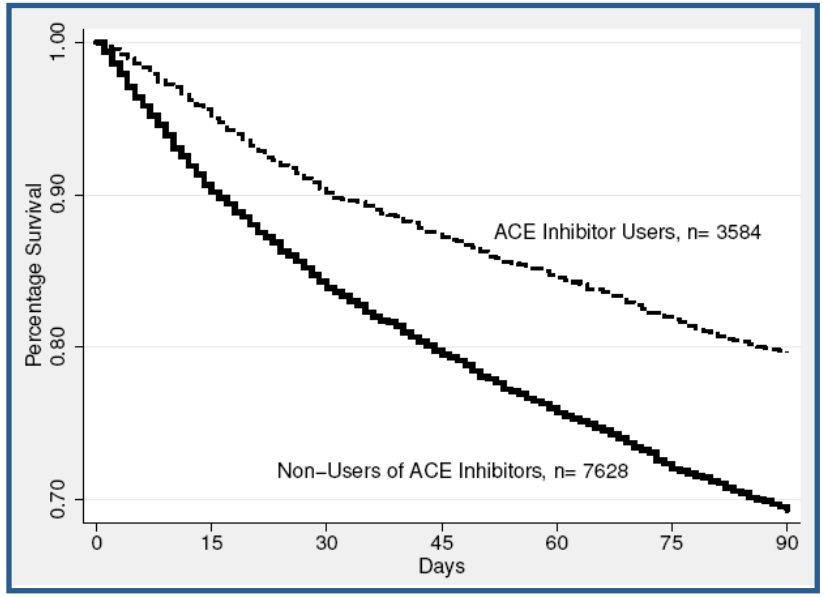




EPOC, inflamación y comorbilidad. XXXII Congreso Nacional de la SEMI. Maspalomas 26-29 octubre 2011

Estatinas e IECAs





Mortensen EM et al. Respir Res 2009; 10: 45

Investigación - Estatinas

Found 8 studies with search of: copd AND STATIN

ClinicalTrials.gov

Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

Rank	Status	Study
1	Recruiting	The Effect of Statins in Patients With Chronic Obstructive Pulmonary Disease (COPD) Condition: Chronic Obstructive Pulmonary Disease Interventions: Drug: Simvastatin; Drug: Lactose tablet
2	Unknown †	Effect of Statin Therapy on C-Reactive Protein Levels in Patients With Chronic Obstructive Lung Disease (COPD) Conditions: COPD; Inflammation Intervention: Drug: simvastatin
3	Recruiting	Simvastatin Therapy for Moderate and Severe COPD Condition: Pulmonary Disease, Chronic Obstructive Interventions: Drug: simvastatin; Drug: Placebo
4	Completed	Effect of Statins on Asthma Control in Smokers With Asthma Conditions: Asthma; COPD; Smoking Interventions: Drug: Atorvastatin; Drug: atorvastatin; Drug: matched placebo
5	Recruiting	Effect of Rosuvastatin Therapy in Patients With Stable Chronic Obstructive Pulmonary Disease Condition: COPD Interventions: Drug: Rosuvastatin; Drug: Placebo
6	Recruiting	LTOT in COPD Patients With Moderate Chronic Hypoxemia and Chronic Heart Failure Conditions: Lung Diseases, Obstructive; Chronic Heart Failure; Chronic Hypoxemia Interventions: Other: LTOT (oxygen therapy); Other: Pharmacological therapy of COPD and CHF
7	Recruiting	Lovastatin as a Potential Modulator of Apoptosis in Chronic Obstructive Pulmonary Disease (COPD) Condition: Chronic Obstructive Pulmonary Disease (COPD) Interventions: Drug: Lovastatin; Drug: Placebo
8	Active, not recruiting	Simvastatin in Chronic Obstructive Pulmonary Disease (COPD) Conditions: COPD; Emphysema Interventions: Drug: Simvastatin; Drug: Placebo

Investigación – IECA o ARA2

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

List Results | Refine Search | Results by Topic | Results on Map | Search Details

Found 2 studies with search of: copd AND ace inhibitor

Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

Rank	Status	Study
1	Recruiting	Angiotensin-converting Enzyme (ACE)-Inhibition and Mechanisms of Skeletal Muscle Weakness in Chronic Obstructive Pulmonary Disease (COPD) Condition: Chronic Obstructive Pulmonary Disease Interventions: Drug: Fosinopril; Other: lactose
2	Recruiting	LTOT in COPD Patients With Moderate Chronic Hypoxemia and Chronic Heart Failure Conditions: Lung Diseases, Obstructive; Chronic Heart Failure; Chronic Hypoxemia Interventions: Other: LTOT (oxygen therapy); Other: Pharmacological therapy of COPD and CHF

Found 2 studies with search of: copd AND ARB

Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

Rank	Status	Study
1	Recruiting	Efficacy of Losartan in Preventing Progression of COPD Conditions: COPD; Emphysema; Chronic Bronchitis; Smoking Interventions: Drug: Losartan; Drug: Placebo
2	Recruiting	Effect of Losartan on Chronic Obstructive Pulmonary Disease (COPD) Conditions: COPD; Emphysema; Chronic Obstructive Pulmonary Disease; Chronic Bronchitis Interventions: Drug: Losartan; Drug: Placebo

Investigación - Roflumilast

ClinicalTrials.gov

Found 30 studies with search of: roflumilast

Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

Rank	Status	Study
1	Recruiting	Pharmacokinetic Study of Single and Repeated Dose of Roflumilast 500 µg , in Healthy Chinese Subjects Condition: Chronic Obstructive Pulmonary Disease Intervention: Drug: Roflumilast
2	Completed Has Results	Effect of Roflumilast in Chronic Obstructive Pulmonary Disease (COPD) Patients Treated With Tiotropium: The HELIOS Study (BY217/M2-128) Condition: Chronic Obstructive Pulmonary Disease Interventions: Drug: Roflumilast; Drug: Placebo
3	Completed Has Results	Effect of Roflumilast on Lung Function in Chronic Obstructive Pulmonary Disease (COPD) Patients Treated With Salmeterol: The EOS Study (BY217/M2-127) Condition: Chronic Obstructive Pulmonary Disease (COPD) Interventions: Drug: Roflumilast; Drug: Placebo
4	Not yet recruiting	Roflumilast and Cognition Condition: Dementia Interventions: Drug: roflumilast (EU: Daxas, USA: Daliresp); Drug: Placebo; Drug: roflumilast
16	Completed	Efficacy of 500µg Roflumilast Once Daily Versus Placebo Over 12 Weeks in Patients With Diabetes Mellitus Type 2. A Double Blind, Parallel Group, Proof of Concept Clinical Study Condition: Diabetes Mellitus Type 2 Intervention: Drug: Roflumilast

Roflumilast y diabetes tipo 2

Table 1. Baseline Characteristics and Demographics

	Roflumilast 500 µg n=107	Placebo n=98
Age, Median years	55	54
Height, Mean m (SD)	1.66 (0.09)	1.66 (0.09)
Weight, Mean kg (SD)	84 (11)	84 (11)
BMI, Mean kg/m² (SD)	30.34 (2.7)	30.56 (3.0)
Male, %	44.9	50.0
HbA_{1c}, Mean % (SD)	7.9 (0.5)	7.9 (0.6)
Mean % of patients with HbA_{1c} ≤8%	67.3	66.3
Mean % of patients with HbA_{1c} >8%	32.7	33.7

BMI = Body Mass Index; HbA_1 = Hemoglobin A_1

Figure 2. Reduction in HbA_{1c} Levels from Baseline to Last Visit with Roflumilast or Placebo

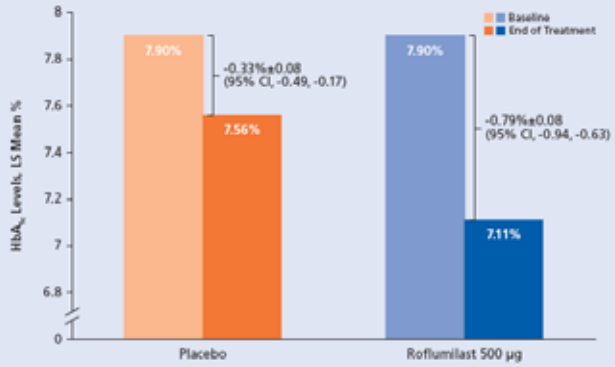


Figure 4. Reduction in Fasting Plasma Glucose Levels from Baseline to End of Treatment with Roflumilast or Placebo

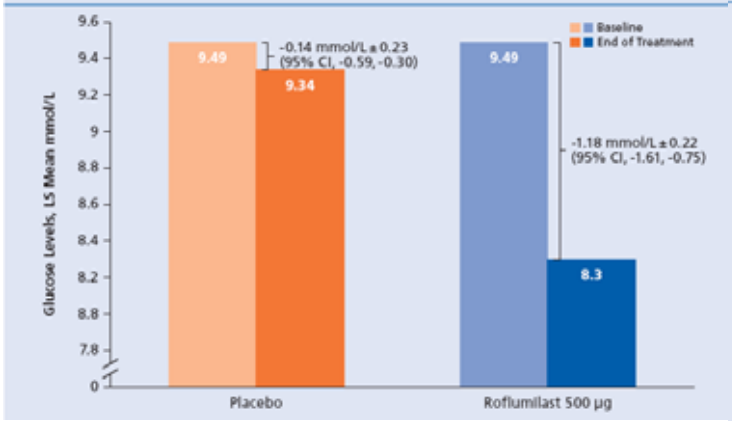


Figure 5. Reduction in Fructosamine Levels from Baseline to End of Treatment with Roflumilast or Placebo

Wouters EFM et al. American Thoracic Society International Conference, May 14 – 19, 2010 | New Orleans, LA

Resumen

- La EPOC es una enfermedad inflamatoria.
- La EPOC es una enfermedad sistémica.
- En el futuro el tratamiento de la EPOC va a superar el ámbito pulmonar y se orientará hacia la inflamación sistémica.

Muchas gracias