Corticoides Inhalados.

¿Cuándo?, ¿Cuánto? ¿Riesgo de Neumonías? EFECTOS ADVERSOS

Dra. Lorena Montero Rivas
Servicio de Medicina Interna
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Parte del material bibliográfico para esta presentación

me ha sido proporcionado por AstraZeneca y GSK

GOLD 2014

La Enfermedad Pulmonar Obstructiva Crónica (EPOC), una enfermedad frecuente prevenible y tratable, se caracteriza por una limitación al flujo aéreo persistente que normalmente es progresiva y se asocia con una **elevada respuesta inflamatoria crónica en las vías respiratorias y el pulmón**, debido a la exposición a gases o partículas nocivas.

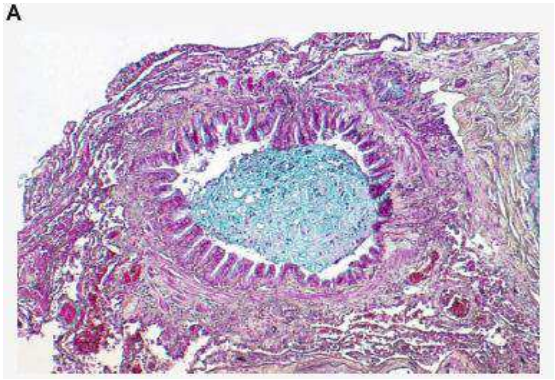
Global Strategy for Diagnosis, Management, and Prevention of COPD (Updated 2014)
http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html

The NEW ENGLAND JOURNAL of MEDICINE

The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease

James C. Hogg, M.D., Fanny Chu, B.Sc., Soraya Utokaparch, B.Sc., Ryan Woods, M.Sc., W. Mark Elliott, Ph.D.,

Progression of COPD is associated with the accumulation of inflammatory mucous exudates in the lumen and infiltration of the wall by innate and adaptive inflammatory immune cells that form lymphoid follicles. These changes are coupled to a repair or remodeling process that thickens the walls of these airways.



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

Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce symptoms

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce risk

OBJETIVOS DEL TRATAMIENTO DE LA EPOC. GesEPOC 2012

Arch Bronconeumol. 2012;48(Supl 1):2-58

ELSEVIER DOYMA

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Guía de Práctica Clínica para el Diagnóstico y Tratamiento de Pacientes con Enfermedad Pulmonar Obstructiva Crónica (EPOC) - Guía Española de la EPOC (GesEPOC)

Clinical Practice Guideline for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) – Spanish Guideline for COPD (GesEPOC)

Objetivos del tratamiento

Los objetivos generales del tratamiento de la EPOC se resumen en tres: reducir los síntomas crónicos de la enfermedad, disminuir la frecuencia y la gravedad de las agudizaciones y mejorar el pronóstico. Se deben alcanzar tanto los beneficios a corto plazo (control de la enfermedad) como los objetivos a medio y largo plazo (reducción del riesgo)[4,170].

Guía española de la EPOC (GesEPOC) Arch Bronconeumol 2012;48(7):247-257

ESTUDIOS DE CORTICOIDES INHALADOS EN EPOC

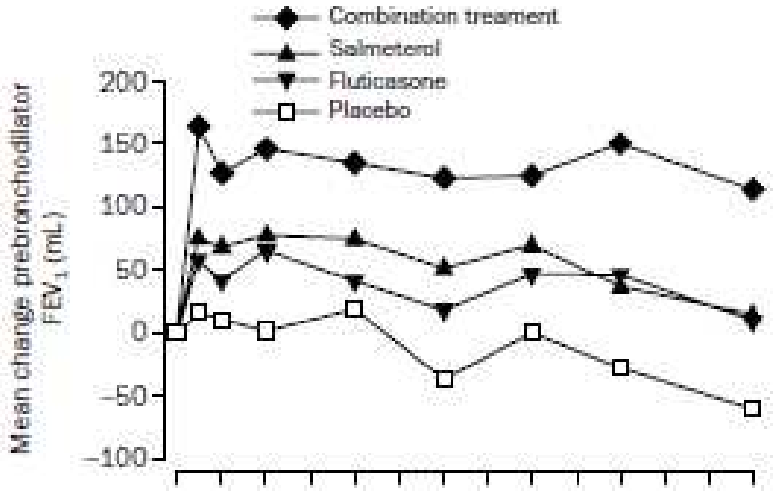
- ✓ **Efecto del CI sobre:**
  - **Función pulmonar**
  - **Reagudizaciones**
  - **Síntomas / Calidad de Vida**
  - **Mortalidad**

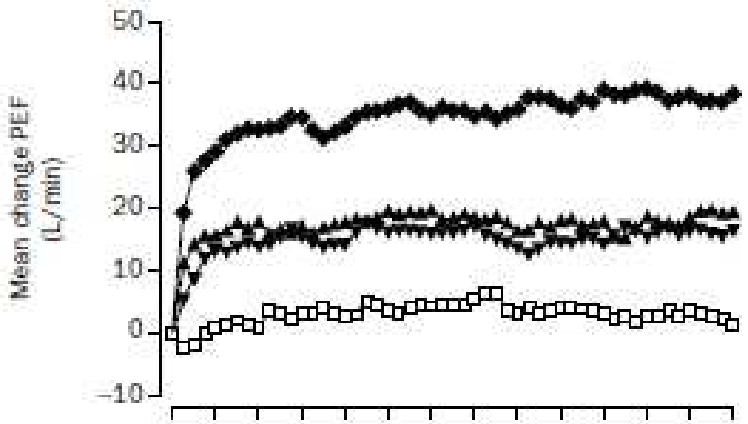
FUNCIÓN PULMONAR (FEV1 predosis y PEF)

THE LANCET ARTICLES

Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial

*Peter Calverley, Romain Pauwels, Jørgen Vestbo, Paul Jones, Neil Pride, Amund Gulsvik, Julie Anderson, Claire Maden for the TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) study group**



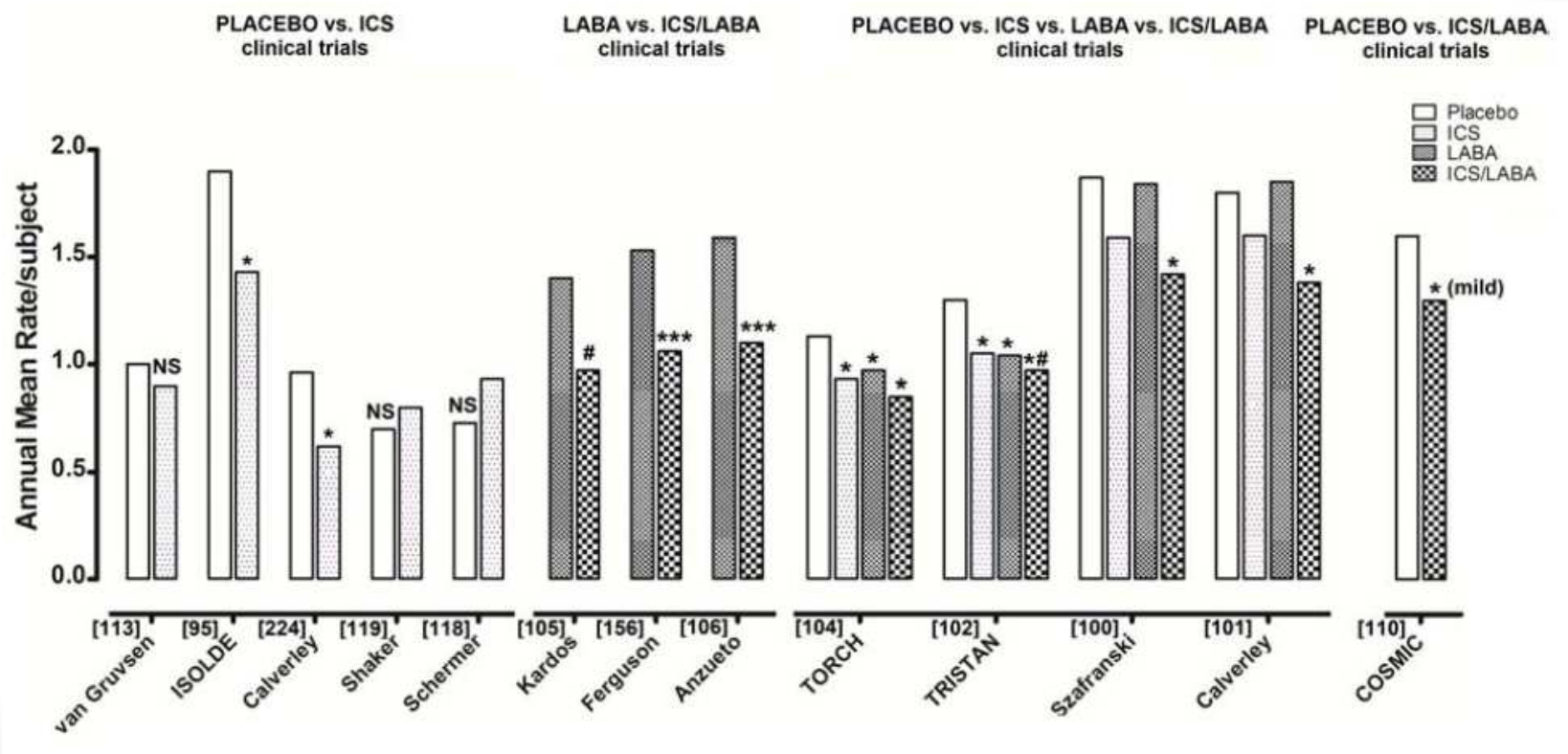


Calverley P et al. Lancet 2003;361: 449–56.

Inhaled Corticosteroids in COPD: Pros and Cons

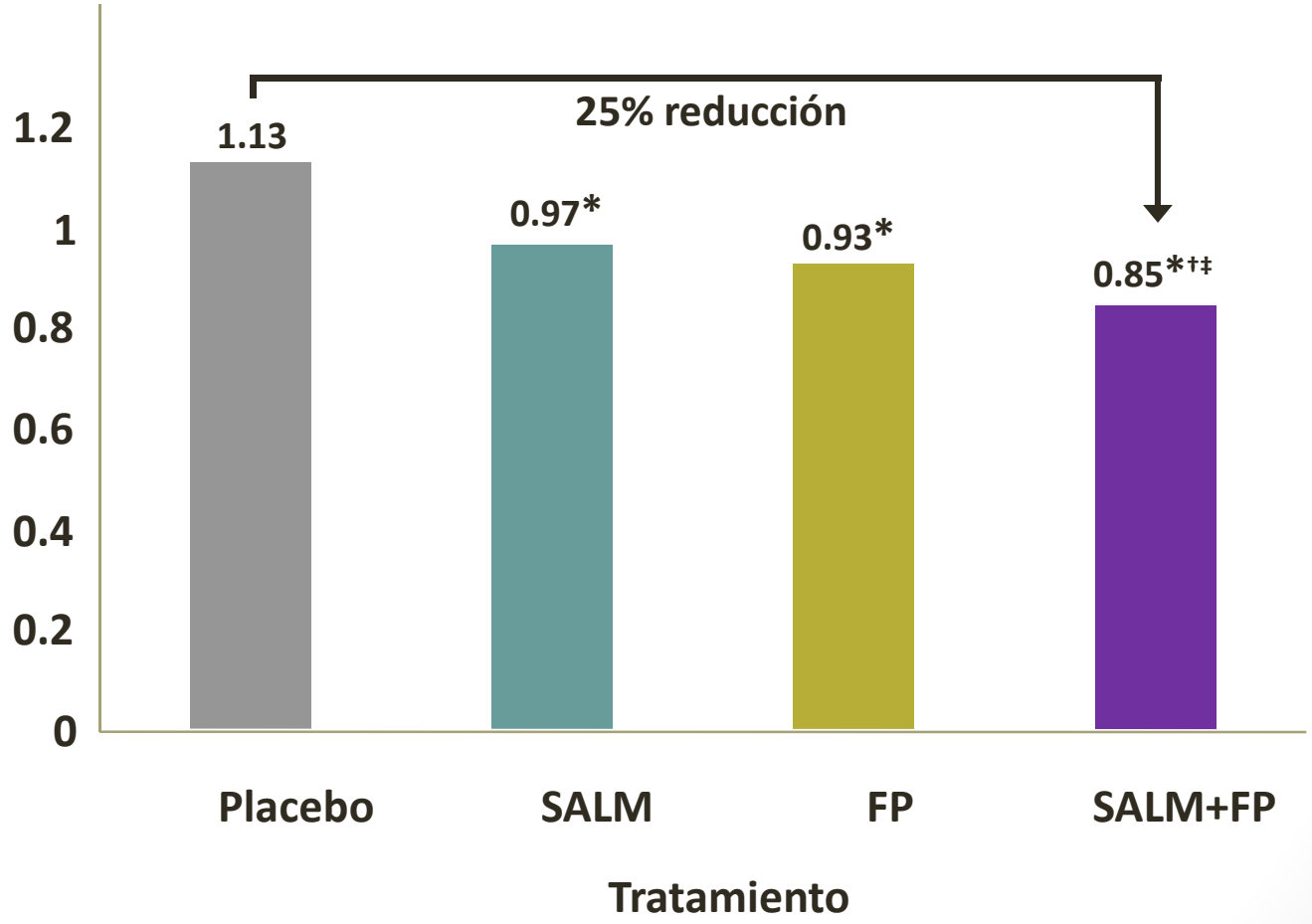
Eleftherios Zervas[1,*], Konstantinos Samitas[1], Mina Gaga[1], Bianca Beghe[2] and Leonardo M. Fabbri[2]

[1]7th Respiratory Medicine Department and Asthma Centre, Athens Chest Hospital, Athens, Greece; [2]Department of Oncology Haematology and Respiratory Diseases University of Modena & Reggio Emilia, Modena, Italy



Current Drug Targets, 2013, 14, 192-224

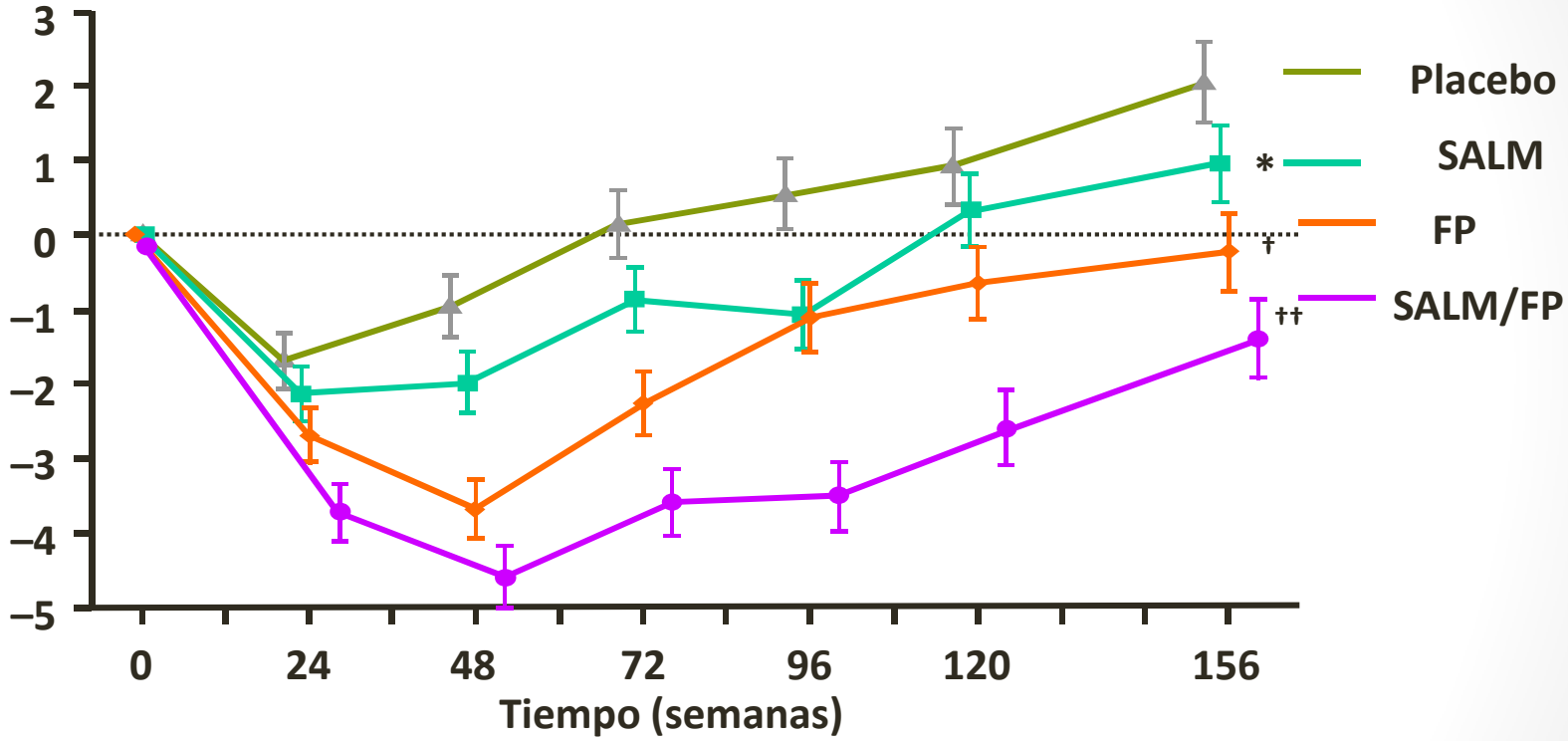
TORCH: Tasa de exacerbaciones moderadas y graves a lo largo de tres años



*p < 0.001 vs. placebo; †p = 0.002 vs. SALM; ‡p = 0.024 vs. FP

Calverley *et al.* NEJM 2007

TORCH: Puntuación total del SGRQ



Número de sujetos						
1149	854	781	726	675	635	569
1148	906	844	807	723	701	634
1155	942	848	807	751	686	629
1133	941	873	814	773	731	681

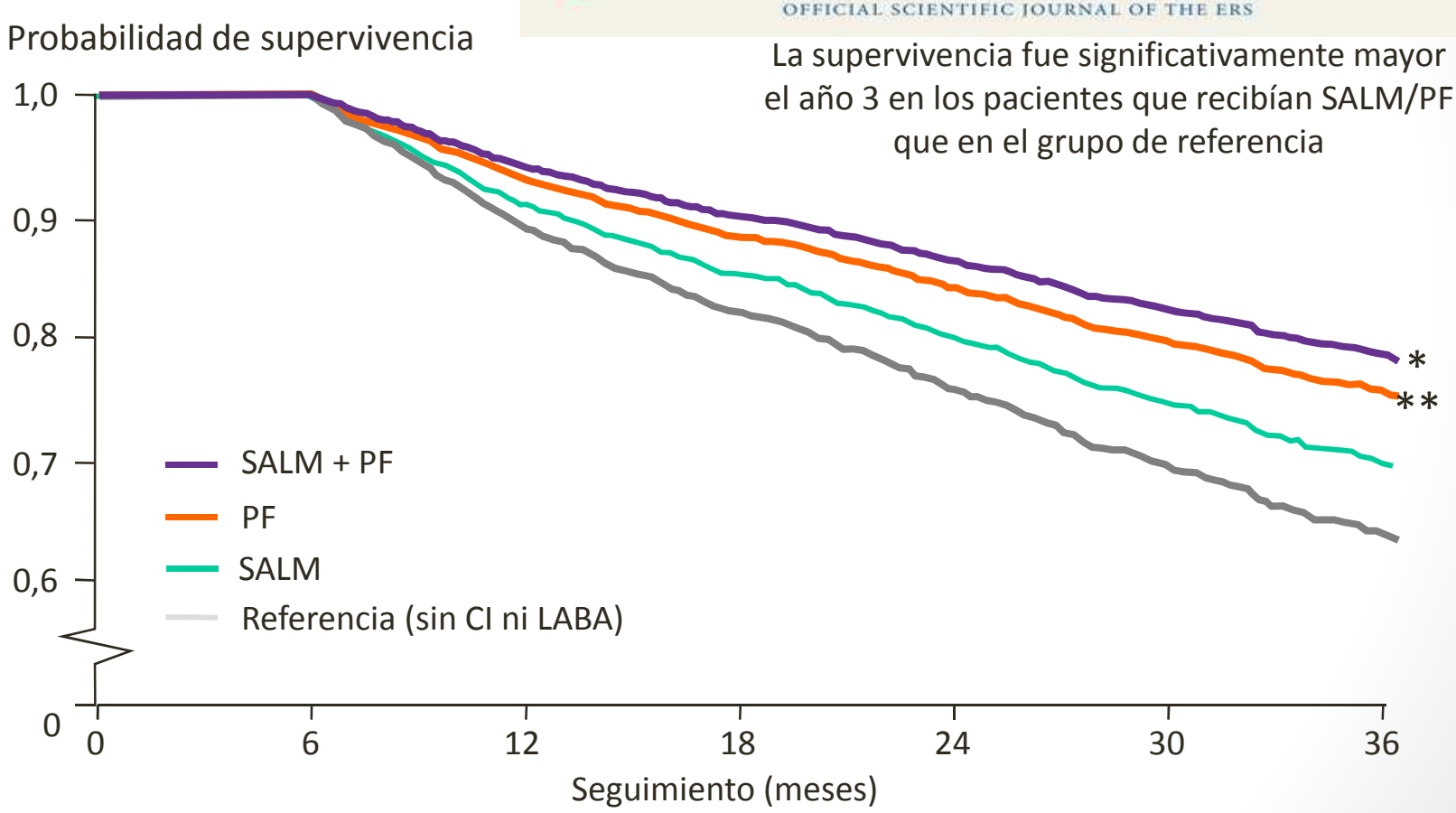
*p = 0.057 vs. placebo; †p < 0.001 vs. placebo; ††p < 0.001 vs. placebo, SALM y FP; barras verticales = error estandar

Calverley *et al.* NEJM 2007

Datos farmacoepidemiológicos: los CI con o sin LABA mejoran la supervivencia

EUROPEAN RESPIRATORY *journal*
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

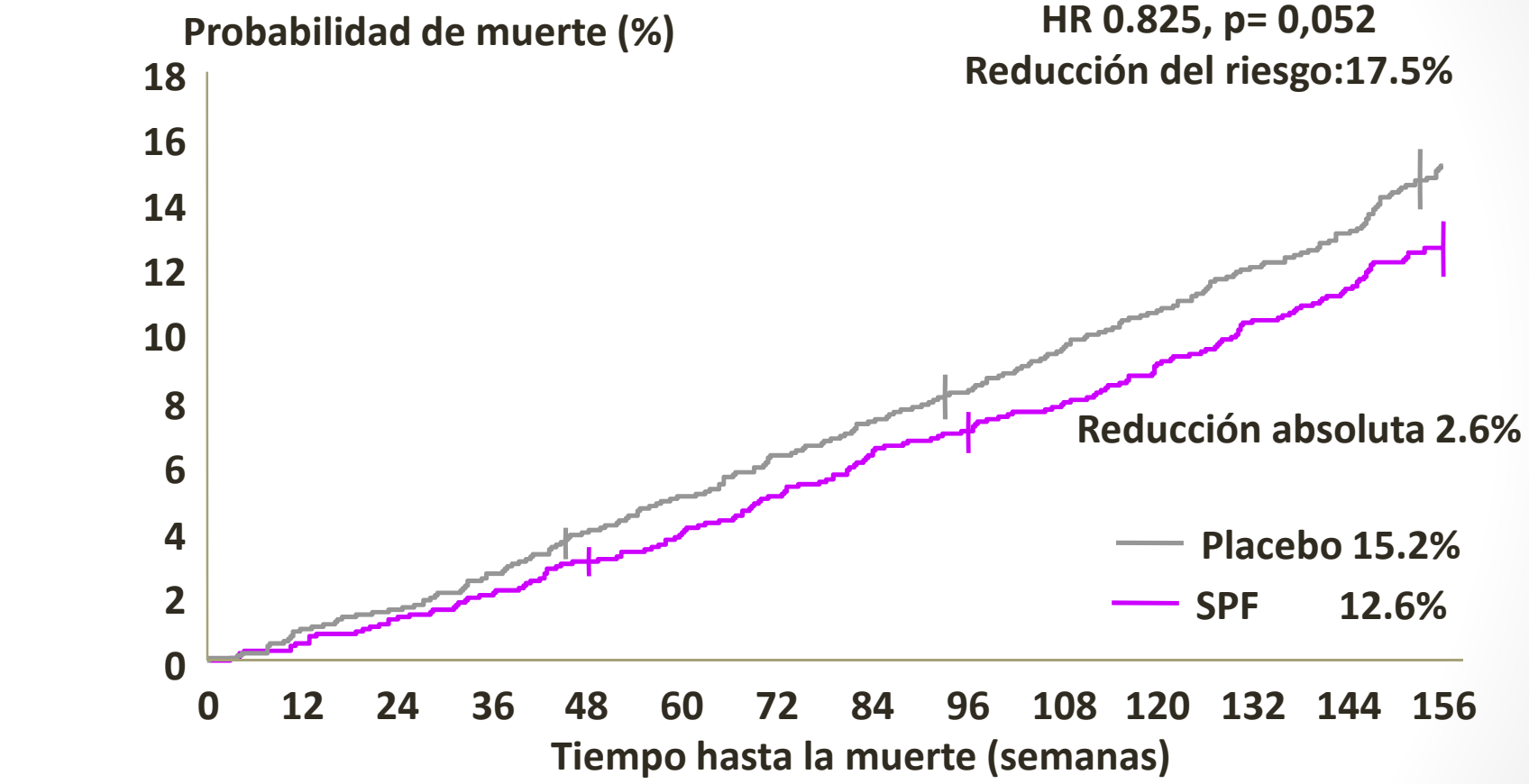
La supervivencia fue significativamente mayor el año 3 en los pacientes que recibían SALM/PF que en el grupo de referencia



* p=0,0008 PF y salmeterol frente al grupo de referencia
** p=0,0028 PF frente al grupo de referencia

Soriano et al. Eur Respir J 2002;20:819–25.

TORCH: Análisis primario: mortalidad a 3 años por todas las causas



Calverley *et al.* NEJM 2007

ESTUDIOS RELACIONADOS CON LA RETIRADA DE CORTICOIDES INHALADOS EN EPOC

RETIRADA DEL CI

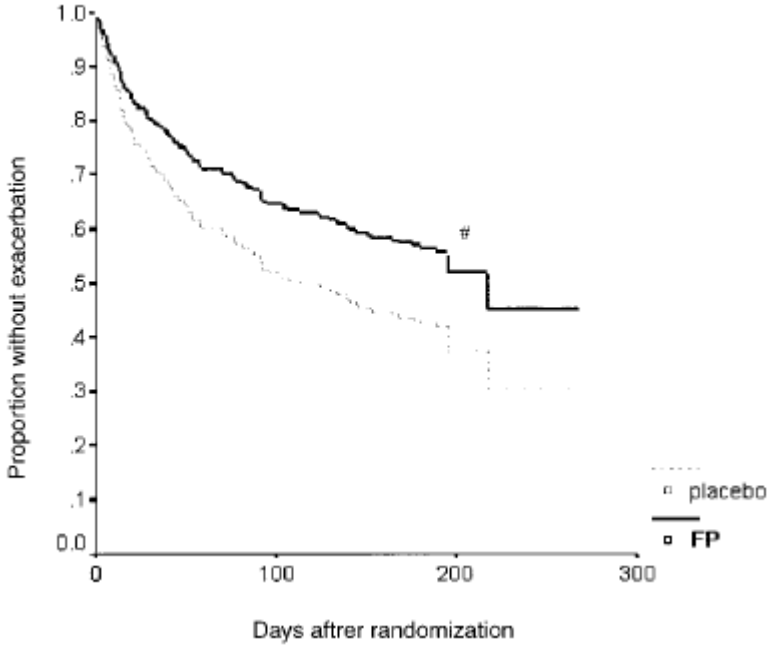
AJRCCM

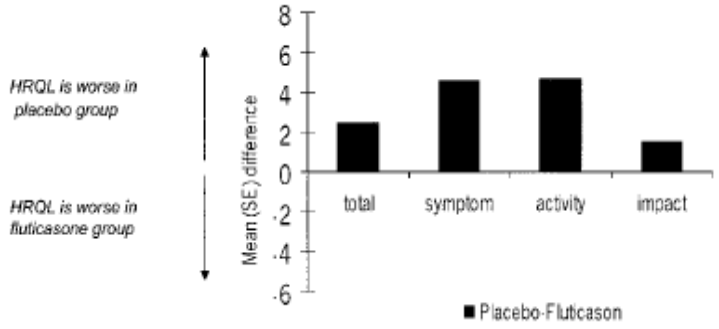
Effect of Discontinuation of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease

The COPE Study

Paul van der Valk, Evelyn Monninkhof, Job van der Palen, Gerhard Zielhuis, and Cees van Herwaarden

Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede; and Departments of Epidemiology and Biostatistics and Pulmonary Medicine, University Medical Center, Nijmegen, The Netherlands





van der Valk P et al. Am J Respir Crit Care Med, 2002;166:1358–1363

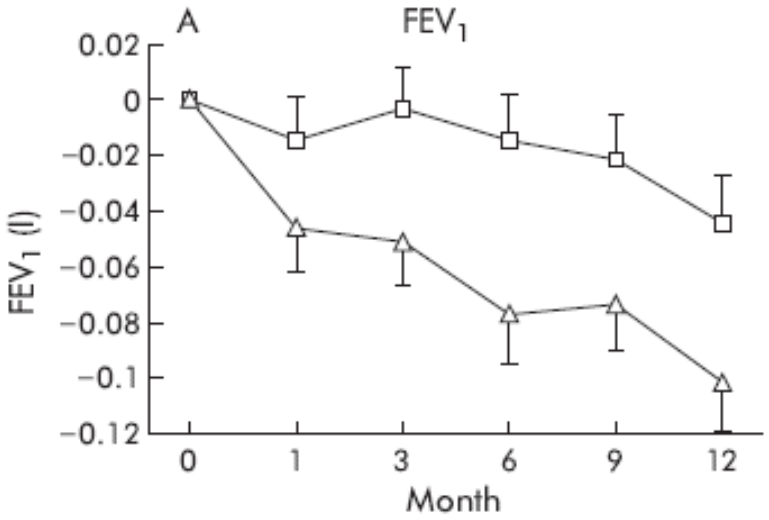
RETIRADA DEL CI

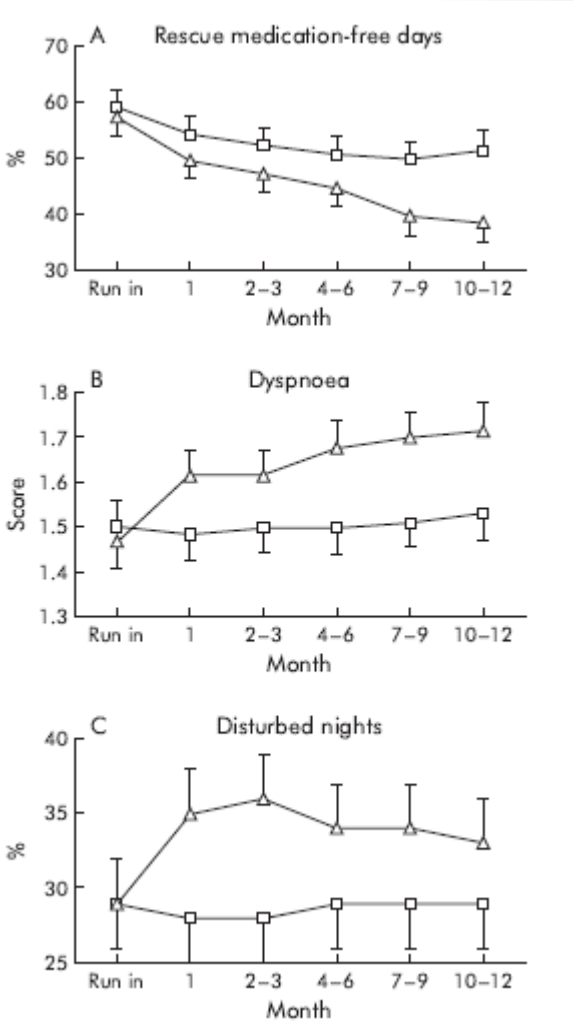
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial

E F M Wouters, D S Postma, B Fokkens†, W C J Hop, J Prins, A F Kuipers, H R Pasma, C A J Hensing, E C Creutzberg, for the COSMIC (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group

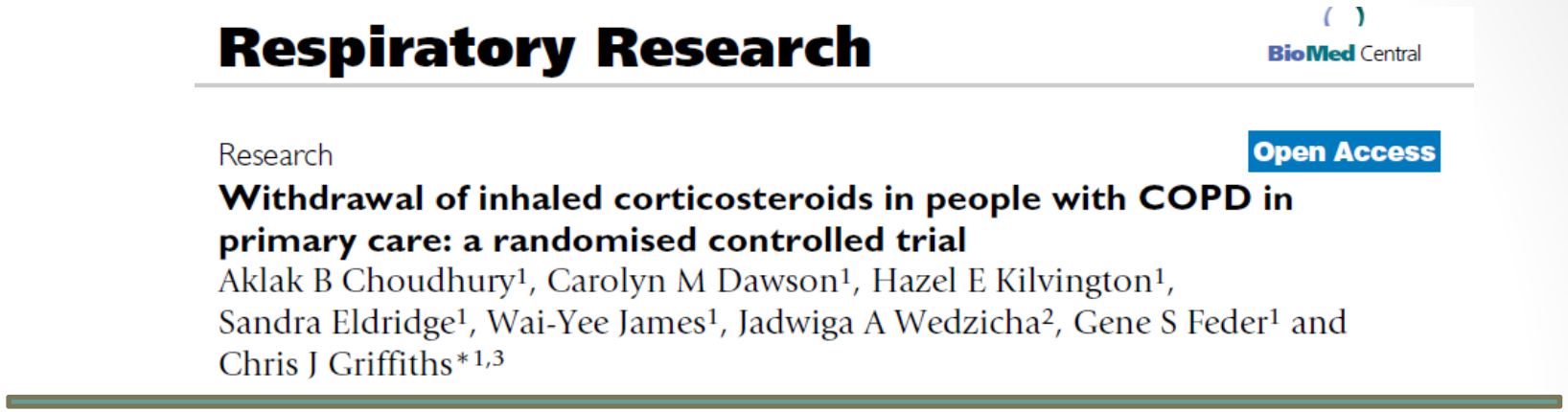
Thorax 2005;60:480–487. doi: 10.1136/thx.2004.034280





Wouters EFM et al. Thorax 2005;60:480–487

RETIRADA DEL CI



Respiratory Research

BioMed Central

Research

Open Access

Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial

Aklak B Choudhury[1], Carolyn M Dawson[1], Hazel E Kilvington[1], Sandra Eldridge[1], Wai-Yee James[1], Jadwiga A Wedzicha[2], Gene S Feder[1] and Chris J Griffiths*[1,3]

- ✓ La retirada del tratamiento de larga duración con CIs:
  - incrementa el riesgo de exacerbaciones
  - acorta el tiempo hasta la primera exacerbación
  - produce un empeoramiento de la sintomatología

- ✓ Los pacientes con EPOC moderada también ven incrementado el riesgo de exacerbar al retirar el tratamiento con CIs

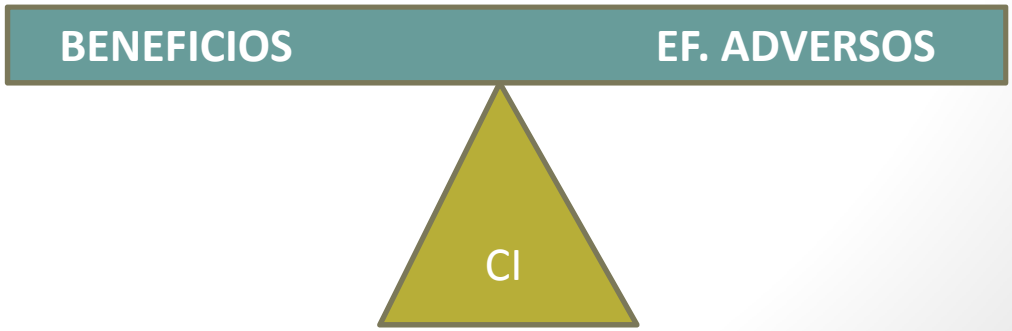
- ✓ Los pacientes mostraron su preferencia a volver a ser tratados con su CI habitual

Respir Res. 2007; 8(1): 93

CORTICOIDES INHALADOS : CUÁNDO ??? MANEJO GUÍAS DE PRACTICA CLÍNICA.

GESEPOC: GENERALIDADES EN EN CUANTO CORTICOIDES INHALADOS

- **CI + BDLD** →disminución significativa del número de agudizaciones
  → mejoría en la calidad de vida
  → No han mostrado un efecto beneficioso sobre la mortalidad.
- **Determinantes del beneficio del uso de CI:**
  - presencia de agudizaciones repetidas,→ fenotipo agudizador,.
  - NO el grado de obstrucción al flujo aéreo.
- **Indicados** : nivel de gravedad II con agudizaciones a pesar de un ttº con uno o dos broncodilatadores de larga duración.
- En la EPOC, los CI se deben utilizar siempre asociados a un BDLD: **CI NUNCA EN MONOTERAPIA**
- **BUSCAR:**



GESEPOC: Tratamiento farmacológico de la EPOC según fenotipos y niveles de gravedad

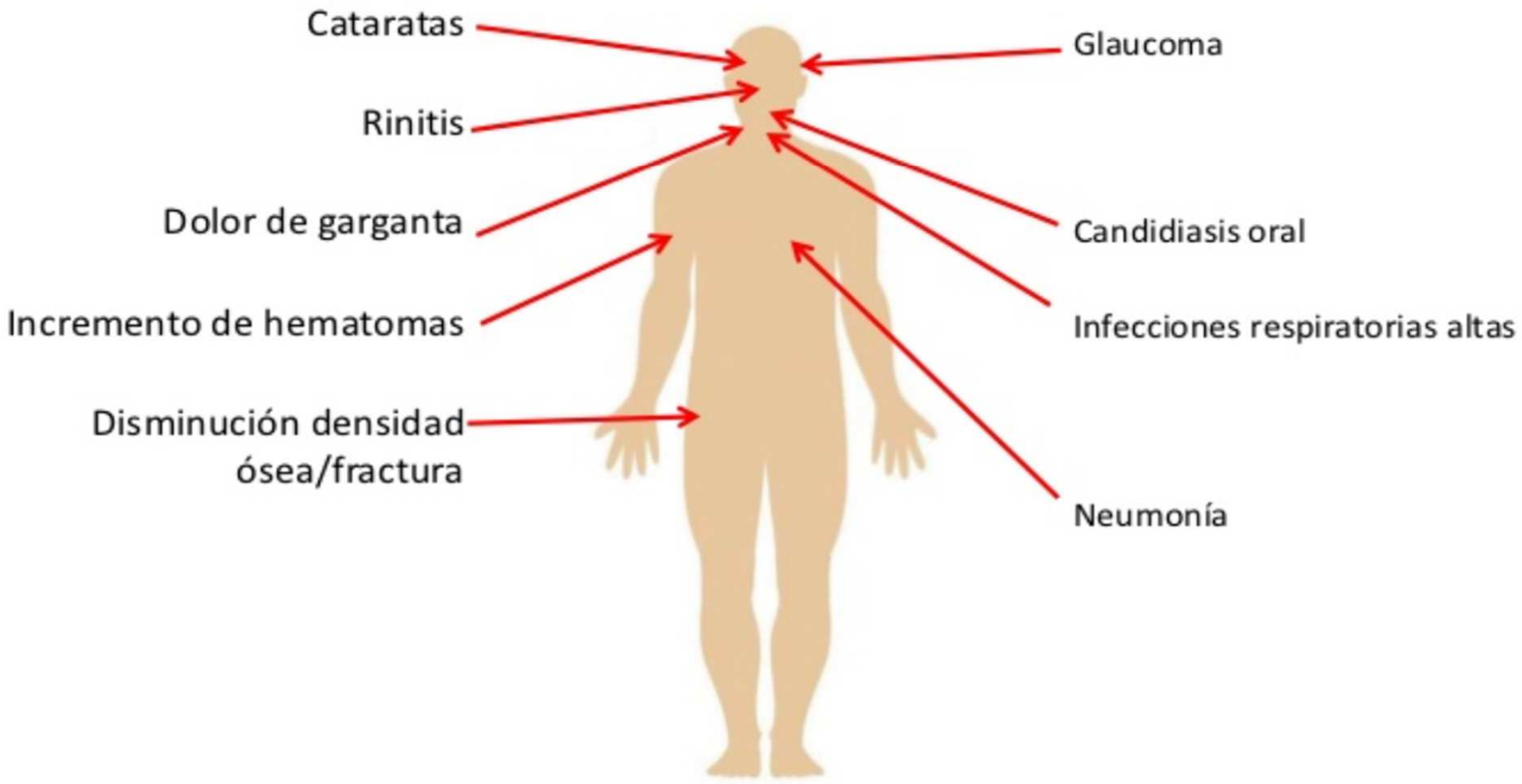
Fenotipo	Estadio de gravedad			
	I	II	III	IV
No agudizador	LAMA o LABA SABA o SAMA*	LAMA o LABA LAMA+ LABA	LAMA + LABA	LAMA + LABA + teofilina
Mixto EPOC-asma	LABA + CI	LABA + CI	LAMA + LABA + CI	LAMA + LABA + CI (valorar añadir teofilina o IPE4 si expectoración y agudizaciones)
Agudizador con enfisema	LAMA o LABA	LABA+ CI LAMA + LABA LAMA o LABA	LAMA + LABA + CI	LAMA + LABA + CI (valorar añadir teofilina)
Agudizador con BC	LAMA o LABA	LABA + CI LAMA + LABA LAMA o LABA (LAMA o LABA) + IPE4	LAMA + LABA + (CI o IPE4) (LAMA o LABA) + CI + IPE4 (valorar añadir carbocisteína)	LAMA + LABA + (CI o IPE4) LAMA + LABA + CI + IPE4 (valorar añadir carbocisteína) Valorar añadir teofilina Valorar añadir antibiótico

Guía española de la EPOC (GesEPOC). Actualización 2014. Arch Bronconeumol 2014;50(Suppl 1):1-16

Global Strategy for Diagnosis, Management and Prevention of COPD Manage Stable COPD: Pharmacologic Therapy (Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	RecommendedFirst choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		Theophylline
B	LAMA *or* LABA	LAMA and LABA		SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.		*C*arbocysteine *SABA and/or* SAMA Theophylline

POTENCIALES EFECTOS SECUNDARIOS DE LA TERAPIA CON CORTICOIDES INHALADOS EN LA EPOC



Efectos sistémicos de los corticoides inhalados

NEUMONIAS

- CI inhiben la producción de mediadores que favorecen reclutamiento de linfocitos y neutrofilos
- CI bloquean la respuesta inmunitaria en la vía aérea inhibiendo el reclutamiento de las células dendríticas y su capacidad de estimular a las células T .
- CI disminución de folículos linfoides en las vías aérea→ supresión de la inmunidad adaptativa→ infecciones.

TODOS LOS CI RECONOCEN EN FICHA TÉCNICA EL RIESGO DE PRODUCIR NEUMONÍA
PERO?????.....

CI se usan en exacerbaciones , la mayoría infecciosas.

CI a pesar de aumentar las tasas de neumonías NO AUMENTAN LAS MORTALIDAD

Inhaled Corticosteroids in COPD: Pros and Cons

Eleftherios Zervas[1,*], Konstantinos Samitas[1], Mina Gaga[1], Bianca Beghe[2] and Leonardo M. Fabbri[2]

[1]7th Respiratory Medicine Department and Asthma Centre, Athens Chest Hospital, Athens, Greece; [2]Department of Oncology Haematology and Respiratory Diseases University of Modena & Reggio Emilia, Modena, Italy

CI→MEUMONIAS

- Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007
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CI ≠ NEUMONIAS

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- Calverley PM, Stockley RA, Seemungal TA, *et al.* Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest 2011
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- Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012

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

Review

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.

Q J Med 2010; 103:379–385

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

EUROPEAN RESPIRATORY *journal*
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

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*,#

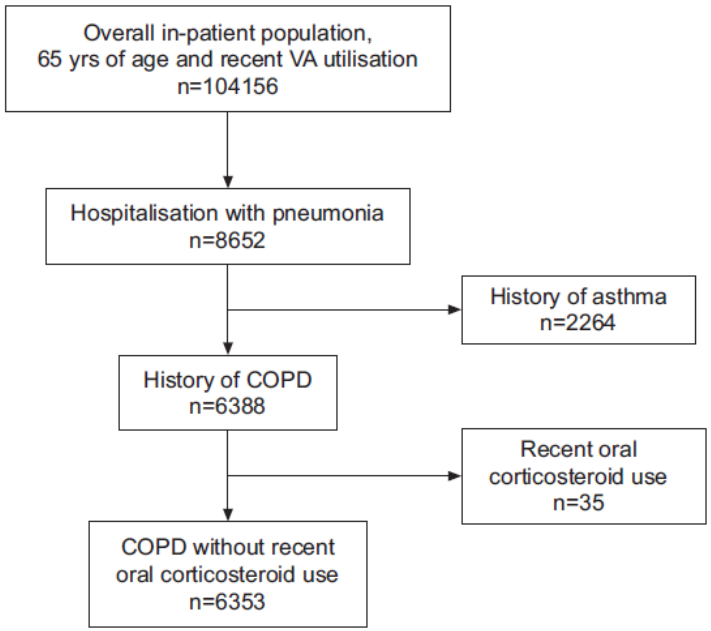

FIGURE 1. Flow diagram of the cohort selection of hospitalised pneumonia patients with chronic obstructive pulmonary disease (COPD). VA: Dept of Veterans Affairs.

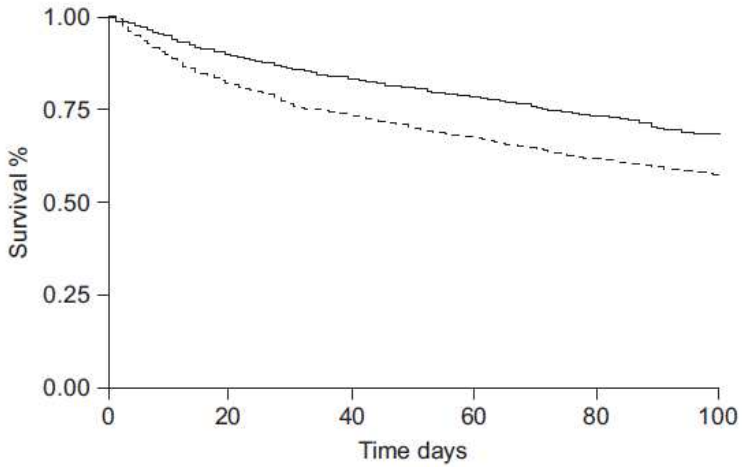

FIGURE 2. Kaplan–Meier curve of the proportion of surviving subjects hospitalised with pneumonia by outpatient inhaled corticosteroid use (—; n=2,420) *versus* non-use (---; n=3,933) ($p<0.001$).

R. Malo de MolinaEur Respir J 2010; 36: 751–757

OPEN ACCESS

ORIGINAL ARTICLE

Inhaled corticosteroids in COPD and the risk of serious pneumonia

Samy Suissa, Valérie Patenaude, Francesco Lapi, Pierre Ernst

Departments of Epidemiology and Biostatistics and of Medicine, Center for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, McGill University, Montreal, Québec, Canada

Correspondence to
Prof Samy Suissa, Centre for Clinical Epidemiology, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Québec, Canada H3T 1E2:

ABSTRACT

Background Inhaled corticosteroids (ICS) are known to increase the risk of pneumonia in patients with chronic obstructive pulmonary disease (COPD). It is unclear whether the risk of pneumonia varies for different inhaled agents, particularly fluticasone and budesonide, and increases with the dose and long-term duration of use.

Methods We formed a new-user cohort of patients with COPD treated during 1990–2005. Subjects were identified using the Quebec health insurance databases and followed through 2007 or until a serious pneumonia event, defined as a first hospitalisation for or death from pneumonia. A nested

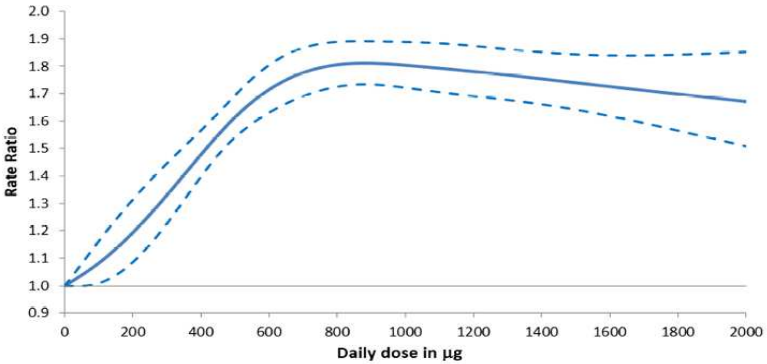

Table 2 Characteristics of controls selected from cohort of patients with COPD, according to current use of fluticasone and budesonide

	Non-use	Fluticasone	Budesonide
Number of subjects	120 890	24 198	9542
Age (years), mean±SD	78.5±7.7	78.1±7.9	76.9±7.4
Follow-up (years), mean±SD	4.3±3.6	4.5±3.7	4.2±3.5
Sex, % men	44.9	47.5	47.6
Hospitalisation for pneumonia in year prior to cohort entry, %	2.9	3.5	2.1
Hospitalisation for COPD in year prior to index date, %	2.1	9.4	4.7
Number of hospitalisations for COPD in year prior to index date (mean±SD)	0.0±0.2	0.1±0.4	0.1±0.3

Suissa S, et al. Thorax 2013;68:1029–1036

ORIGINAL ARTICLE

MAYO CLINIC

Prehospital Use of Inhaled Corticosteroids and Point Prevalence of Pneumonia at the Time of Hospital Admission: Secondary Analysis of a Multicenter Cohort Study

Emir Festic, MD; Vikas Bansal, MBBS, MPH; Ognjen Gajic, MD, MS; and Augustine S. Lee, MD; on behalf of the United States Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS)

Abstract

Objective: To address clinical concern regarding the use of inhaled corticosteroids (ICSs) and the risk for pneumonia, particularly among patients with chronic obstructive pulmonary disease (COPD) and asthma.

Patients and Methods: A multicentered prospective cohort of patients admitted to the hospital from March 1, 2009, through August 31, 2009, with pneumonia or another risk factor for acute respiratory distress syndrome was analyzed to determine the risk for pneumonia requiring hospitalization among patients taking ICSs. The adjusted risk (odds ratio [OR]) for developing pneumonia because of ICSs was determined in a multiple logistic regression model.

Results: Of the 5584 patients in the cohort, 495 (9%) were taking ICSs and 1234 (22%) had pneumonia requiring hospitalization. In univariate analyses, pneumonia occurred in 222 (45%) of the patients on ICSs vs 1012 (20%) in those who were not (OR, 3.28; 95% CI, 2.71-3.96; $P<.001$). After adjusting in the logistic regression model, prehospital ICS use was not significantly associated with pneumonia in the whole cohort (OR, 1.20; 95% CI, 0.93-1.53; $P=.162$), among the subset of 589 patients with COPD (OR, 1.40; 95% CI, 0.95-2.09; $P=.093$), among the 440 patients with asthma (OR, 1.07; 95% CI, 0.61-1.87; $P=.81$), nor among the remaining 4629 patients without COPD or asthma (OR, 1.32; 95% CI, 0.88-1.97; $P=.179$).

Conclusion: When adjusted for multiple confounding variables, ICS use was not substantially associated with an increased risk for pneumonia requiring admission in our cohort.

 ■ Mayo Clin Proc. 2014;89(2):154-162

Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease (Review)

Nannini LJ, Poole P, Milan SJ, Kesterton A

THE COCHRANE COLLABORATION®

Cochrane Database of Systematic Reviews 2013, Issue 8.

✓En los participantes con EPOC moderada y grave, el beneficio clínico es evidente cuando LABA y CI se administran conjuntamente en lugar de solos CI.

✓Los pacientes pueden vivir más tiempo y tienen menos exacerbaciones con tratamiento combinado en comparación con CI solos .

✓La reducción en las exacerbaciones varía, dependiendo de la frecuencia de estos eventos en pacientes individuales.

✓El beneficio en la mortalidad necesita al menos dos años a ser evidente.

✓La administración de CI sin LABA es una estrategia no válida en el tratamiento de la EPOC.

✓La dosis mínima efectiva de los CI no está clara.

✓ Los tres inhaladores de combinación mostraron efectos similares sobre resultados de la revisión, incluidos los efectos adversos.

Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease (Review)

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THE COCHRANE COLLABORATION®

Cochrane Database of Systematic Reviews 2012, Issue 9.

✓En pacientes con EPOC moderada y grave la terapia de combinación conlleva:

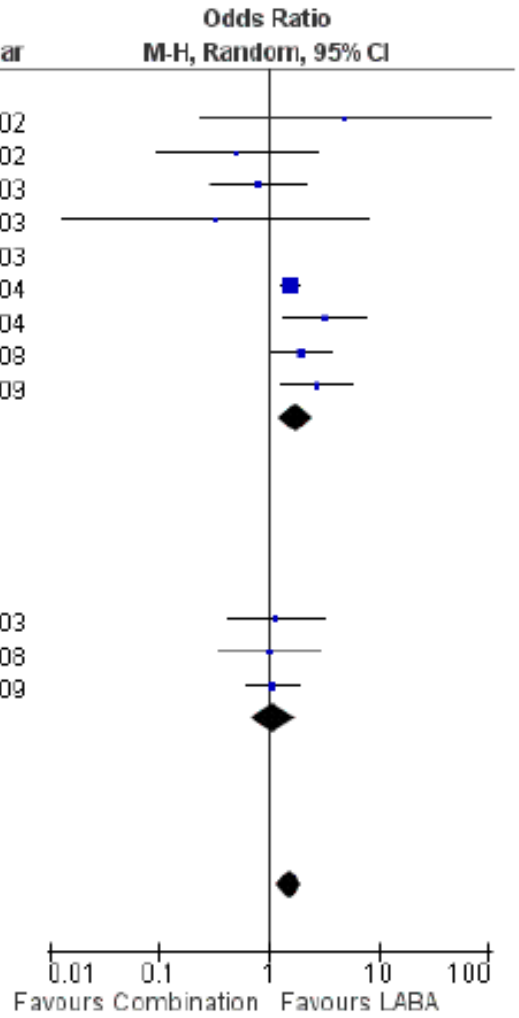
- Menor número de exacerbaciones
- Mejor calidad de vida
- Mejoría de la función pulmonar
- Mejoría de síntomas
- Menor uso de medicación de rescate,que con acción prolongada beta2-agonista de tratamiento solo.

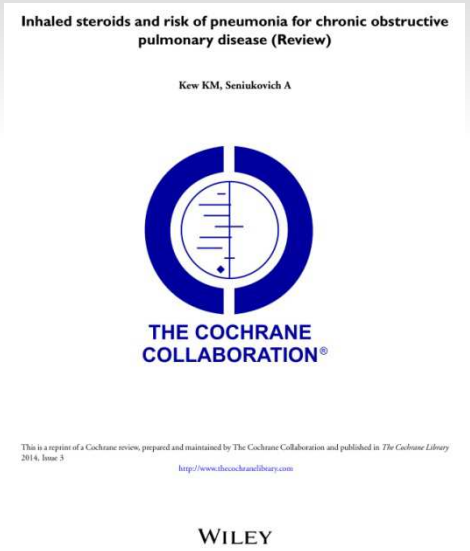
✓Las tasas de efectos secundarios fueron similares entre la terapia de combinación y los beta2 agonistas de acción prolongada, con la excepción de la candidiasis oral, infección del tracto respiratorio superior y un aumento del riesgo de neumonía observada con tratamiento combinado.

✓Los médicos y los pacientes deben sopesar los beneficios de la terapia de combinación en términos de reducción de las exacerbaciones de la EPOC con el riesgo que supone en términos del posible aumento del riesgo de neumonía.

Figure 6. Forest plot of comparison: 1 Combined inhalers versus long-acting beta2-agonists (primary outcomes), outcome: 1.3 Pneumonia.

Study or Subgroup	Combination Events	Combination Total	LABA Events	LABA Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.5.1 Fluticasone/salmeterol							
Mahler 2002	2	165	0	160	0.7%	4.91 [0.23, 103.04]	2002
SCO100470	2	518	4	532	2.2%	0.51 [0.09, 2.81]	2002
TRISTAN	7	358	9	372	5.9%	0.80 [0.30, 2.18]	2003
Hanania 2003	0	178	1	177	0.6%	0.33 [0.01, 8.15]	2003
O'Donnell 2006	0	62	0	59		Not estimable	2003
TORCH	303	1546	205	1542	36.7%	1.59 [1.31, 1.93]	2004
Kardos 2007	23	507	7	487	7.7%	3.26 [1.39, 7.67]	2004
Ferguson 2008	29	394	15	388	12.1%	1.98 [1.04, 3.75]	2008
Anzueto 2009	26	394	10	403	9.6%	2.78 [1.32, 5.84]	2009
Subtotal (95% CI)		**4122**		**4120**	**75.6%**	**1.75 [1.25, 2.45]**	
Total events	392		251				
Heterogeneity: Tau² = 0.06; Chi² = 10.03, df = 7 (P = 0.19); I² = 30%							
Test for overall effect: Z = 3.23 (P = 0.001)							
1.5.2 Budesonide/formoterol							
Calverley 2003	8	254	7	255	5.6%	1.15 [0.41, 3.23]	2003
Tashkin 2008	10	558	5	284	5.1%	1.02 [0.34, 3.01]	2008
Rennard 2009	37	988	17	495	13.8%	1.09 [0.61, 1.96]	2009
Subtotal (95% CI)		**1800**		**1034**	**24.4%**	**1.09 [0.69, 1.73]**	
Total events	55		29				
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.37 (P = 0.71)							
Total (95% CI)		**5922**		**5154**	**100.0%**	**1.55 [1.20, 2.01]**	
Total events	447		280				
Heterogeneity: Tau² = 0.04; Chi² = 12.84, df = 10 (P = 0.23); I² = 22%							
Test for overall effect: Z = 3.32 (P = 0.0009)							
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%							





[Intervention Review]

Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease

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Authors' conclusions

Budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls. The safety concerns highlighted in this review should be balanced with recent cohort data and established randomised evidence of efficacy regarding exacerbations and quality of life. Comparison of the two drugs revealed no statistically significant difference in serious pneumonias, mortality or serious adverse events. Fluticasone was associated with higher risk of any pneumonia when compared with budesonide (i.e. less serious cases dealt with in the community), but variation in the definitions used by the respective manufacturers is a potential confounding factor in their comparison.

Primary research should accurately measure pneumonia outcomes and should clarify both the definition and the method of diagnosis used, especially for new formulations such as fluticasone furoate, for which little evidence of the associated pneumonia risk is currently available. Similarly, systematic reviews and cohorts should address the reliability of assigning 'pneumonia' as an adverse event or cause of death and should determine how this affects the applicability of findings.

Efectos sistémicos de los corticoides inhalados

OSTEOPOROSIS Y FRACTURAS

OP: Edad
Tabaquismo,
Actividad física,
Toma de medicación (corticoides)
Enfermedades crónicas con inflamación sistémica de baja intensidad .

EPOC
Tabaquismo
el sedentarismo
Ciclos de esteroides sistémicos / Inhalados

CORTICOIDES Y OP

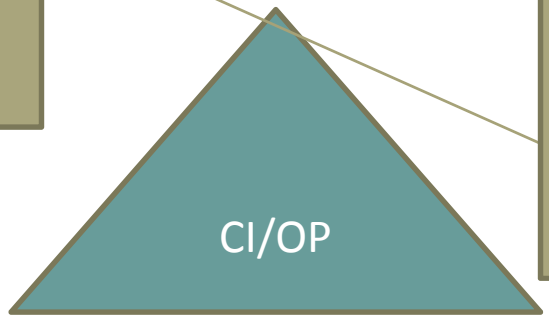
Disminución de la apoptosis de los osteoclastos,
Fomento de la apoptosis de los osteocitos
Inhibición de la proliferación y la maduración de los osteoblastos.
Aumentarían NF-kB ligando→ estimulo para la diferenciación y actividad osteoclastos.
Atrofia muscular.
Alteraciones hormonales
Inhibición de la absorción de Ca

Pérdida de densidad ósea.

Efectos sistémicos de los corticoides inhalados

OSTEOPOROSIS Y FRACTURAS

The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;



Pauwels RA. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med. 1999;340:1948-53

Ferguson GT. Prevalence and progression of osteoporosis in patients with COPD: results from the towards a revolution in COPD health study. Chest. 2009.- TORCH

La prevalencia de osteoporosis y osteopenia era muy alta en EPOC moderada-grave .
Sólo un 10 % de los pacientes recibían tratamiento

Efectos sistémicos de los corticoides inhalados

FRACTURAS

Riesgo de fracturas en la EPOC por la toma de CI.

Edad avanzada
Escasa movilidad
Tabaquismo
Bajo peso

→ EPOC GRAVE

Riesgo de fractura es menor que con otros fármacos: antipsicótica (2,8 veces mayor) o uso de hipnóticos (1,7) .

TORCH :
Fracturas escasas
Origen traumático.
No se encontraron diferencias estadísticamente significativas entre los grupos con ttº y con placebo en la tasa de fracturas.

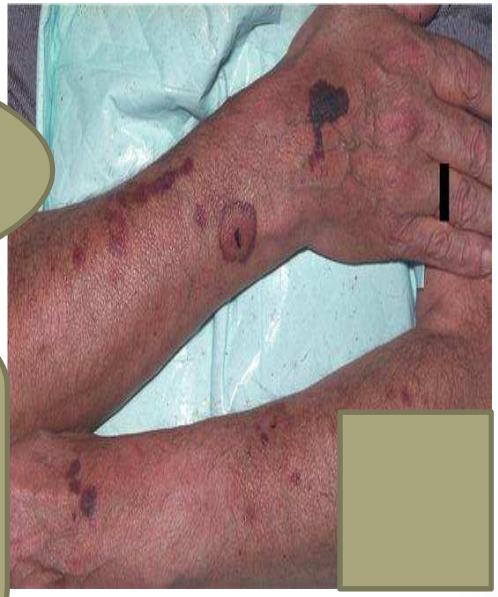
Metaanálisis Drummond MB en JAMA. 2008→ no se encontraron diferencias en el riesgo de fracturas entre los que utilizaron CI y los que no.

Metanálisis Weatherall M en Clin Exp Allergy. 2008→ asociación entre la toma de CI y la presencia de fracturas no vertebrales

Efectos sistémicos de lo corticoides inhalados

EQUIMOSIS Y ALTERACIONES CUTÁNEAS: (aumento del 1% por cada año de empleo)

Tashkin DP and Cia. Skin manifestations of inhaled corticosteroidsin COPD patients: results from Lung Health Study II. Chest. 2004.



Capewell S and Cia. Purpura and dermal thinning associated with high dose inhaled corticosteroids. BMJ. 1990

Cuestión estética???
Manifestaciones cutáneas →absorción y efecto sistémicos de los CI.
ESTAS MANIFESTACIONES CUTÁNEAS COMO MARACADORES DE TOXICIDAD SISTÉMICA.

Efectos sistémicos de los corticoides inhalados

SUPRESIÓN SUPRARRENAL

TRASTORNOS PSIQUIÁTRICOS: ansiedad, trastornos del sueño y alteraciones del comportamiento, tales como hiperactividad e irritabilidad

GLAUCOMA y CATARATAS:

CI→ Cataratas nuclear y subcapsular posterior.

- Cumming RG. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med. 1999
- Garbe E. Association of inhaled corticosteroid use with cataract extraction in elderly patients. JAMA. 1998
- Jick SS. The risk of cataract among users of inhaled steroids. Epidemiology. 2001
- Smeeth L A population based case-control study of cataract and inhaled corticosteroids. Br J Ophthalmol. 2003.
- Ernst P. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. Eur Respir J. 2006.
- Weatherall M. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta- analysis. Respirology. 2009
- Wang JJ. Use of inhaled and oral corticosteroids and the long-term risk of cataract. Ophthalmology. 2009

Efectos adversos locales de los corticoides inhalados

- DISFONÍA (2% de aumento por cada año de empleo)
- FARINGITIS
- CANDIDIASIS OROFARINGEA
- SEQUEDAD FARINGEAS
- TOS (4%)

Fluticasona /Budesonida > Beclometasona

Valorar siempre en los pacientes orofaringe y la técnica de inhalado ,así como medidas higiénicas en cada consulta

CONCLUSIONES

Cuando???

GesEPOC
guía española de la EPOC

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

La Medicina Interna es una especialidad médica que aporta una ATENCION GLOBAL al enfermo, asumiendo la COMPLETA RESPONSABILIDAD de la misma, de una forma CONTINUA desde la consulta externa a las unidades de hospitalización. En principio, al médico internista deben INTERESARLE TODOS los problemas de los enfermos, y muy concretamente la VISION DEL MISMO COMO UN TODO, siendo consciente de que frecuentemente va a ser precisa la intervención de otros especialistas para poder llegar a diagnósticos correctos y poder efectuar tratamientos adecuados. Lo que más caracteriza a esta especialidad es esta VISIÓN DE CONJUNTO Y DE SÍNTESIS.

CONCLUSIONES

- Cuánto???

- Reacciones adversas

La Medicina es una ciencia estadística en la que predomina la incertidumbre

CONCLUSIONES

Ayres JG. Cost-effectiveness of fluticasone propionate in the treatment of chronic obstructive pulmonary disease: a double-blind randomized, placebo-controlled trial. Respir Med 2003.

Paltiel AD, Fuhlbrigge AL, Kitch BT, *et al.* Cost-effectiveness ofinhaled corticosteroids in adults with mild-to-moderate asthma: results from the asthma policy model. J Allergy Clin Immunol2001.

Hertel N, *et al*. Cost-effectiveness of available treatment options forpatients suffering from severe COPD in the UK: a fully incrementalanalysis. Int J Chron Obstruct Pulmon Dis 2012.

Dal NR, *et al*. Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients. Int J Chron Obstruct Pulmon Dis 2007.

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Akazawa M, *et al*. Assessing treatment effects of inhaled corticosteroids on medical expenses and exacerbations among COPD patients: longitudinal analysis of managed care claims. Health Serv Res 2008.

EL FUTURO ES PRESENTE

COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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The COPD Pipeline XXIII

Nicholas Gross

LAMA/LABA Combinations		
Forest	Aclidinium/formoterol DPI	Ph III
GSK/Theravance	Umeclidinium/vilanterol (Anoro) DPI	NDA*
BI	Olodaterol/tiotropium Respimat	Ph III
Novartis	Glycopyrrolate/indacaterol DPI	Ph III
Pearl	Glycopyrrolate/formoterol MDI	Ph II
ICS/LABA Combinations		
Merck	Mometasone/formoterol MDI	NDA*
GSK/Theravance	Fluticasone/vilanterol (Relvar/Breo)	Approved
Mylan Specialty	Fluticasone/formoterol Neb soln	Ph II ->III
Pearl	PT002/009 MDI	Preclinical
Novartis	Mometasone/indacaterol DPI	Ph II
MABA+		
GSK/Theravance	GSK961081	Ph II
AstraZeneca	AZD2115	Ph II
ICS/LAMA/LABA Triple Combinations		
GSK	Fluticasone/vilanterol/umeclidinium	Ph I
GSK	Fluticasone/GSK961081	Ph II
GSK	Advair/umeclidinium	Ph III
Pearl	PT010 ICS/LABA/LAMA	Preclinical

*NDA, New Drug Application.
+MABA, muscarinic antagonist/beta agonist.

COPD, 10:545–546, 2013

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