XXXIV Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

XXIX Congreso de la Sociedad Andaluza de Medicina Interna (SADEMI)

Cumplimentación del tratamiento en EPOC con comorbilidades

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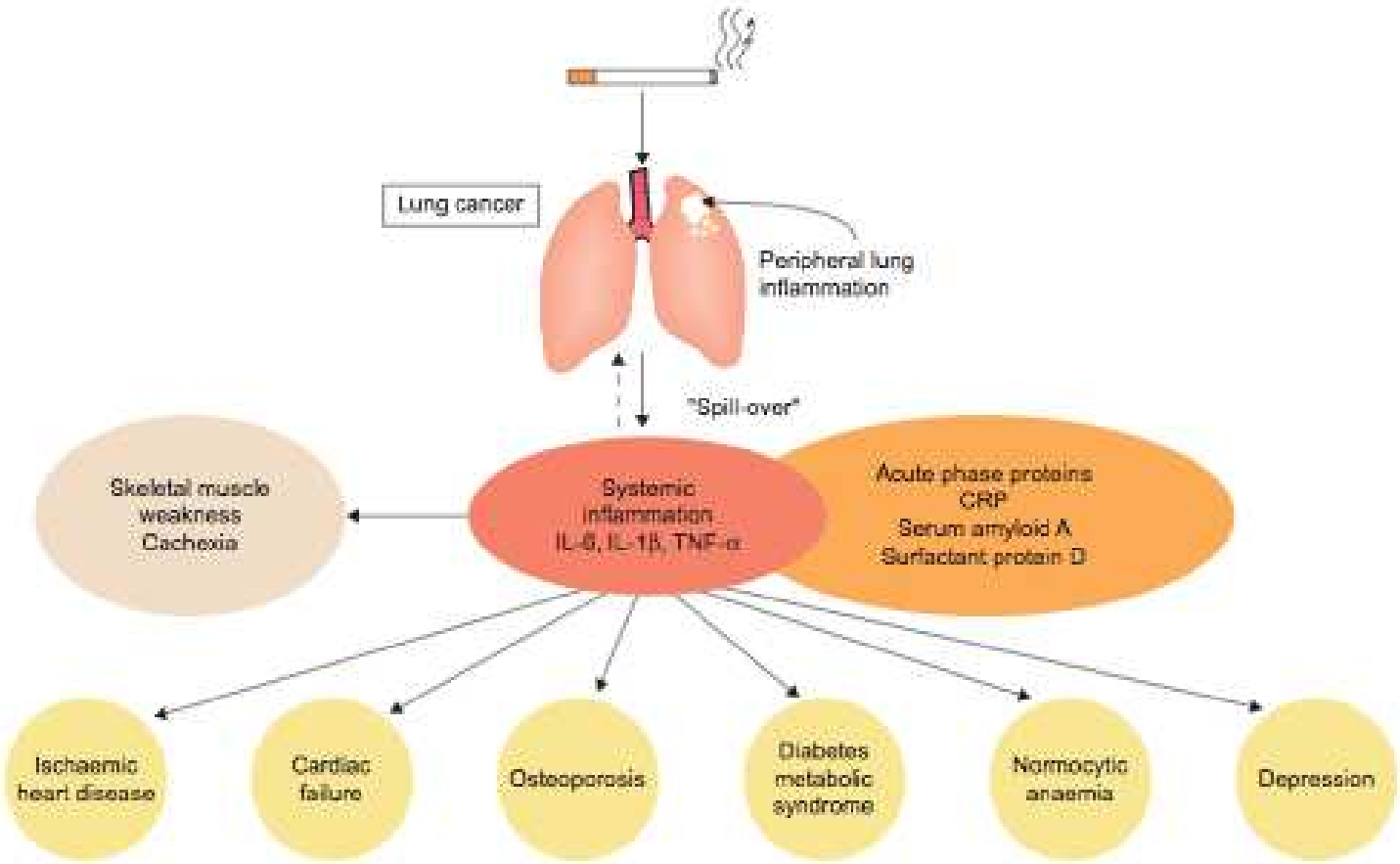
Conflicto de intereses: fondos por ponencias, colaboraciones científicas o asistencia a congresos de Boehringer Ingelheim, Pfizer y Menarini.

Guión

- Concepto de comorbilidad
- Significado clínico de la comorbilidad
- Comorbilidad en la guías de EPOC
- Los pacientes EPOC en la “vida real”
- Tratamiento de las comorbilidades (cardiovascular)
    - seguridad CV del tratamiento de la EPOC
        - agonistas adrenérgicos
        - anticolinérgicos
    - influencia del tratamiento de la ECV en pacientes con EPOC

Systemic manifestations and comorbidities of COPD

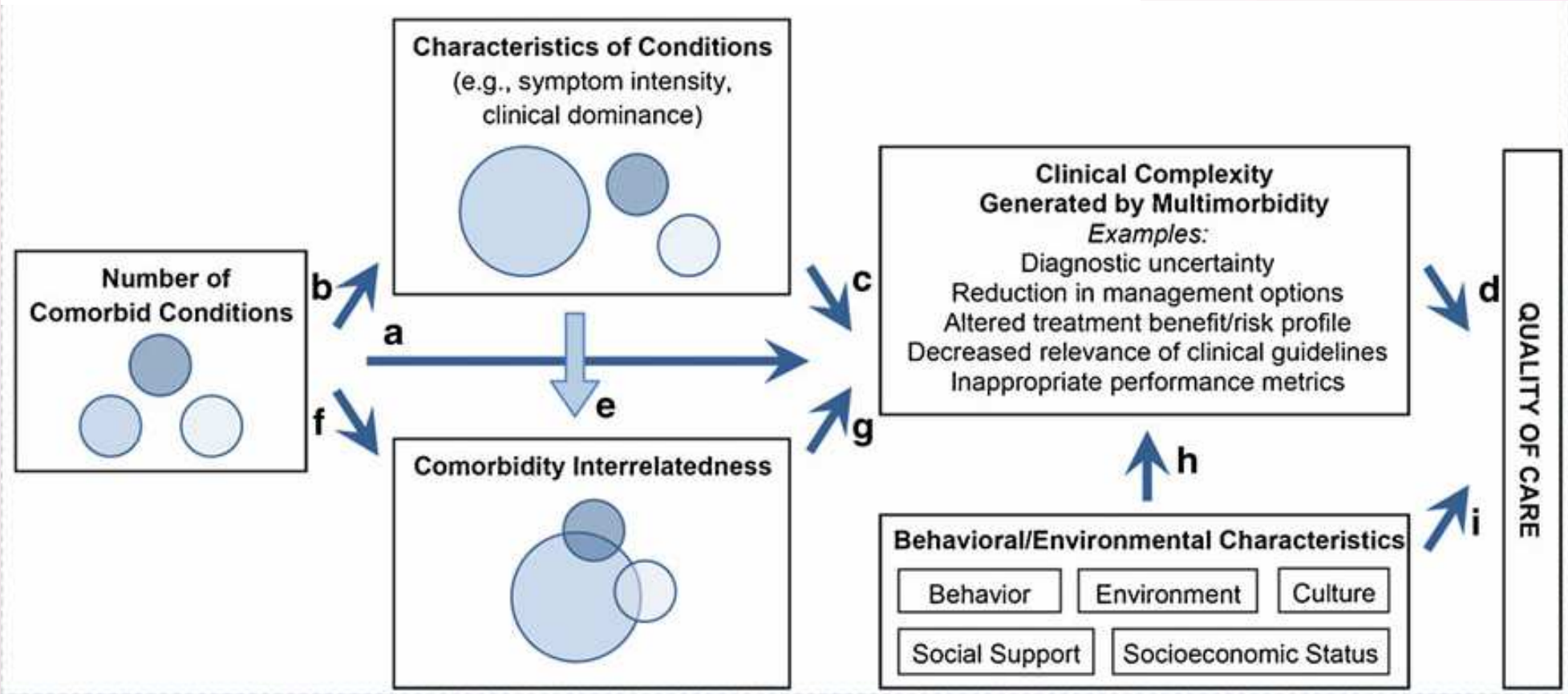


Eur Respir J 2009; 33: 1165–1185
DOI: 10.1183/09031936.00128008

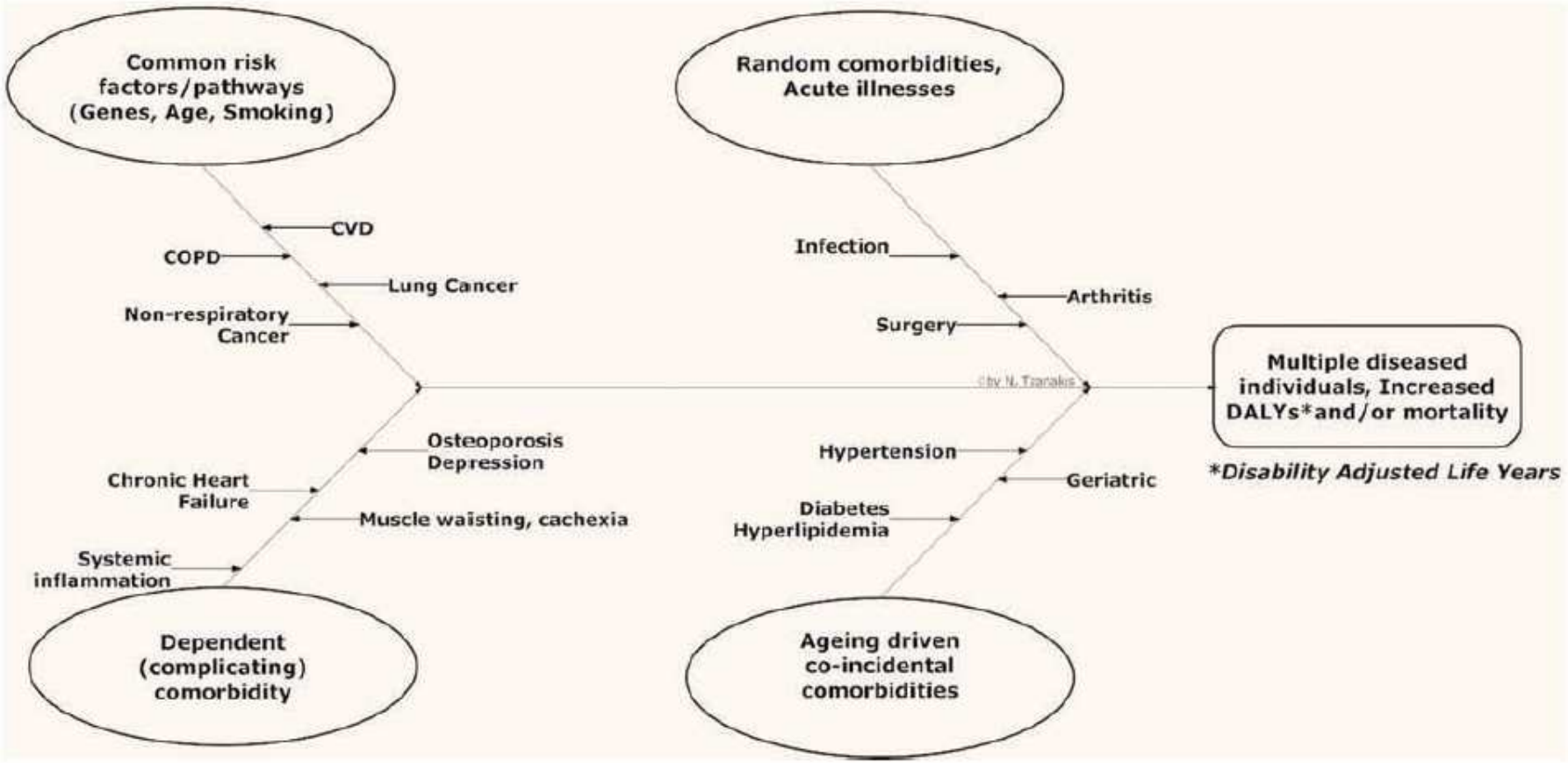
Comorbilidad

Asociación de cualquier patología a una entidad nosológica principal, tanto aguda como crónica, que modula el diagnóstico y tratamiento.

Quality of Care for Patients with Multiple Chronic Conditions: The Role of Comorbidity Interrelatedness



J Gen Intern Med DOI: 10.1007/s11606-013-2616-9


Common risk factors/pathways (Genes, Age, Smoking)
Random comorbidities, Acute illnesses
CVD
COPD
Lung Cancer
Non-respiratory Cancer
Infection
Arthritis
Surgery
© by N. Tzanakis
Multiple diseased individuals, Increased DALYs*and/or mortality
*Disability Adjusted Life Years
Osteoporosis
Depression
Chronic Heart Failure
Muscle waisting, cachexia
Systemic inflammation
Hypertension
Geriatric
Diabetes
Hyperlipidemia
Dependent (complicating) comorbidity
Ageing driven co-incidental comorbidities

FEV1 < 35%

PT # 1
58 y
FEV1: 28 %
MRC: 2/4
PaO2: 70 mmHg
6MWD: 540 mt
BMI: 30
HTA, SAOS

PT # 2
62 y
FEV1: 33%
MRC: 2/4
PaO2: 57 mmHg
6MWD: 400 m
BMI: 21
IAM, DLP, A.Prost, Hepatitis C

PT # 3
69 y
FEV1: 35%
MRC: 3/4
PaO2: 66 mmHg
6MWD: 230 m
BMI: 34
DMNID, HTA, SHO, Depresión, RGE

PT # 4
72 y
FEV1: 34%
MRC: 4/4
PaO2: 60 mmHg
6MWD: 154 m
BMI: 24
Ca. Prostata, ACxFA, HTA, Psoriasis

C.Cote


Mira la luna,
no el dedo que apunta a la luna
Mira al paciente,
no a su función pulmonar
Fabbri L, AMJRCCM 2013

XXXIV Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

XXIX Congreso de la Sociedad Andaluza de Medicina Interna (SADEMI)

21-23 Noviembre 2013 Palacio de Ferias y Congresos de Málaga. Málaga

¿QUÉ DICEN LAS GUÍAS SOBRE COMORBILIDADES EN EPOC?

GesEPOC
guía española de la EPOC

Global Strategy for Diagnosis, Management and Prevention of COPD

Diagnosis and Assessment: Key Points

- The goals of COPD assessment are to determine the severity of the disease, including the severity of airflow limitation, the impact on the patient's health status, and the risk of future events.
- Comorbidities occur frequently in COPD patients, and should be actively looked for and treated appropriately if present.

Global Strategy for Diagnosis, Management and Prevention of COPD

Assess COPD Comorbidities

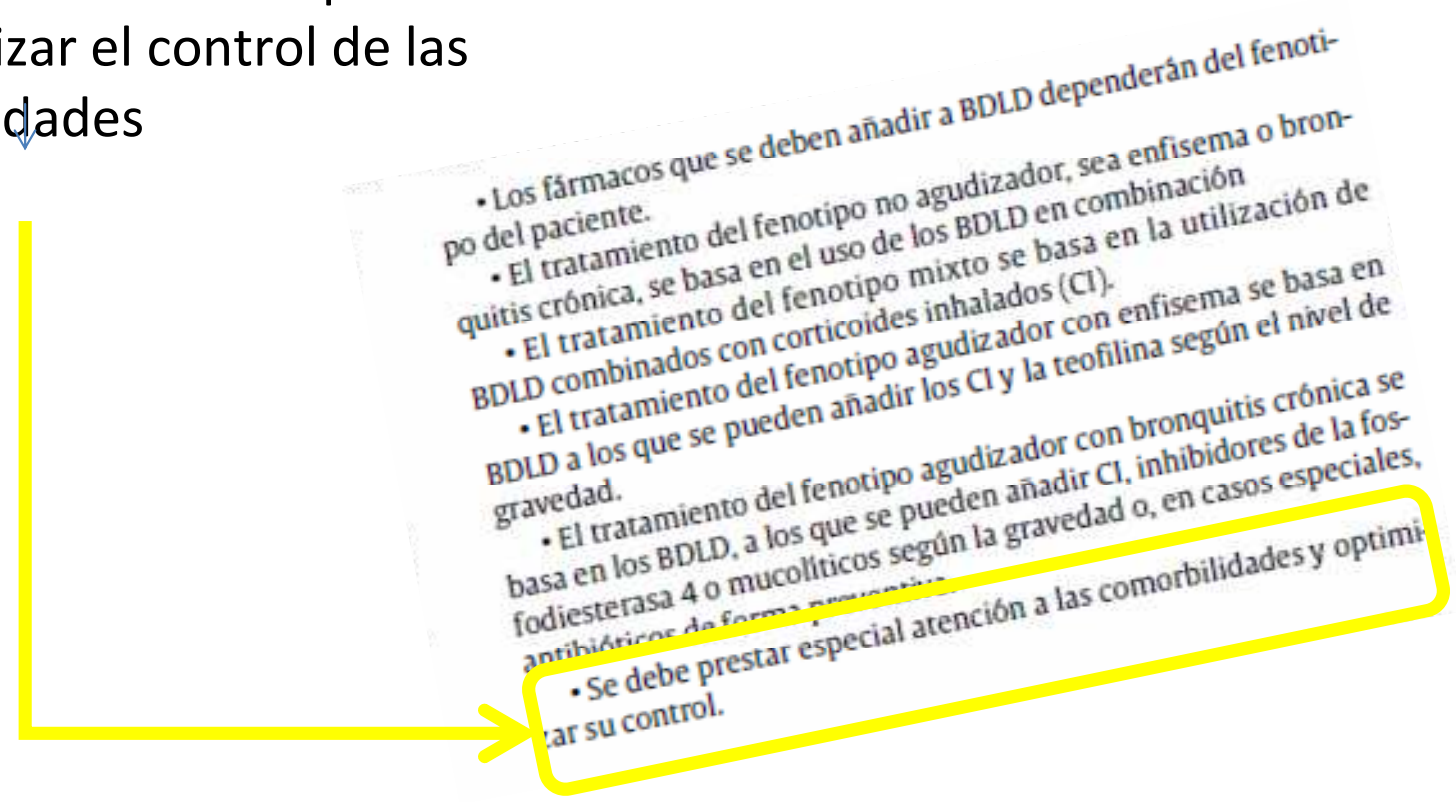
COPD patients are at increased risk for:

- Cardiovascular diseases
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- Lung cancer

These comorbid conditions may influence mortality and hospitalizations and should be looked for routinely, and treated appropriately.

GesEPOC
guía española de la EPOC

- Solo se menciona la importancia de optimizar el control de las comorbilidades



• Los fármacos que se deben añadir a BDLD dependerán del fenotipo del paciente.
• El tratamiento del fenotipo no agudizador, sea enfisema o bronquitis crónica, se basa en el uso de los BDLD en combinación
• El tratamiento del fenotipo mixto se basa en la utilización de BDLD combinados con corticoides inhalados (CI).
• El tratamiento del fenotipo agudizador con enfisema se basa en BDLD a los que se pueden añadir los CI y la teofilina según el nivel de gravedad.
• El tratamiento del fenotipo agudizador con bronquitis crónica se basa en los BDLD, a los que se pueden añadir CI, inhibidores de la fosfodiesterasa 4 o mucolíticos según la gravedad o, en casos especiales, antibióticos de forma preventiva.
• Se debe prestar especial atención a las comorbilidades y optimizar su control.

¿CÓMO SON NUESTROS ENFERMOS?

¿SON RELEVANTES LAS COMORBILIDADES?

Comorbilidad en EPOC en los servicios de Medicina Interna

Comorbilidad	ECCO[1]	ESMI[2] (%)
Hipertensión	55	65,6
Anemia	33	27,1
Diabetes Mellitus	29,5	37,1
Insuficiencia cardíaca	27	35,5
Arrítmia	27	25,8
Cardiopatía isquémica	17	22
Enfermedad arterial periférica	12,6	17,4
Enfermedad cerebrovascular	9,5	12,2
Insuficiencia renal	6,5	16,8

[1] Rev Clin Esp 2010;210(3):101-108
[2] CHEST 2012; 142(5):1126–1133

RELEVANCIA PRONÓSTICA DE LAS COMORBILIDADES

EPOC/IC

FUENTE-AUTOR/POBLACIÓN ESTUDIADA	RIESGO ATRIBUIDO A EPOC/IC
ESMI[3]/EPOC	La presencia de IC se asoció con - Un aumento de la mortalidad en los 90 días posteriores al alta (HR 2,31; IC 95% 1,05-5,1)
ValHeFT/IC[10]	La presencia de EPOC es: - Predictor de mortalidad no cardiovascular (HR 2.50 [IC95% 1.58–3.96])
OPTIMIZE-HF/IC[8]	La presencia de EPOC: - Incrementó la mortalidad intrahospitalaria - Sin diferencia en los 2 meses tras el alta
Macchia 2012/EPOC[11]	La presencia de IC: - Aumentó el riesgo de mortalidad en presencia de disfunción ventricular (HR 2.34, [IC 95% 0.99–5.5])
ECHOS-Lung/IC[12]	La EPOC: Infradiagnosticada en presencia de IC. La espirometria identifica enfermos de alto riesgo
Ather 2012/IC[13] Finkelstein[14]	La EPOC: -En pacientes con FE preservada se asocia a un aumento del riesgo de mortalidad (HR: 1.62 [IC95%: 1.36-1.92]) - Aumento del riesgo de IC (OR 3.9, [IC 95% 0.99–5.5])

Factors associated with mortality in patients with exacerbation of chronic obstructive pulmonary disease hospitalized in General Medicine departments

Intern Emerg Med (2011) 6:47–54

ECCO Working Group on COPD, Spanish Society of Internal Medicine

…suggested an **inadequate** use of most recommended **treatments for COPD**, not only prior to admission but also during hospitalization.

…association of **increased risk of death** during hospitalization with three previously diagnosed comorbid conditions: **pneumonia, coronary heart disease, and stroke**. No association was found with the other study variables, including those reflecting the advanced stage of COPD that was present in a large percentage of our patients.

Table 2 Treatments received by patients prior to admission and during hospitalization

	Prior to [illegible] Patients (%)	During [illegible] Patients (%)
Oxygen therapy	146 (36.7)	367 (92.2)
Inhaled β_2 agonists	337 (84.7)	270 (67.8)
Inhaled anticholinergics	290 (72.9)	274 (68.8)
[illegible]	[illegible]	[illegible]
Inhaled corticosteroids	250 (62.8)	138 (34.7)
Oral corticosteroids	262 (65.8)	349 (87.7)
Macrolides	67 (16.8)	82 (20.6)
Antibiotics	24 (6.0)	352 (88.4)
[illegible]	[illegible]	[illegible]
Antacid agents	202 (50.8)	332 (83.4)
ACEI or ARB	113 (28.4)	110 (27.6)
β Blockers	28 (7.0)	28 (7.0)
Digoxin	50 (12.6)	65 (16.3)
Oral anticoagulants	58 (14.6)	59 (14.8)
Platelet antiaggregants	79 (19.8)	82 (20.6)
Fractionated heparin, prophylactic	2 (0.5)	58 (14.6)
Psychoactive drugs	60 (15.1)	63 (15.8)
Calcium channel blockers	39 (9.8)	36 (9.0)
Statins	38 (9.5)	43 (10.8)
Alpha adrenergic antagonists	27 (6.8)	27 (6.8)
Amiodarone	14 (3.5)	15 (3.8)

ACEI angiotensin-converting enzyme inhibitors, *ARb* angiotensin II receptor blockers

Table 4 Comorbidity diagnosed prior to admission in the study patients

	Patients (%)
Coronary heart disease	79 (19.8)
Heart failure	107 (26.9)
[illegible]	[illegible]
Stroke	39 (9.8)
[illegible]	[illegible]
Thromboembolic disease	13 (3.3)
Arrhythmia	108 (27.1)
[illegible]	[illegible]
Connective tissue disease	7 (1.8)
[illegible]	49 (12.3)
Chronic liver disease	38 (9.5)
Diabetes mellitus	117 (29.4)
Chronic renal failure	26 (6.5)
Cancer	43 (10.8)
HIV infection	1 (0.3)
Osteoporosis	37 (9.3)
Pneumonia	51 (12.8)

CHEST Original Research

COPD

Comorbidities and Short-term Prognosis in Patients Hospitalized for Acute Exacerbation of COPD

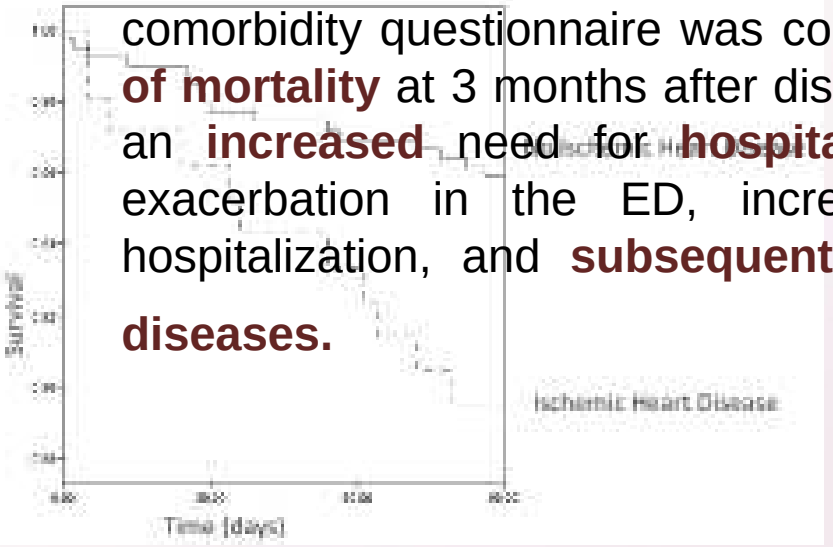
The EPOC en Servicios de Medicina Interna (ESMI) Study

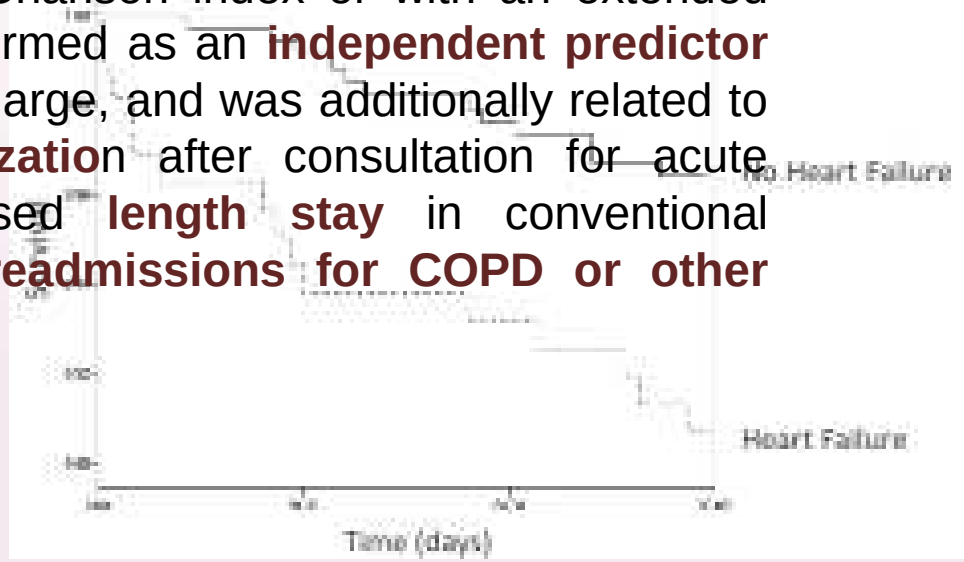
Table 4—*Mortality: Multivariate Analysis (Cox Regression)*

Variables	*P* Value	HR	95% CI
Age	.06	1.05	0.99-1.1
Katz index	.04	0.75	0.60-0.96
FEV_1	.03	1.95	1.05-3.62
Charlson index	.003	1.23	1.09-1.35

See Table 1 and 3 legends for expansion of abbreviations.
*FEV$_1$ stratified according GOLD guidelines.

… comorbidity measured by the Charlson index or with an extended comorbidity questionnaire was confirmed as an **independent predictor of mortality** at 3 months after discharge, and was additionally related to an **increased** need for **hospitalization** after consultation for acute exacerbation in the ED, increased **length stay** in conventional hospitalization, and **subsequent readmissions for COPD or other diseases.**





CHEST 2012; 142(5):1126–1133

¿Qué dicen las guías del tratamiento de las comorbilidades?

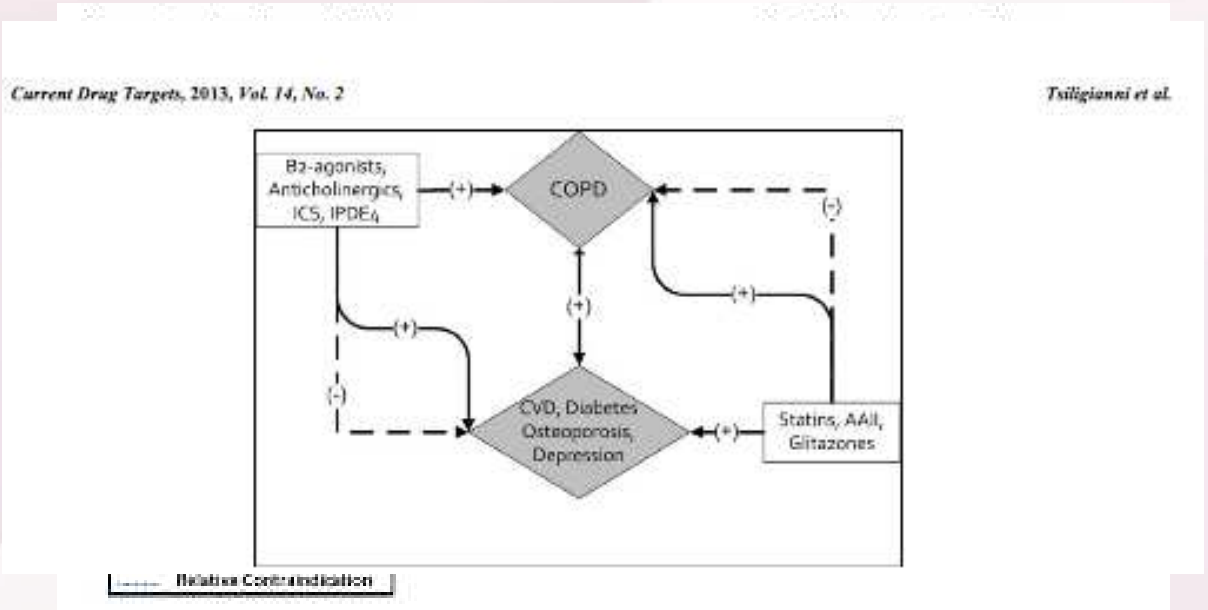
¿Cómo tratamos a nuestros enfermos?

Manage Comorbidities

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis. In general, presence of comorbidities should not alter COPD treatment and comorbidities should be treated as if the patient did not have COPD.

Manage Comorbidities

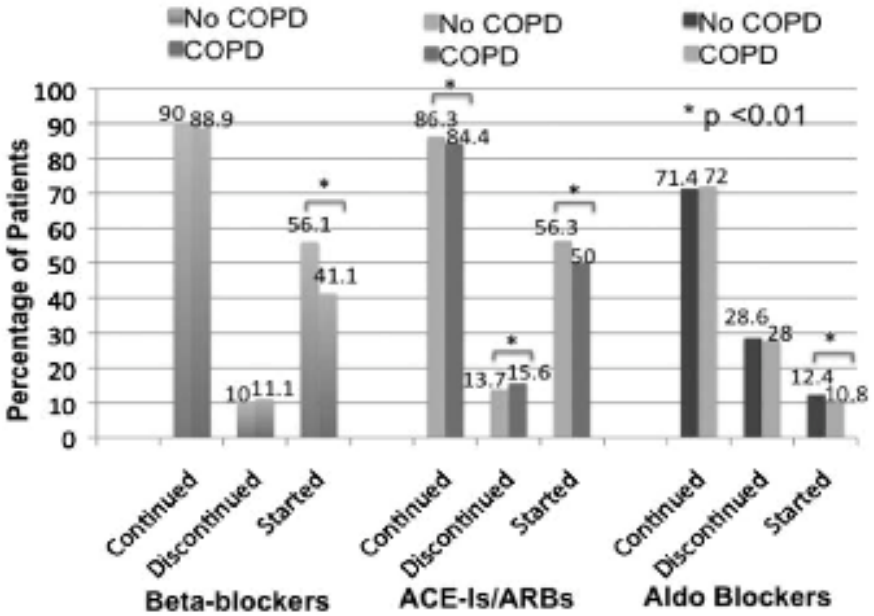
Cardiovascular disease (including ischemic heart disease, heart failure, atrial fibrillation, and hypertension) is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD. Benefits of cardioselective beta-blocker treatment in heart failure outweigh potential risk even in patients with severe COPD.



Current Drug Targets, 2013, 14, 158-176
J Gen Intern Med DOI: 10.1007/s11606-013-2616-9

Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF

Medication	At admission			At discharge		
	No COPD (n = 15 061)	COPD (n = 5057)	P-value	No COPD (n = 15 061)	COPD (n = 5057)	P-value
Beta-blockers	57.1	52.0	<0.001	75.4	65.9	<0.001
ACE-I/ARB	54.4	54.0	0.65	72.7	68.7	<0.001



➢ Those with COPD were less likely to be receiving a beta-blocker on admission or to have a beta-blocker added during hospitalization. Interestingly, beta-blocker cessation rates were no different between those with and without COPD.

➢ Improved utilization of beta-blockers in HF patients with COPD is warranted and should involve cardioselective agents as we await more definitive data.

➢..patients with COPD were less likely to be initiated on an ACE-I/ARB or aldosterone blocker during admission and were more likely to have their ACE-I/ARB discontinued.

European Journal of Heart Failure (2012) 14, 395–403

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El tratamiento de la EPOC¿es seguro, además de eficaz en la ECV?

¿Influye la presencia de EPOC en el tratamiento de la ECV?

Are beta2-agonists responsible for increased mortality in heart failure?

- B2A use is associated with excess HF hospitalizations as well as increased risk of all-cause mortality in patients with left ventricular dysfunction (LVSD).

Chest 2003; 123:1964 - 1969.

- A retrospective analysis of the CHARM dataset showed a concerning 26% excess risk of mortality when using bronchodilators.

Eur J Heart Fail 2010;12:557–565.

- A long-term inhaled salmeterol therapy (100 µg twice daily) improved pulmonary function, without augmentation of neurohormonal systems or ventricular ectopy, in symptomatic heart failure patients with a left ventricular ejection fraction of less than 40%.

Cardiovasc Pharmacol 2002 40:140–45.

- A longitudinal, retrospective cohort study of patients suggest that inhaled B2As are not associated with increased mortality in community-managed HF patients.
- Safety data pooled from three clinical trials: there was no relevant effect of indacaterol versus placebo on the development of arrhythmias.

Eur J Heart Fail 2011;13:885–891.

Am J Respir Crit Care Med. 2010;182:155–162.

Thorax. 2010;65:473–479.

Eur Respir J. 2011;37:273–279.

Do Inhaled Anticholinergics Increase or Decrease the Risk of Major Cardiovascular Events?

A Synthesis of the Available Evidence

Shelley R. Salpeter[1,2]

" treatment has been shown to substantially increase the risk of the development of dry mouth, urinary retention and sinus tachycardia, indicating significant systemic effects of inhaled anticholinergics.
For this reason, it is possible that inhaled anticholinergics can exert adverse systemic cardiovascular effects.Inhaled anticholinergics increase the incidenceof sinus tachycardia, which is a supraventriculararrhythmia"

There have been conflicting data concerning the cardiovascular risk associated with the inhaled anticholinergic agents ipratropium bromide and tiotropium bromide. Observational studies and some randomized trials have shown an increase in adverse cardiovascular events, whereas pooled data from all available trials show no significant effect on the proportion of patients with adverse cardiovascular events and a trend towards reduced incidence of events over time

Drugs 2009; 69 (15): 2025-2033

CHEST

Original Research

COPD

Cardiovascular Safety of Tiotropium in Patients With COPD

Bartolome Celli, MD, FCCP; Marc Decramer, MD; Inge Leimer, PhD; Ulrich Vogel, MD; Steven Kesten, MD; and Donald P. Tashkin, MD, FCCP

The primary objective … to examine whether there were specific events that might show either a decreased or an increased risk with tiotropium. Attention was focused on selected CV events, including a composite CV end point and mortality.

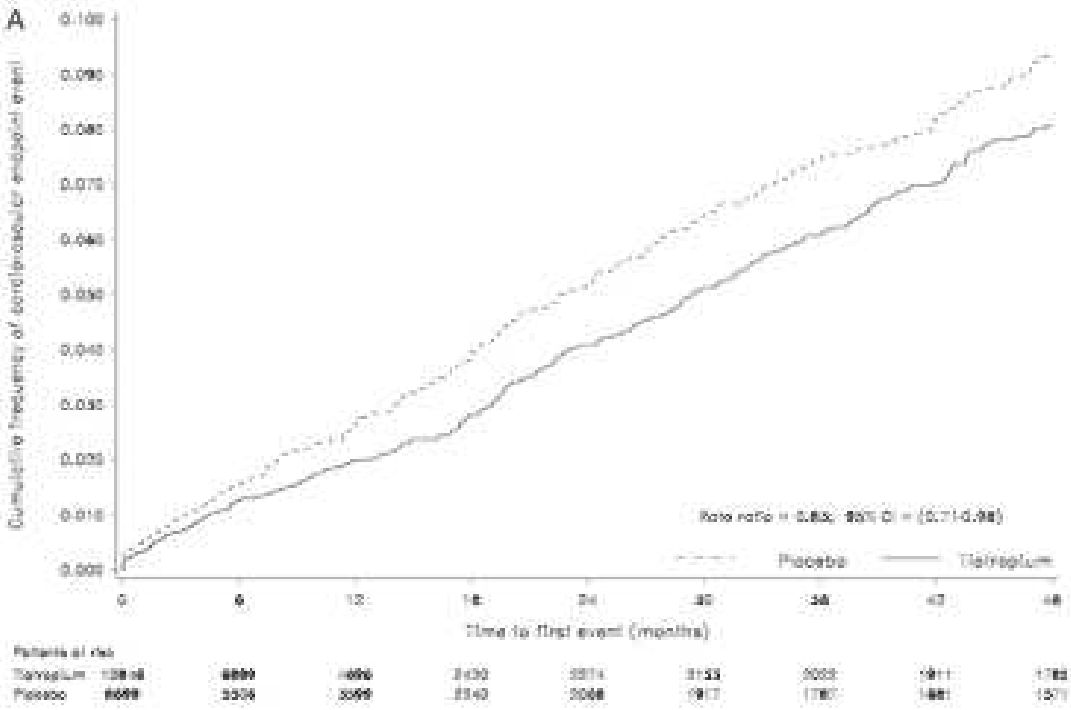
Table 4—*IRs, RRs, and 95% CIs for Cardiac Adverse Events in the Pooled Analysis of 30 Trials*

	Placebo n = 8,699		Tiotropium n = 10,546		
Cardiac Events	No.	IR	No.	IR	RR (95% CI)
Cardiac disorders (SOC)	788	7.23	907	6.04	0.91 (0.83-1.01)
Ischemic heart disease	290	2.53	322	2.30	0.93 (0.79-1.08)
Atrial fibrillation/flutter	147	1.26	159	1.15	0.92 (0.74-1.16)
Cardiac arrest	31	0.26	23	0.16	0.68 (0.36-1.16)
Cardiac failure	261	2.26	252	1.82	0.82 (0.69-0.95)*
Myocardial infarction	111	0.85	101	0.72	0.78 (0.59-1.02)
Palpitations	58	0.49	95	0.61	1.16 (0.83-1.64)
Supraventricular tachycardia	28	0.24	37	0.26	1.09 (0.67-1.79)
Tachycardia (nonventricular)	52	0.44	66	0.47	1.03 (0.71-1.50)
Ventricular tachycardia/fibrillation	28	0.24	22	0.16	0.67 (0.38-1.19)

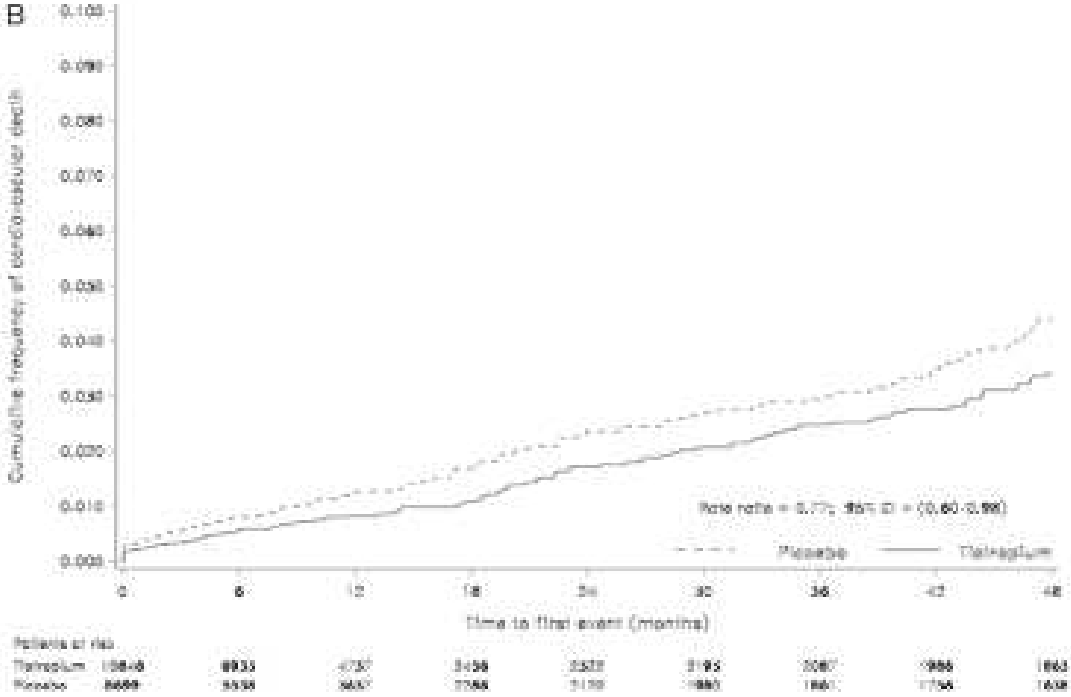
Chest 2010;137;20-30

Cardiovascular Safety of Tiotropium in Patients With COPD

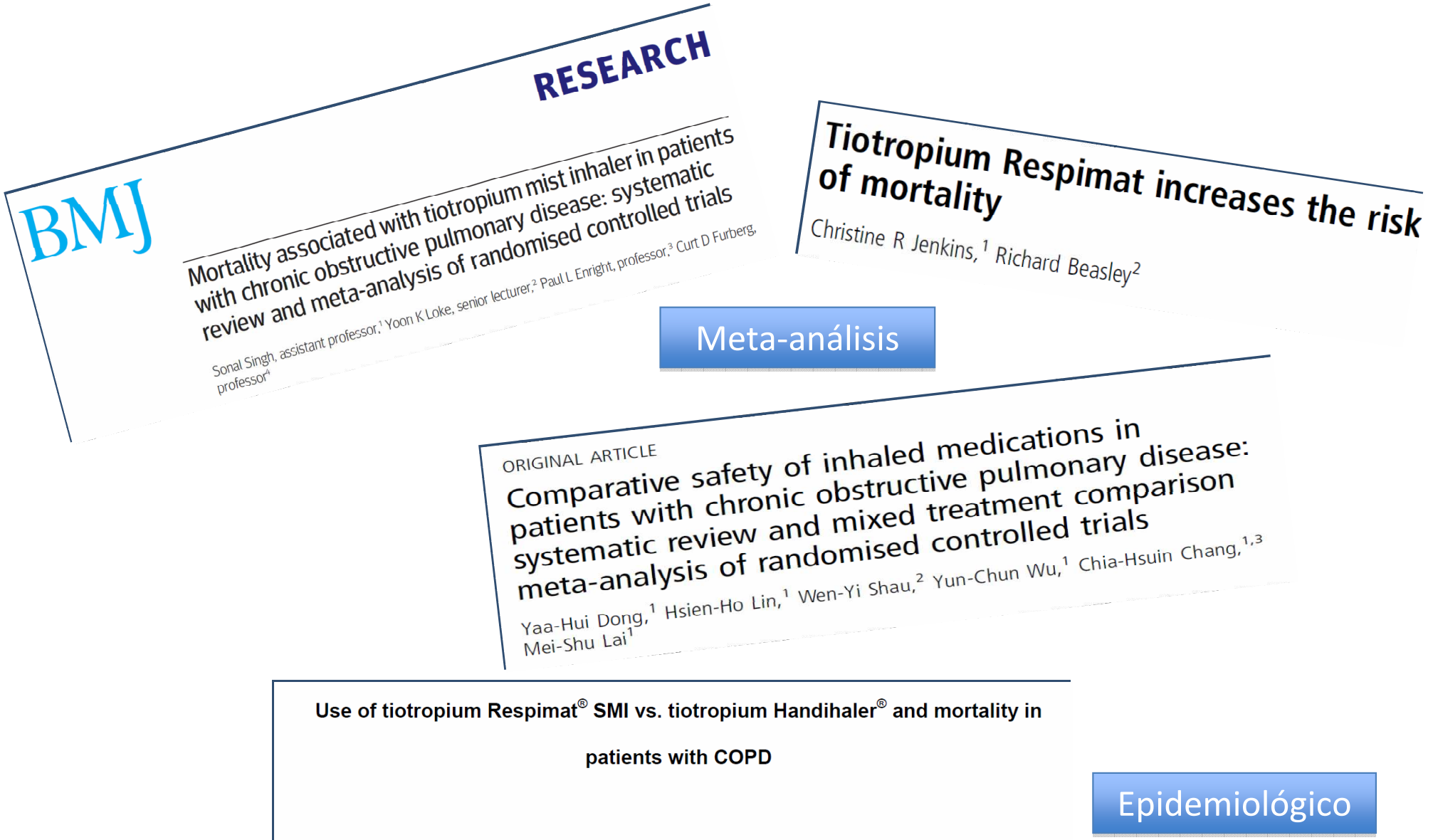
Cardiovascular events



Cardiovascular deaths



Chest 2010;137;20-30


RESEARCH
BMJ
Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials
Sonal Singh, assistant professor,[1] Yoon K Loke, senior lecturer,[2] Paul L Enright, professor,[3] Curt D Furberg, professor[4]
Tiotropium Respimat increases the risk of mortality
Christine R Jenkins,[1] Richard Beasley[2]
Meta-análisis
ORIGINAL ARTICLE
Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials
Yaa-Hui Dong,[1] Hsien-Ho Lin,[1] Wen-Yi Shau,[2] Yun-Chun Wu,[1] Chia-Hsuin Chang,[1,3] Mei-Shu Lai[1]
Use of tiotropium Respimat® SMI vs. tiotropium Handihaler® and mortality in patients with COPD
KMC. Verhamme[1*], MD, PhD; A. Afonso[*], VetD[1], PhD; S. Romio, PhD[1]; B.Ch Stricker[2], MD, PhD; GGO Brusselle[3], MD, PhD; MCJM. Sturkenboom[1,2], PharmD, PhD
Epidemiológico

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Respimat Inhaler and the Risk of Death in COPD

- Tiotropio administrado con el inhalador Respimat® no se asoció a una mayor mortalidad en comparación con HandiHaler®, incluidos los pacientes con
  - antecedentes de cardiopatía
  - arritmia cardíaca en situación basal
- No se observó ninguna diferencia entre grupos de tratamiento en el tiempo hasta la primera exacerbación, el tiempo hasta la primera exacerbación grave (hospitalización) o la frecuencia de exacerbaciones

Table 1. Baseline Characteristics of the Patients in the As-Treated Population.*

Characteristic	Tiotropium Respimat 2.5 μg (N=5724)	Tiotropium Respimat 5 μg (N=5705)	Tiotropium HandiHaler 18 μg (N=5687)
Male sex (%)	71.1	72.5	71.0
Age (yr)	65.1±9.1	64.9±9.1	65.0±9.0
Current smoker (%)	37.9	38.7	37.7
Smoking history (pack-yr)	43.6±24.6	44.1±25.0	43.7±24.7
Spirometry after bronchodilation			
FEV_1			
Mean (liters)†	1.328±0.481	1.352±0.481	1.338±0.473
Percent of predicted value	48.0±13.9	48.5±13.8	48.4±13.9
FVC (liters)	2.696±0.848	2.726±0.843	2.716±0.843
Ratio of FEV_1 to FVC	0.498±0.115	0.501±0.114	0.498±0.114
Previous cardiac arrhythmia (%)	10.6	10.8	10.7
Previous myocardial infarction (%)	5.9	5.9	6.1
Previous stroke (%)	2.2	2.4	2.2
Previous ischemic heart disease or coronary artery disease (%)	14.8	15.0	15.7
Use of respiratory medication (%)			
Any	90.8	90.3	90.7
Long-acting inhaled beta-agonist‡	61.9	61.2	62.3
Inhaled glucocorticoid‡	58.9	58.8	59.4

Under-use of beta-blockers in COPD patients

- "despite the clear evidence of the effectiveness of BB, there is a general reluctance to use them in patients with COPD, due to a perceived contraindication and fear of inducing adverse reactions and bronchspasm"

- < 30% of HF patients received β blockers

- Long-term BB is underused in CHF … due to the entrenched belief that it may precipitate respiratory deterioration when COPD coexists with CHF. Beta-blockers remain underprescribed to patients with CHF and COPD… despite extensive safety data in patients with moderate to severe COPD.

N Engl J Med 1998;339:489-97
Int J Clin Pharmacol Ther 2001;39:383-8
Q J Med 2005; 98:493–497
J Am Coll Cardiol 2007;49:171–80

Use of β blockers and the risk of death in hospitalised patients with acute exacerbations of COPD

To examine the use of b blockers (both cardioselective and non-cardioselective) in patients admitted to a university hospital with acute exacerbations of COPD and to determine whether the administration of these drugs was associated with in-hospital mortality.

Table 3 Predictors of in-hospital mortality

Parameter	Unadjusted OR for death (95% CI)	p Value	Adjusted OR for death (95% CI)	p Value
β blocker use	1.10 (0.50 to 2.44)	0.80	0.39 (0.14 to 0.98)	0.049
Short-acting β agonist use	0.08 (0.04 to 0.17)	<0.001	0.08 (0.02 to 0.30)	<0.001
Age (per year of life)	1.05 (1.02 to 1.08)	0.001	1.05 (1.02 to 1.09)	0.004
Number of prior AECOPD	1.27 (1.12 to 1.44)	<0.001	1.22 (1.01 to 1.47)	0.037
Length of stay (per day)	1.06 (1.04 to 1.09)	<0.001	1.05 (1.02 to 1.08)	<0.001
Respiratory failure	11.5 (6.04 to 22.0)	<0.001	10.2 (4.56 to 22.6)	<0.001
Congestive heart failure	3.58 (1.92 to 6.67)	<0.001	4.54 (1.53 to 13.5)	0.006
Cerebrovascular disease	3.41 (1.25 to 9.32)	0.016	12.9 (3.10 to 53.3)	<0.001
Chronic liver disease	3.42 (0.73 to 15.9)	0.12	12.1 (2.05 to 71.5)	0.006

OR, odds ratio; CI, confidence interval; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

40% reduction in mortality

"the use of b blockers in patients admitted with acute exacerbations of COPD is not deleterious and may be associated with a beneficial effect on mortality. These results have direct implications for the use of b blockers in patients hospitalised for acute exacerbations of COPD and suggest that they can be safely continued in this setting".

Thorax 2008;63:301–305

Association between β-blocker therapy and outcomes in patients hospitalised with acute exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension

n= 35082; median age: 72 years, 59% were women.

- only 40% of patients with AE-COPD who had an evidence-based indication for chronic b-blocker therapy (an ICD-9 code of prior MI) were given a b blocker during hospitalisation.

- …continuing a b1-selective b blocker among patients who are chronic users appears to be safe during a hospitalisation for AE-COPD.

- Compared with b1-selective agents, non-selective b blockers were associated with an increased risk of 30-day readmission.

In summary

among patients with COPD and coexistent IHD, CHF or HTN, continuing b1-selective b-blocker therapy among chronic users appears **to be safe during a hospitalisation** for AE-COPD. Until additional evidence becomes available, clinicians should consider **choosing b1-selective rather than non-selective b blockers in patients with COPD**. Given the large number of patients with COPD and concurrent CHF and IHD, clinical trials assessing the riskebenefit of b blockers in this population would be valuable.

Thorax 2012;67:977-984

Manage Comorbidities

Osteoporosis and *anxiety/depression:* often under-diagnosed and associated with poor health status and prognosis.

Lung cancer: frequent in patients with COPD; the most frequent cause of death in patients with mild COPD.

Serious infections: respiratory infections are especially frequent.

Metabolic syndrome and manifest *diabetes:* more frequent in COPD and the latter is likely to impact on prognosis.

Mensajes para recordar

- Visión global de la EPOC, no sólo del funcionalismo pulmonar.
- La comorbilidad condiciona el pronóstico de los enfermos.
- Es necesario el diagnóstico y correcto tratamiento de la comorbilidad de origen cardiovascular.
- El tratamiento broncodilatador es eficaz y seguro: pautar LAMA y LABA.
- La EPOC no es una contraindicación del tratamiento con BB
    - Mantener el tratamiento con BB durante las agudizaciones de la EPOC es seguro y disminuye la mortalidad.
    - tratamiento preferentemente con BB cardioselectivos

Gracias por su presencia y atención