HOSPITAL Sant Joan de Déu MARTORELL

Insuficiencia cardíaca y EPOC. Controversias terapéuticas

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Definición de EPOC

Table 2.5. Classification of Severity of Airflow Limitation in COPD (Based on Post-Bronchodilator FEV_1)

In patients with $FEV_1/FVC < 0.70$:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

GOLD 2014

Definición de insuficienca cardíaca

Table I Diagnosis of heart failure

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Reduced LVEF
The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)

HF = heart failure; HF-PEF = heart failure with 'preserved' ejection fraction; HF-REF = heart failure and a reduced ejection fraction; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction.

[a]Signs may not be present in the early stages of HF (especially in HF-PEF) and in patients treated with diuretics (see Section 3.6).

McMurray. Eur Heart J 2012

Prevalencia de IC en pacientes EPOC

Table 2 Frequencies of comorbidities, by gender.

Comorbidity	Men $N = 353$ (89%)	Women $N = 45$ (11%)	Total	p
Myocardial infarction	32 (9.1%)	2 (4.4%)	34 (9%)	0.2
Ischemic Heart disease	66 (18.7%)	2 (4.4%)	68 (17%)	0.008
Chronic heart failure	89 (25.2%)	18 (40%)	107 (27%)	0.03
Peripheral vascular disease	48 (13.6%)	2 (4.4%)	50 (13%)	0.06
Cerebrovascular disease	31 (8.8%)	7 (15.6%)	38 (10%)	0.1
Dementia	13 (3.7%)	2 (4.4%)	15 (4.4%)	0.5
Connective tissue disease	6 (1.5%)	1 (0.3%)	7 (2%)	0.6
Peptic ulcer	46 (13%)	3 (6.7%)	49 (12%)	0.16
Mild liver disease	28 (8%)	1 (2.2%)	29 (7.3%)	0.13
Diabetes without complications	85 (24%)	18 (40%)	103 (26%)	0.02
Diabetes with organ damage	12 (3.4%)	2 (4.4%)	14 (3.5%)4	0.48
Hemiplegia	3 (1%)	2 (2.2%)	4 (1%)	0.38
Moderate kidney failure	24 (6.8%)	2 (4.4%)	26 (6.5%)	0.4
Solid tumor without metastasis	24 (6.8%)	2 (4.4%)	26 (6.5%)	0.4
Leukemia	6 (1.7%)	0 (0%)	6 (1.5%)	0.5
Lymphoma	2 (0.6%)	0 (0%)	2(0.5%)	0.8
Moderate or serious liver disease	9 (2.5%)	0 (0%)	9(2.3%)	0.3
Solid tumor with metastasis	6 (1.7%)	1 (2.2%)	71(8%)	0.6
AIDS	1 (0.3%)	0 (0%)	1 (0.3%)	0.9
Charlson index, average (DE)	2.8 (1.7)	2.6 (1.2)	2.7 (2.0)	0.6

Almagro. Respir Med 2010

Prevalencia de IC en pacientes EPOC

Table 2—*Frequencies of Comorbidities by Charlson Index Data and Global Questionnaire*

Comorbidities	Previous Diagnosis, No. (%)
Included in Charlson index	
Acute myocardial infarction	70 (11.6)
Heart failure	199 (32.8)
Peripheral vascular disease	102 (16.8)
Cerebrovascular disease	71 (11.7)
Dementia	22 (3.6)
COPD	606 (100)
Connective tissue disease	15 (2.5)
Ulcer disease	63 (10.4)
Liver disease (mild)	35 (5.8)
DM without organ damage	172 (28.4)
Kidney disease (creatinine < 3)	94 (15.5)
Hemiplegia	10 (1.7)
Kidney disease (creatinine > 3)	4 (0.7)
DM with organ damage	45 (7.4)
Malignant solid tumor	73 (12)
Leukemia	2 (0.3)
Lymphoma	4 (0.7)
Liver disease (severe)	3 (0.5)
Malignant solid tumor with metastases	7 (1.2)
AIDS	4 (0.7)

Almagro. Chest 2012

Prevalencia de IC en pacientes EPOC

Table 2—*Prevalence of Baseline Comorbidities, Case Patients, and Control Subjects*

Comorbidities	Case Patients		Control Subjects		OR (95% CI)
	No.	%	No.	%	
Obesity	3,779	8.2	1,398	3.0	2.86 (2.68–3.04)
Diabetes	753	1.6	501	1.1	1.51 (1.35–1.69)
Hypertension	8,387	18.2	5,163	11.2	1.76 (1.70–1.83)
Hyperlipidemia	3,998	8.7	3,279	7.1	1.24 (1.18–1.30)
VT/VF/cardiac arrest	347	0.8	44	0.1	7.94 (5.80–10.87)
Atrial fibrillation	2,169	4.7	510	1.1	4.41 (4.00–4.87)
Other arrhythmia	1,254	2.7	310	0.7	4.13 (3.65–4.68)
Angina	461	1.0	106	0.2	4.38 (3.55–5.42)
MI	823	1.8	189	0.4	4.42 (3.77–5.17)
Stroke	553	1.2	228	0.5	2.44 (2.09–2.85)
Pulmonary embolism	117	0.3	25	0.1	4.69 (3.04–7.22)
CHF	3,311	7.2	417	0.9	8.48 (7.65–9.40)
Renal disease	259	0.6	101	0.2	2.57 (2.04–3.24)
Asthma	18,371	40.0	1,206	2.6	24.71 (23.27–26.24)

Sydney. Chest 2005

Prevalencia de EPOC en pacientes con IC

25%

Características basales de los enfermos con insuficiencia cardiaca

	Global (n = 391)	EPOC (n = 98)	Sin EPOC (n = 293)	p
Varones/mujeres	152/239	69/29	83/210	< 0,05
Edad (años), media (DE)	77,9 (9,4)	78,0 (9,5)	77,9 (9,4)	0,95
Tabaquismo, n (%)	120 (30,7)	57 (58,2)	63 (21,5)	< 0,001
Índice de Charlson, media (DE)	2,9 (1,9)	3,7 (1,9)	2,7 (1,9)	0,04
Hipertensión arterial, n (%)	311 (79,5)	76 (77,5)	237 (80,8)	0,46
Diabetes, n (%)	193 (49,4)	43 (43,9)	150 (51,2)	0,24
Cardiopatía isquémica, n (%)	139 (35,5)	36 (36,7)	103 (35,1)	0,87
Fibrilación auricular, n (%)	181 (46,3)	47 (47,9)	134 (45,7)	0,73
Filtrado glomerular < 60 ml, n (%)	177 (45,3)	53 (54,1)	124 (42,3)	0,02
Inicio de IC, n (%)	127 (32,5)	23 (23,5)	104 (35,5)	0,03
FEVI (%), media (DE)	50,6 (16,8)	48,5 (17,8)	51,3 (16,5)	0,18
NYHA, media (DE)	2,6 (0,8)	2,67 (0,8)	2,6 (0,8)	0,89
Hemoglobina (g/l), media (DE)	11,9 (2,1)	12,3 (1,9)	11,9 (2,1)	0,12
Sodio (mEq/l), media (DE)	138,6 (4,3)	138,6 (4,8)	138,5 (4,1)	0,87
Potasio (mEq/l), media (DE)	4,4 (0,6)	4,4 (0,7)	4,3 (0,6)	0,51
IMC, media (DE)	28,4 (5,9)	26,9 (5,2)	28,8 (6,1)	0,028

DE: desviación estándar; EPOC: enfermedad pulmonar obstructiva crónica; FEVI: fracción de eyección del ventrículo izquierdo; IC: insuficiencia cardiaca; IMC: índice de masa corporal; NYHA: New York Heart Association.

Recio. Med Clin 2010

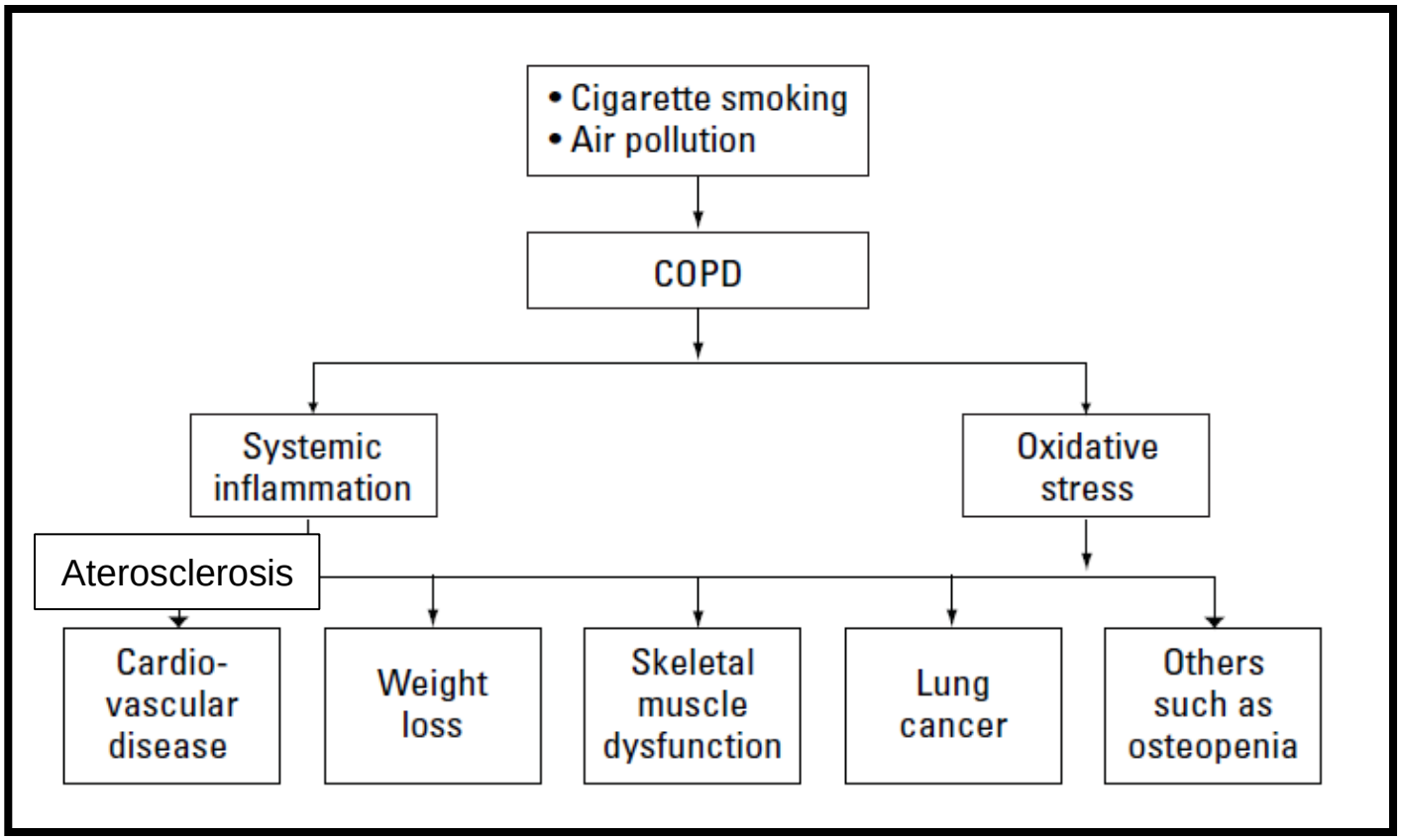
Prevalencia de EPOC en pacientes con IC

	All patients (n = 3226)	≤1 co-morbidiy (n = 1417)	>1 co-morbidity (n = 1167)	*P*-value
Age (years)	66 ± 14	63 ± 14	71 ± 11	<0.001
Male sex (%)	2268 (70)	1029 (73)	797 (68)	0.02
Body mass index (kg/m^2)	28 ± 5	28 ± 5	28 ± 5	0.12
NYHA class				<0.001
I (%)	511 (16)	299 (21)	103 (9)	
II (%)	1797 (56)	828 (59)	600 (52)	
III (%)	854 (26)	277 (20)	431 (37)	
IV (%)	56 (2)	11 (1)	28 (2)	
Co-morbidities				
Chronic kidney disease	1035 (41)	211 (15)	780 (73)	<0.001
eGFR	68 ± 26	79 ± 23	54 ± 22	<0.001
Anaemia	727 (29)	124 (9)	589 (55)	<0.001
Haemoglobin	13.4 ± 1.9	14.1 ± 1.5	12.6 ± 1.9	<0.001
Diabetes	934 (29)	165 (12)	697 (54)	<0.001
COPD	484 (15)	75 (5)	363 (31)	<0.001
Stroke	337 (11)	52 (4)	244 (21)	<0.001
Sleep apnoea	128 (4)	19 (1)	104 (9)	<0.001
Hypothyroidism	272 (9)	37 (3)	199 (18)	<0.001
Hyperthyroidism	101 (3)	21 (2)	68 (6)	<0.001

The HF Pilot Survey of the EUR*Observational* Research Programme (EORP) of the European Society of Cardiology (ESC) was a prospective, multicentre, observational survey.[9] The aim was to include a

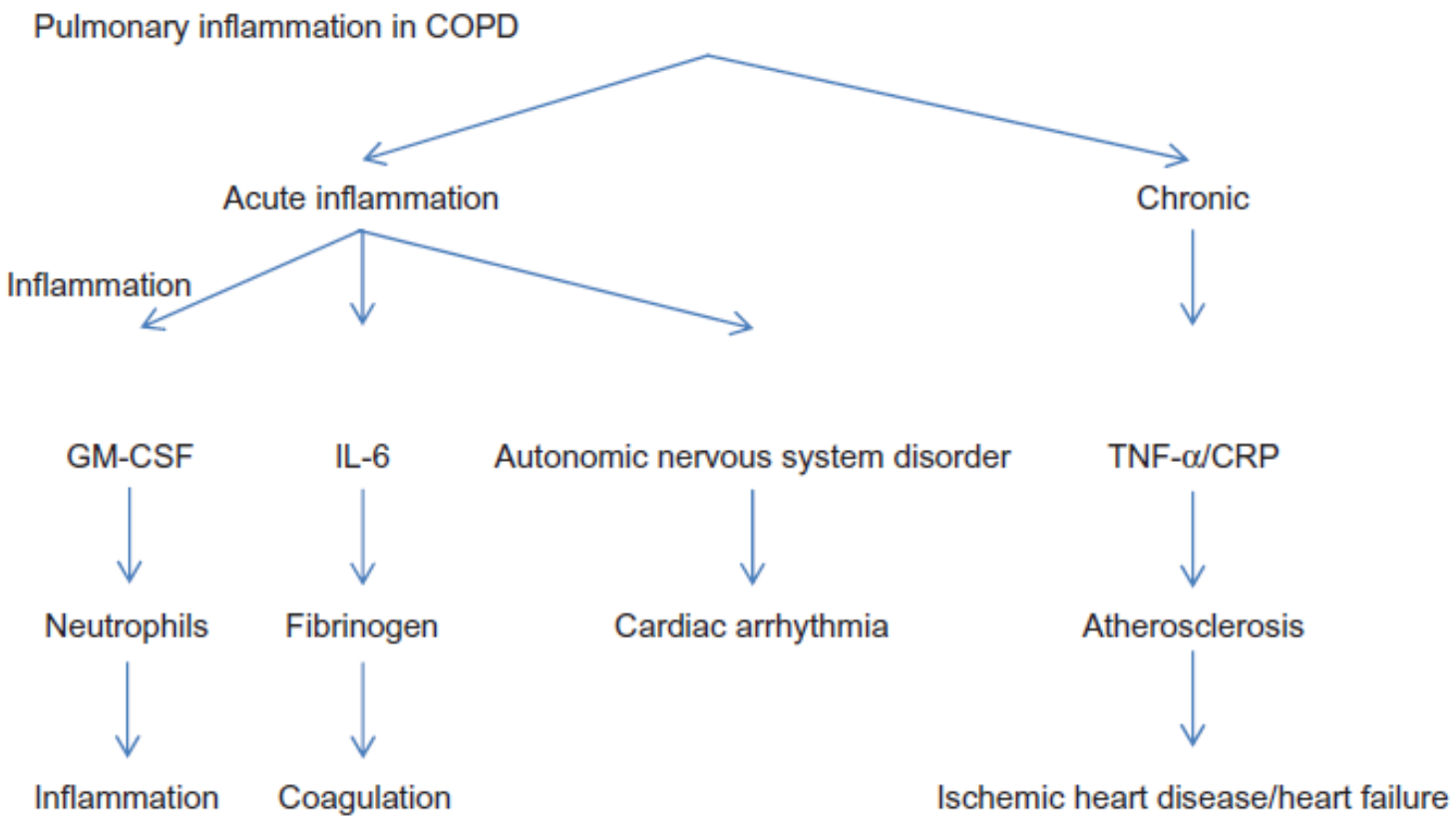
Van Deursen. Eur J Heart Fail 2014

Fisiopatologia



Gan. BMCJ 2008

Fisiopatologia



Diez. Int J COPD 2013

Fisiopatologia de la función respiratoria

EPOC	EPOC+IC	IC
Patrón obstrutivo	Alteración de la V/Q	Patrón restrictivo
Taquipnea		Vd/Vt aumentado
Aumento de CRF		VCO_2 aumentado
PaO_2 disminuida	Alteración del intercambio	PaO_2 disminuida
$PaCO_2$ aumentada	gaseoso	$PaCO_2$ disminuida o aumentada
DLCO normal o disminuida	Alteración de la DLCO	DLCO disminuida

CRF: capacidad funcional residual; DLCO: capacidad de difusión del monóxido de carbono; $PaCO_2$: presión arterial de CO_2; PaO_2: presión arterial de O_2; V/Q: ventilación/perfusión; Vd/Vt: espacio muerto.

Villar. Arch Bronconeumol 2009

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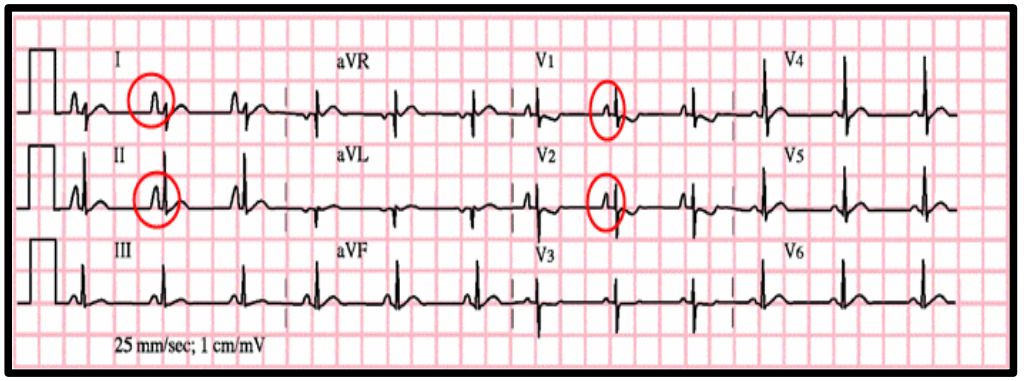
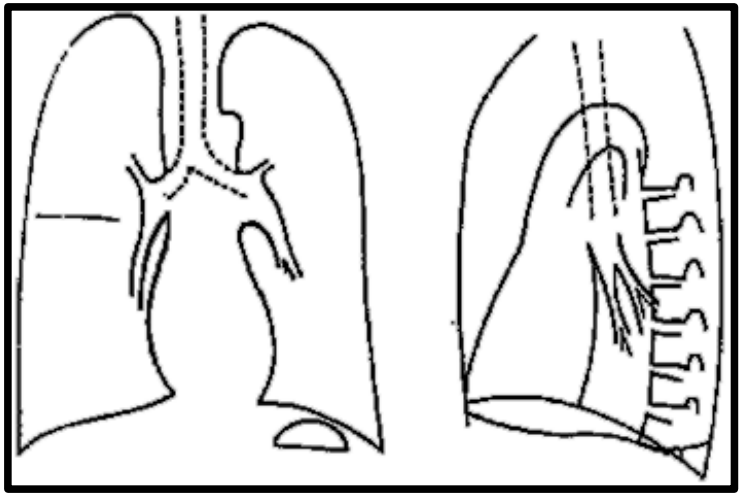
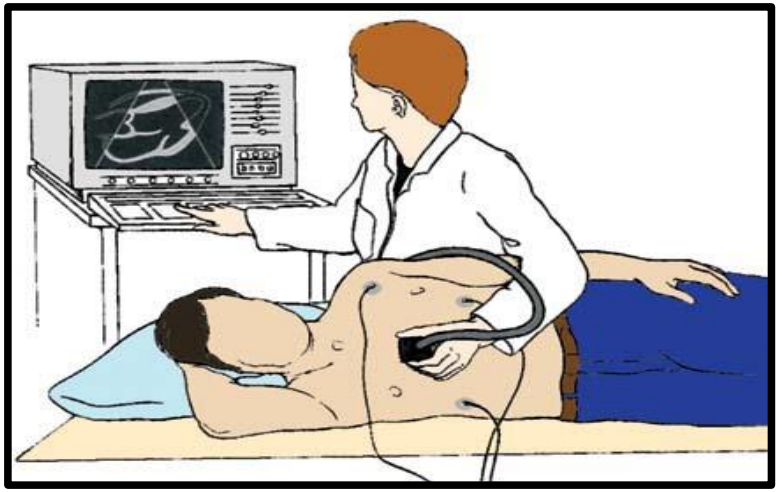
Errores en la valoración de eecc

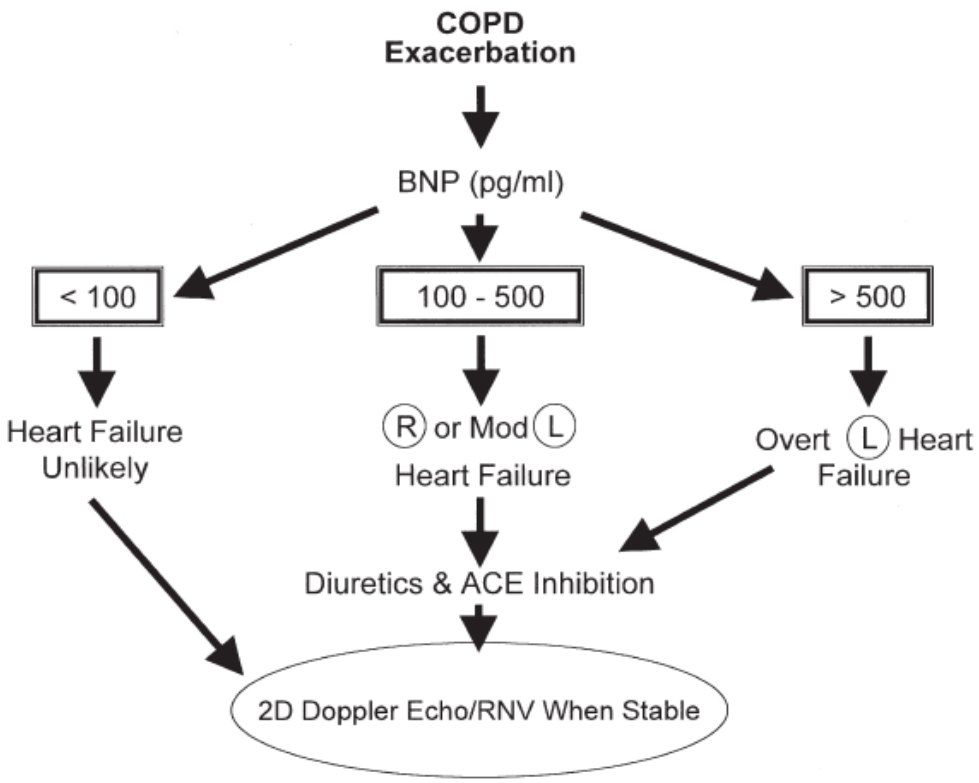






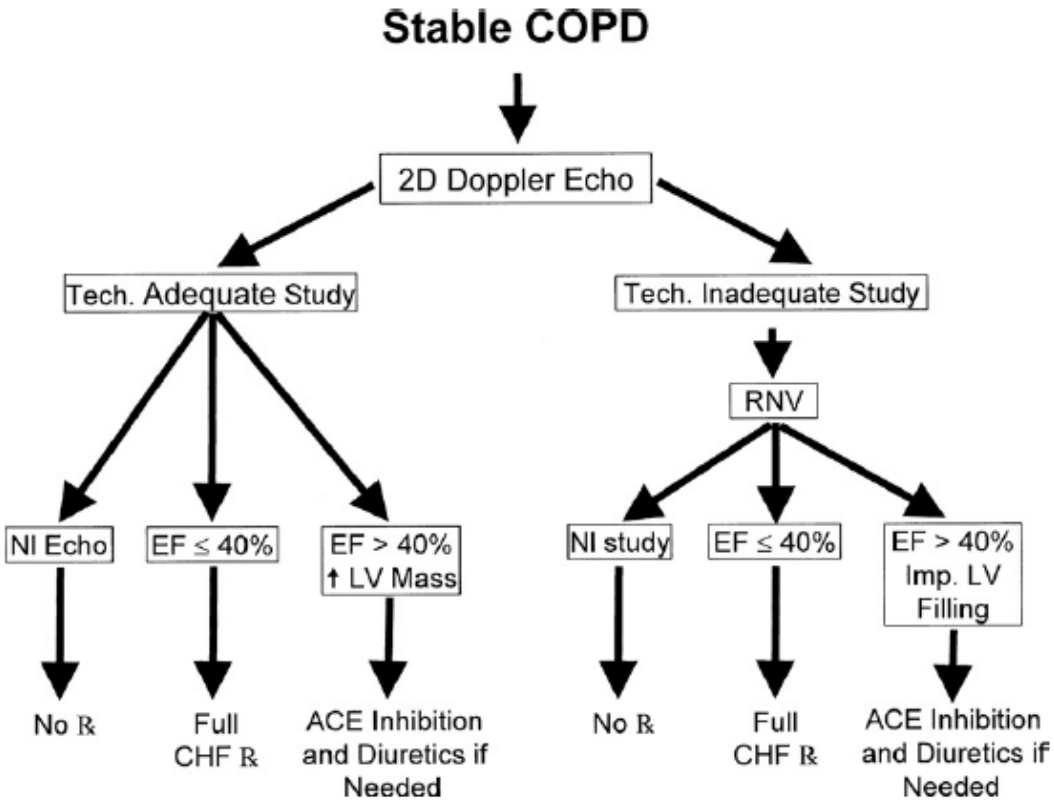
Cabau Rubies. Med Int 2. Síndromes 2011

Evaluación de IC durante exacerbación EPOC



Le Jemtel. JACC 2207

Evaluación de IC en EPOC estable



Le Jemtel. JACC 2207

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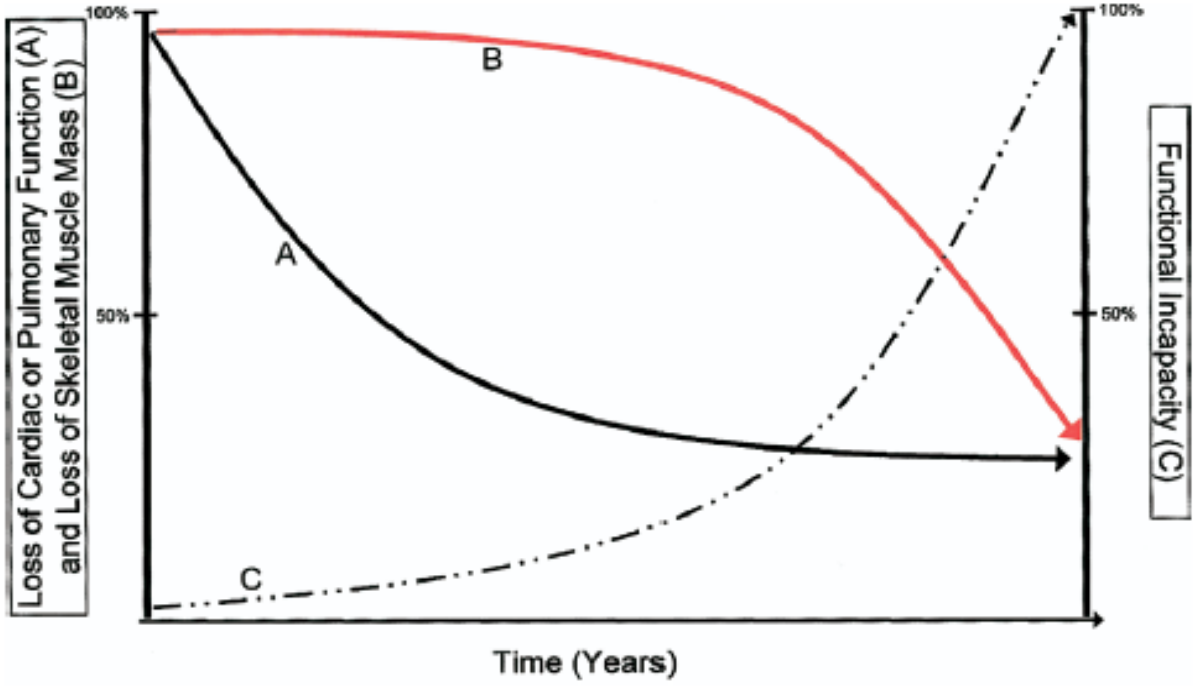
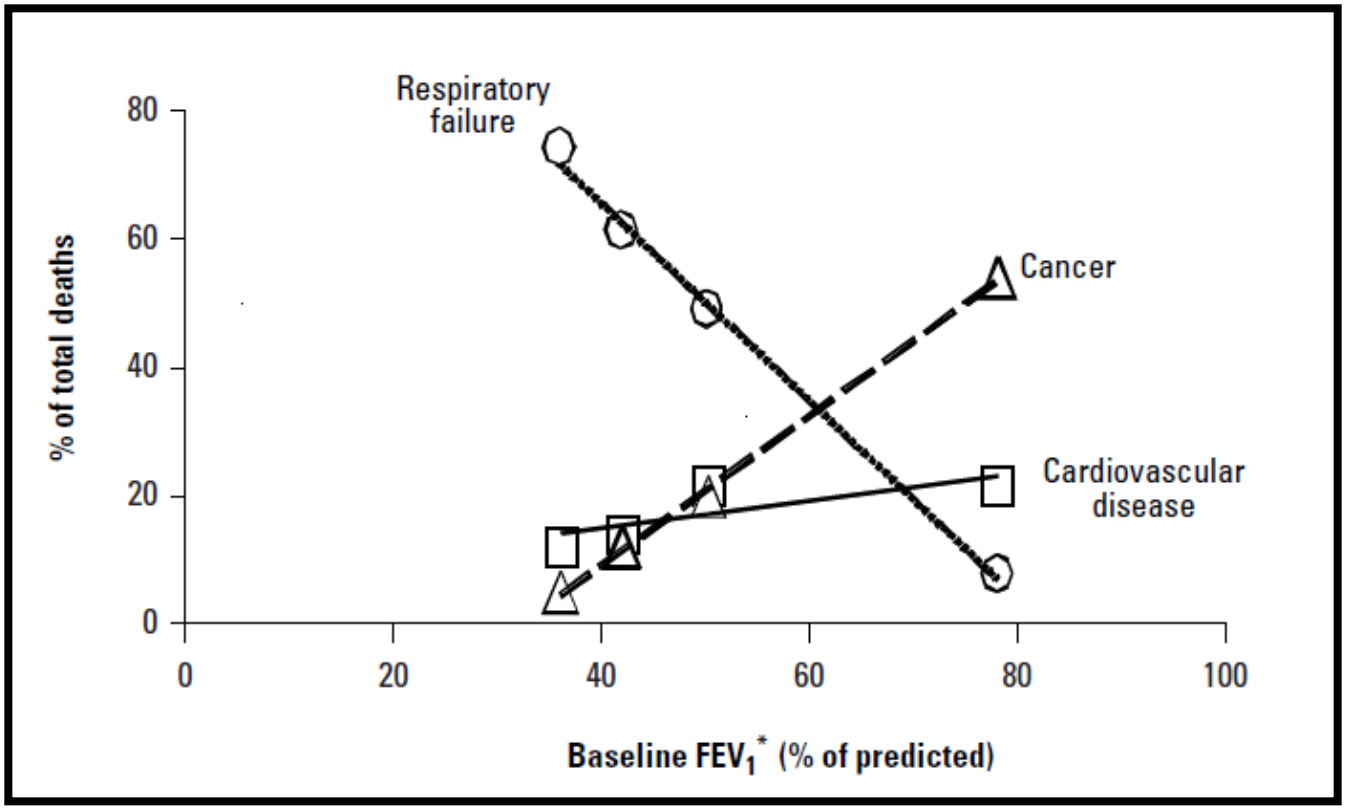
Progresión IC y EPOC



Le Jemtel. JACC 2007

Causas de mortalidad



Sinn. Eur Resp J 2005

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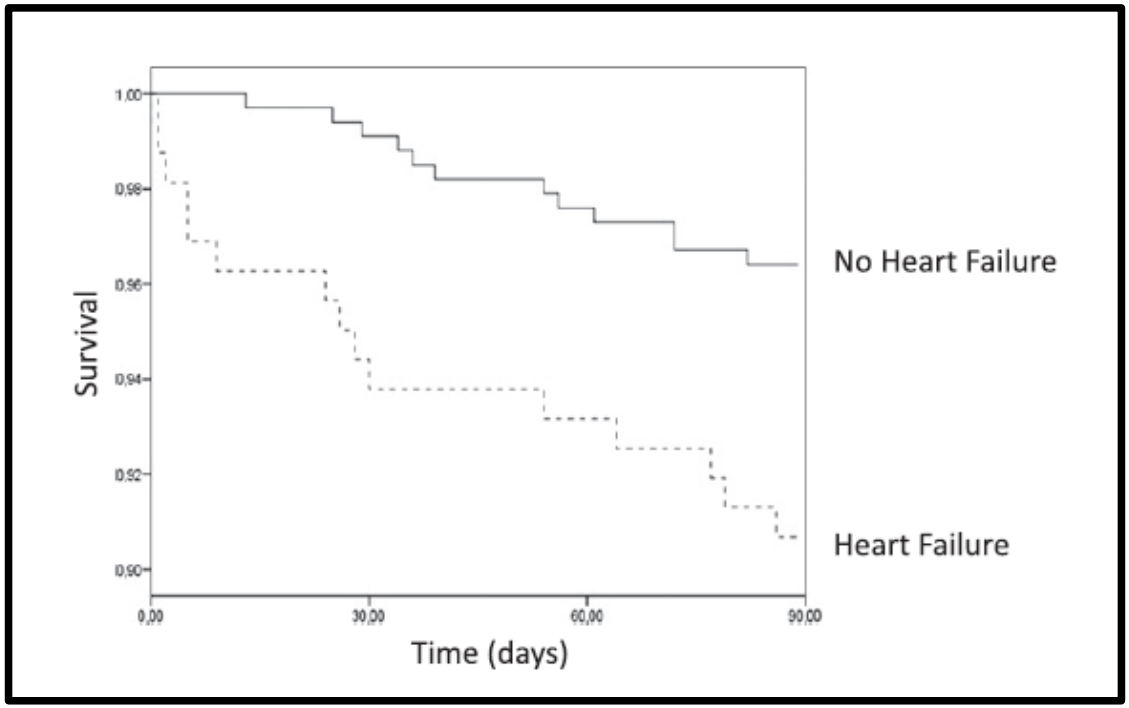
Mortalidad



Almagro. Chest 2012

Influencia del tratamiento de la IC en la EPOC

Beta bloqueantes

Cardioselective beta-blockers for chronic obstructive pulmonary disease (Review)

Salpeter SR, Ormiston TM, Salpeter EE

Beta-blocker treatment reduces mortality in patients with cardiovascular disease. The available data from controlled trials indicate that cardioselective beta-blocker use in patients with COPD has no significant adverse effects on FEV1, respiratory symptoms or response to beta2-agonists, even for those with severe chronic airways obstruction.

NICE y ESC

Salpeter. Cochrane 2005

Beta bloqueantes y mortalidad

Characteristic	No. (%) All Patients (N=2230)	No. (%) β-Blocker Use (n=665)	No. (%) No β-Blocker Use (n=1565)	*P* Value
Cardiovascular diseases				
Angina pectoris	363 (16.3)	217 (32.6)	146 (9.3)	<.001
Myocardial infarction	104 (4.7)	64 (9.6)	40 (2.6)	<.001
Ischemic heart disease[c]	439 (19.7)	255 (38.3)	184 (11.8)	<.001
Atrial fibrillation	222 (10.0)	125 (18.8)	97 (6.2)	<.001
Heart failure	546 (24.5)	213 (32.0)	333 (21.3)	<.001
Stroke	155 (7.0)	60 (9.0)	95 (6.1)	.01
Peripheral arterial disease	162 (7.3)	75 (11.3)	87 (5.6)	<.001

2230 pacientes EPOC. BB en 29,8%

Rutten. Arch Int Med 2010

Beta bloqueantes y mortalidad

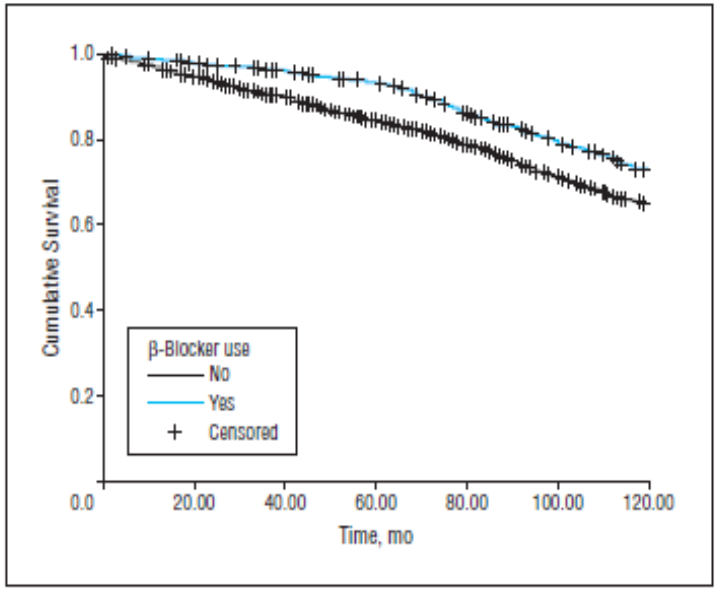


Figure 1. Cumulative survival of patients with chronic obstructive pulmonary disease according to β-blocker use.

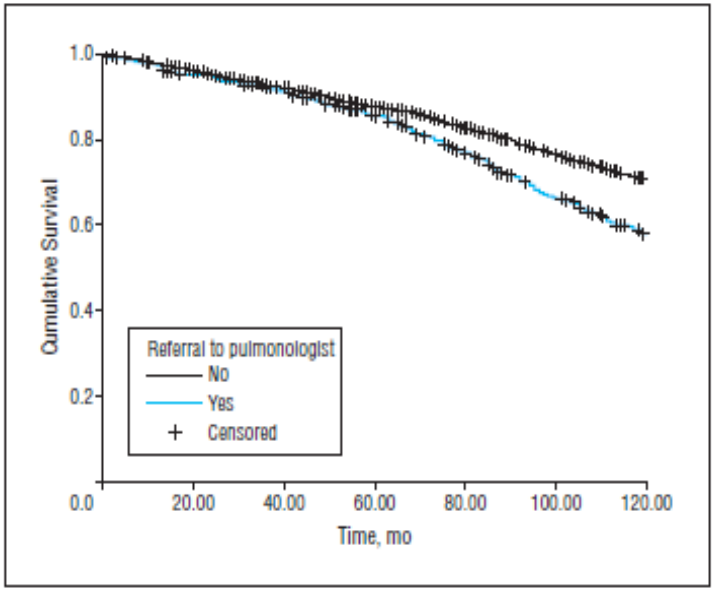


Figure 2. Cumulative survival of patients with chronic obstructive pulmonary disease according to referral to a pulmonologist.

Rutten. Arch Int Med 2010

Beta bloqueantes y mortalidad

Table 3. Crude and Adjusted Hazard Ratios (HRs) for Mortality According to β-Blocker Use in Subgroups of Patients With a Diagnosis of Chronic Obstructive Pulmonary Disease (COPD)

Variable	HR (95% Confidence Interval)
No overt cardiovascular disease (n=1229); 241(19.6%) died	Any β-blocker (n=239)
Unadjusted (crude)	0.60 (0.41-0.87)
Adjusted with Cox[a]	0.67 (0.45-0.99)
Adjusted with propensity score[b]	0.68 (0.46-1.02)
Patients who used 2 or more pulmonary drugs (n=1419); 442 (31.1%) died	Any β-blocker (n=417)
Unadjusted (crude)	0.66 (0.53-0.82)
Adjusted with Cox[a]	0.62 (0.48-0.80)
Adjusted with propensity score[b]	0.60 (0.49-0.74)
Patients who used β_2-sympathicomimetics (n=1288); 384 (29.8%) died	Any β-blocker (n=349)
Unadjusted (crude)	0.66 (0.52-0.83)
Adjusted with Cox[a]	0.64 (0.49-0.85)
Adjusted with propensity score[b]	0.60 (0.46-0.79)
Patients who inhaled anticholinergic agents (n=1357); 463 (34.1%) died	Any β-blocker (n=432)
Unadjusted (crude)	0.68 (0.56-0.84)
Adjusted with Cox[a]	0.68 (0.53-0.87)
Adjusted with propensity score[b]	0.60 (0.48-0.76)
Incident cases of COPD (n=1670); 472 (28.3%) died	Any β-blocker (n=530)
Unadjusted (crude)	0.73 (0.59-0.89)
Adjusted with Cox[a]	0.73 (0.57-0.92)
Adjusted with propensity score[b]	0.63 (0.50-0.79)
Patients who were referred to a pulmonologist (n=575); 233 (40.5%) died	Any β-blocker (n=151)
Unadjusted (crude)	0.80 (0.59-1.08)
Adjusted with Cox[a]	0.72 (0.51-1.03)
Adjusted with propensity score[b]	0.81 (0.58-1.13)

Rutten. Arch Int Med 2010

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Beta bloqueantes y exacerbaciones

Table 4. Crude and Adjusted Hazard Ratios (HRs) for Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) According to β-Blocker Use in 2230 Patients With a Diagnosis of COPD[a]

Variable	HR (95% Confidence Interval)		
	Any β-Blocker	Cardioselective β-Blocker	Nonselective β-Blocker
Unadjusted (crude)	0.73 (0.63-0.83)	0.75 (0.65-0.87)	0.72 (0.57-0.90)
Covariates included in the Cox model to calculate adjusted HRs +			
Age	0.71 (0.62-0.82)	0.74 (0.64-0.86)	0.71 (0.56-0.89)
Sex	0.71 (0.62-0.81)	0.74 (0.64-0.85)	0.70 (0.56-0.89)
Current or former smoker	0.70 (0.61-0.80)	0.73 (0.63-0.84)	0.71 (0.56-0.89)
Diabetes, hypertension, cardiovascular diseases	0.63 (0.54-0.74)	0.68 (0.58-0.80)	0.66 (0.52-0.84)
Cardiovascular drugs other than β-blocker	0.58 (0.50-0.68)	0.64 (0.54-0.75)	0.66 (0.52-0.84)
Pulmonary drugs	0.67 (0.57-0.79)	0.72 (0.61-0.85)	0.72 (0.56-0.91)
Referral to a pulmonologist	0.71 (0.60-0.83)	0.78 (0.66-0.92)	0.74 (0.58-0.94)
Adjusted with propensity score[b]	0.64 (0.55-0.75)	0.68 (0.58-0.80)	0.70 (0.56-0.89)

Rutten. Arch Int Med 2010

Propiedades de los betabloqueantes

Cardioselectividad	Lipofilia	Intervalo dosis (horas)	Actividad simpaticomimética	Vasodilatación
SI Mayor afinidad receptores beta 1				
Acebutolol	Moderada	12-24	Sí	No
Atenolol	Baja	12-24	No	No
Bisoprolol	Moderada	24	No	No
Celiprolol	Moderada	24	Sí	Sí
Metropolol	Alta	12-24	No	No
Nebivolol	Moderada	24	No	Sí
Esmolol	Baja	Uso i.v.	No	No
NO				
Carteolol	Baja	12-24	Sí	No
Carvedilol	Moderada	12	No	Sí
Labetalol	Baja	12	Sí	Sí
Nadolol	Baja	24	No	No
Oxprenolol	Moderada	12	Sí	No
Pindolol	Alta	12	Sí	No
Propanolol	Alta	12	No	No
Sotalol	Baja	12	No	No
Timolol	Alta	12	No	No

Hawkins. J Am Coll Cardiol 2011

Ivabradina

Abstract

Background

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) frequently coexist, with undefined prognostic and therapeutic implications. We investigated clinical profile and outcomes of patients with chronic HF and COPD, notably the efficacy and safety of ivabradine, a heart rate-reducing agent.

Methods

6505 ambulatory patients, in sinus rhythm, heart rate ≥ 70 bpm and stable systolic HF were randomised to placebo or ivabradine (2.5 to 7.5 mg bid). Multivariate Cox model analyses were performed to compare the COPD (n = 730) and non-COPD subgroups, and the ivabradine and placebo treatment effects.

Results

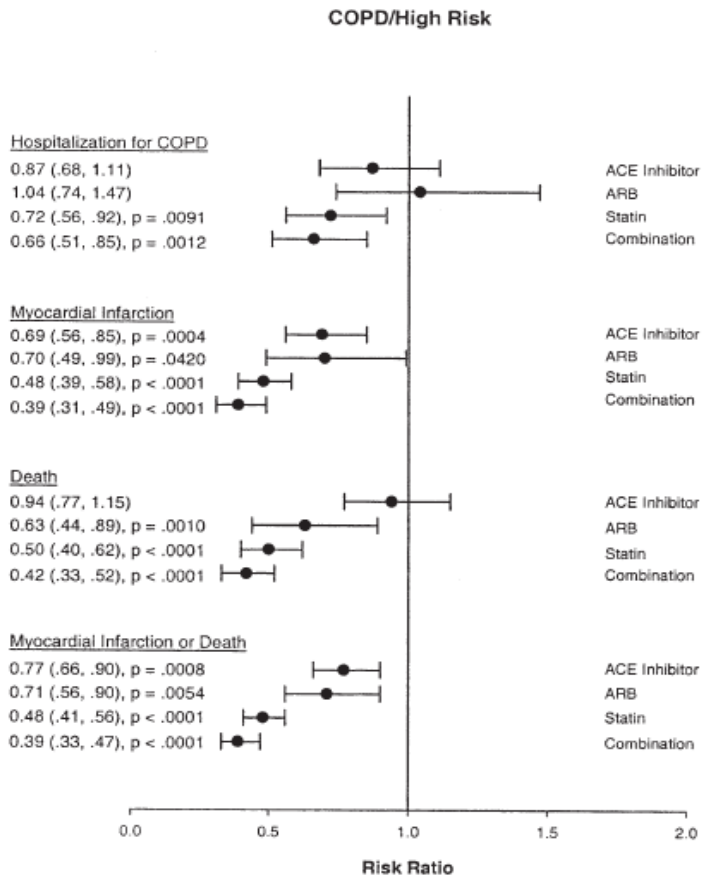
COPD patients were older and had a poorer risk profile. Beta-blockers were prescribed to 69% of COPD patients and 92% of non-COPD patients. The primary endpoint (PEP) and its component, hospitalisation for worsening HF, were more frequent in COPD patients (HRs f, 1.22 [p = 0.006]; and 1.34 [p < 0.001]) respectively, but relative risk was reduced similarly by ivabradine in both COPD (14%, and 17%) and non-COPD (18% and 27%) patients (p interaction = 0.82, and 0.53, respectively). Similar effect was noted also for cardiovascular death. Adverse events were more common in COPD patients, but similar in treatment subgroups. Bradycardia occurred more frequently in ivabradine subgroups, with similar incidence in patients with or without COPD.

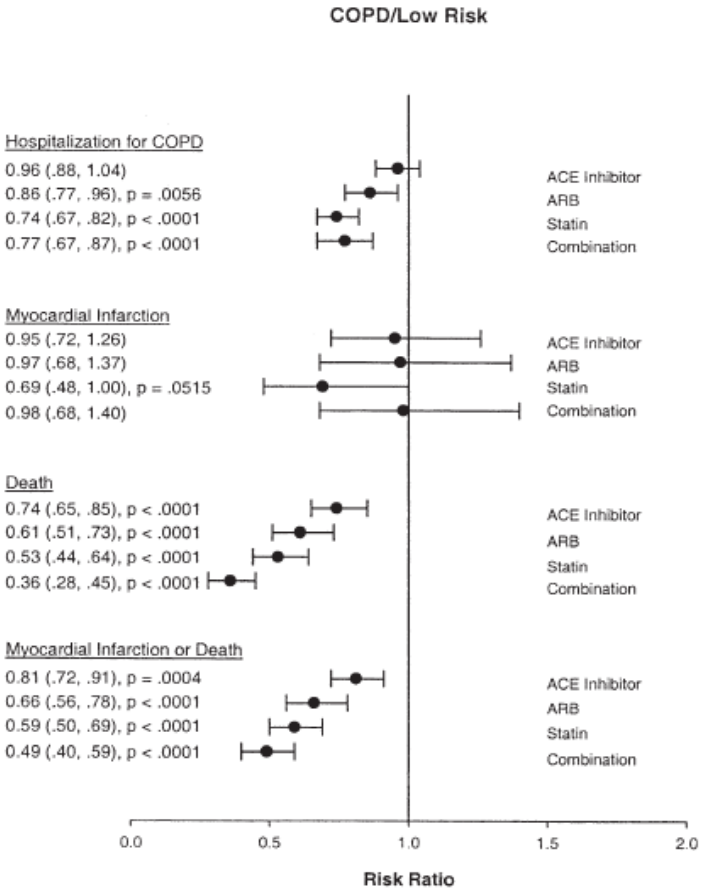
Conclusions

The association of COPD and HF results in a worse prognosis, and COPD represents a barrier to optimisation of beta-blocker therapy. Ivabradine is similarly effective and safe in chronic HF patients with or without COPD, and can be safely combined with beta-blockers in COPD

Tavazzi. Int J Cardiol 2013

IECAS / ARA II / estatinas





Mancini. J Am Coll Cardiol 2006

Simvastatina

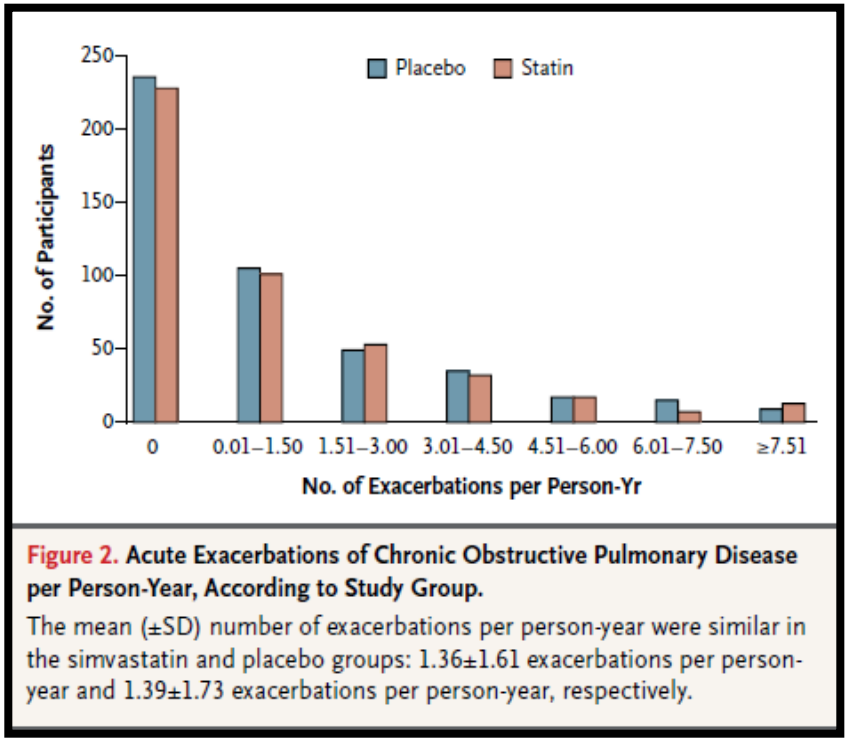


Figure 2. Acute Exacerbations of Chronic Obstructive Pulmonary Disease per Person-Year, According to Study Group.

The mean (±SD) number of exacerbations per person-year were similar in the simvastatin and placebo groups: 1.36±1.61 exacerbations per person-year and 1.39±1.73 exacerbations per person-year, respectively.

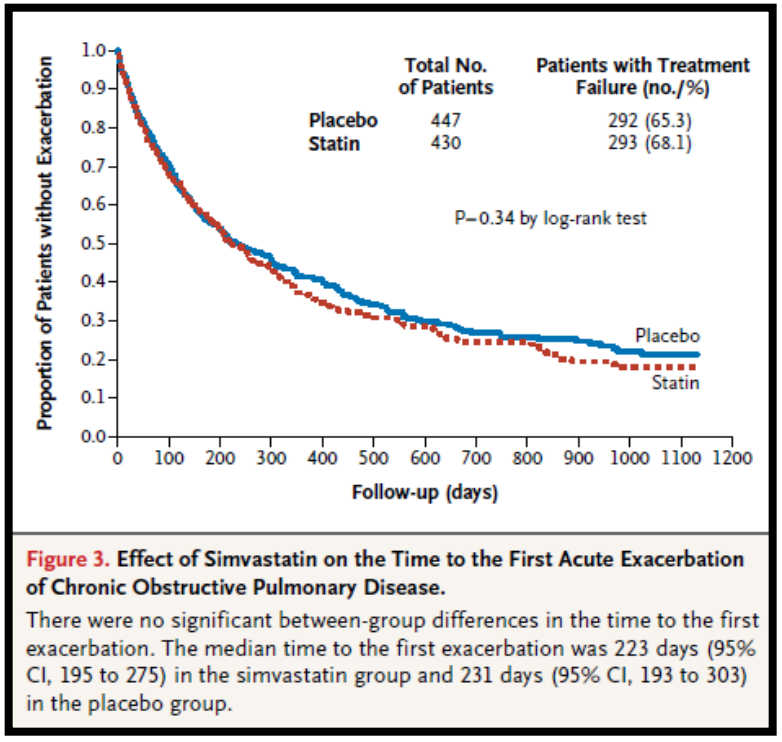


Figure 3. Effect of Simvastatin on the Time to the First Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

There were no significant between-group differences in the time to the first exacerbation. The median time to the first exacerbation was 223 days (95% CI, 195 to 275) in the simvastatin group and 231 days (95% CI, 193 to 303) in the placebo group.

30 muertes en el grupo placebo
28 en el grupo estatinas p = 0,89

Criner. NEJM 2014

Simvastatina

ABSTRACT

Background We tested the hypothesis that statin use in individuals with COPD is associated with a reduced risk of exacerbations.

Methods We identified 5794 individuals with COPD and a measurement of C reactive protein (CRP) in the Copenhagen General Population Study (2003–2008). During 3 years of follow-up we recorded exacerbations with hospital admissions or oral corticosteroid treatment. In a nested case-control design, matching on age, gender, smoking, COPD severity and comorbidity, we estimated the association between statin use and exacerbations. In addition, we examined the association between statin use and high CRP (>3 mg/L), and the association between high CRP and exacerbations during follow-up.

Results Statin use was associated with reduced odds of exacerbations in crude analysis, OR=0.68 (95% CI 0.51 to 0.91, p=0.01), as well as in multivariable conditional logistic regression analysis, OR=0.67 (0.48 to 0.92, p=0.01). However, in the subgroup with the most severe COPD and without cardiovascular comorbidity, we observed a null association between statin use and exacerbations, OR=1.1 (0.5 to 2.1, p=0.83). Furthermore, statin use was associated with reduced odds of a high CRP, OR=0.69 (0.56 to 0.85, p<0.001), and a high CRP was associated with an increased risk of exacerbations, HR=1.62 (1.35 to 1.94, p<0.001). We estimated the percentage of excess risk of the association of statin use with exacerbations possibly mediated through a reduction of CRP to be 14% (4–51%).

Ingebrigsten. Thorax 2015

Simvastatina

Conclusions Statin use was associated with reduced odds of exacerbations in individuals with COPD from the general population, although this was not apparent in those with the most severe COPD without cardiovascular comorbidity. Statins may thus only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease.

Ingebrigsten. Thorax 2015

Otros

Diuréticos:

- ✓ **Inducen alcalosis hipopotasémica**
- ✓ **En pacientes con insuficiencia respiratoria hipercápnica facilitan más retención de CO2 para compensar el pH, sobretodo a dosis altas**

Digoxina:

- ✓ **Produce vasoconstricción pulmonar**
- ✓ **Importante ajustar la digoxinemia a una ventana terapéutica de 0,5-0,8 ug/ml (aproximadamente 1/2 comprimido al día)**

Influencia del tratamiento de la EPOC en la IC

Propiedades farmacológicas de los beta 2

Table I. Summary of some pharmacological properties of selected β_2-adrenoceptor agonists[21-25]

β_2-Adrenoceptor agonist	Affinity for β_2-adrenoceptor (K_i, nmol/L)	Efficacy at β_2-adrenoceptor[a]	Potency at β_2-adrenoceptor[b]	Selectivity ratio ($\beta_2 : \beta_1$-adrenoceptor)	Intrinsic efficacy (%)	Approximate onset of action (min)	Approximate duration of action
Isoprenaline	200	(100)	(1)	1 : 1	100	2–5	<20 min
Salbutamol	2500	86	0.55	1 : 1375	4.9	2–3	4–6h
Fenoterol	ND	100	ND	1 : 120	42	2–4	4–6h
Terbutaline	ND	65–85	ND	ND	ND	2–4	4–6h
Salmeterol	53	63	8.5	1 : 85 000	<2.0	30	>12h
Formoterol	76	100	20	1 : 120	20	2–3	>12h

a Relative to isoprenaline as 100%.

b Relative to isoprenaline.

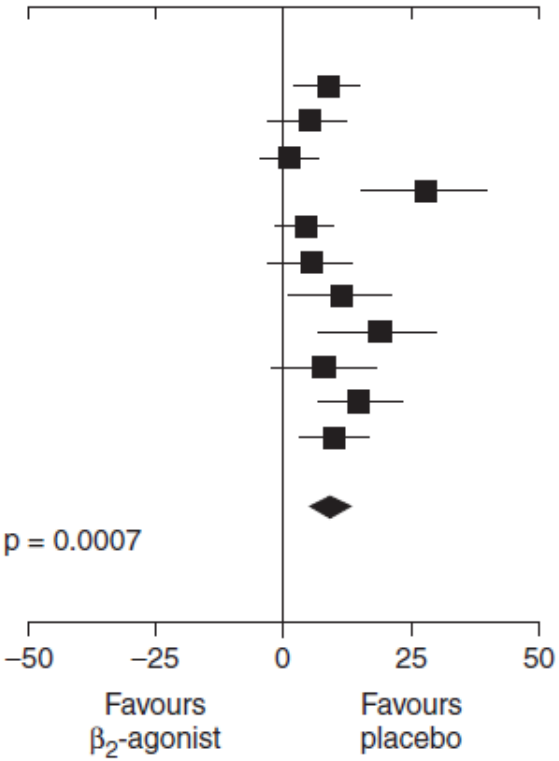
ND = no data available.

Cazzola. Drugs 2005

Efectos cardiovasculares. FC

Study	β_2-Agonist (n)	Placebo (n)	Weighted mean difference (95% CI random)	Weight (%)	Weighted mean difference (95% CI random)
Bennett et al. (1994)	12	12		10.7	7.97 (2.12, 13.82)
Braden et al. (1998)	8	8		9.7	5.00 (–2.00, 12.00)
Braun and Levy (1991)	72	72		11.6	0.70 (–4.20, 5.60)
Buch and Bundgaard (1984)	8	8		6.2	28.00 (16.47, 39.53)
Burgess et al. (1998)	20	20		11.9	4.30 (–0.32, 8.92)
Burggraaf et al. (2001)	8	8		9.1	5.20 (–2.40, 12.80)
Chan et al. (1988)	10	10		7.6	11.00 (1.54, 20.46)
Jartti et al. (1997)	8	8		6.5	18.00 (6.93, 29.07)
Marlin et al. (1978)	6	8		7.2	8.00 (–2.06, 18.06)
Vathenen et al. (1988)	30	30		9.2	15.10 (7.51, 22.69)
Wong et al. (1990)	10	10		10.3	9.90 (3.59, 16.21)
Total (95% CI)	192	194		100.0	9.12 (5.32, 12.92)

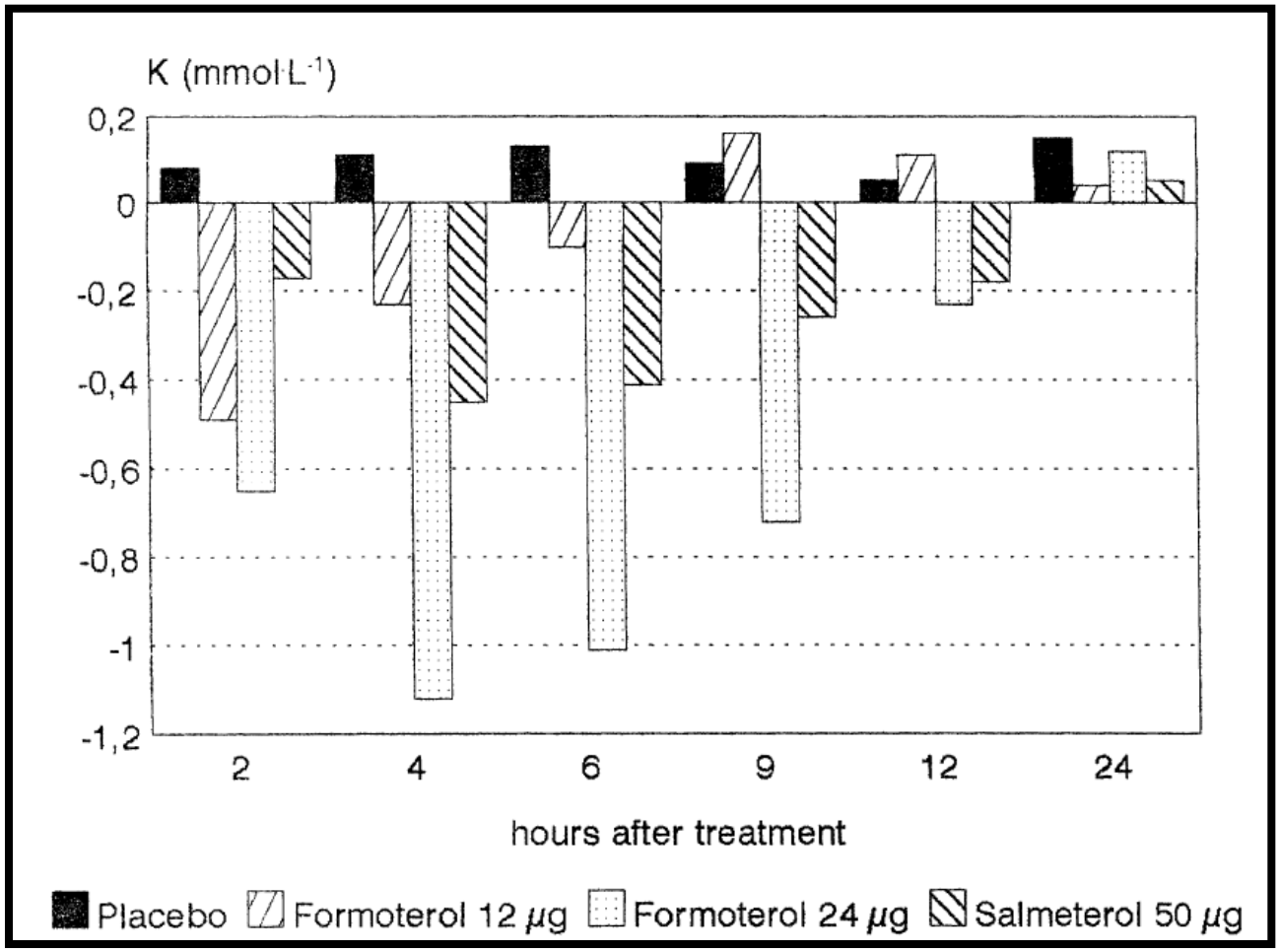
Test for heterogeneity chi-square = 30.62; df = 10; p = 0.0007
Test for overall effect z = 4.70; p < 0.00001



Frecuencia cardíaca

Cazzola M. Drugs 2005

Hipopotasemia



Cazzola M. Chest 1998

HOSPITAL Sant Joan de Déu MARTORELL

Beta 2 y hospitalización por IC y muerte

Table 2—*Risk of Chronic Heart Failure Hospital Admission Within 1 Year of Entry Associated With Inhaled β-Agonist Use***

Average No. of Canisters Filled per Month	CHF Hospital Admission (n = 391)	No CHF Hospital Admission (n = 1,138)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
0	269	897	Referent	Referent
1	34	83	1.4 (0.9–2.0)	1.3 (0.9–2.0)
2	47	92	1.7 (1.2–2.5)	1.7 (1.2–2.5)
≥ 3	41	66	2.1 (1.4–3.1)	2.0 (1.3–3.0)

*Adjusted for age, ACE inhibitor use, β-blocker use, diabetes, acute myocardial ischemia, cardiovascular disease, hypertension, and alcohol abuse. See Table 1 for expansion of abbreviation.

Table 3—*Risk of All-Cause Death Within 1 Year of Entry Associated With Inhaled β-Agonist Use***

Average No. of Canisters Filled per Month	Dead (n = 259)	Alive (n = 1,270)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
0	185	981	Referent	Referent
1	17	100	0.9 (0.5–1.5)	0.9 (0.5–1.6)
2	28	111	1.3 (0.9–2.1)	1.4 (0.9–2.2)
≥ 3	29	78	2.0 (1.3–3.1)	2.0 (1.3–3.2)

*Adjusted for age, ACE inhibitor use, β-blocker use, diabetes, acute myocardial ischemia, cardiovascular disease, hypertension, and alcohol abuse.

Au. Chest 2003

HOSPITAL Sant Joan de Déu MARTORELL

Asociación entre beta2 y IC

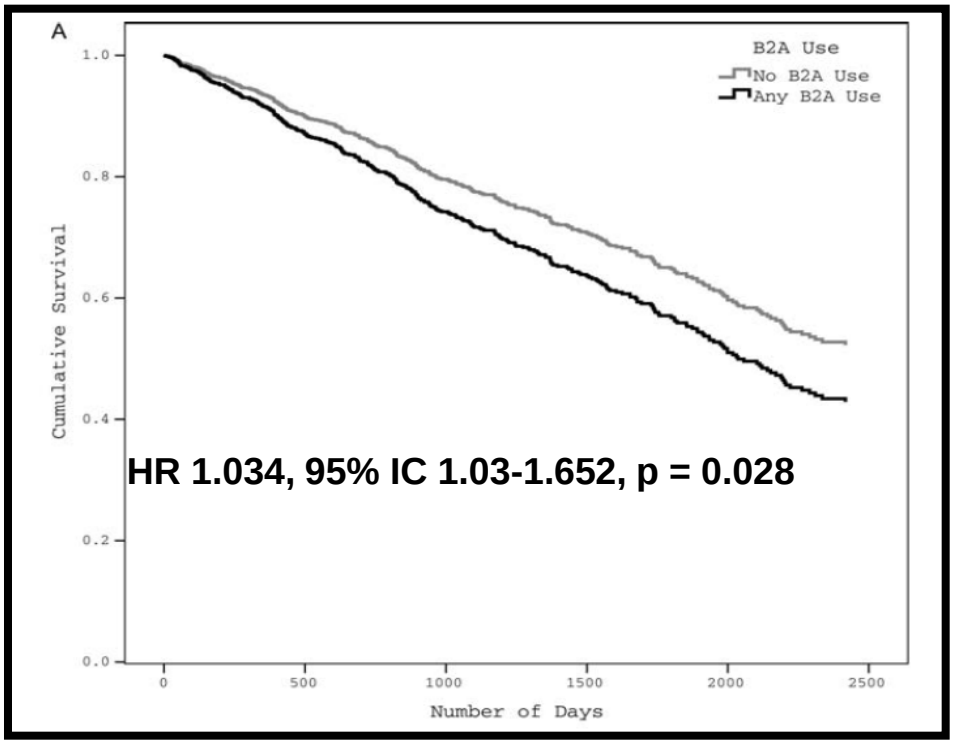
First Author (Ref. #)	Population	Route	Bronchodilator	Study Design	N	Outcome	Risk Associated With Bronchodilator Use (95% CI)
Martin et al. (43)	Asthma	Oral	Bambuterol	Cohort	8,098	HF	RR: 3.41 (1.99–5.86), $p < 0.0001$
		Inhaled	Salmeterol	Cohort	15,407	HF	RR: 1.10 (0.63–1.91), $p = 0.7$
Coughlin et al. (44)	General population	Oral	Beta-agonist	Case control	387	DCM	OR: 3.4 (1.1–11.0)
		Inhaled nebulized	Beta-agonist	Case control	387	DCM	OR: 3.2 (1.4–7.1)
Sengstock et al. (38)	Cardiology clinic	Inhaled	Beta-agonist	Case control	190	DCM	OR: 1.0
Macie et al. (87)	COPD or asthma	Inhaled	Beta-agonist	Case control	59,336	HF hospitalization	OR: 1.74 (1.60–1.91)
Au et al. (37)	HF	Inhaled	Beta-agonist	Case control	1,121	HF hospitalization	OR: 1.5 (0.8–2.8), 1–2 canisters OR: 2.1 (1.0–4.3), ≥3 canisters
	General medical clinics	Inhaled	Beta-agonist	Case control	13,012	HF hospitalization	OR: 1.3 (0.9–1.8), 1–2 canisters OR: 1.1 (0.8–1.6), ≥3 canisters
Au et al. (36)	LVSD	Inhaled	Beta-agonist	Cohort	1,529	Death	RR: 0.9 (0.5–1.6), 1 canister/month RR: 1.4 (0.9–2.2), 2 canisters/month RR: 2.0 (1.3–3.2), 3 canisters/month
Singer et al. (101)	Acute HF without COPD	Inhaled	Any bronchodilator	Cohort	7,299	Death IV Vasodilator use Ventilation	OR: 1.02 (0.67–1.56) OR: 1.40 (1.18–1.67) OR: 1.69 (1.21–2.37)

CI = confidence interval; DCM = idiopathic dilated cardiomyopathy; HF = heart failure; LVSD = left ventricular systolic dysfunction; OR = odds ratio; RR = relative risk; other abbreviations as in Table 2.

Hawkins. J Am Coll Cardiol 2011

LABA y mortalidad en IC

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



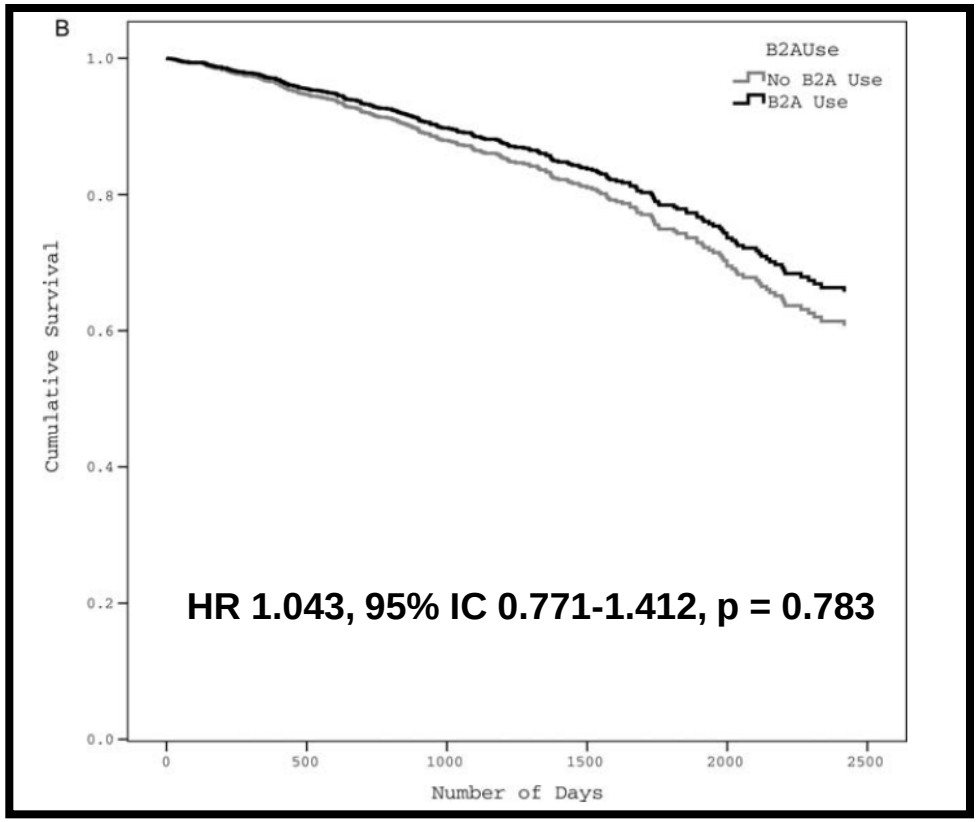
Cohorte retrospectiva

1294 pacientes

Modelo ajustado por:
- **edad**
- **sexo**
- **uso betabloqueantes**

Bermingham M. ERJHF 2011

LABA y mortalidad en IC



1294 pacientes

Modelo ajustado por:

- **edad**
- **sexo**
- **uso betabloqueantes**
- **comorbilidades**
- **hábito tabáquico**
- **severidad IC**
- **severidad EPOC**
- **BNP**

Bermingham M. ERJHF 2011

Tiotropio

Table 2.– Adverse event profile

	Tiotropium	Placebo
Subjects n	550	371
Adverse events n (%)	495 (90.0)	338 (91.1)
Adverse events considered drug related n (%)	104 (18.9)	34 (9.2)*
Dry mouth n (%)	88 (16.0)	10 (2.7)*
Deaths n (%)	7 (1.3)	7 (1.9)
Serious adverse events n (%)	99 (18.0)	78 (21.0)
Adverse events leading to discontinuation n (%)	53 (9.6)	51 (13.7)

*: $p<0.05$.

excluded if they had a recent history of myocardial infarction ($\leqslant$1 yr), heart failure ($\leqslant$3 yrs) or cardiac arrhythmia requiring drug therapy.

Casaburi. Eur Resp J 2002

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Tiotropio

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).
† $P<0.05$.

Tashkin. NEJM 2008

Tiotropio

Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials

Results Five randomised controlled trials were eligible for inclusion. Tiotropium mist inhaler was associated with a significantly increased risk of mortality (90/3686 *v* 47/2836; relative risk 1.52, 95% confidence interval, 1.06 to 2.16; P=0.02; I^2=0%). Both 10 µg (2.15, 1.03 to 4.51; P=0.04; I^2=9%) and 5 µg (1.46, 1.01 to 2.10; P=0.04; I^2=0%) doses of tiotropium mist inhaler were associated with an increased risk of mortality. The overall estimates were not substantially changed by sensitivity analysis of the fixed effect analysis of the five trials combined using the random effects model (1.45, 1.02 to 2.07; P=0.04), limiting the analysis to three trials of one year's duration each (1.50, 1.05 to 2.15), or the inclusion of additional data on tiotropium mist inhaler from another investigational drug programme (1.42, 1.01 to 2.00). The number needed to treat for a year with the 5 µg dose to see one additional death was estimated to be 124 (95% confidence interval 52 to 5682) based on the average control event rate from the long term trials.

Signh. BMJ 2011

Tiotropio

Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials

Conclusions This meta-analysis explains safety concerns by regulatory agencies and indicates a 52% increased risk of mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease.

Signh. BMJ 2011

LAMA y LABA (hospitalización / urg)

Long-Acting Bronchodilator Class	Reference Group	% of Subjects			OR (95% CI)		
		Cases (n = 26 628)	Controls (n = 26 628)	Absolute Difference	Matched[a]	Adjusted[b]	*P* Value
New use of LAAs	Nonuse of LAAs or LABAs	2.8	2.4	0.4	1.18 (1.06-1.32)	1.14 (1.01-1.28)	.03
New use of LABAs	Nonuse of LAAs or LABAs	1.7	1.4	0.4	1.28 (1.11-1.47)	1.31 (1.12-1.52)	<.001
New use of LABAs vs LAA use	New use of LAAs (nonusers of LABAs)	NA	NA	NA	1.08 (0.91-1.29)	1.15 (0.95-1.38)	.16

Gershon. JAMA 2013

LAMA y LABA

Cardiovascular Event	Matched Cases With Cardiovascular Outcome as First Event, %	OR (95% CI)				
		New Use of LAAs[a]		New Use of LABAs[a]		New Use of LABAs vs LAAs, Adjusted[c]
		Matched[b]	Adjusted[c]	Matched[b]	Adjusted[c]	
ACS, including acute MI						
Cases	35.5	1.32 (1.08-1.61)	1.30 (1.04-1.62)	1.23 (0.96-1.56)	1.43 (1.08-1.89)	1.10 (0.78-1.56)
P value		.006	.02	.10	.01	.58
Heart failure						
Cases	29.1	1.32 (1.11-1.58)	1.31 (1.08-1.60)	1.48 (1.17-1.86)	1.42 (1.10-1.83)	1.08 (0.79-1.47)
P value		.002	.006	.001	.008	.64
Arrhythmias						
Cases	16.3	1.21 (0.91-1.61)	1.26 (0.91-1.75)	1.17 (0.79-1.73)	1.17 (0.74-1.83)	0.93 (0.54-1.59)
P value		.19	.17	.43	.50	.77
Ischemic stroke						
Cases	19.1	0.73 (0.55-0.96)	0.68 (0.50-0.91)	1.05 (0.74-1.50)	1.17 (0.78-1.74)	1.73 (1.06-2.83)
P value		.02	.01	.77	.58	.03

Gershon. JAMA 2013

Corticoides

Table 3. New-Onset Atrial Fibrillation and Corticosteroid Therapy in Different Patient Groups

Corticosteroid Prescription*	Cases, No. (n = 385)	OR† (95% CI)	OR‡ (95% CI)
In patients with asthma and/or COPD			
None	43	1.00	1.00
Low-intermediate dose	13	1.46 (0.78-2.76)	1.40 (0.73-2.70)
High dose	13	4.71 (2.51-8.81)	4.02 (2.07-7.81)
In patients with other diseases			
None	299	1.00	1.00
Low-intermediate dose	1	0.78 (0.11-5.55)	0.57 (0.08-4.24)
High dose	16§	10.78 (6.50-17.83)	7.90 (4.47-13.98)

Van der Hooft, Arch Int Med 2006

Conclusiones

- ✓ **Asociación frecuente que empeora el pronóstico. Pensar en cardiopatia isquémica subyacente.**
- ✓ **Dificultades diagnósticas y nuevas herramientas para casos dudosos.**
- ✓ **No se deberían denegar los efectos beneficiosos de los betabloqueantes cardioselectivos en pacientes con EPOC y IC.**
- ✓ **Estatinas, IECAS y ARA II disminuyen la morbi mortalidad.**
- ✓ **Precaución en el uso de beta 2 agonistas y anticolinérgicos.**