XVII Reunión
Insuficiencia Cardiaca
y Fibrilación Auricular

¿Aportan los nuevos broncodilatadores un beneficio adicional en el paciente con IC y EPOC?

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Conflicto de intereses: fondos por colaboraciones, ponencias o asistencia a congresos de: Almirall, Boehringer, Chiesi, GSK, Menarini, Takeda

XVII Reunión
Insuficiencia Cardiaca y Fibrilación Auricular

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

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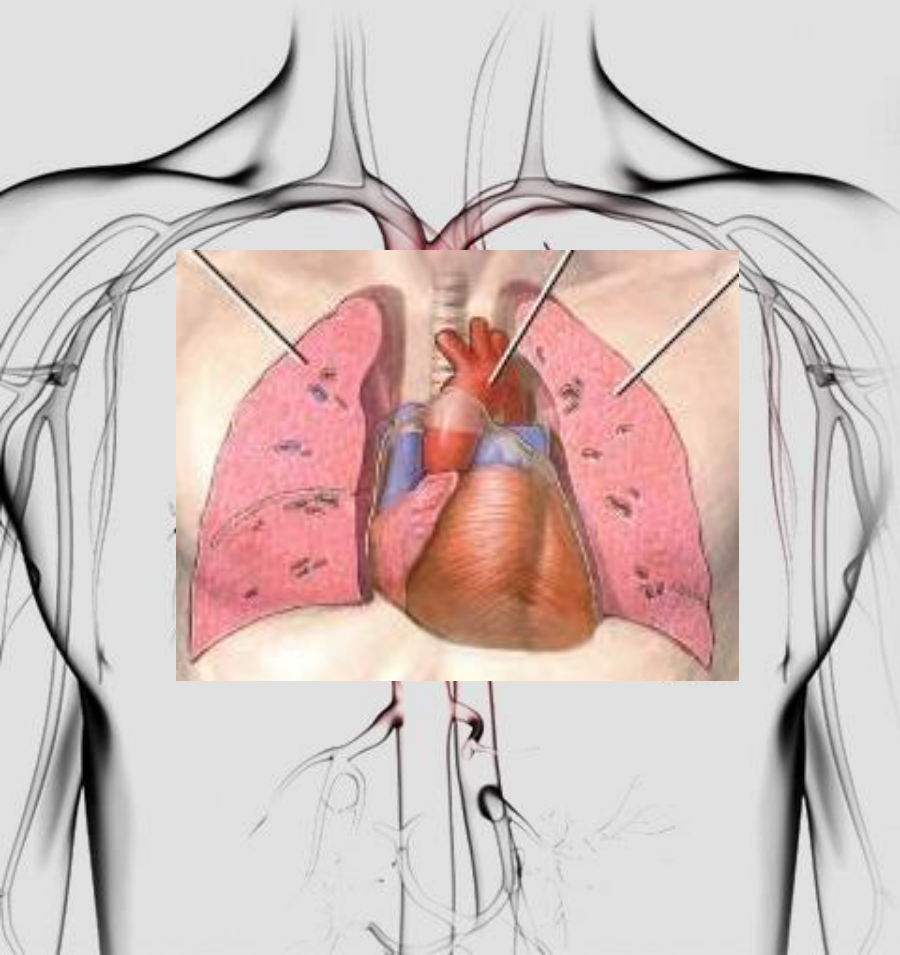
FUNDACIÓN ESPAÑOLA DE MEDICINA INTERNA

GRUPO DE INSUFICIENCIA CARDÍACA Y FIBRILACIÓN AURICULAR

16-17 de Abril de 2015
Hotel Holiday Inn-Madrid



- ✓¿Qué sabemos de la EPOC en el paciente con IC?
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Relación entre EPOC y la IC

Systemic inflammation has been proposed as having a potential role in explaining the association between COPD and increased risk of CVD. Other factors have also been implicated, including :

- autonomic imbalance,
- vascular endothelial dysfunction,
- lower arterial compliance
- arrhythmias.

It is, however, also possible that the decreased physical activity associated with even mild COPD may increase the risk of CVD, as well as other comorbidities.

Eur Respir J 2013; 41: 1017–1022

From a clinical perspective, they support the need to consider CVD in the routine assessment of patients with COPD, and that patients with CVD should also be routinely screened for COPD

¿Es frecuente la coexistencia IC-EPOC?

Grupo de IC de la SEMI

- Registro SEMI- IC 2002: 30% — Med Clin (Barc) 2002;118(16):605-10
- Estudio ATICA 2006: 29% — An Med Interna (Madrid) 2006; 23: 478-482
- Estudio GESAIC: 25% — Med Clin (Barc) 2010;134(10):427–432

A nivel mundial: (> año 2000)

- 9-52% registros — Eur J Heart Fail 2009;11:130–139
- Ensayos clínicos 7-13% — Am Heart J 2008;156:662-673
- 20-30% (ADHERE; OPTIMIZE-HF) — Am Heart J 2007;153: 1021-1028; Eur J Heart Fail 2012;14, 395–403

	ECCO [1]	ESMI [2]
Edad (años)	75	72,6
FEV1 postBD (%)	43,2	43
Comorbilidad	(%)	(%)
Hipertensión	55	65,6
Anemia	33	27,1
Diabetes Mellitus	29,5	37,1
Insuf cardíaca	27	35,5
Arrítmia	27	25,8
C. isquémica	17	22
Enf arterial periférica	12,6	17,4
Enf 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

¿Es un factor pronóstico la coexistencia de EPOC en IC?

- **Val-HeFT trial : Chronic obstructive pulmonary disease strongly predicted non-cardiovascular mortality (HR 2.50 [1.58– 3.96) and hospitalizations (HR1.71[1.43–2.06].**

- **Escasa influencia en el pronóstico a corto plazo (1año):**
  Disminución de un 20% en la supervivencia a 5 años

- **OPTIMIZE-HF: COPD was associated with increased in-hospital non-CV mortality but similar 60-day mortality**

- **FEV_1 had independent prognostic value…. provides significant prognostic information for all-cause mortality in patients admitted with HF…**

Spirometry therefore seems to be worth considering for all patients admitted with HF in order to identify patients at high risk.

- **Comorbidities had similar impacts on mortality in patients with HFpEF compared with those with HFrEF, except for chronic obstructive pulmonary disease, which was associated with a higher hazard (1.62 [95% confidence interval: 1.36 to 1.92] vs. 1.23 [95% confidence interval: 1.11 to 1.37], respectively, p < 0.01 for interaction) in patients with HFpEF.**

J Card Fail 2007;13:797–804.
Am J Cardiol 2008;101:353–358
Eur J Heart Fail 2009 11, 130–139
Eur J Heart Fail 2012;14, 395–403
J Am Coll Cardiol 2012;59:998–1005

Table 5. Factors Associated With Postdischarge Mortality

Factor	All Patients		Incident Cases	
	HR	95% CI	HR	95% CI
Age, y				
<65	1.00	—	1.00	—
65 to 74	1.43	1.21 to 1.70	1.62	1.52 to 1.73
75 to 84	1.89	1.64 to 2.18	2.22	1.96 to 2.51
≥85	2.62	2.29 to 2.99	3.16	2.75 to 3.63
Male	1.06	1.02 to 1.10	1.24	1.04 to 1.47
White race	1.39	1.22 to 1.59	1.61	1.38 to 1.86
Incident case	0.74	0.65 to 0.83	—	—
Medical history				
Anemia	1.13	1.06 to 1.20	1.23	1.04 to 1.44
Coronary heart disease	1.00	0.95 to 1.06	0.99	0.93 to 1.06
Chronic obstructive pulmonary disease	1.26	1.19 to 1.34	1.48	1.35 to 1.63
Diabetes	1.08	1.01 to 1.15	1.09	0.98 to 1.18
Hypertension	0.88	0.84 to 0.92	0.89	0.77 to 1.01
Peripheral vascular disease	1.09	1.01 to 1.18	1.14	1.07 to 1.20
Renal disease	1.11	1.04 to 1.20	1.11	0.98 to 1.26
Stroke	1.19	1.14 to 1.24	1.22	1.08 to 1.38
Estimated GFR, mL/min per 1.73 m^2				
<30	1.21	1.04 to 1.42	1.30	0.89 to 1.89
30 to 59	1.08	1.01 to 1.14	1.10	1.03 to 1.18
≥60	1.0	—	1.0	—
Serum glucose, mg/dL				
<140	1.00	—	1.00	—
140 to 199	1.00	0.95 to 1.05	0.99	0.90 to 1.09
≥200	1.02	0.91 to 1.14	1.14	0.92 to 1.41
Systolic BP, mm Hg				
<100	1.0	—	1.0	—
100 to 159	0.78	0.73 to 0.84	0.89	0.76 to 1.04
≥160	0.66	0.60 to 0.72	0.75	0.61 to 0.92
Diastolic BP, mm Hg				
<60	1.0	—	1.0	—
60 to 89	0.99	0.94 to 1.04	0.93	0.89 to 0.98
≥90	0.96	0.90 to 1.02	0.97	0.90 to 1.04
Heart rate, bpm				
<60	1.0	—	1.0	—
60 to 99	1.05	0.91 to 1.21	1.14	0.93 to 1.40
≥100	1.16	1.05 to 1.28	1.16	0.96 to 1.42

Journal of the American Heart Association
OPEN ACCESS

Improved Survival After Heart Failure: A Community–Based Perspective

Samuel W. Joffe, Kristy Webster, David D. McManus, Michael S. Kiernan, Darleen Lessard, Jorge Yarzebski, Chad Darling, Joel M. Gore and Robert J. Goldberg

J Am Heart Assoc. 2013;2:e000053; originally published May 15, 2013;

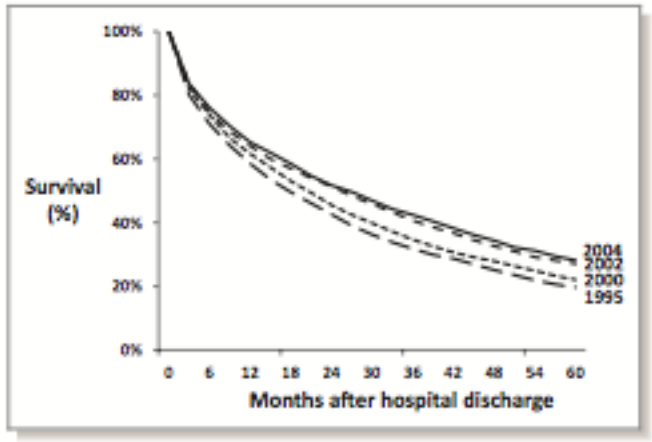
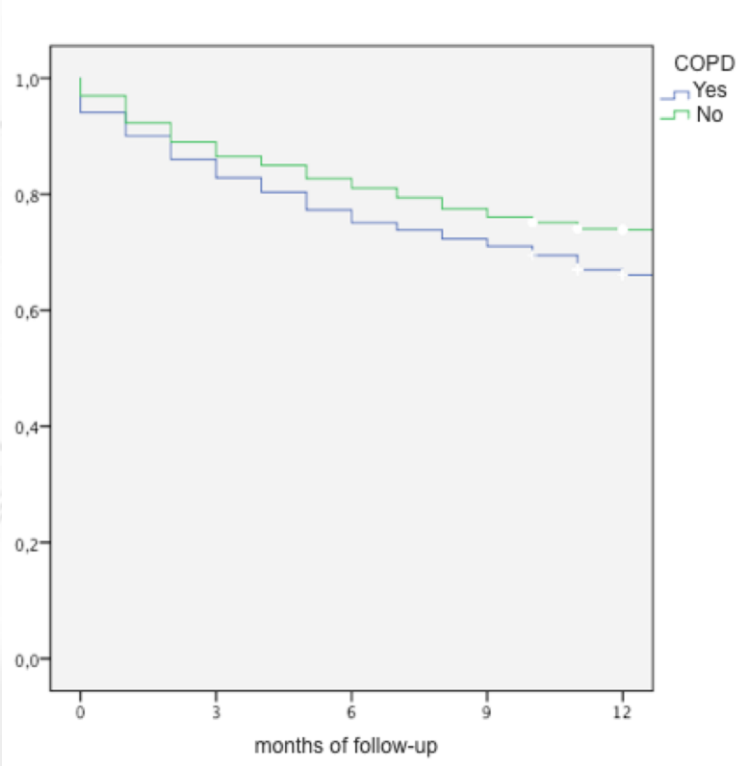


Figure. Long-term survival after hospital discharge for acute decompensated heart failure.

Prognostic influence of chronic obstructive pulmonary disease in elderly patients with heart failure. Data from the Spanish RICA registry.

Development	Total n=1165	COPD (n=321)	Without COPD n=844	RR (95% CI)	p-value
Death n (%)	365 (31.3)	118 (36.8)	247 (29.3)	1.26 (1.05-1.50)	0.014
Hospital readmission	509 (43.7)	143 (44.5)	366 (43.4)	1.03 (0.89-1.19)	0.716



In press

¿Es un factor pronóstico la coexistencia de IC en la EPOC

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 3—*Crude Mortality Predictors at 3 mo*

Variables	*P* Value	HR	95% CI
Age	< .007	1.068	1.02-1.1
Hospitalization for COPD in previous year	< .001	1.4	1.2-1.7
Hospitalization for other causes in previous year	< .05	1.3	1.15-1.57
Dyspnea	< .0001	2.36	1.57-3.55
Chronic oxygen therapy	< .003	3.4	1.5-7.5
Charlson index	< .0001	1.35	1.18-1.57
Global comorbidity scale	< .003	1.32	1.15-1.52
Katz index	< .0001	0.7	0.58-0.85
FEV_1 stratified GOLD	< .04	1.78	1.02-3.11
Ischemic heart disease	< .01	1.29	1.04-1.61
Heart failure	< .01	2.31	1.05-5.1
Peripheral vascular disease	< .002	3.83	1.71-8.57
Cerebrovascular disease	< .006	3.44	1.49-7.99
Dementia	< .001	5.17	1.76-15.28
Chronic kidney disease	< .005	3.91	1.75-8.73
Hemiplegia	< .0001	32.2	10.2-101
Depression	< .012	3.24	1.24-7.56
Atrial fibrillation	< .001	2.8	1.28-6.15

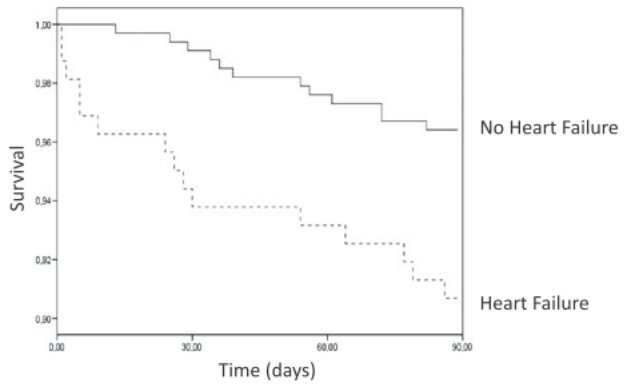
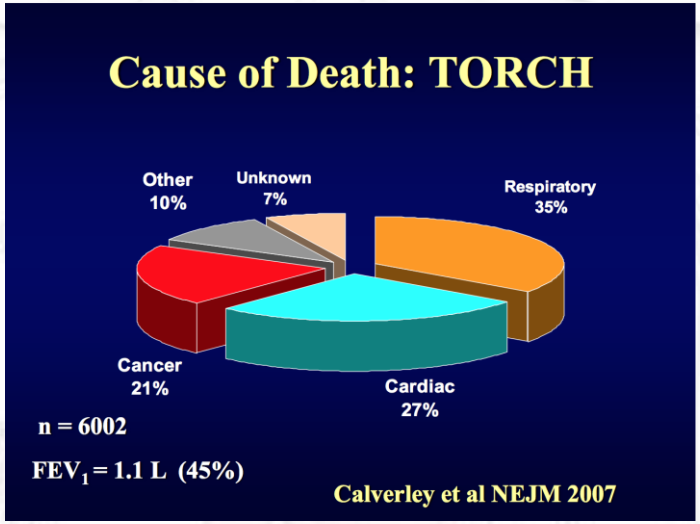


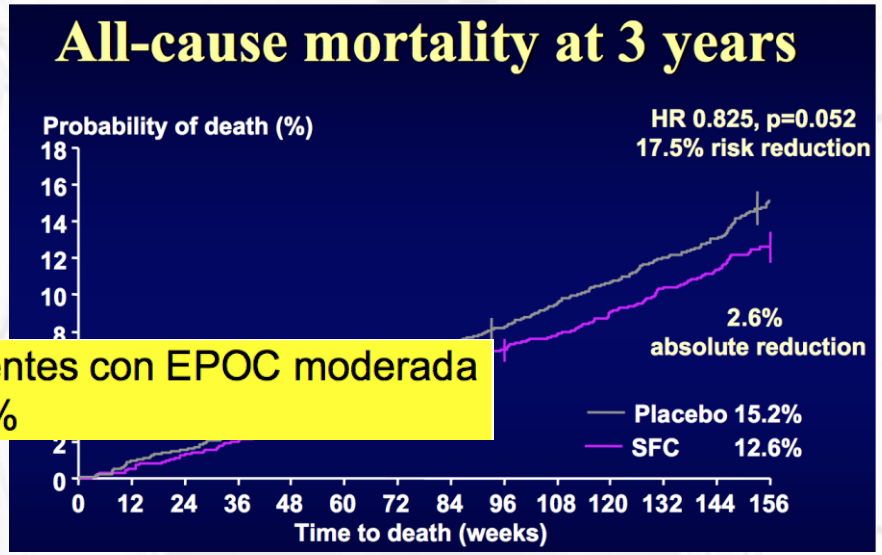
FIGURE 3. Mortality and heart failure.

CHEST 2012;142:1126–1133

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease





La disminución del riesgo en pacientes con EPOC moderada y riesgo cardiovascular fue del 49%

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Seguridad cardiovascular de los broncodilatadores

CHEST Original Research

COPD

Bronchodilator Use and the Risk of Arrhythmia in COPD

CHEST 2012; 142(2):305–311

Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease

A Systematic Review and Meta-analysis

JAMA. 2008;300:1439-1450

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

A Synthesis of the Available Evidence

Shelley R. Salpeter[1,2]

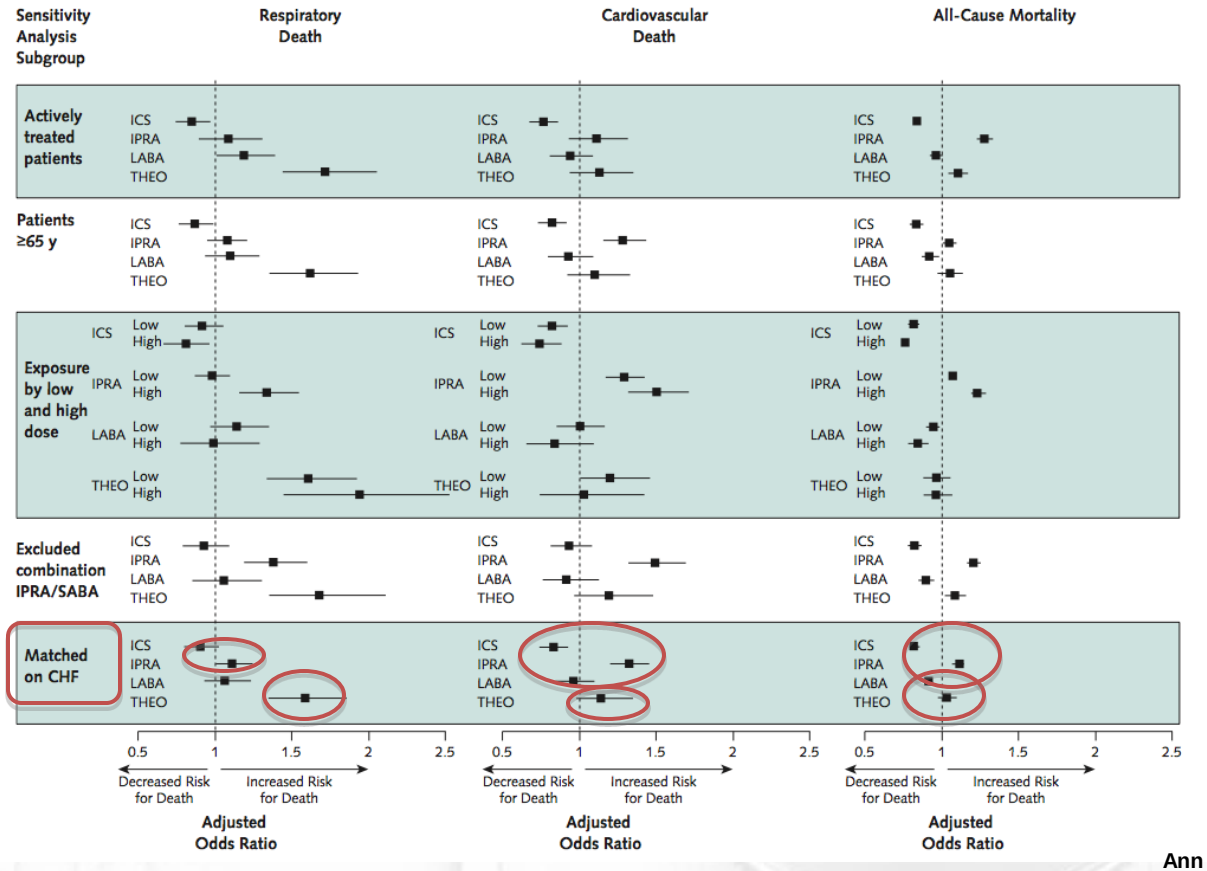
Drugs 2009; 69: 2025-2033

ARTICLE

Annals of Internal Medicine

Risk for Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease

Figure 2. Risk for mortality associated with respiratory medications in the sensitivity analyses for each study end point.



Ann Intern Med. 2008;149:380-390

Adverse events LABA

- Increase risk of unstable angina, myocardial infarction
- Increase cardiovascular and cardiac failure risk
- When LVSD is present are associated with an increased risk of heart failure and hospitalization
- In preexisting cardiac arrhythmias and hypoxemia, LABA may have adverse effects on the myocardium
- Could increase heart rate, decrease potassium concentration, risk of sinus tachycardia and cardiovascular events

Chest 2003; 123:1964–1969
Am Heart J 2001; 142:E11.
Chest 2004; 125:2309–2321

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 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 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 longitudinal, retrospective cohort study of patients suggest that inhaled B2As are not associated with increased mortality in community-managed HF patients.

Eur J Heart Fail 2011;13:885–891.

Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease (Review)

formoterol

Outcome: 7 Mortality (all-cause)

Study or subgroup	LABA n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Formoterol 12 µ g twice daily				
Bogdan 2011	0/199	0/208		0.0 [0.0, 0.0]
Nelson 2007	0/114	0/114		0.0 [0.0, 0.0]
Dahl 2001	0/192	0/100		0.0 [0.0, 0.0]
Vogelmeier 2008	0/210	1/209		0.13 [0.00, 6.79]
Tashkin 2008 [SHINE]	1/284	1/300		1.06 [0.07, 16.95]
Campbell 2005	2/215	0/217		7.49 [0.47, 120.19]
Rossi 2002	3/211	0/110		4.62 [0.42, 50.53]
Tashkin 2012	3/209	1/212		2.78 [0.39, 19.86]
Doherty 2012	4/243	2/236		1.90 [0.38, 9.52]
Dahl 2010	3/435	4/432		0.74 [0.17, 3.29]
Rennard 2009	4/495	4/481		0.97 [0.24, 3.90]
Szafranski 2003	6/201	9/205		0.67 [0.24, 1.89]
Calverley 2003a	13/255	5/256		2.52 [0.98, 6.45]
Subtotal (95% CI)	**3263**	**3080**		**1.41 [0.87, 2.30]**
Total events: 39 (LABA), 27 (Placebo)				
Heterogeneity: Chi^2 = 8.77, df = 9 (P = 0.46); I^2 =0.0%				
Test for overall effect: Z = 1.38 (P = 0.17)				
2 Formoterol 24 µ g twice daily				
Dahl 2001	0/191	0/100		0.0 [0.0, 0.0]
Rossi 2002	1/214	0/110		4.54 [0.07, 285.14]
Subtotal (95% CI)	**405**	**210**		**4.54 [0.07, 285.14]**

salmeterol

Study or subgroup	LABA n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
3 Salmeterol 50 µ g twice daily				
SLMF4010 2005	0/17	0/17		0.0 [0.0, 0.0]
Mahler 1999	0/135	0/143		0.0 [0.0, 0.0]
Hanania 2003	0/177	0/185		0.0 [0.0, 0.0]
Hanrahan 2008	0/293	0/294		0.0 [0.0, 0.0]
Rennard 2001	0/132	1/135		0.14 [0.00, 6.98]
Mahler 2002	0/160	3/181		0.15 [0.02, 1.46]
Kornmann 2011	0/334	3/335		0.13 [0.01, 1.30]
Calverley 2003b [TRISTAN]	3/372	7/361		0.43 [0.12, 1.50]
Brusasco 2003	6/405	5/400		1.19 [0.36, 3.90]
Calverley 2007 [TORCH]	205/1521	232/1524		0.87 [0.71, 1.06]
Subtotal (95% CI)	**3546**	**3575**		**0.83 [0.69, 1.01]**

global

Total (95% CI)	**7214**	**6865**	**0.90 [0.75, 1.08**

The Cochrane Library 2013

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*

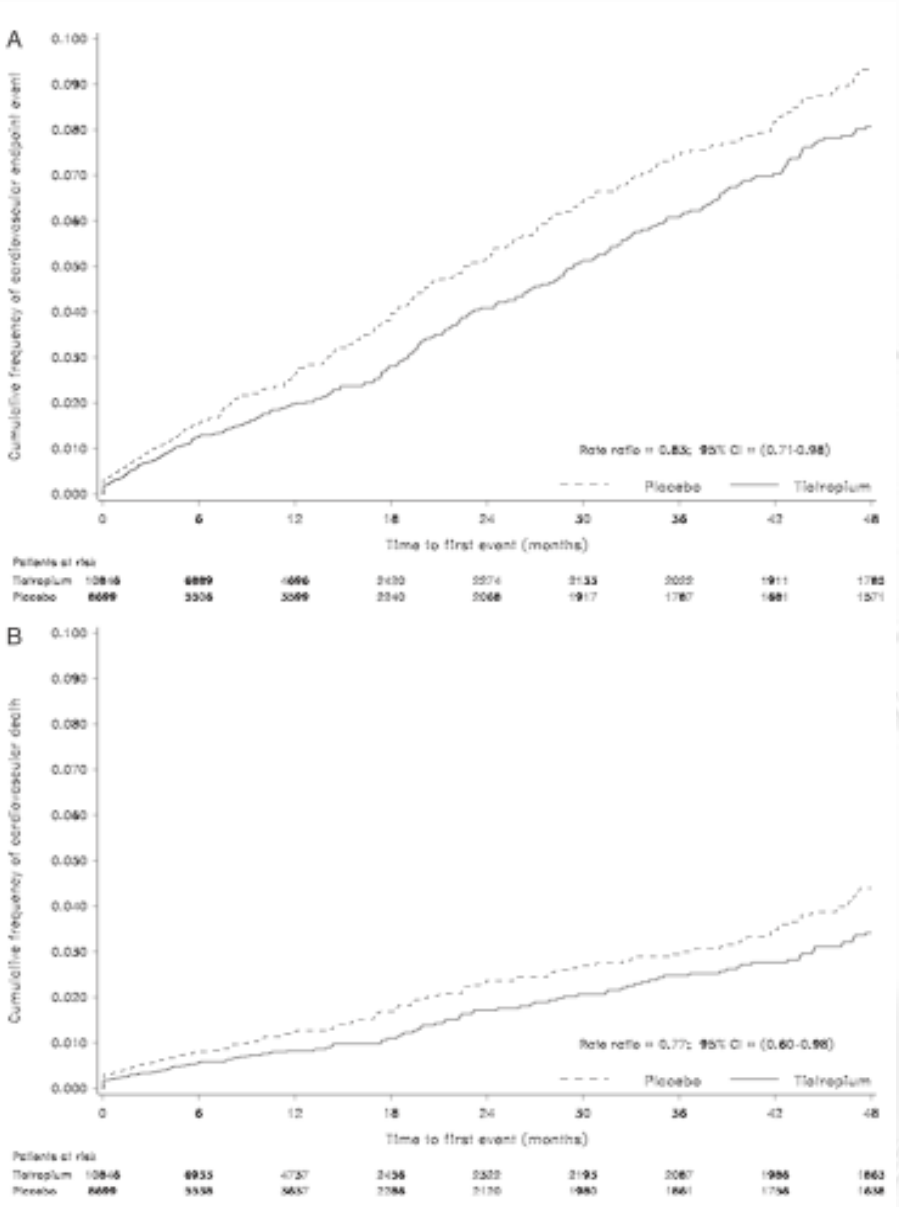
	Placebo n = 8,699		Tiotropium n = 10,646		
Cardiac Events	No.	IR	No.	IR	RR (95% CI)
Cardiac disorders (SOC)	788	7.23	967	6.64	0.91 (0.83-1.01)
Ischemic heart disease	290	2.53	322	2.36	0.93 (0.79-1.09)
Atrial fibrillation/flutter	147	1.26	159	1.15	0.92 (0.74-1.16)
Cardiac arrest	31	0.26	23	0.16	0.68 (0.39-1.16)
Cardiac failure	261	2.26	252	1.82	0.82 (0.69-0.98)*
Myocardial infarction	111	0.95	101	0.72	0.78 (0.59-1.02)
Palpitations	58	0.49	85	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

The NEW ENGLAND JOURNAL of MEDICINE

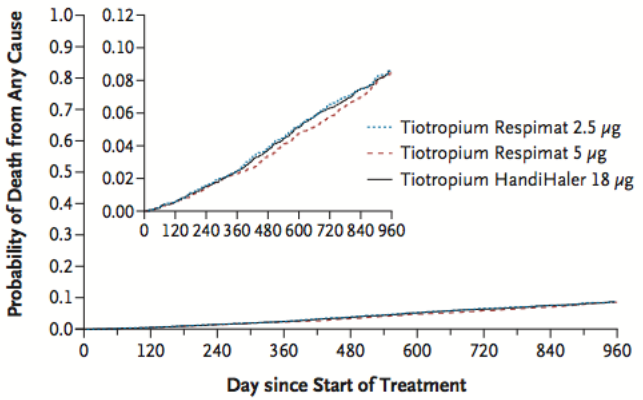
ORIGINAL ARTICLE

Tiotropium Respimat Inhaler and the Risk of Death in COPD

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

A Death during Follow-up



No. at Risk

Tiotropium Respimat 2.5 μg	5730	5694	5637	5582	5499	5423	5157	3575	504
Tiotropium Respimat 5 μg	5711	5675	5626	5576	5510	5429	5167	3585	467
Tiotropium HandiHaler 18 μg	5694	5660	5601	5544	5471	5388	5097	3544	488

N Engl J Med 2013.DOI: 10.1056/NEJMoa1303342

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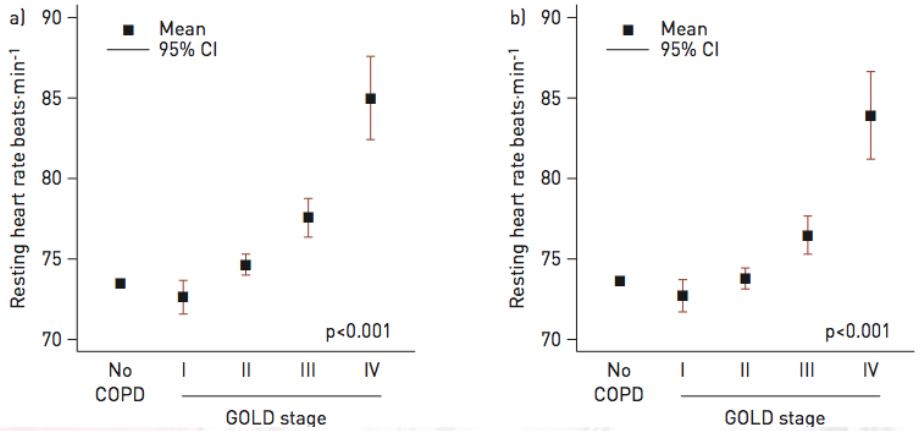
Resting heart rate is a predictor of mortality in COPD

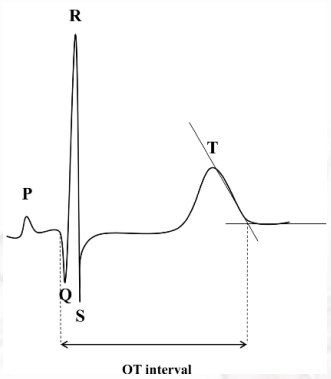
Resting heart rate and mortality

Resting heart rate was highly significantly associated with both cardiovascular and all-cause mortality in both uni- and multivariate models (table 2). There was no interaction between COPD severity and heart rate with



	Resting heart rate beats·min^{-1}			
	<64	65–74	75–84	⩾85
All-cause mortality				
Univariate	1¶	1.11 (1.05–1.17)	1.30 (1.23–1.37)	1.51 (1.42–1.60)
Multivariate#	1¶	1.16 (1.10–1.22)	1.31 (1.24–1.38)	1.51 (1.43–1.60)
Cardiovascular mortality				
Univariate	1¶	1.08 (1.00–1.17)	1.34 (1.24–1.45)	1.57 (1.45–1.70)
Multivariate#	1¶	1.16 (1.07–1.25)	1.36 (1.26–1.48)	1.57 (1.45–1.71)

Eur Respir J 2013; 42: 341–349

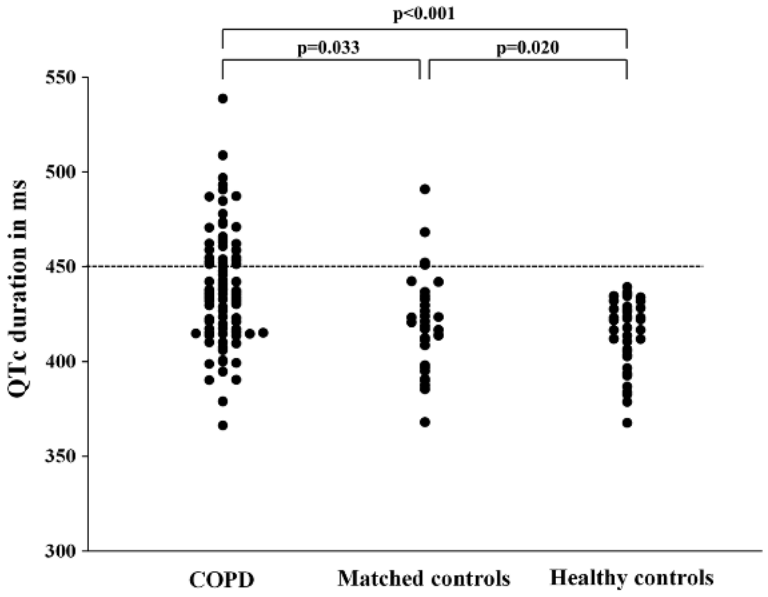


Sievi *et al. BMC Pulmonary Medicine* 2014, **14**:55
http://www.biomedcentral.com/1471-2466/14/55

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

High prevalence of altered cardiac repolarization in patients with COPD

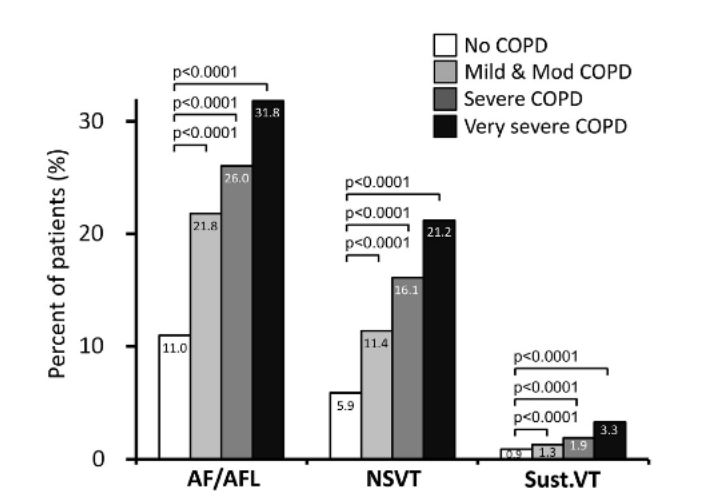


Discussion

This study investigated the prevalence of altered cardiac repolarization in a heterogeneous group of COPD patients and evaluated possible underlying risk factors. The main findings of this study are that approximately one third of a typical COPD population has altered cardiac repolarization and increased dispersion of repolarization, which may be related to hypoxia. Altered cardiac repolarization may expose these patients to an increased risk for malignant ventricular arrhythmias and SCD.

Relation of Chronic Obstructive Pulmonary Disease to Atrial and Ventricular Arrhythmias

Variable	COPD			
	No COPD (n = 4,320)	Mild/Mod. (n = 2,239)	Severe (n = 698)	Very Severe (n = 184)
Atrial fibrillation/flutter				
Univariate	1*	2.27 (1.93–2.67)	2.85 (2.27–3.57)	3.78 (2.53–5.55)
Multivariate	1*	1.39 (1.17–1.66)	1.56 (1.22–1.99)	2.10 (1.36–3.18)
Nonsustained ventricular Tachycardia				
Univariate	1*	2.06 (1.72–2.47)	3.05 (2.39–3.86)	4.29 (2.91–6.18)
Multivariate	1*	1.34 (1.10–1.63)	1.74 (1.34–2.24)	2.24 (1.49–3.30)
Sustained ventricular tachycardia				
Univariate	1*	1.49 (0.92–2.40)	2.08 (1.06–3.82)	3.70 (1.39–8.23)
Multivariate	1*	0.92 (0.55–1.52)	1.11 (0.55–2.10)	1.80 (0.66–4.14)

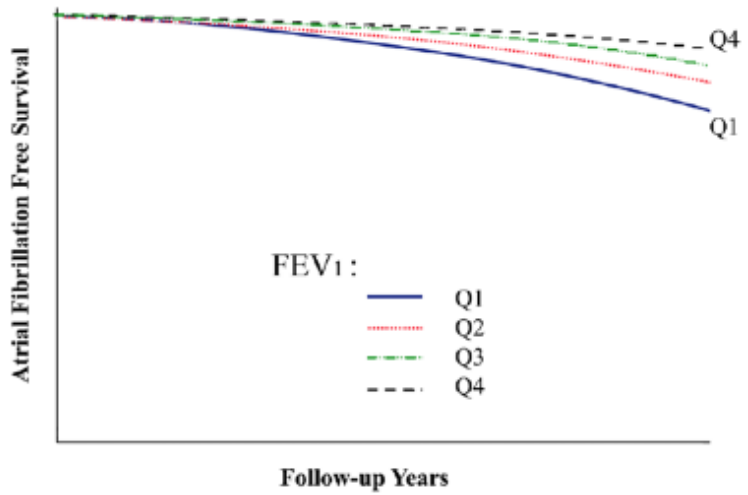


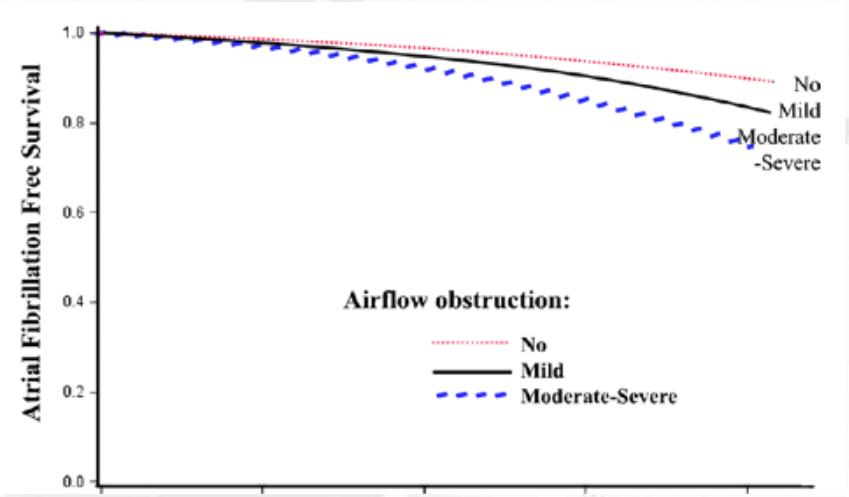
Am J Cardiol 2014;114:272-277

Airflow Obstruction, Lung Function, and Incidence of Atrial Fibrillation

The Atherosclerosis Risk in Communities (ARIC) Study

The ARIC study is a multicenter population-based prospective study of risk factors for atherosclerosis and the burden of cardiovascular disease. From 1987 to 1989, 15 792 adults (55.2% women) 45 to 64 years of age from 4 US communities were enrolled and completed a home interview and clinic visit. Participants were from the following





Circulation 2014;129:971-980

OPEN ACCESS

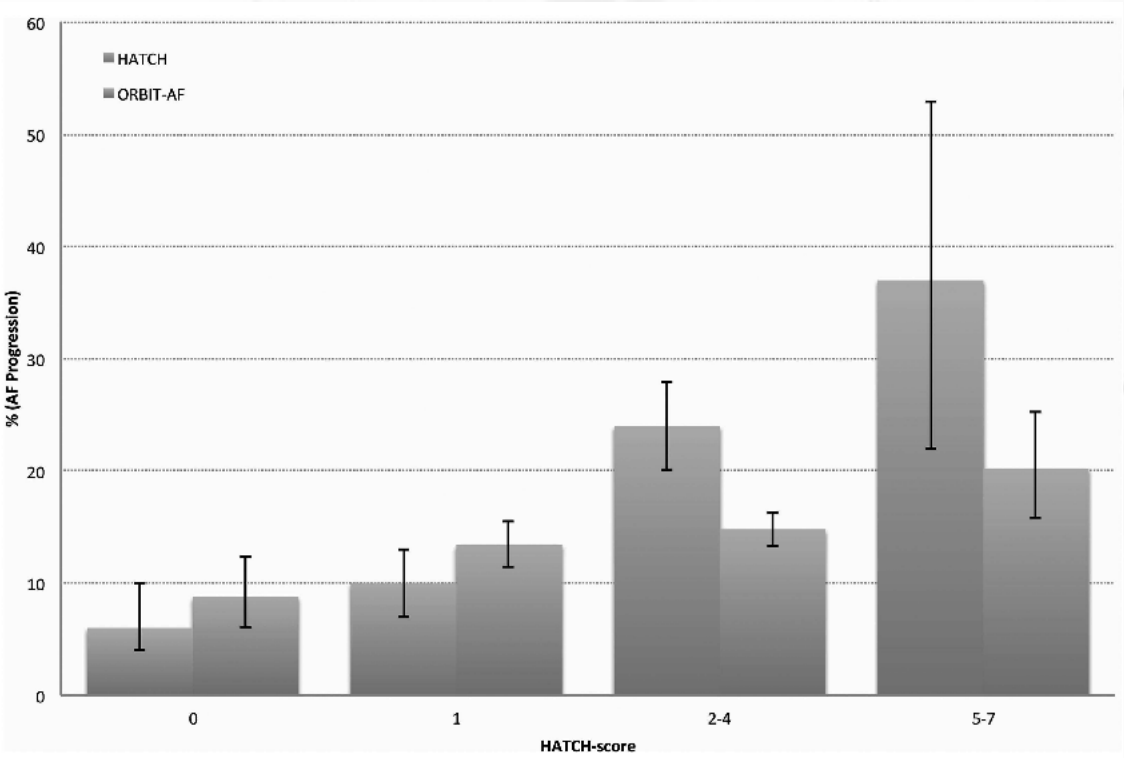
ORIGINAL ARTICLE

Heart rate is associated with progression of atrial fibrillation, independent of rhythm

Table 4 Descriptive of AF progression across four HATCH score group among patients with paroxysmal AF at baseline and 12 month follow-up

HATCH score*		Overall N=3958		No AF progression N=3393		AF progression N=565	
Score	Risk	N	(%)	N	(%)	N	(%)
0	Very low	341	(8.6)	311	(9.2)	30	(5.3)
1	Low	1128	(29)	977	(29)	151	(27)
2–4	Moderate	2192	(55)	1868	(55)	324	(57)
5–7	High	297	(7.5)	237	(7.0)	60	(11)

*HATCH score=Hypertension+(Age >75 years)+(TIA or stroke)×2+Chronic obstructive pulmonary disease+(congestive heart failure)×2.[6]
AF, atrial fibrillation; HATCH, *h*ypertension, *a*ge, *T*IA/stroke, *c*hronic obstructive pulmonary disease, *h*eart failure.



Heart 2015;0:1–6. doi:10.1136/heartjnl-2014-307043

- ✓¿Qué sabemos de la EPOC en el paciente con IC?
- ✓¿Qué sabemos del tratamiento de la EPOC en el paciente con IC?
- ✓¿Qué sabemos del riesgo de arritmias en el paciente con EPOC?
- ✓¿Qué nos dicen las guías?
- ✓¿Qué sabemos de los nuevos broncodilatadores?

European Heart Journal (2012) 33, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

11. Importance and management of other co-morbidity in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

11.7 Chronic obstructive pulmonary disease

COPD and asthma may cause diagnostic difficulties, especially in HF-PEF.[24,25] These conditions are associated with worse functional status and a worse prognosis. Beta-blockers are contraindicated in asthma but not in COPD, although a selective beta-1 adrenoceptor antagonist (i.e. bisoprolol, metoprolol succinate, or nebivolol) is preferred.[195] Oral corticosteroids cause sodium and water retention, potentially leading to worsening of HF, but this is not believed to be a problem with inhaled corticosteroids. COPD is an independent predictor of worse outcomes in HF.

Global Strategy for Diagnosis, Management and Prevention of COPD

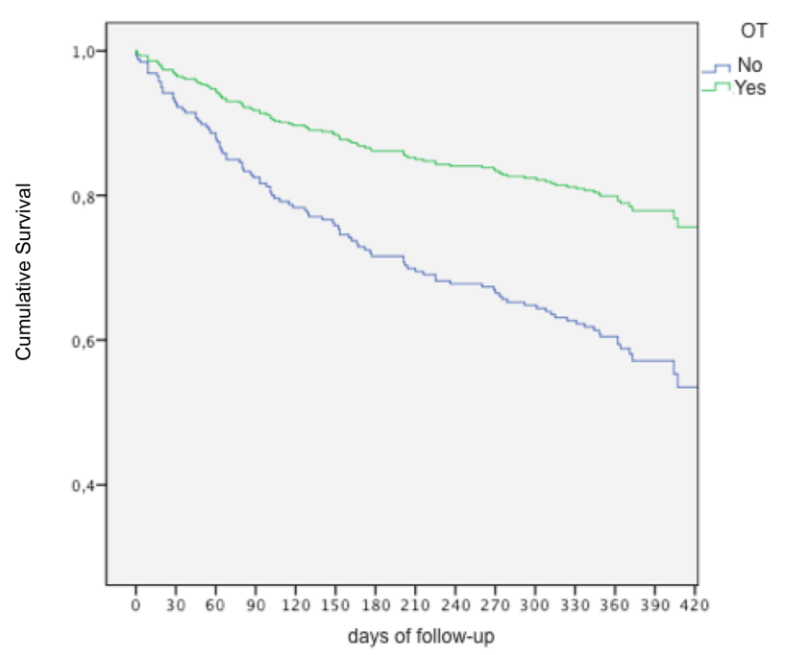
Manage Comorbidities. Update 2015

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.

Cardiovascular disease should be treated according to usual guidelines

Prognostic influence of chronic obstructive pulmonary disease in elderly patients with heart failure. Data from the Spanish RICA registry.

Drug	Total n=1165 n (%)	COPD (n=321) n (%)	Without COPD (n=844) n (%)	p-value
BB	714 (61.3)	165 (51.4)	549 (64.8)	<0.0001
ACEI	627(53.8)	183 (57.0)	444 (52.6)	0.12
ARBs	417 (35.8)	112 (34.9)	305 (36.1)	0.69
Antialdosterone	402 (34.5)	118 (36.8)	284 (33.6)	0.32
Optimised*	603 (51.8)	141 (43.9)	462 (54.7)	<0.0001



In press

- ✓¿Qué sabemos de la EPOC en el paciente con IC?
- ✓¿Qué sabemos del tratamiento de la EPOC en el paciente con IC?
- ✓¿Qué sabemos del riesgo de arritmias en el paciente con EPOC?
- ✓¿Qué nos dicen las guías?
- ✓¿Qué sabemos de los nuevos broncodilatadores?

COPD drug development standards and regulatory guidance recommendations

Recomendaciones de la guía de desarrollo de fármacos para EPOC[1,2,3]
Deberían reflejar a la población de pacientes EPOC y sus tratamientos en el mundo real.
Las variables de eficacia deberían incluir: **Evaluación de la función pulmonar** **Evaluación de los beneficios en control de síntomas**

1. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
2.European Medicines Agency
3. ATS/ERS task force. *Eur Respir J*. 2008;31(2):416-469

BJP British Journal of Pharmacology
Themed Issue: Respiratory Pharmacology

REVIEW

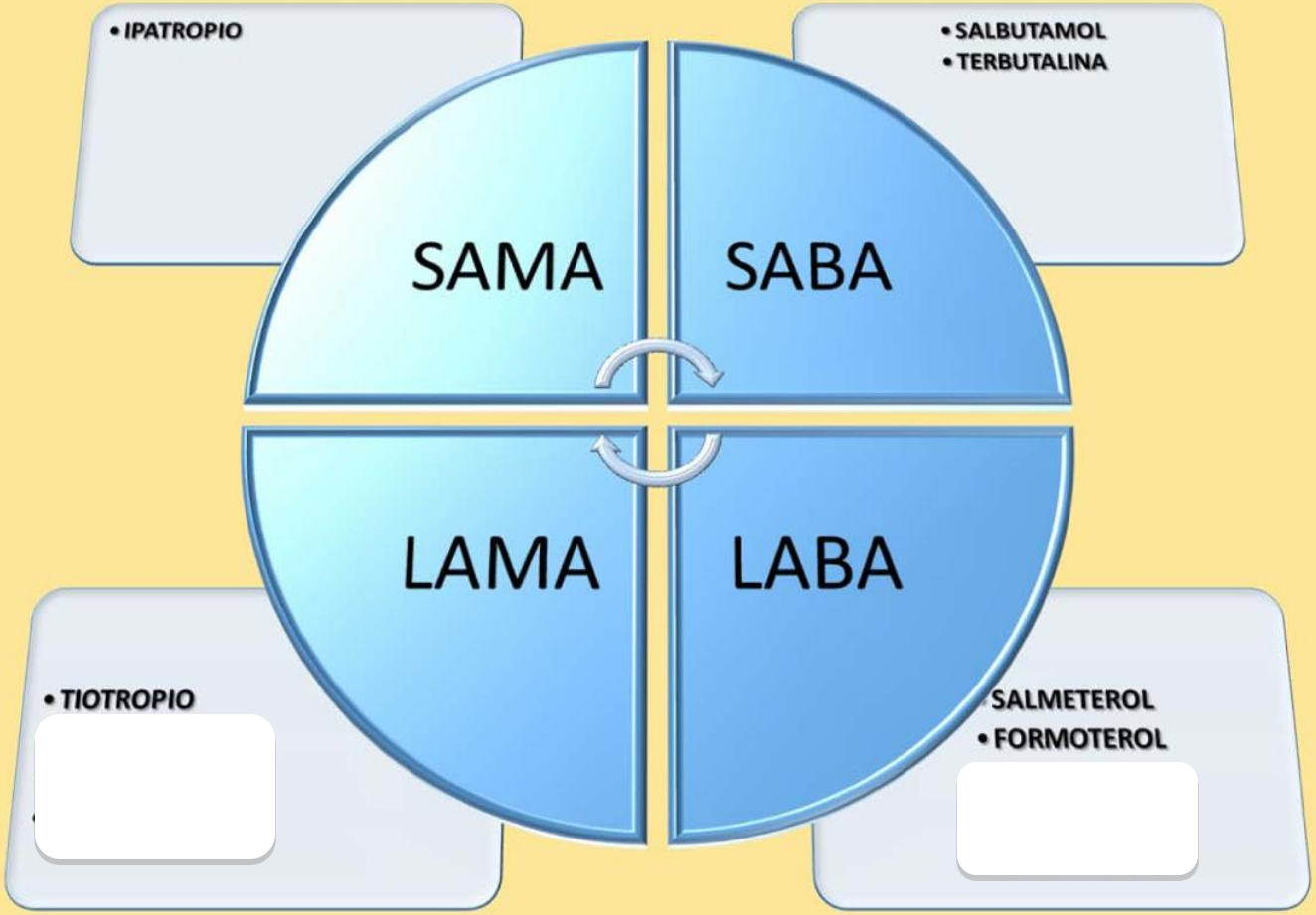
β_2-adrenoceptor agonists: current and future direction

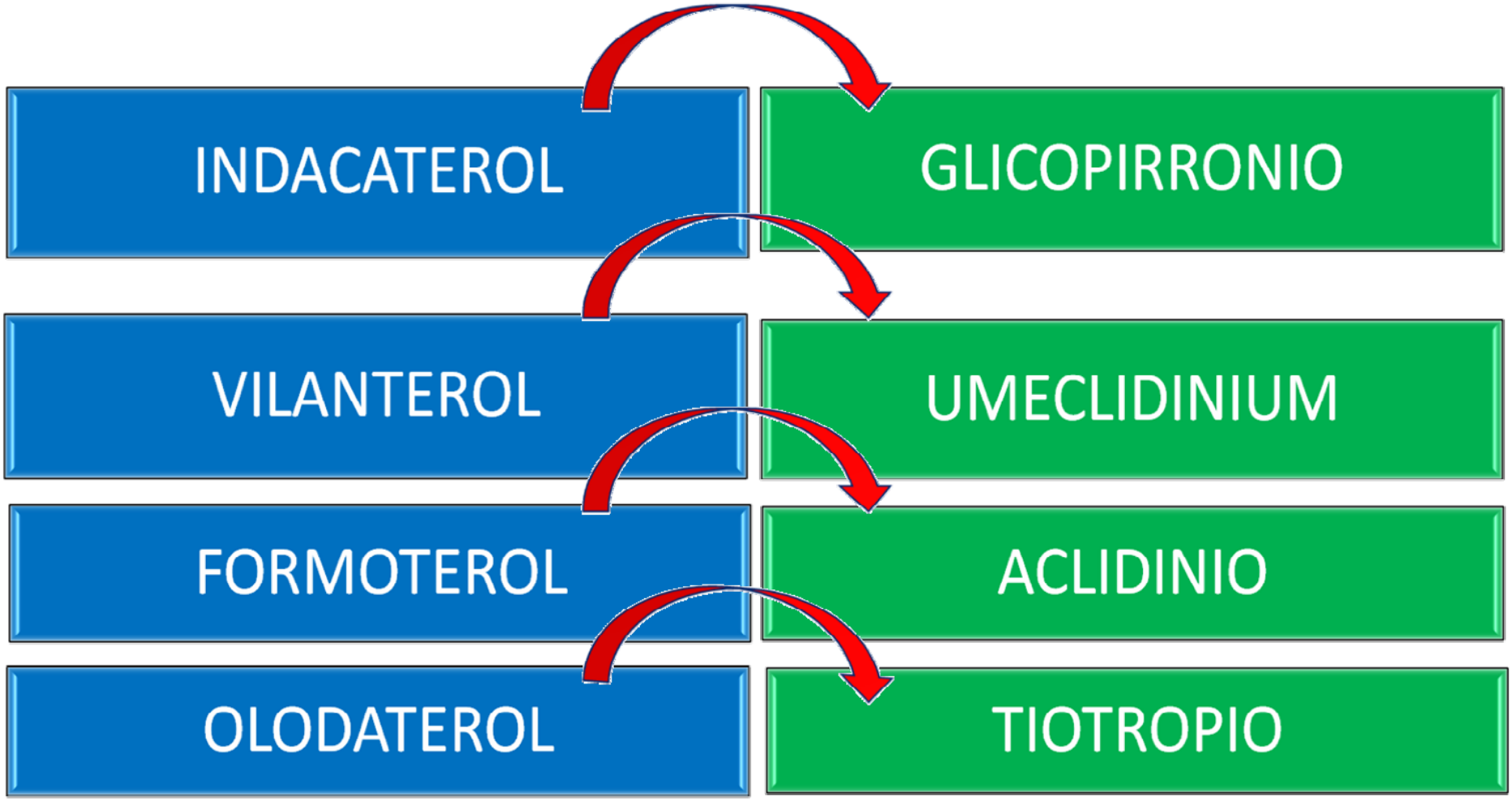
Table 1
Designing a new LABA for COPD

Criteria for a new β_2-adrenoceptor agonist could include:
- Longer duration of action (compared with existing LABAs)
  - True 24 h sustained bronchodilator efficacy
  - Allowing once-daily dosing
- Fast onset of action
- Superior efficacy compared with existing LABAs
- Favourable safety and tolerability profile
- Efficient and convenient device
  - Breath actuated
  - With effective feedback to indicate successful inhalation

Such an ultra-LABA should provide flexibility to prescribers and could be used alone or in combination with a once-daily long-acting muscarinic antagonist. Obviously, an ideal ultra-LABA should be well tolerated with a favourable safety profile. Thus, a new entry to the market must ensure that potential cardiac effects are minimized, especially taking into account that mainly COPD patients are often older and may have cardiovascular comorbidities.

British Journal of Pharmacology (2011);163:4-17


• IPATROPIO
• SALBUTAMOL
• TERBUTALINA
SAMA
SABA
LAMA
LABA
• TIOTROPIO
SALMETEROL
• FORMOTEROL


INDACATEROL
GLICOPIRRONIO
VILANTEROL
UMECLIDINIUM
FORMOTEROL
ACLIDINIO
OLODATEROL
TIOTROPIO

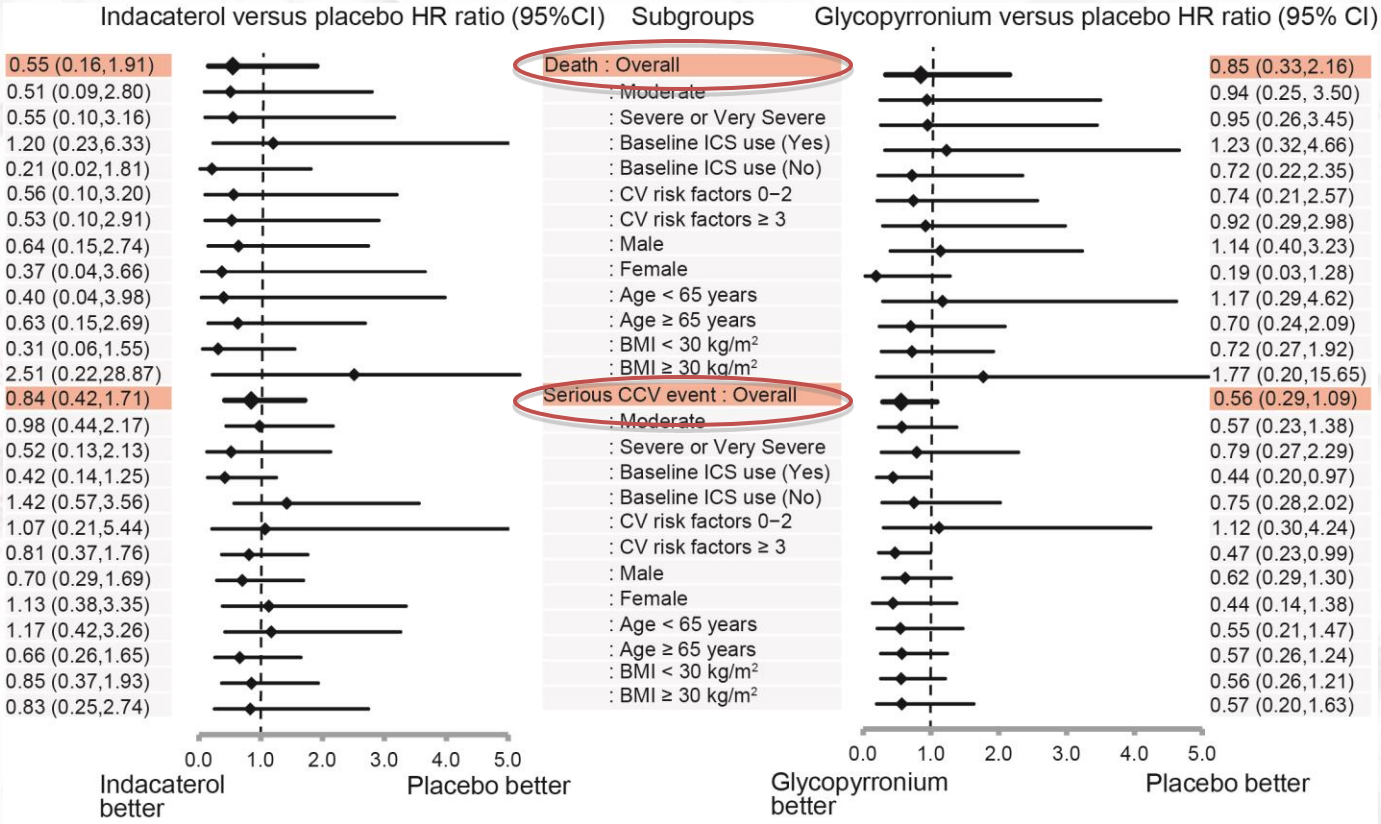
Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients

Parameter	QVA149 110/50 μg (n = 1547)	Indacaterol 150 μg (n = 2528)	Glycopyrronium 50 μg (n = 2411)	Tiotropium 18 μg (n = 2777)	Placebo (n = 2141)
Mean (SD) age in years	63.8 (8.51)	63.8 (8.90)	63.9 (8.82)	63.8 (8.33)	64.0 (8.93)
Age (years)					
<65	818 (52.9)	1298 (51.3)	1235 (51.2)	1467 (52.8)	1082 (50.5)
65 to <75	554 (35.8)	927 (36.7)	900 (37.3)	1025 (36.9)	810 (37.8)
≥75	175 (11.3)	303 (12.0)	276 (11.4)	285 (10.3)	249 (11.6)
Sex					
Male	1206 (78.0)	1799 (71.2)	1821 (75.5)	1963 (70.7)	1551 (72.4)
Female	341 (22.0)	729 (28.8)	590 (24.5)	814 (29.3)	590 (27.6)
Number of CV risk factors[a]					
0–2	1072 (69.3)	1122 (44.4)	1282 (53.2)	1449 (52.2)	961 (44.9)
≥3	475 (30.7)	1405 (55.6)	1129 (46.8)	1328 (47.8)	1180 (55.1)
History of diabetes mellitus	151 (9.8)	254 (10.1)	283 (11.7)	282 (10.2)	220 (10.3)
CCV condition[b]	157 (10.2)	302 (12.0)	273 (11.3)	314 (11.3)	253 (11.8)
Hyperlipidaemia	376 (24.3)	602 (23.8)	593 (24.6)	725 (26.1)	514 (24.0)
Hypertension	700 (45.2)	1027 (40.6)	1079 (44.8)	1221 (44.0)	877 (41.0)

In this pooled analysis across multiple safety databases that included data from 11,404 patients, the incidence of deaths, serious CCV events, MACEs, pneumonia, exacerbations requiring hospitalisation and atrial flutter/fibrillation was comparable between QVA149 and placebo, with no increase in the overall risk being observed for any of the investigated safety endpoints for any of the drugs versus placebo.

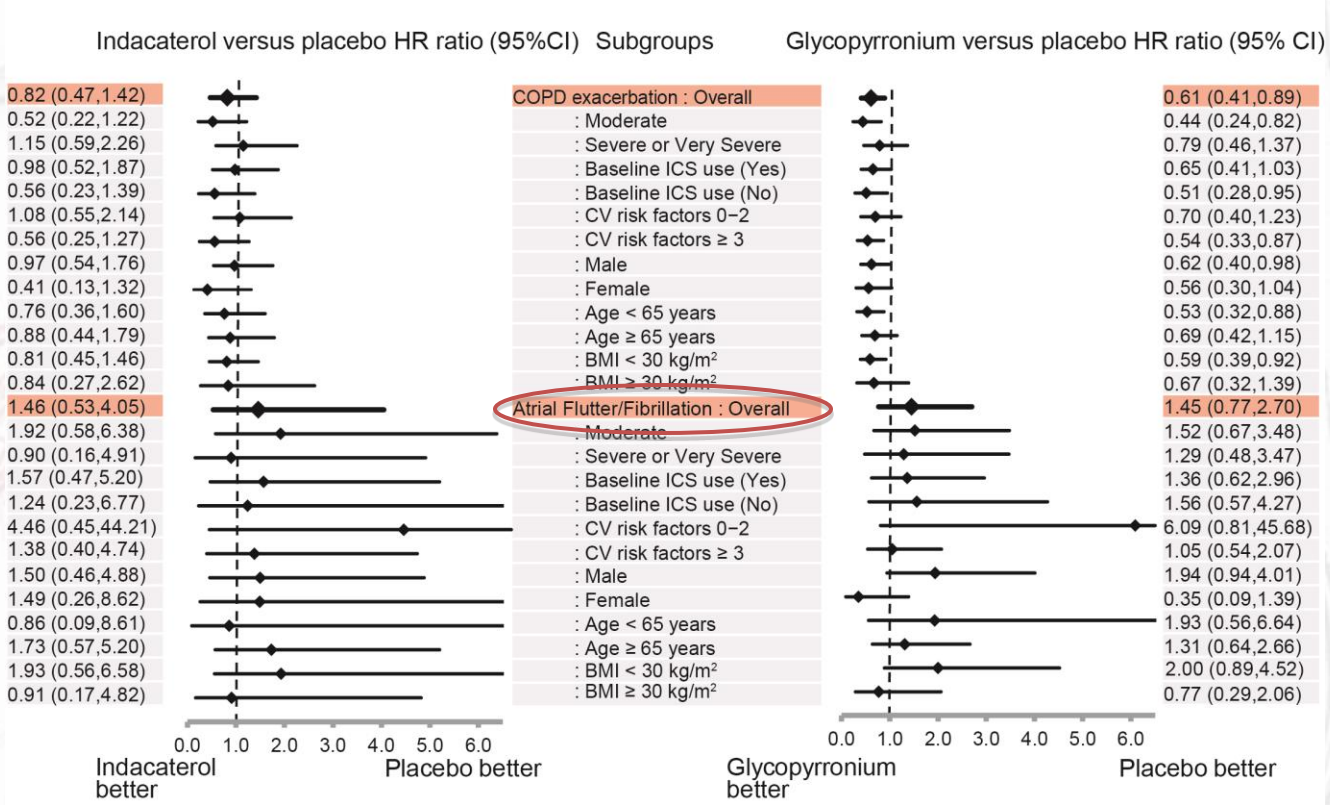
Respiratory Medicine 2014;108:1498-1507

Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients



Respiratory Medicine 2014;108:1498-1507

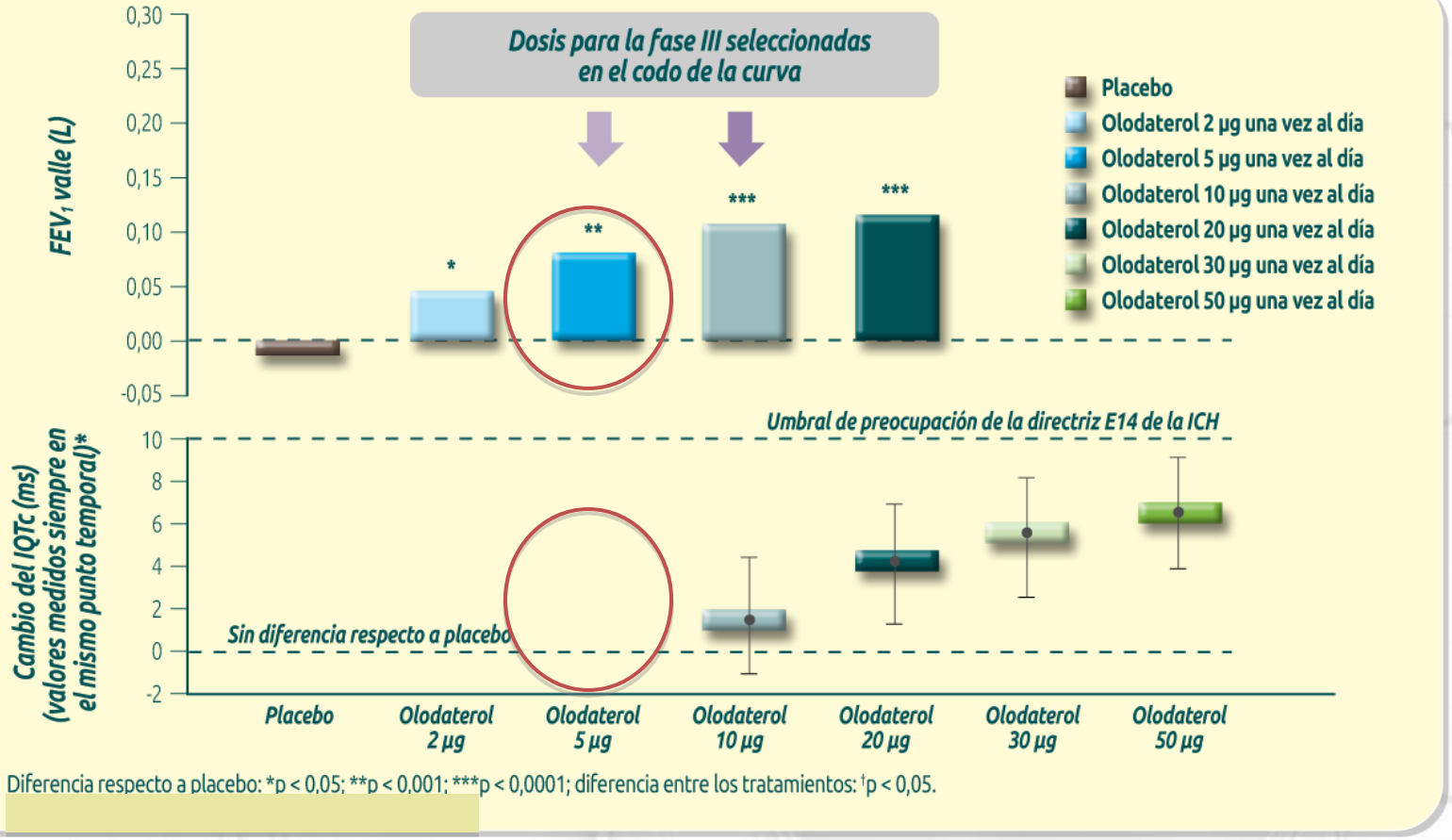
Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients



Respiratory Medicine 2014;108:1498-1507

Olodaterol

Adecuado beneficio/riesgo en los estudios de búsqueda de dosis



Diferencia respecto a placebo: *p < 0,05; **p < 0,001; ***p < 0,0001; diferencia entre los tratamientos: †p < 0,05.

Troost J. Poster P13-05951, ATS 2013.

COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
COPD, 00:1–10, 2015
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2014.991864

ORIGINAL RESEARCH

One-Year Safety of Olodaterol Once Daily via Respimat® in Patients with GOLD 2–4 Chronic Obstructive Pulmonary Disease: Results of a Pre-Specified Pooled Analysis

Table 6. Incidence of cardiac and vascular AEs and serious AEs in patients with cardiac disorder at baseline or cardiac history

	Cardiac history				No cardiac history			
	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol
Patients, n	204	219	229	92	681	657	654	368
Total AEs, n (%)	152 (74.5)	162 (74.0)	185 (80.8)	66 (71.7)	475 (69.8)	460 (70.0)	457 (69.9)	252 (68.5)
Cardiac disorders	23 (11.3)	34 (15.5)	31 (13.5)	12 (13.0)	44 (6.5)	35 (5.3)	33 (5.0)	14 (3.8)
Vascular disorders	15 (7.4)	21 (9.6)	20 (8.7)	6 (6.5)	32 (4.7)	29 (4.4)	25 (3.8)	12 (3.3)
Total serious AEs, n (%)	35 (17.2)	43 (19.6)	44 (19.2)	17 (18.5)	110 (16.2)	95 (14.5)	103 (15.7)	52 (14.1)
Cardiac disorders	10 (4.9)	12 (5.5)	8 (3.5)	6 (6.5)	16 (2.3)	7 (1.1)	9 (1.4)	1 (0.3)
Vascular disorders	4 (2.0)	5 (2.3)	3 (1.3)	1 (1.1)	4 (0.6)	3 (0.5)	2 (0.3)	3 (0.8)

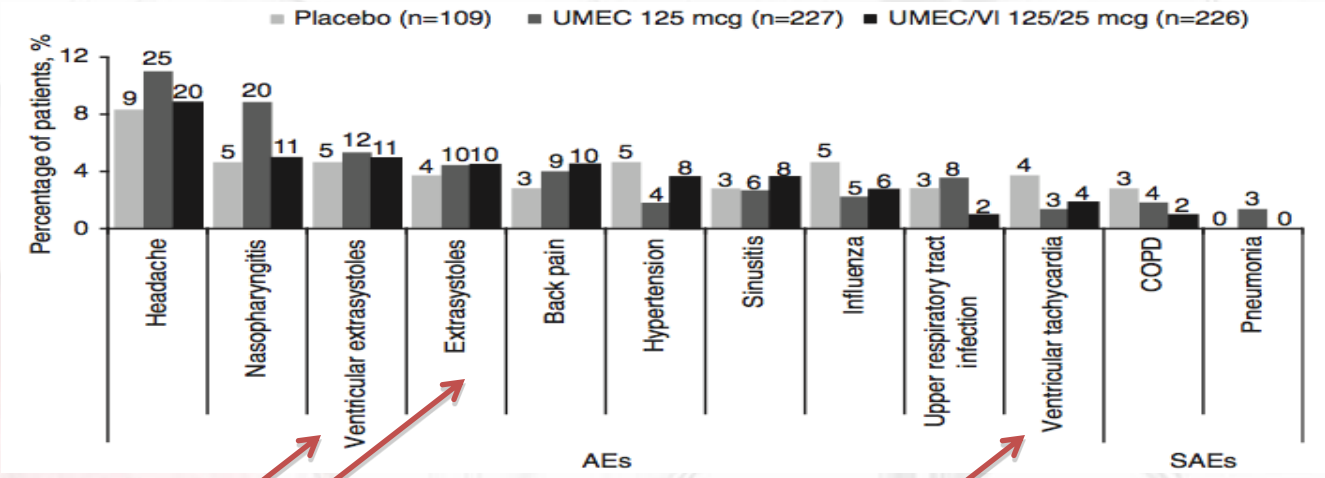
AE = adverse event.

Table 7. Incidence of cardiac and vascular AEs and serious AEs in concomitant β-blocker medication subgroup

	Concomitant β-blocker medication				No concomitant β-blocker medication			
	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol
Patients, n[a]	90	81	85	34	766	766	770	419
Total AEs, n (%)	71 (78.9)	65 (80.2)	70 (82.4)	28 (82.4)	553 (72.2)	552 (72.1)	568 (73.8)	288 (68.7)
Cardiac disorders	23 (25.6)	17 (21.0)	19 (22.4)	7 (20.6)	44 (5.7)	50 (6.5)	45 (5.8)	19 (4.5)
Vascular disorders	9 (10.0)	12 (14.8)	9 (10.6)	4 (11.8)	38 (5.0)	38 (5.0)	36 (4.7)	14 (3.3)
Total serious AEs, n (%)	27 (30.0)	23 (28.4)	21 (24.7)	6 (17.6)	118 (15.4)	115 (15.0)	126 (16.4)	63 (15.0)
Cardiac disorders	11 (12.2)	8 (9.9)	10 (11.8)	4 (11.8)	15 (2.0)	11 (1.4)	7 (0.9)	3 (0.7)
Vascular disorders	2 (2.2)	3 (3.7)	2 (2.4)	2 (5.9)	6 (0.8)	5 (0.7)	3 (0.4)	2 (0.5)

[a]Only patients with non-missing values for β-blocker use at baseline were included.
AE = adverse event.

Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study



The proportions of patients with one or more abnormal, clinically significant Holter ECG interpretation at any time post-baseline was similar across all treatment groups (52–55%). Holter ECG recordings showed that the incidence of atrial arrhythmias with UMEC/VI 125/25 mcg was similar to placebo, but that some arrhythmias had a ≥2% greater incidence with UMEC 125 mcg compared with placebo; these included ectopic supraventricular beats, sustained supraventricular tachycardia and ectopic supraventricular rhythm.

Respiratory Research 2014

RESEARCH Open Access

Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study

The number of Major Adverse Cardiac Events (MACEs), based on blinded adjudication, TEAEs and SAEs, were infrequent and occurred at similar incidences across all treatment groups. All adjudicated MACEs were SAEs with the exception of 1 report of moderate nonfatal stroke in the placebo group. Based on adjudicated SAEs, a total of 12 MACEs were reported for 12 patients. MACEs based on adjudicated SAEs were reported in 2 (0.6%) and 4 (1.2%) patients in the aclidinium/formoterol FDC 400/12 μg and 400/6 μg treatment groups. A total of 2 (0.6%) patients in the placebo group, 1 (0.3%) patient in the aclidinium group, and 3 (0.9%) patients in the formoterol group reported MACEs. All MACEs were considered unrelated to treatment.

Mean changes from baseline in clinical laboratory parameters, vital signs, and ECGs were small and of no clinical relevance. Holter monitoring did not show any findings of an ECG effect for patients in any group, and no differences were observed between the treatment arms.

Table 2 Treatment-emergent adverse events[a] (≥2% in any treatment group)

	PBO (n = 332)	ACL400/FOR12 FDC (n = 335)	ACL400/FOR6 FDC (n = 333)	ACL400 (n = 337)	FOR 12 (n = 332)
Patients with ≥1 TEAE, n (%)	181 (54.5)	215 (64.2)	203 (61.0)	210 (62.3)	189 (56.9)
TEAEs by preferred term, n (%)					
Cough[b]	12 (3.6)	17 (5.1)	13 (3.9)	7 (2.1)	10 (3.0)
Headache[b]	11 (3.3)	16 (4.8)	14 (4.2)	13 (3.9)	12 (3.6)
Nasopharyngitis	12 (3.6)	16 (4.8)	17 (5.1)	12 (3.9)	22 (6.6)
Urinary tract infection[b,c]	10 (3.0)	15 (4.5)	7 (2.1)	11 (3.3)	9 (2.7)
Back pain	9 (2.7)	10 (3.0)	5 (1.5)	4 (1.2)	6 (1.8)
Upper respiratory tract infection	5 (1.5)	10 (3.0)	13 (3.9)	11 (3.3)	9 (2.7)
Diarrhea	8 (2.4)	9 (2.7)	10 (3.0)	9 (2.7)	6 (1.8)
Muscle spasms[b]	3 (0.9)	9 (2.7)	4 (1.2)	2 (0.6)	6 (1.8)
Sinusitis	7 (2.1)	9 (2.7)	8 (2.4)	12 (3.6)	6 (1.8)
Dry mouth[c]	1 (0.3)	8 (2.4)	5 (1.5)	2 (0.6)	3 (0.9)
Tooth abscess	2 (0.6)	8 (2.4)	2 (0.6)	2 (0.6)	0
Musculoskeletal pain	2 (0.6)	7 (2.1)	0	2 (0.6)	3 (0.9)
Oropharyngeal pain	10 (3.0)	7 (2.1)	6 (1.8)	4 (1.2)	6 (1.8)
Dizziness	7 (2.1)	6 (1.8)	4 (1.2)	5 (1.5)	8 (2.4)
Insomnia[b]	2 (0.6)	6 (1.8)	3 (0.9)	3 (0.9)	9 (2.7)
Dyspnea	6 (1.8)	5 (1.5)	11 (3.3)	6 (1.8)	3 (0.9)
Nausea	4 (1.2)	5 (1.5)	15 (4.5)	12 (3.6)	14 (4.2)
Hypertension[b]	6 (1.8)	4 (1.2)	9 (2.7)	10 (3.0)	9 (2.7)
Constipation[b,c]	6 (1.8)	3 (0.9)	4 (1.2)	7 (2.1)	4 (1.2)
Pain in extremity	0	3 (0.9)	3 (0.9)	7 (2.1)	2 (0.6)
Vomiting	2 (0.6)	3 (0.9)	7 (2.1)	5 (1.5)	3 (0.9)
Fatigue	8 (2.4)	2 (0.6)	6 (1.8)	4 (1.2)	7 (2.1)
Gastroenteritis viral	8 (2.4)	2 (0.6)	5 (1.5)	3 (0.9)	2 (0.6)

Respiratory Research 2014

Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/ salmeterol (250/50 mcg) in COPD patients

Table 3 Number (and %) of on-treatment AEs and events of special interest by treatment arm (intent-to-treat population).

	Pooled data	
	FF/VI 100/25 mcg *n* = 931	FP/SAL 250/50 mcg *n* = 927
On-treatment AEs		
Any AE	250 (27)	261 (28)
Headache[a]	46 (5)	50 (5)
Nasopharyngitis[a]	44 (5)	38 (4)
Oral candidiasis[a]	8 (<1)	19 (2)
Back pain	11 (1)	11 (1)
Oropharyngeal candidiasis[a]	7 (<1)	11 (1)
Any non-fatal serious AE	19 (2)	27 (3)
Any fatal AE	2 (<1)	4 (<1)
Treatment-related AEs[b]	28 (3)	43 (5)
AEs leading to study withdrawal	23 (2)	24 (3)

No clinically relevant abnormalities were demonstrated for any laboratory or electrocardiogram assessment, or urinary cortisol measurement, in any of the studies. In Study 1 a significant difference in 0–4 h wm pulse rate (bpm) was observed at Week 12 between FF/VI and FP/SAL

Respiratory Medicine 2014; 108:1171-1179

Original Investigation

Cardiovascular Safety of Inhaled Long-Acting Bronchodilators in Individuals With Chronic Obstructive Pulmonary Disease

Table 6. Bronchodilator Class and Risk of Hospitalization or ED Visit for Cardiovascular Events

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

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Para recordar

- 1 de cada 3-4 enfermos con IC tiene EPOC.
- La EPOC condiciona un peor pronóstico.
- La presencia de EPOC no debe interferir el tratamiento de la IC.
- La EPOC se acompaña de un riesgo de desarrollo de arrítmias.
- El tratamiento de la EPOC con los nuevos LAMA y LABA es eficaz y seguro.


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