Cardiovascular disease (CVD) in COPD

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2017 GOLD

- Assessment of concomitant chornic diseases (comorbidities)
    - Common comorbidities include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer
- COPD & Comordidities
    - Pts c CHF have greater morbidity and mortality

Cardiovascular disease (CVD)

- heart failure
- arrhythmias
- ischemic heart disease
- peripheral vascular disease
- HT

Heart failure (I)

- Prevalence of systolic or diastolic heart failure in COPD patients : 20 to 70%
- Annual incidence :3-4%

- Predictor of all-cause mortality

- 40% of COPD patients that are mechanically ventilated because of hypercapnic respiratory failure have evidence of left ventricular dysfunction
  - mimic or accompany acute exacerbations of COPD

-Bhatt SP, et al. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res* 2013; 162(4): 237-51

-Matamis D, et al. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. J Crit Care 2014 ; 29(2): 315.e7-14.
-MacDonald Ml, et al. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. The Lancer Respiratory medicine 2016 ; 4(2): 138

Prevalence of systolic and 'isolated' diastolic heart failure by age and sex

	Systolic heart failure ($n = 42$)	'Isolated' diastolic heart failure ($n = 41$)	All heart failure ($n = 83$)
Males			
Age (years)			
65–74 ($n = 150$)	26 [17.3% (11.6–24.4)]	11 [7.3% (3.7–12.7)]	37 [4.7% (18.0–32.4)]
≥75 ($n = 73$)	9 [12.3% (5.8–22.1)]	5 [6.8% (2.3–15.3)]	14 [19.2% (10.9–30.1)]
All ages ($n = 223$)	35 [15.7% (11.1–21.1)]	16 [7.2% (4.2–11.4)]	51 [22.9% (17.5–28.9)]
Females			
Age (years)			
65–74 ($n = 112$)	4 [3.6% (1.0–8.9)]	7 [6.3% (2.5–12.5)]	11 [9.8% (5.0–16.9)]
≥75 ($n = 70$)	3 [4.3% (0.9–12.0)]	18 [25.7% (16.0–37.6)]	21 [30.0% (19.6–42.1)]
All ages ($n = 182$)	7 [3.8% (1.6–7.8)]	25 [13.7% (9.1–19.6)]	32 [17.6% (12.3–23.9)]
All males and females			
Age (years)			
65–74 ($n = 262$)	30 [11.5% (7.9–15.9)]	18 [6.9% (4.1–10.6)]	48 [18.3% (13.8–23.5)]
≥75 ($n = 143$)	12 [8.4% (4.4–14.2)]	23 [16.1% (10.5–23.2)]	35 [24.5% (17.7–32.4)]
All ages ($n = 405$)	42 [10.4% (7.6–13.8)]	41 [10.1% (7.4–13.5)]	83 [20.5% (16.7–24.8)]

Numbers with per cent and 95% CI.
Seven females and three males were aged ≥85.

- FH.Rutten et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. European Heart Journal (2005) 26, 1887–1894

Data on the in-ICU and the in-hospital mortality and 6-month outcome among the 4 study groups

	Patients with normal systolic function (n = 26; 24.3%)	Patients with isolated RV failure (n = 37; 34.5%)	Patients with isolated LV failure (n = 24; 22.4%)	Patients with biventricular failure (n = 20; 18.8%)
ICU/Hospital deaths (n)	10/1	14/2	4/0	7/0
In-hospital mortality (%)	39	43.2	16.6*	35.0
Time of death (d)	27 ± 24	18 ± 9	8 ± 2*	8 ± 3*
Cause of death (n)				
VAP/Sepsis	8	11	1	2
Heart failure	–	5	3	5
Pulmonary embolism	2	–	–	
Unknown	1	–		–

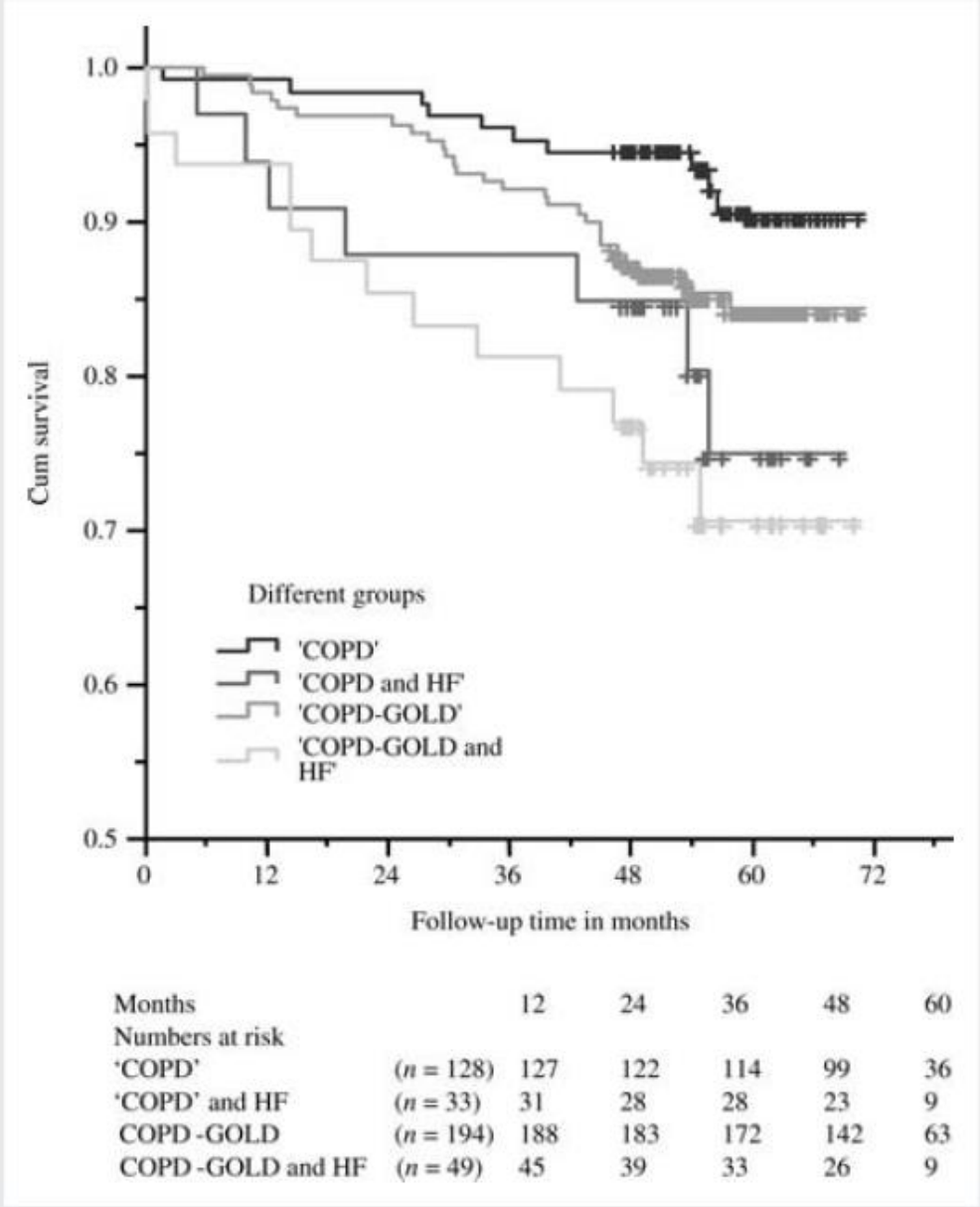
-Matamis D, et al. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. J Crit Care 2014 ; 29(2): 315.e7-14.

Table 3 All-cause mortality, causes of death, admission to hospital, exacerbation, and pneumonia during follow-up of 404 patients with a general practitioner's diagnosis of COPD

	GP's diagnosis of COPD with HF ($n = 82$)	GP's diagnosis of COPD without HF ($n = 322$)	*P*-value
All-cause mortality	25.6	12.1	0.002
Cause of death			
Cardiovascular	6.1	4.0	0.01
Sudden death	1.2	0.9	0.81
(Worsening) heart failure	2.4	0.6	0.14
Other cardiovascular	3.7	0.3	0.006
Respiratory	7.3	3.4	0.12
Respiratory insufficiency	6.1	1.2	0.008
Lung carcinoma	1.2	1.6	0.82
Other respiratory	—	0.6	0.47
Other diseases	7.3	4.7	0.33
Malignancy	2.4	2.2	0.89
Unknown	2.4	2.2	0.89
Admission to hospital			
Cardiology	15.9	9.9	0.14
Respiratory	24.4	14.9	0.04
Exacerbations of chronic obstructive pulmonary disease	32.9	37.9	0.40
Pneumonia	18.3	18.2	0.98

Values are percentages, unless stated otherwise. Cardiovascular death includes sudden death, death caused by myocardial infarction, heart failure, stroke, pulmonary embolism, or other cardiovascular disease. Other diseases includes death caused by malignancy not located in the lungs or unknown cause of mortality.

- The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. European Journal of Heart Failure (2009) 11, 1182–1188



Months		12	24	36	48	60
Numbers at risk						
'COPD'	(n = 128)	127	122	114	99	36
'COPD' and HF	(n = 33)	31	28	28	23	9
COPD -GOLD	(n = 194)	188	183	172	142	63
COPD -GOLD and HF	(n = 49)	45	39	33	26	9

Figure 1 Kaplan–Meier survival curves of 404 patients with a general practitioner's diagnosis of chronic obstructive pulmonary disease.

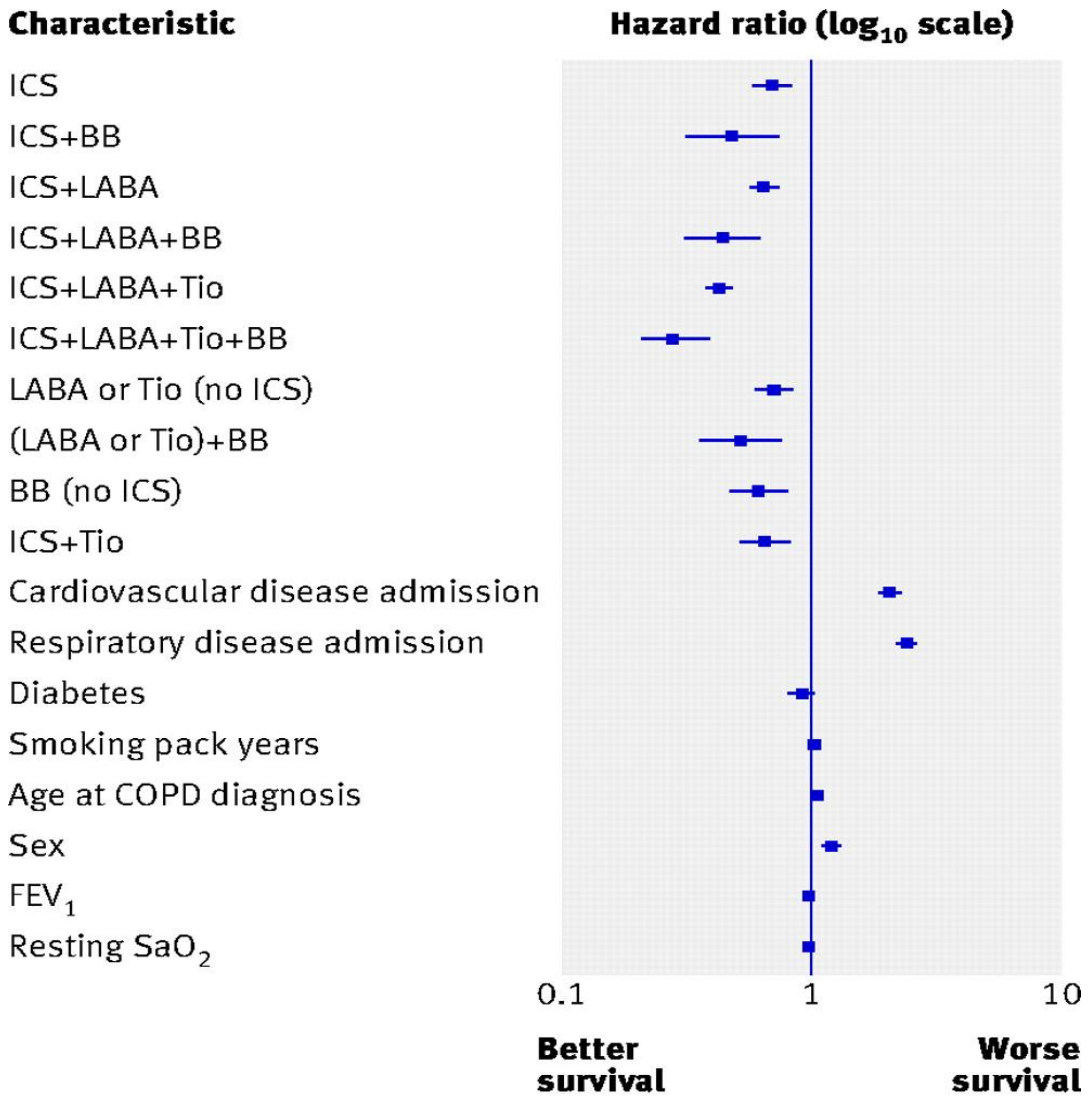
- The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. European Journal of Heart Failure (2009) 11, 1182–1188

Heart failure (II)

- Tx of Chronic heart failure
- No evidence that should be treated differently
- Selective B1-blockers : safe in COPD

-Beta-blockers in COPD: time for reappraisal. Eur RespirJ 2016 ; 48(3): 880-8

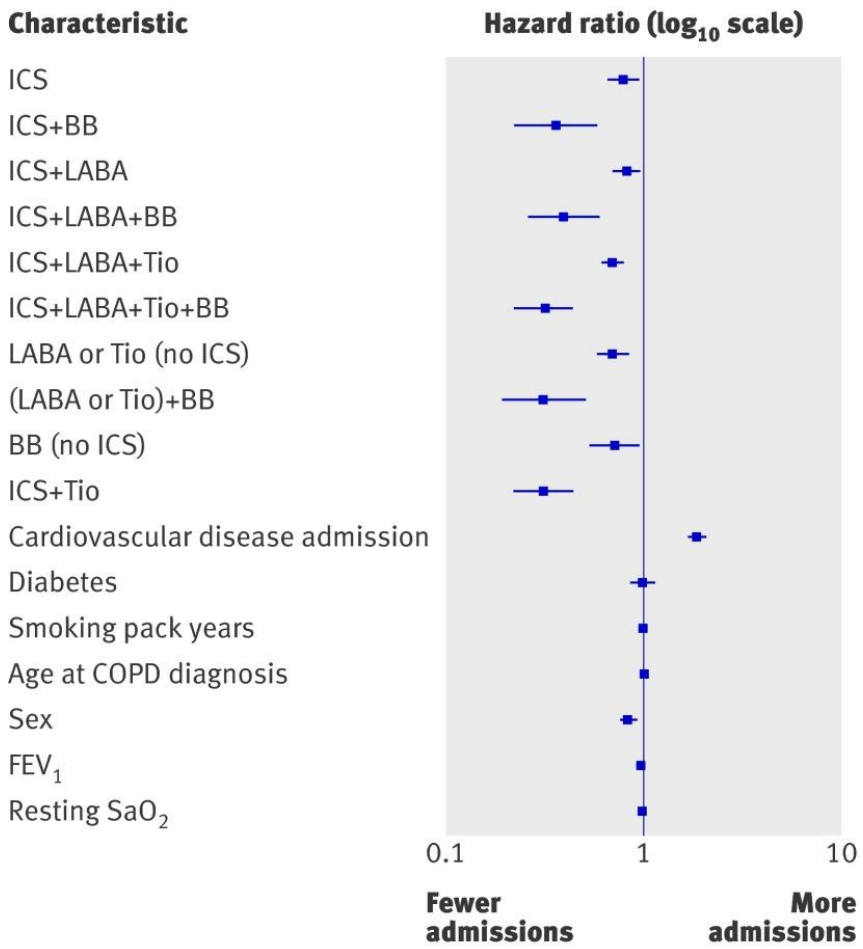
Adjusted hazard ratios for all cause mortality among patients with COPD in reference to the control group (who received only inhaled therapy with short acting β agonists or antimuscarinics).



ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV_1=forced expiratory volume in one second, SaO_2=arterial oxygen saturation

Philip M Short et al. BMJ 2011;342:bmj.d2549

Adjusted hazard ratios for hospital admissions due to respiratory disease among patients with COPD



ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV_1=forced expiratory volume in one second, SaO_2=arterial oxygen saturation

Philip M Short et al. BMJ 2011;342:bmj.d2549

- Potential cardiac targets for beta-blockers in COPD
  - Improved left ventricular systolic and diastolic function
  - Reduced left ventricular dilatation
  - Protection against myocardial ischaemia
  - Reduced left ventricular mass
  - Reduced heart rate
  - Anti-arrhythmic effects
  - Inhibition of myocyte apoptosis
  - Protection against hypoxic sympathetic drive
  - Protection against adverse effects of beta-agonists

- Potential noncardiac targets for beta-blockers in COPD
  - Inhibition of endothelin-1 release
  - Reduction in circulating pro-inflammatory cytokines
  - Inhibition of neutrophil chemotaxis and respiratory burst
  - Reduction in goblet cell number and mucus release

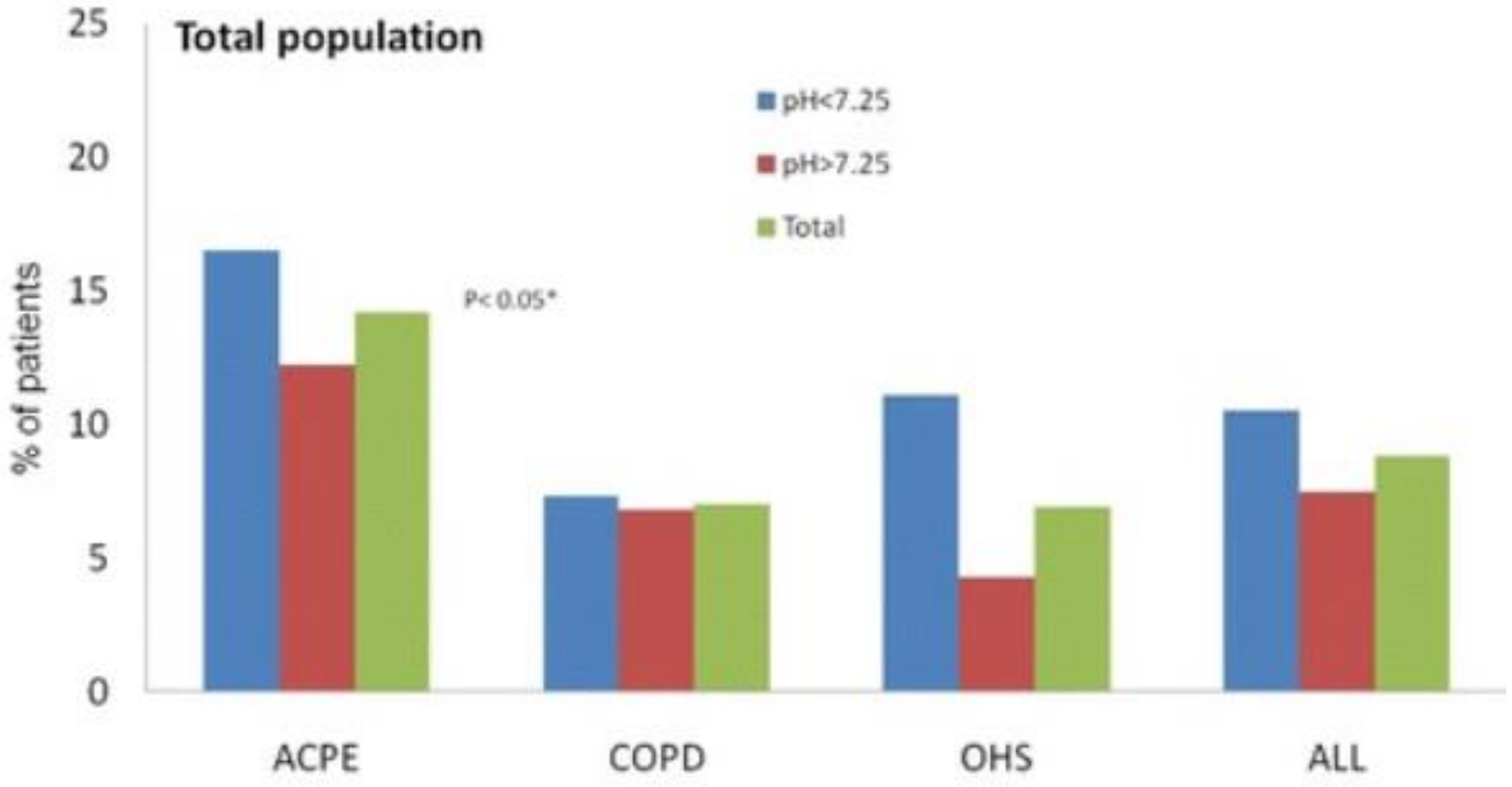
-Beta-blockers in COPD: time for reappraisal. Eur RespirJ 2016 ; 48(3): 880-8

Heart failure (III)

- Tx of acute heart failure
  - According to usual HF guidelines
  - NIV
    - Improves outcome for HF with acute pul edema.

- Masa JF et al. Noninvasive ventilation for severely acidotic patients in respiratory intermediate care units: Precision medicine in intermediate care units. BMC Pulm Med 2016

The percentages of patients experiencing NIV treatment failure during hospitalization



N=969 patients (240 with ACPE, 540 with COPD and 189 with OHS).

Abbreviations: NIV = noninvasive ventilation, ACPE = acute cardiogenic pulmonary edema, COPD = chronic obstructive pulmonary disease, OHS = obesity hypoventilation syndrome

BMC Pulm Med. 2016; 16: 97.

Arrhythmias

- Common in COPD
- Atrial fibrillation
  - frequent & associated with FEV1
    - *- P. Buch et al. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003; 21(6): 1012-6.*
  - a trigger or a consequence of COPD AE
    - *-Atrial fibrillation in the acute, hypercapnic exacerbations of COPO. Eur Rev Med Pharmacol Sd 2014 ; 18(19): 2908-17*

Presence of atrial fibrillation (AF) at baseline, at re-examination and at incident hospitalisations according to lung function

	FEV_1 % pred		
	<60%	60-80%	≥80%
At baseline			
Subjects n	1253	3904	8351
Presence of AF	15 (1.20)	32 (0.82)	31 (0.37)
At re-examination			
Subjects n	809	2947	6910
Presence of AF	9 (1.11)	25 (0.85)	28 (0.41)
At hospital admission			
Subjects n	1167	3699	8315
All cases of AF	47 (4.03)	96 (2.60)	147 (1.77)
AF as main diagnosis	46 (3.94)	28 (0.76)	19 (0.23)

Data are presented as n (%) unless otherwise stated

- P. Buch et al. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003; 21(6): 1012-6.

Variables	COPD (n=130)	COPD and AF (n=30)	*p*-value
FEV_1 %	76 ±8.3	57.1 ± 7.5	0.05 [a]
pH	7.38 ± 0.02	7.32 ± 0.03	0.2 [a]
PaO_2 mmHg	60.2±4.6	58.5±2.96	0,52 [a]
$PaCO_2$ mmHg	50.2 ± 3.5	70.6 ±5.3	0.05 [a]
HCO^{3-} mmol/L	30.2 ± 3.2	35.9±5.3	0.256 [a]
SO_2 %	91.5±2.2	90.2±2.7	0.33 [a]
EF %	51.2±2.7	41.3±6.3	0.652 [a]
PASP mmHg	35.2 ±2.3	45.3 ± 3.5	0.05 [b]

→ Impaired pulmonary function, hypercapnia and high values of PASP are independent predictors of incident AF.

-C. TERZANO, et al. Atrial fibrillation in the acute, hypercapnic exacerbations of COPO. Eur Rev Med Pharmacol Sd 2014

- atrial fibrillation does not alter the treatment of COPD

- Bronchodilators : previously described as potentially pro-arrhythmic agents;
  - *Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. Chest 2012; 142(2): 30S-11*
  - *Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergics medications. Thorax 2013;68(1):114-6*
- long-acting beta2-agonists, anticholinergic drugs (and inhaled corticosteroids) : overall acceptable safety profile
  - *Tiotropium Respimat inhaler and the risk of death in COPD. N EngtJ Med 2013; 369(16): 1491-501.*
  - *Cardiovascular events in patients with COPD: TORCH study results. Thorax 2010;65(8)*
  - *Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. The Lancet 2016; 387*

- short-acting beta2- agonists & theophylline
  - caution is advised
  - may precipitate AF and make control of the ventricular response rate difficult
    - *Bronchodilator use and the risk of arrhythmia in COPD. part 1: Saskatchewan cohort study. Chest 2012; 142(2): 298-304*
    - *Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004; 125(6): 2309-21*
    - *A prospective clinical study of theophylline safety in 3810 elderly with asthma or COPD. Respir Med 2004; 98(10): 1016-24*

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ORIGINAL ARTICLE

Tiotropium Respimat Inhaler and the Risk of Death in COPD

Robert A. Wise, M.D., Antonio Anzueto, M.D., Daniel Cotton, M.S., Ronald Dahl, M.D., Theresa Devins, Dr.Ph., Bernd Disse, M.D., Daniel Dusser, M.D., Elizabeth Joseph, M.P.H., Sabine Kattenbeck, Ph.D., Michael Koenen-Bergmann, M.D., Gordon Pledger, Ph.D., and Peter Calverley, D.Sc., for the TIOSPIR Investigators*

N Engl J Med 2013; 369:1491-1501 | October 17, 2013 | DOI: 10.1056/NEJMoa1303342

Serious Adverse Events and Major Adverse Cardiovascular Events.

Table 4. Serious Adverse Events and Major Adverse Cardiovascular Events.*

Event	Tiotropium Respimat 2.5 μg (N=5724)	Tiotropium Respimat 5 μg (N=5705)	Tiotropium HandiHaler 18 μg (N=5687)	Tiotropium Respimat 2.5 μg vs. HandiHaler		Tiotropium Respimat 5 μg vs. HandiHaler	
				Hazard Ratio (95% CI)†	P Value	Hazard Ratio (95% CI)†	P Value
	number of patients (percent)						
Any serious adverse event	1937 (33.8)	1846 (32.4)	1842 (32.4)				
Respiratory, thoracic, or mediastinal disorder	1017 (17.8)	957 (16.8)	964 (17.0)				
Infection or infestation	497 (8.7)	502 (8.8)	495 (8.7)				
Cardiac disorder	293 (5.1)	273 (4.8)	270 (4.7)				
Major adverse cardiovascular events ‡	224 (3.9)	222 (3.9)	202 (3.6)	1.11 (0.91–1.34)	0.30	1.10 (0.91–1.33)	0.33
Stroke	56 (1.0)	52 (0.9)	57 (1.0)	0.98 (0.68–1.41)	0.90	0.91 (0.63–1.33)	0.63
Transient ischemic attack	25 (0.4)	30 (0.5)	20 (0.4)	1.24 (0.69–2.24)	0.47	1.50 (0.85–2.65)	0.16
Myocardial infarction	70 (1.2)	73 (1.3)	52 (0.9)	1.34 (0.94–1.92)	0.11	1.41 (0.98–2.00)	0.06

* Events are listed according to the system organ class in the Medical Dictionary for Regulatory Activities. A complete list of serious adverse events is provided in Table S4 in Section 9 in the Supplementary Appendix.
† Hazard ratios and P values are provided for all prespecified analyses.
‡ Major adverse cardiovascular events include stroke, transient ischemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death, or fatal event in system organ classes for cardiac and vascular disorders. Data for patients who died from a fatal major adverse cardiovascular event are listed in Table 2.

Wise RA et al. N Engl J Med 2013;369:1491-1501.

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Articles

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Prof Jørgen Vestbo, DMSc, Julie A Anderson, MA, Robert D Brook, MD, Prof Peter M A Calverley, DSc, Bartolome R Celli, MD, Courtney Crim, MD, Fernando Martinez, MD, Julie Yates, BS, Prof David E Newby, DSc on behalf of the SUMMIT Investigators

Published: 30 April 2016

Reported adverse events among 16 568 patients in the safety population

	Placebo (n=4131)	Fluticasone furoate (n=4157)	Vilanterol (n=4140)	Combination therapy (n=4140)
Any adverse event	2782 (67%)	2820 (68%)	2809 (68%)	2780 (67%)
Adverse event leading to discontinuation of study medication	397 (10%)	367 (9%)	370 (9%)	342 (8%)
Serious adverse event	918 (22%)	929 (22%)	972 (23%)	961 (23%)
Fatal adverse event	192 (5%)	183 (4%)	198 (5%)	182 (4%)
Total exposure to study medication (patient-years)	6614	6889	6955	7038
Adverse events of special interest*				
Local steroid events	146 (4%) [2·7, 2·3–3·1]	209 (5%) [3·9, 3·4–4·4]	152 (4%) [2·5, 2·1–2·9]	225 (5%) [4·2, 3·8–4·7]
All cardiovascular events	695 (17%) [16·4, 15·4–17·4]	699 (17%) [15·7, 14·8–16·7]	707 (17%) [15·7, 14·8–16·6]	735 (18%) [16·3, 15·4–17·3]
Cardiac arrhythmias	211 (5%) [4·1, 3·6–4·6]	229 (6%) [4·1, 3·6–4·6]	224 (5%) [3·9, 3·4–4·4]	209 (5%) [3·9, 3·4–4·3]

Ischaemic heart disease (IHD)

- Ischaemic heart disease should be considered in all COPD patients depending on their risk factor profile.

- The cardiovascular risk may be assessed by the global risk calculator, which can be found on the US National Heart Blood Lung Institute website and treatment initiated based on the current

  - *National Heart Lung & Blood Institute. Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack 2016. http://cvdrisk.nhlbi.nih.gov/ (accessed 14 August 2016)*

- During acute COPD exacerbations, there is an increased risk of myocardial damage in patients with concomitant ischemic heart disease. Patients who demonstrate abnormal cardiac troponins in isolation are at increased risk of adverse outcomes including short-term (30day) and long-term mortality.

  -Hoiseth AD, et al. Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease. Thorax 2011; 66(9): 775-81.

- Tx according to guidelines irrespective of the presence of COPD.

Peripheral vascular disease

- Peripheral artery disease (PAD) is an atherosclerotic process that refers to the occlusion of the arteries in the lower limbs
- Worse functional activity , worse quality of life in PAD patients with COPD
- 8.8% were diagnosed with PAD in COPD vs 1.8% non-COPD controls
  - *Peripheral Artery Disease and its Clinical Relevance in Patients with COPO in the COSYCONET Study. Am J Respir Crit Care Med 2016; EPub 17 Aug 2016*

Hypertension

- most frequently occurring comorbidity in COPD and may have implications for prognosis
  - *Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186(2): 15S-61*
- Diastolic dysfunction as a result of optimally treated hypertension may be associated with exercise intolerance and mimic symptoms associated with an acute exacerbation
  - *Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162(4): 237-51*
  - *High Prevalence of Left Ventricle Diastolic Dysfunction in Severe COPD Associated with A Low Exercise Capacity: A Cross-Sectional Study. PLoS One, 2013;8(6)*
- Hypertension should be treated according to usual guidelines

Summary

- Cardiovasvular diseases (CHF, arrhythmias, CAD etc) are common and important comorbidities in COPD
- A high index of suspicion for coexisting CVD should be maintained in all patients with COPD
- CVD should be treated according to usual guidelines