EXCEL IN PULMONOLOGY

the advanced training program in Respiratory Medicine

COPD@ATHENS

3

Management of stable and exacerbated COPD

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Disclosures

Speaker and Consulting fees from

- Novartis
- ELPEN
- Menarini
- AstraZeneca
- GlaxoSmithKline
- Chiesi
- Boehringer Ingelheim
- Specialty Therapeutics
- Guidotti

COPD definition GOLD 2023

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.

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Goals of COPD treatment

- Relieve Symptoms
- Improve health status
- Improve exercise tolerance
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

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Therapeutic interventions for COPD

Non pharmacological interventions

✓Smoking cessation

✓Rehabilitation

✓Vaccination

✓Oxygen therapy, NIV,LVRS/LVRB,
- nutritional support

✓Education

Pharmacological interventions

✓Medications for COPD

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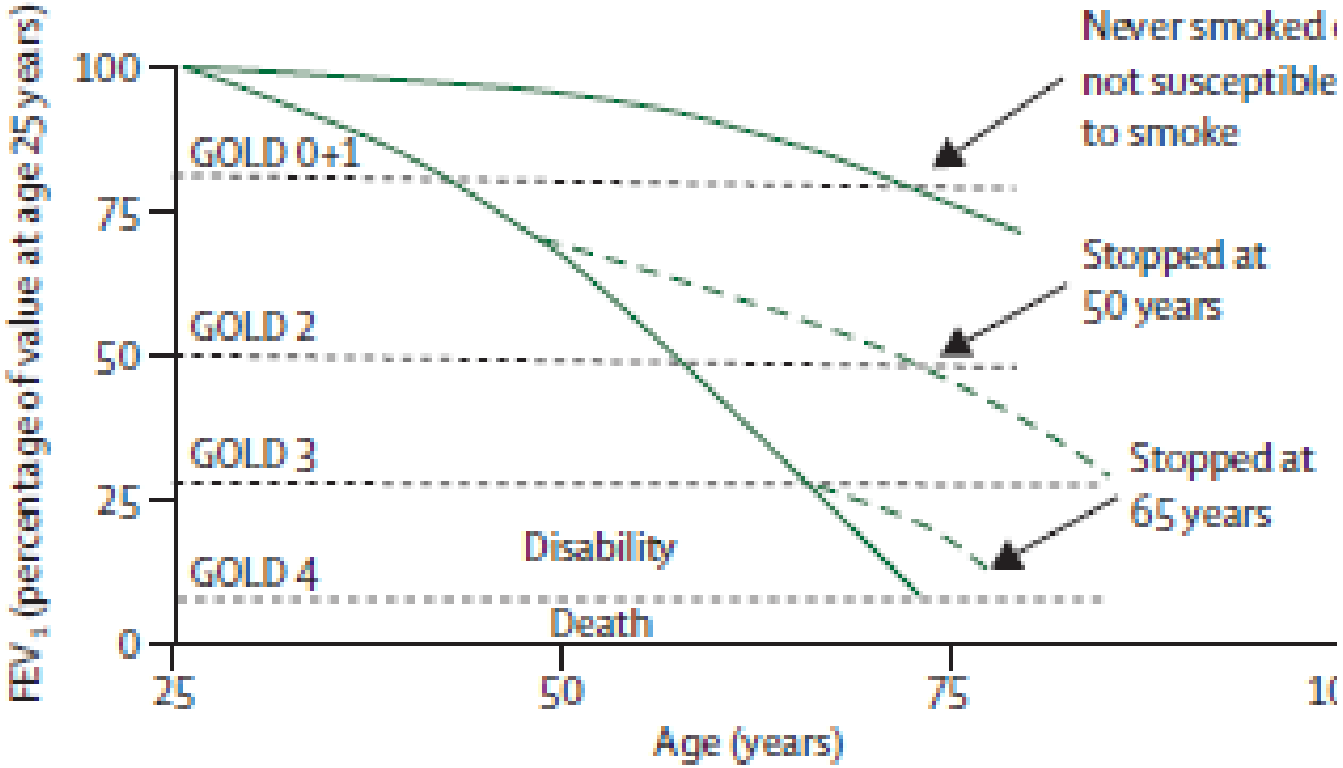
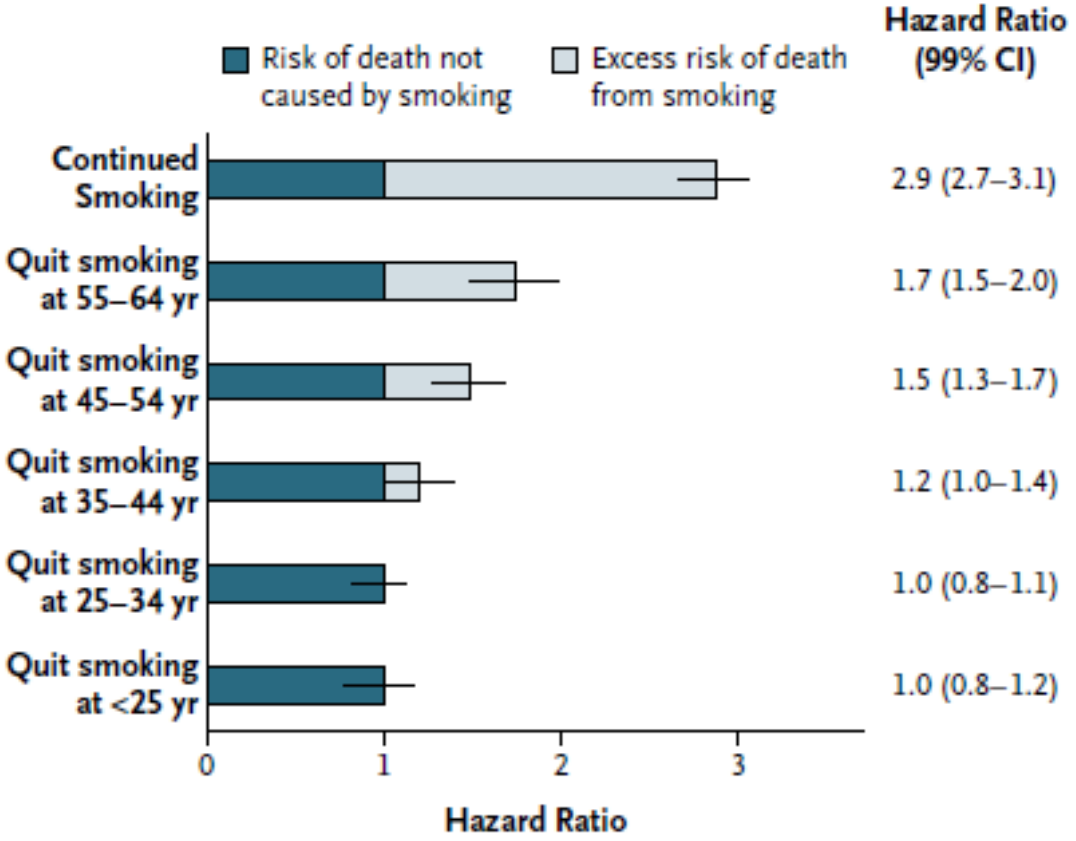
Smoking cessation- the first intervention which alters disease course





Tonnesen P et al ERJ 2007
Jha P et al Nature reviews Cancer 2009
Rigotti NA et al Lancet Resp Med 2013

Therapeutic interventions for smoking cessation

Brief Strategies to Help the Patient Willing to Quit

Table 3.1

ASK	Systematically identify all tobacco users at every visit *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented*
ADVISE	Strongly urge all tobacco users to quit *In a clear, strong, and personalized manner, urge every tobacco user to quit*
ASSESS	Determine willingness and rationale of patient's desire to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days)*
ASSIST	Aid the patient in quitting *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials*
ARRANGE	Schedule follow-up contact *Schedule follow-up contact, either in person or via telephone*

- **Nicotine replacement products** (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge)
  - Contraindications: recent myocardial infarction or stroke (treatment can be started after 2w)
- **Medications**
  - Bupropion, nortriptyline

The combination of pharmacotherapy and behavioral support increases smoking cessation rates

Vaping is not suggested as an intervention for smoking cessation!

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Pulmonary Rehabilitation

- Decreased exercise capacity in COPD patients is related to
  - Low HRQoL
  - Depression
  - Increased exacerbation Frequency
  - Increased mortality

- Pulmonary rehabilitation programs include the following
  - exercise training to increase in muscle strength
  - Respiratory physiotherapy- breathing patterns
  - Nutritional support
  - Psychological support (cognitive behavioral psychotherapy)
  - Education

Spruit M A et al AJRCCM 2014

Pulmonary Rehabilitation

HRQoL

Analysis 4.5. Comparison 4 Rehabilitation versus usual care (sensitivity analysis by allocation concealment and incomplete outcome), Outcome 5 QoL - Low Risk SGRQ (Total).

Review: Pulmonary rehabilitation for chronic obstructive pulmonary disease

Comparison: 4 Rehabilitation versus usual care (sensitivity analysis by allocation concealment and incomplete outcome)

Outcome: 5 QoL - Low Risk SGRQ (Total)

Study or subgroup	Pulmonary rehab N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Boxall 2005	23	-5.8 (11.8)	23	-1.4 (13.3)		10.2 %	-4.40 [-11.67, 2.87]
Engstrom 1999	26	0.3 (17.3)	24	0.5 (16.2)		7.1 %	-0.20 [-9.49, 9.09]
Griffiths 2000	93	-7.1 (15.5)	91	1.3 (11.7)		19.8 %	-8.40 [-12.36, -4.44]
Gurgun 2013	30	-6.45 (8.0638)	16	-0.18 (0.7)		24.3 %	-6.27 [-9.18, -3.36]
Karapolat 2007	26	-16.8 (15.2)	19	-3.7 (17.3)		6.6 %	-13.10 [-22.83, -3.37]
Theander 2009	12	7.6 (10.8)	14	2.6 (12.2)		7.7 %	5.00 [-3.84, 13.84]
Van Wetering 2010	87	-3.9 (10.26)	88	0.3 (9.38)		24.3 %	-4.20 [-7.11, -1.29]
Total (95% CI)	**297**		**275**			**100.0 %**	**-5.15 [-7.95, -2.36]**

Heterogeneity: Tau² = 6.17; Chi² = 12.19, df = 6 (P = 0.06); I² =51%

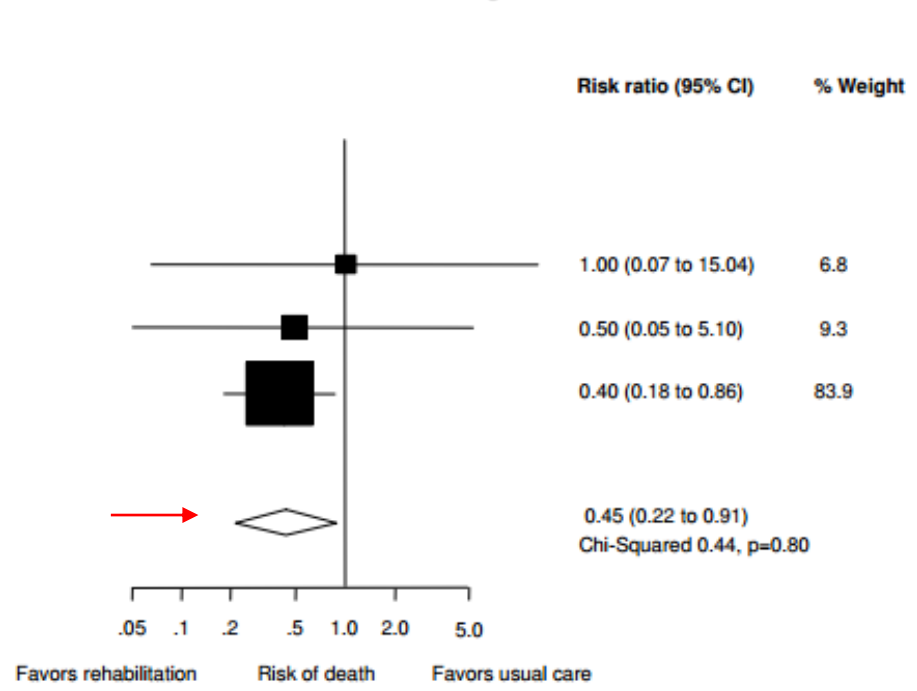
Test for overall effect: Z = 3.61 (P = 0.00030)

Test for subgroup differences: Not applicable

-20 -10 0 10 20

Favours pulmonary rehab | Favours usual care

Mortality



- ✓ **Symptom improvement**
- ✓ **Improvement of HRQoL**
- ✓ **Decrease of mortality**

McCarthy B et al Cochrane Database Syst Rev 2015
Puhan MA et al Resp Res 2005

Vaccination for Stable COPD

Vaccination for Stable COPD

Table 3.2

- Influenza vaccination is recommended in people with COPD **(Evidence B)** **Influenza**
- The WHO and CDC recommends SARS-CoV-2 (COVID-19) vaccination for people with COPD **(Evidence B)** **SARS-Cov-2**
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) in people with COPD **(Evidence B)** ***S pneumoniae***
- Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations in people with COPD **(Evidence B)** ***S pneumoniae***
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence **(Evidence B)**, and Zoster vaccine to protect against shingles for people with COPD over 50 years **(Evidence B)** **dTaP, V-ZV**

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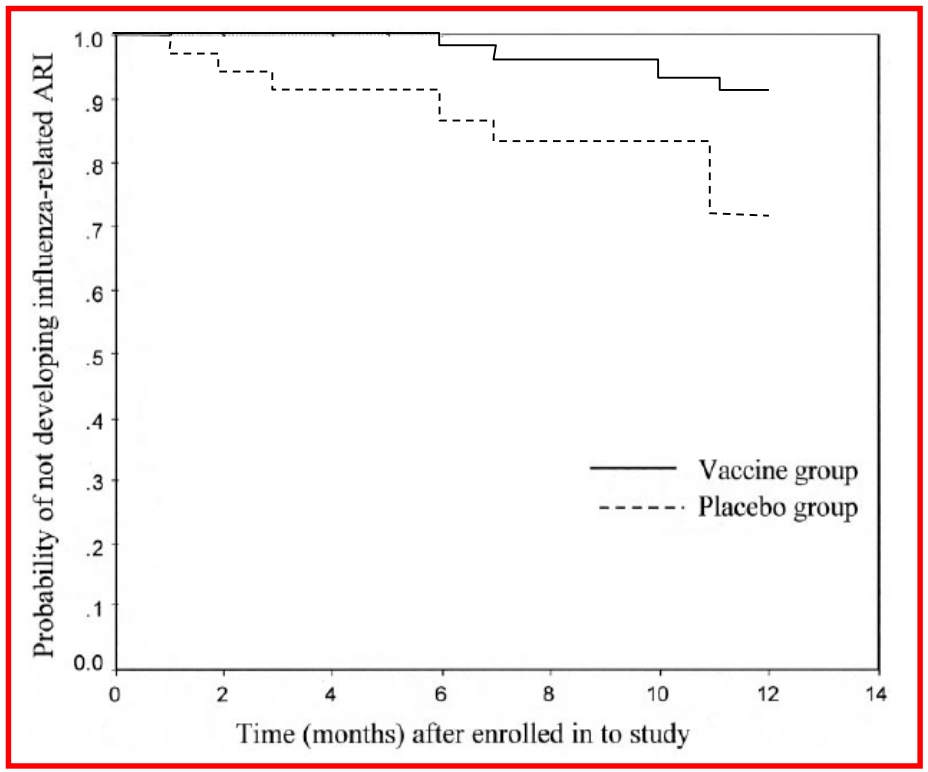
The effect of influenza vaccination in COPD exacerbations

- COPD patients (especially those with CV comorbidities) are at increased risk of complications when infected with the influenza virus

Crohskopf LA et al CDC recommendations 2014

- Influenza A & B are responsible for 5.4% of exacerbations

Seemungal T, Am J Respir Crit Care Med 2001



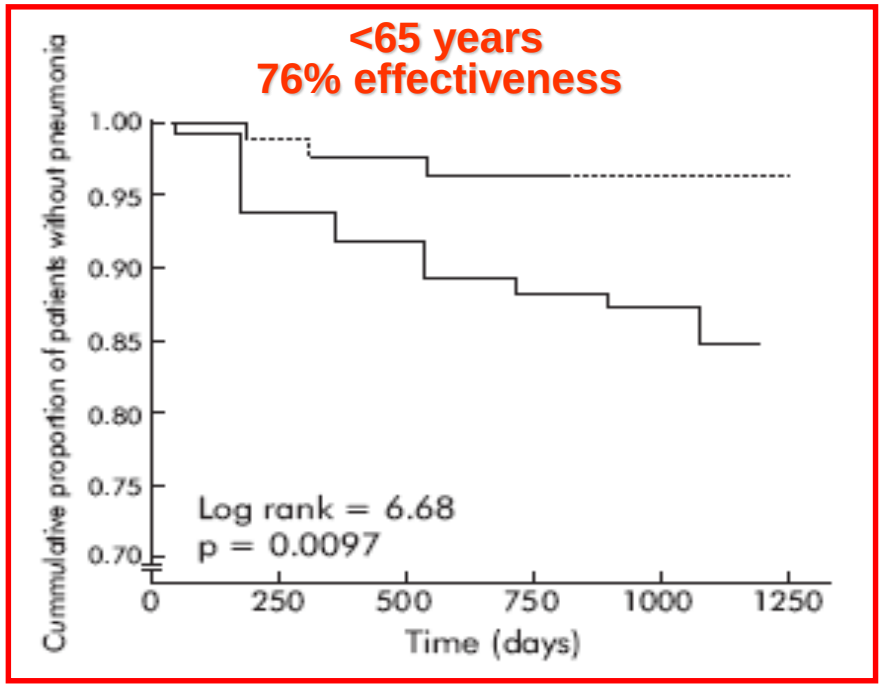
76% Decrease of AECOPD related with (IRR = 0.24)

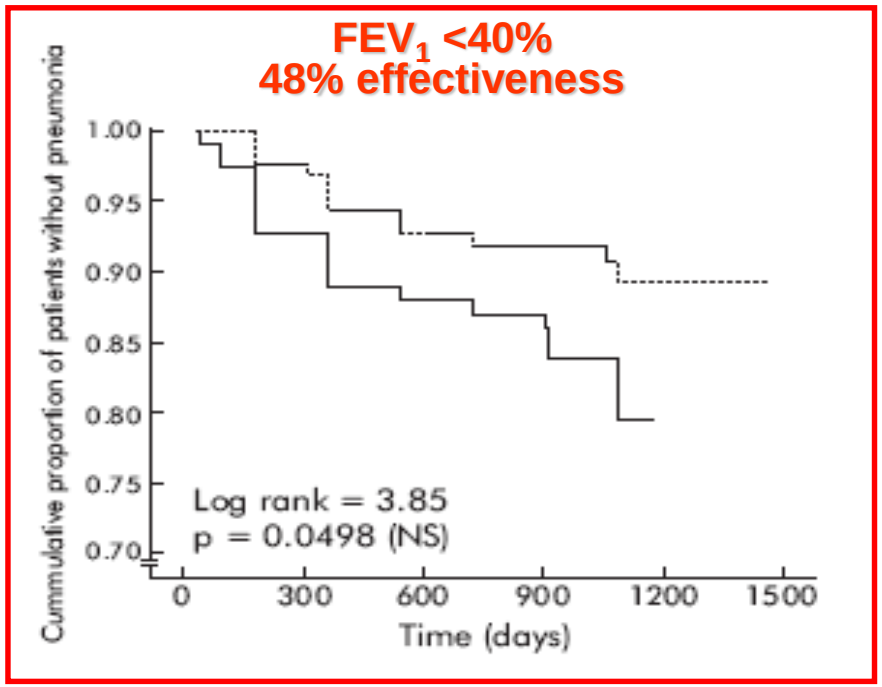
- Best time of immunization September-November
- Protection lasts for one period.
- Annual vaccination is required

Bekkat-Berkani R, et al. BMC Pulm Med. 2017

Wongsurakiat P. Chest 2004

Pneumococal vaccination and exacerbations





91% effectiveness in COPD patients <65 years with FEV_1 <40%

Alfageme I, Thorax 2006

LTOT

Indications:

Stable COPD with

- PaO_2 ≤55mmHg or
- PaO_2 ≤60mmHg + AND
  - Peripheral oedema
  - Polycythemia (Ht ≥55) or
  - Pulmonary hypertension

2 measurements are required - 3 w intervals

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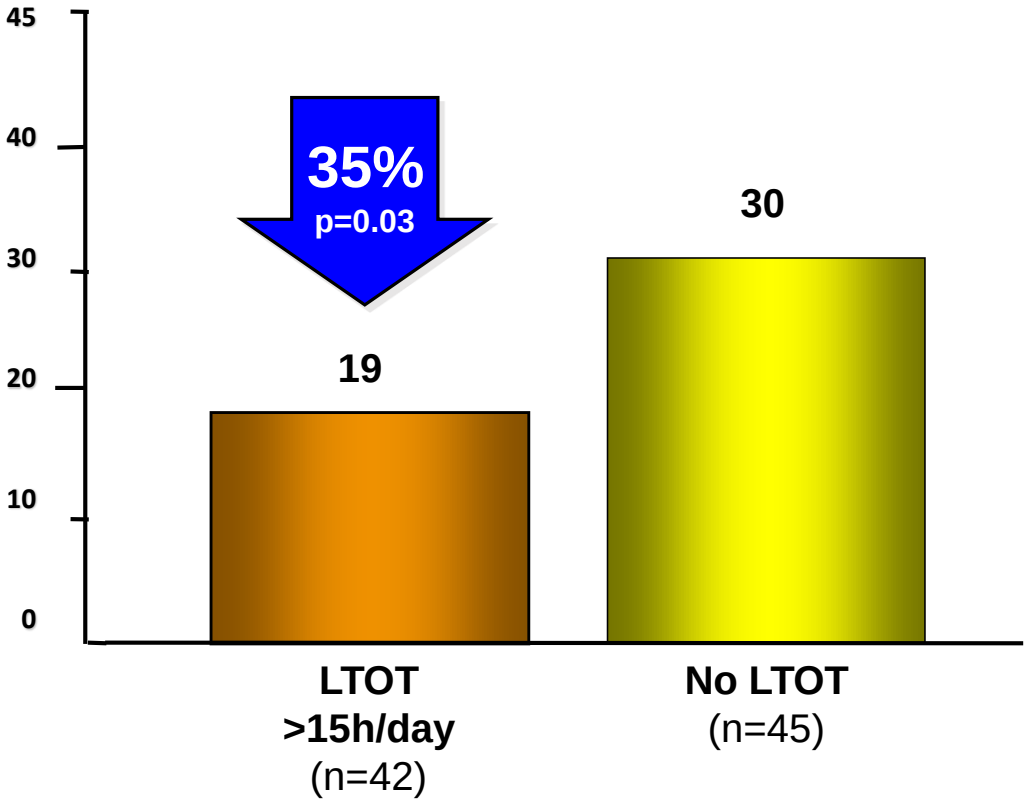
Hardinge M et al Thorax 2015

LTOT ≥ 15h/day

Patients which have been prescribed LTOT after a AECOPD should be re-evaluated after 60-90 days



Medical Research Council Working Party, Lancet 1981

NIV in stable COPD

- It can be prescribed in patients in which the acute cause of AECOPD has been resolved

but

  - They cannot be weaned from NIV for 8 consecutive days (due to clinical deterioration, increase in PaCO2, respiratory acidosis)

  - Recurring episodes of acute respiratory failure without precise cause

- In COPD patients with concomitant OSA

- In patients with prolonged daytime hypercarbia ($PCO_2 \geq 52mmHg$) and a recent hospitalization for AECOPD

Roberts CM et al Clin Med 2008
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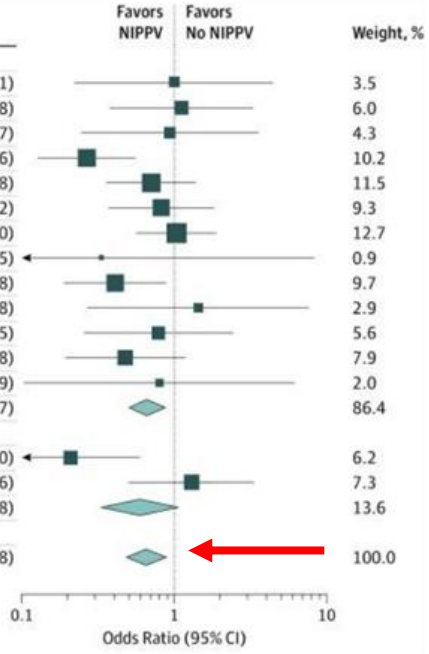
The benefits of NIV in stable COPD

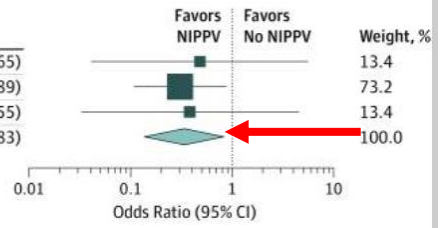
Survival

Study	Study Design	NIPPV Events/Patients	No NIPPV Events/Patients	Odds Ratio (95% CI)	Weight, %
BPAP vs no device					
Casanova et al,[19] 2010	RCT	4/26	4/26	1.00 (0.22-4.51)	3.5
Clini et al,[23] 2002	RCT	8/43	8/47	1.11 (0.38-3.28)	6.0
Duiverman et al,[26] 2011	RCT	5/37	5/35	0.94 (0.25-3.57)	4.3
Köhnlein et al,[36] 2014	RCT	12/102	31/93	0.27 (0.13-0.56)	10.2
McEvoy et al,[38] 2009	RCT	40/72	46/72	0.71 (0.36-1.38)	11.5
Murphy et al,[6] 2017	RCT	16/57	19/59	0.82 (0.37-1.82)	9.3
Struik et al,[7] 2014	RCT	30/101	29/100	1.03 (0.56-1.90)	12.7
Zhou et al,[46] 2017	RCT	0/57	1/58	0.33 (0.01-8.35)	0.9
Budweiser et al,[18] 2007	Observational	24/99	18/41	0.41 (0.19-0.88)	9.7
Clini et al,[22] 1996	Observational	4/17	3/17	1.44 (0.27-7.68)	2.9
Clini et al,[21] 1998	Observational	13/28	11/21	0.79 (0.25-2.45)	5.6
Galli et al,[32] 2014	Observational	8/78	17/88	0.48 (0.19-1.18)	7.9
Tsolaki et al,[44] 2008	Observational	2/27	2/22	0.80 (0.10-6.19)	2.0
Subtotal (I^2 = 5.9%; P = .39)				0.66 (0.50-0.87)	86.4
HMV vs no device					
Heinemann et al,[35] 2011	Observational	6/39	20/43	0.21 (0.07-0.60)	6.2
Paone et al,[42] 2014	Observational	13/48	10/45	1.30 (0.50-3.36)	7.3
Subtotal (I^2 = 84.3%; P = .01)				0.56 (0.29-1.08)	13.6
NIPPV (BPAP and HMV) vs no device					
Overall (I^2 = 27.3%; P = .16)				0.65 (0.48-0.88)	100.0



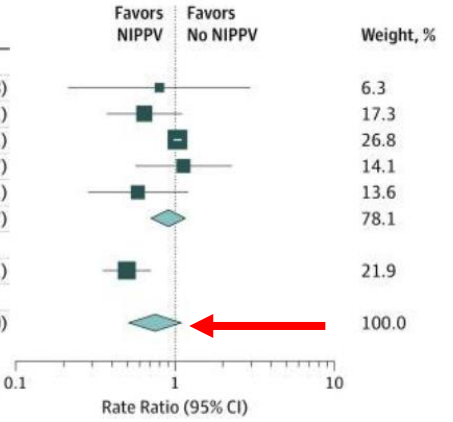
Intubation

BPAP vs No Device	Study Design	NIPPV Events/Patients	No NIPPV Events/Patients	Odds Ratio (95% CI)	Weight, %
Casanova et al,[19] 2010	RCT	1/26	2/26	0.48 (0.04-5.65)	13.4
Galli et al,[32] 2014	Observational	5/78	16/88	0.31 (0.11-0.89)	73.2
Tsolaki et al,[44] 2008	Observational	1/27	2/22	0.38 (0.03-4.55)	13.4
Subtotal (I^2 = 0.0%; P = .94)				0.34 (0.14-0.83)	100.0



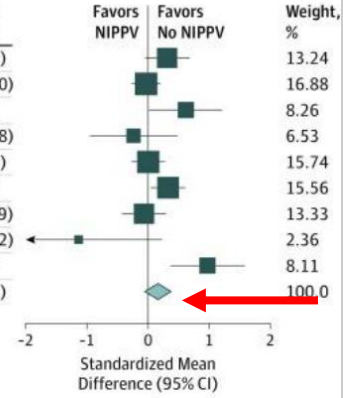
Hospital readmission

Study	Study Design	No. of Patients NIPPV	No. of Patients No NIPPV	Rate Ratio (95% CI)	Weight, %
BPAP vs no device					
Casanova et al,[19] 2010	RCT	26	26	0.80 (0.21-2.98)	6.3
Clini et al,[23] 2002	RCT	23	24	0.64 (0.37-1.11)	17.3
McEvoy et al,[38] 2009	RCT	72	72	1.04 (0.98-1.11)	26.8
Clini et al,[22] 1996	Observational	17	17	1.13 (0.57-2.27)	14.1
Tsolaki et al,[44] 2008	Observational	27	22	0.59 (0.29-1.21)	13.6
Subtotal (I^2 = 27.2%; P = .240)				0.91 (0.71-1.17)	78.1
HMV vs no device					
Paone et al,[42] 2014	Observational	48	45	0.50 (0.35-0.71)	21.9
NIPPV (BPAP and HMV) vs no device					
Overall (I^2 = 76.6%; P = .001)				0.75 (0.52-1.10)	100.0



Health Related Quality of Life

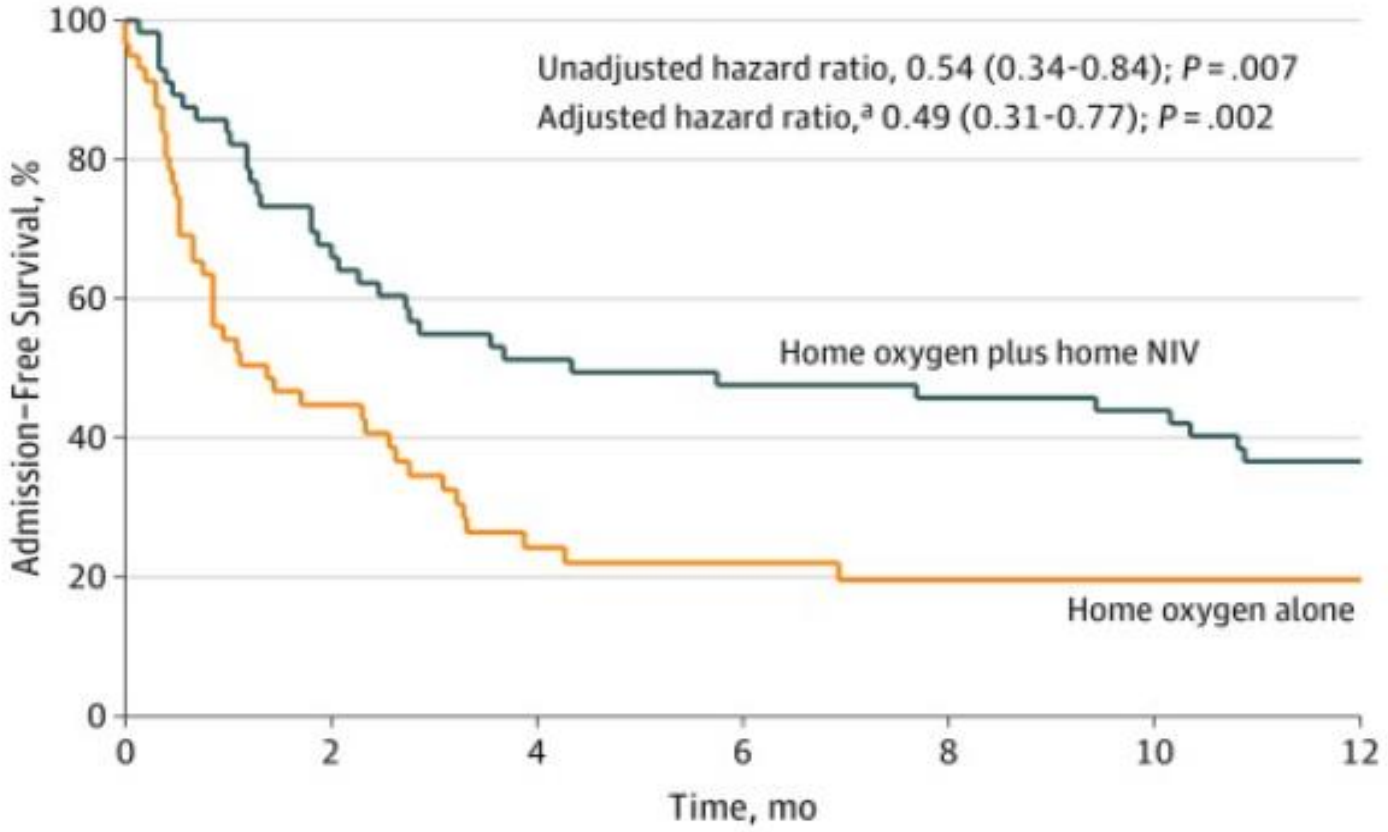
BPAP vs No Device	Study Design	No. of Patients NIPPV	No. of Patients No NIPPV	Quality of Life Scale	Standardized Mean Difference (95% CI)	Weight, %
Zhou et al,[46] 2017	RCT	57	58	COPD assessment test	0.31 (-0.06 to 0.68)	13.24
Duiverman et al,[26] 2011	RCT	37	35	Chronic Respiratory Disease Questionnaire	-0.04 (-0.27 to 0.20)	16.88
Garrod et al,[33] 2000	RCT	23	22	Chronic Respiratory Disease Questionnaire	0.62 (0.02 to 1.21)	8.26
Márquez-Martín et al,[37] 2014	RCT	15	15	Chronic Respiratory Disease Questionnaire	-0.24 (-0.96 to 0.48)	6.53
Struik et al,[7] 2014	RCT	101	100	Chronic Respiratory Disease Questionnaire	0.00 (-0.28 to 0.28)	15.74
Köhnlein et al,[36] 2014	RCT	102	93	St George's Respiratory Questionnaire	0.32 (0.04 to 0.61)	15.56
Murphy et al,[6] 2017	RCT	57	59	St George's Respiratory Questionnaire	-0.07 (-0.43 to 0.29)	13.33
Oscroft et al,[41] 2010	RCT	5	5	St George's Respiratory Questionnaire	-1.14 (-2.50 to 0.22)	2.36
Tsolaki et al,[44] 2008	Observational	27	22	SF-36 physical component summary	0.97 (0.36 to 1.58)	8.11
Overall (I^2 = 61.7%; P = .007)					0.16 (-0.06 to 0.38)	100.0



Wilson EM et al JAMA 2020

The benefits of NIV in stable COPD

- **Randomized controlled trial**
- **13 centers in UK (2010-2015)**
- **Patients with persistent hypercarbia ($PaCO_2$ >53 mm Hg) 2-4w after resolution of acidosis**

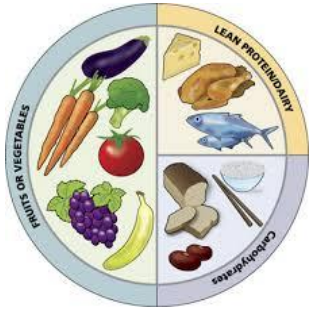


No. at risk							
Home oxygen plus home NIV	57	37	28	26	25	24	16
Home oxygen alone	59	23	11	10	8	8	6

Murphy PB et al JAMA 2017

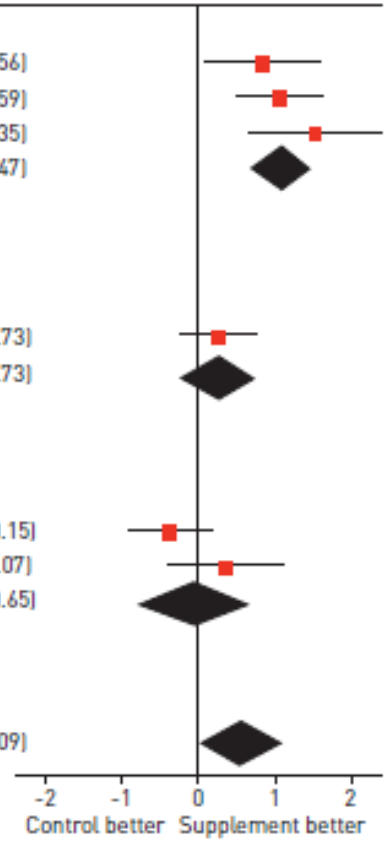
Nutritional support

- Important for cachectic patients



FFMI

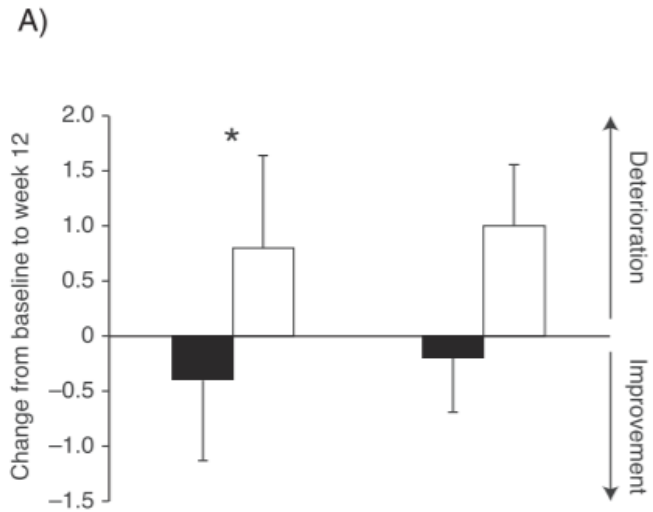
First author [ref.]	Difference mean±SE	Experimental total	Control total	Weight %	Std mean difference IV, random (95% CI)
Undernourished					
Sugawara [74]#	0.8329±0.3713	17	15	15.5	0.83 (0.11–1.56)
Schols [73]¶	1.0495±0.2735	39	25	17.9	1.05 (0.51–1.59)
Hoogendoorn [75], van Wetering [76–89]#	1.5066±0.4282	15	14	14.1	1.51 (0.67–2.35)
Subtotal (95% CI)		71	54	47.5	1.08 (0.70–1.47)
Heterogeneity: Tau-squared 0.00; Chi-squared 1.45, df 2 (p=0.48); I^2=0%					
Test for overall effect: Z=5.54 (p<0.00001)					
Adequately nourished					
Schols [73]	0.2651±0.239	33	38	18.7	0.27 (-0.20–0.73)
Subtotal (95% CI)		33	38	18.7	0.27 (-0.20–0.73)
Heterogeneity: not applicable					
Test for overall effect: Z=1.11 (p<0.27)					
Combined population of undernourished and nourished patients					
Steiner [84–86]	-0.3712±0.2642	25	35	18.1	-0.37 (-0.89–0.15)
Sugawara [87, 88]	0.3532±0.3641	17	14	15.7	0.35 (-0.36–1.07)
Subtotal (95% CI)		42	49	33.8	-0.05 (-0.76–0.65)
Heterogeneity: Tau-squared 0.16; Chi-squared 2.59, df 1 (p=0.11); I^2=61%					
Test for overall effect: Z=0.15 (p<0.88)					
Total (95% CI)		146	141	100.0	0.57 (0.04–1.09)
Heterogeneity: Tau-squared 0.33; Chi-squared 22.28, df 5 (p=0.0005); I^2=78%					
Test for overall effect: Z=2.11 (p=0.03)					
Test for subgroup differences: Chi-squared 11.33, df 2 (p=0.003); I^2=82.3%					



Schols AM et al ERJ 2014

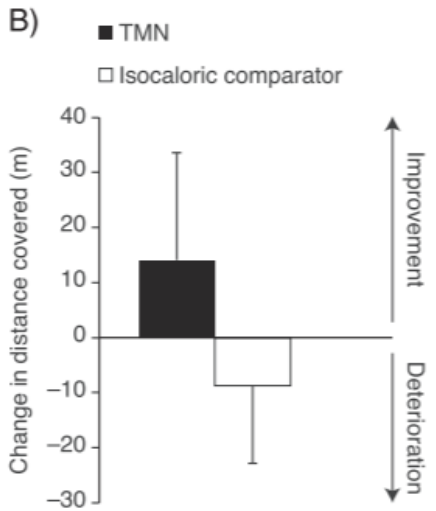
Nutritional support

Dyspnea **Fatigue**



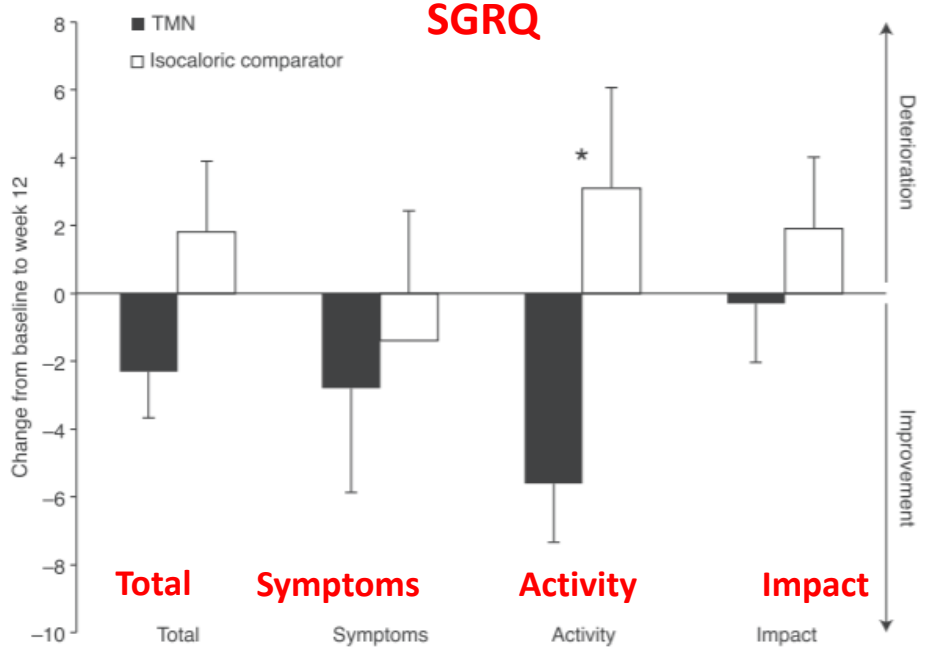
	Post-walk fatigue		Post-walk dyspnoea	
	TMN	Comparator	TMN	Comparator
Mean baseline value:	2.5	3.6	3.4	4.0
Mean week 12 value:	2.3	4.3	3.2	4.8
Estimated effect size, mean (95% CI):	−1.91 (−3.68, −0.14)		−1.37 (−2.77, 0.04)	
p value:	0.0352		0.0565	

Distance (m)



	TMN	Comparator
Mean baseline value:	388.1	389.0
Mean week 12 value:	385.3	389.8
Estimated effect size, mean (95% CI):	13.5 (−29.0, 56.1)	
p value:	0.5219	

SGRQ



Total **Symptoms** **Activity** **Impact**

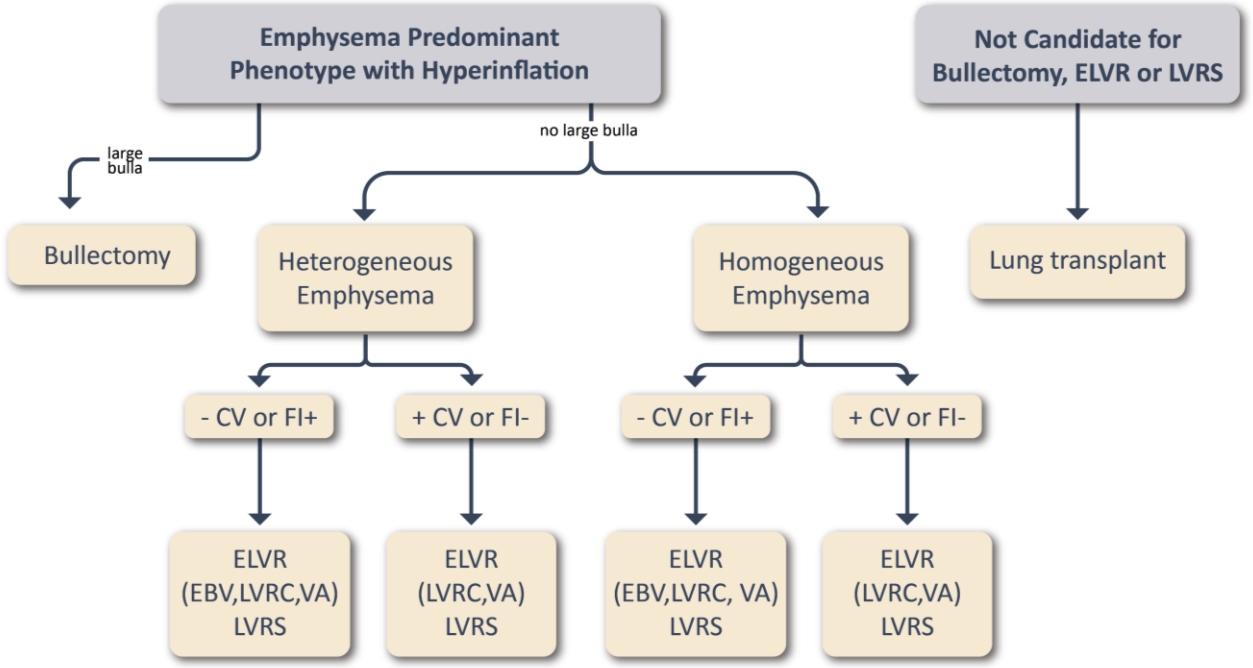
	Total score		Symptoms subscale		Activity subscale		Impact subscale	
	TMN	Comparator	TMN	Comparator	TMN	Comparator	TMN	Comparator
Mean baseline value:	37.1	37.8	59.1	59.7	49.4	48.3	22.2	24.2
Mean week 12 value:	35.9	40.6	57.5	58.0	43.4	52.3	23.9	27.7
Estimated effect size, mean (95% CI):	−4.09 (−9.4, 1.21)		−1.56 (−11.2, 8.11)		−8.65 (−15.9, −1.4)		−2.3 (−8.0, 3.5)	
p value:	0.1259		0.7449		0.0214		0.4225	

Calder PC et al J Cachexia Sarcopenia Muscle 2018

Interventional therapy in stable COPD

Surgical and Interventional Therapies in Advanced Emphysema

Figure 4.6



Note: not all therapies are clinically available in all countries. Long term ELVR outcomes or direct comparisons to LVRS are unknown.

Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; ELVR, Endoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017

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Education

1. Information about smoking cessation
2. Correct use of device
3. Recognition of AECOPD
4. Action plans to relieve symptoms and AECOPD
5. Education on when to seek medical help

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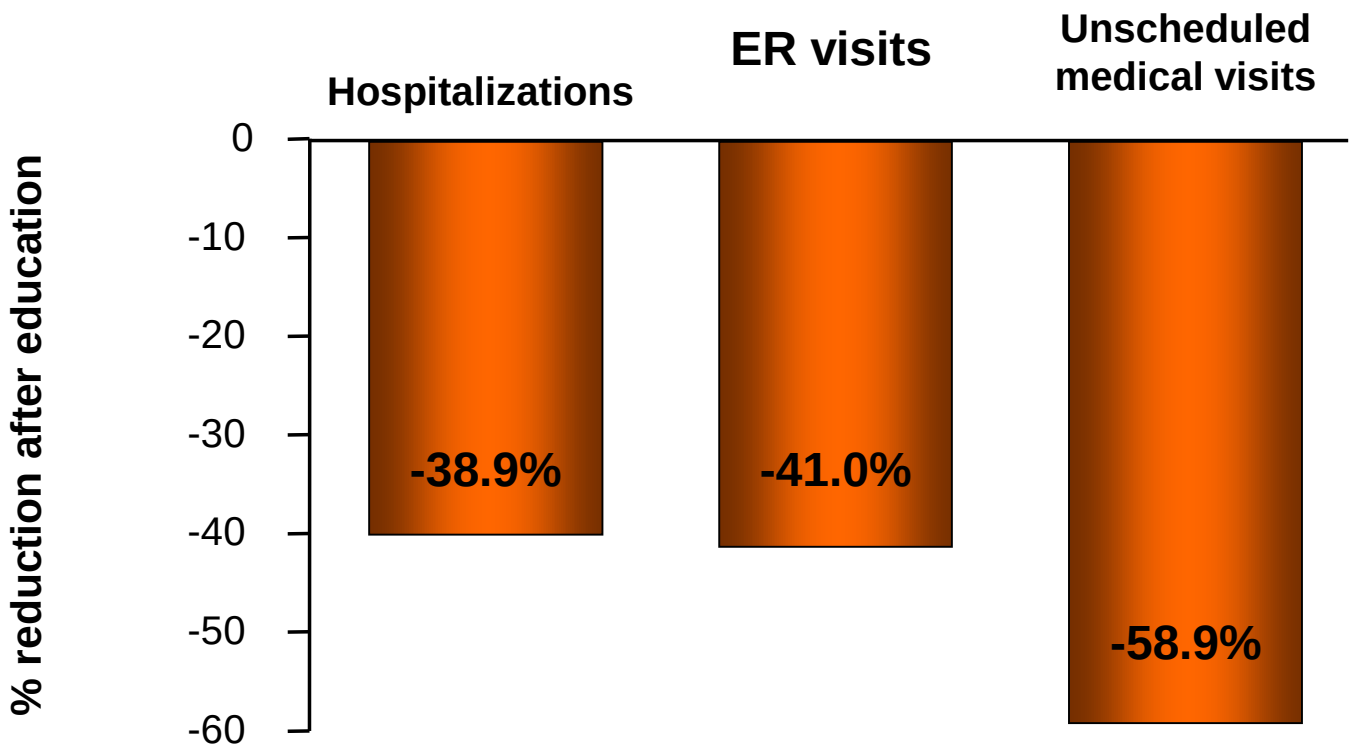
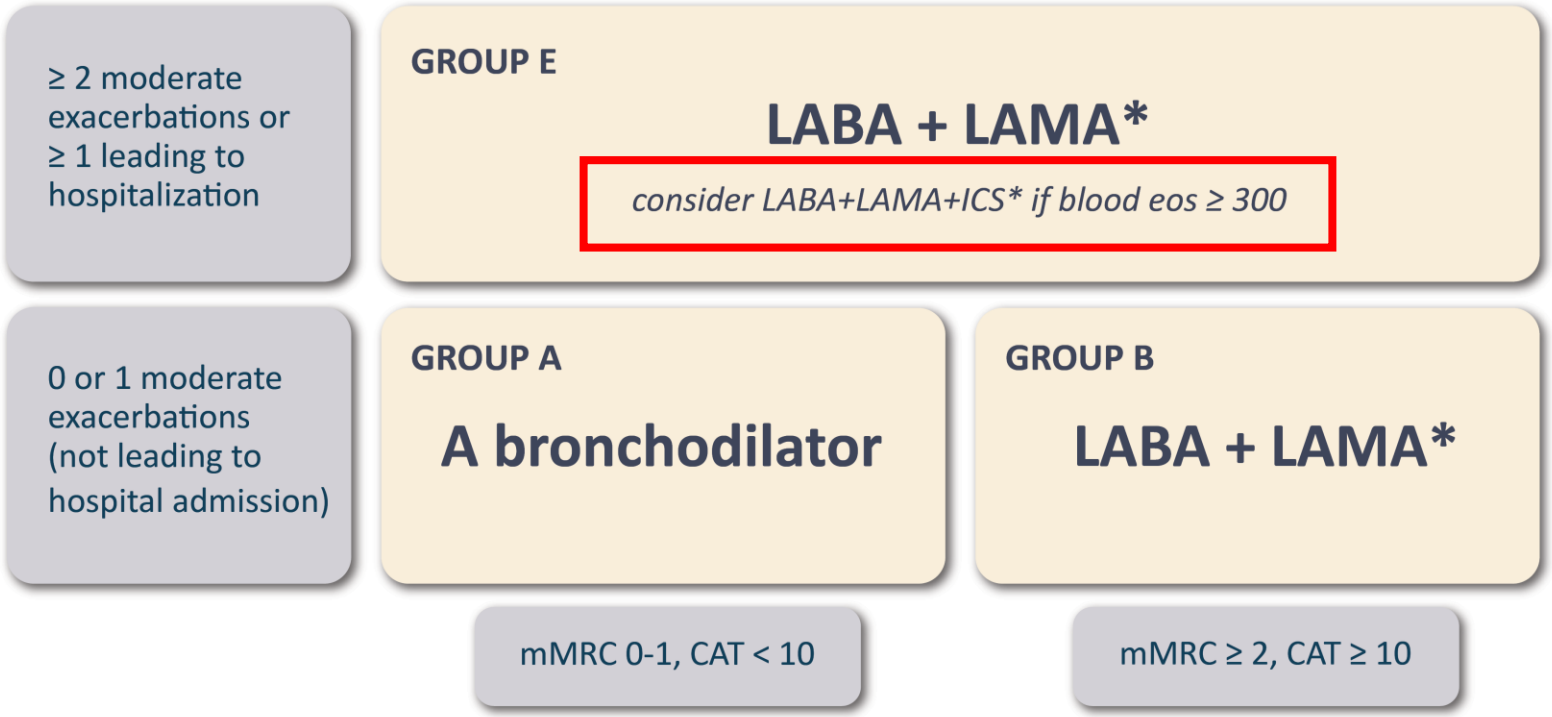


n=191 COPD pts with ≥1 AECOPD in the past year
Education and self-management plan vs. usual care

Bourbeau J, Arch Intern Med 2003

Initial Pharmacological Treatment

Figure 4.2



*single inhaler therapy may be more convenient and effective than multiple inhalers
Exacerbations refers to the number of exacerbations per year

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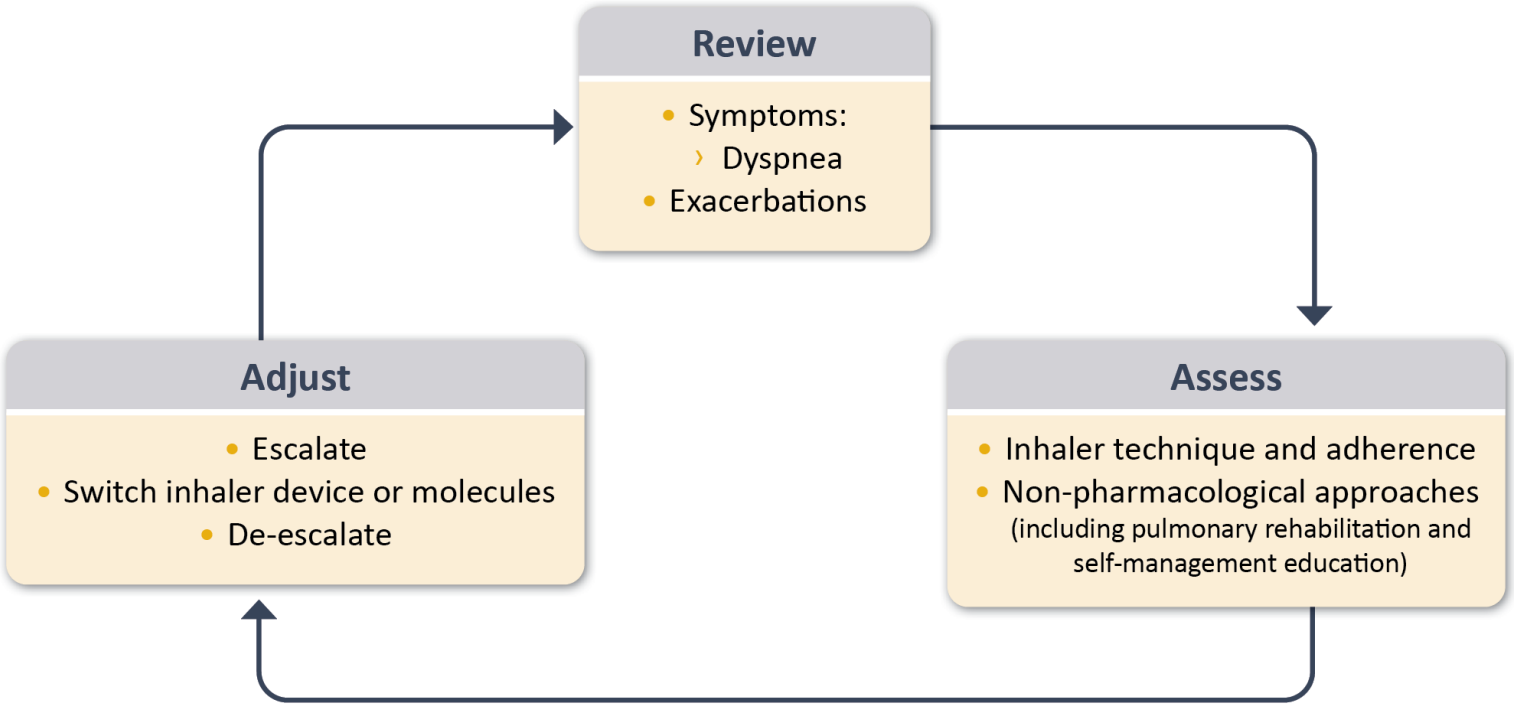
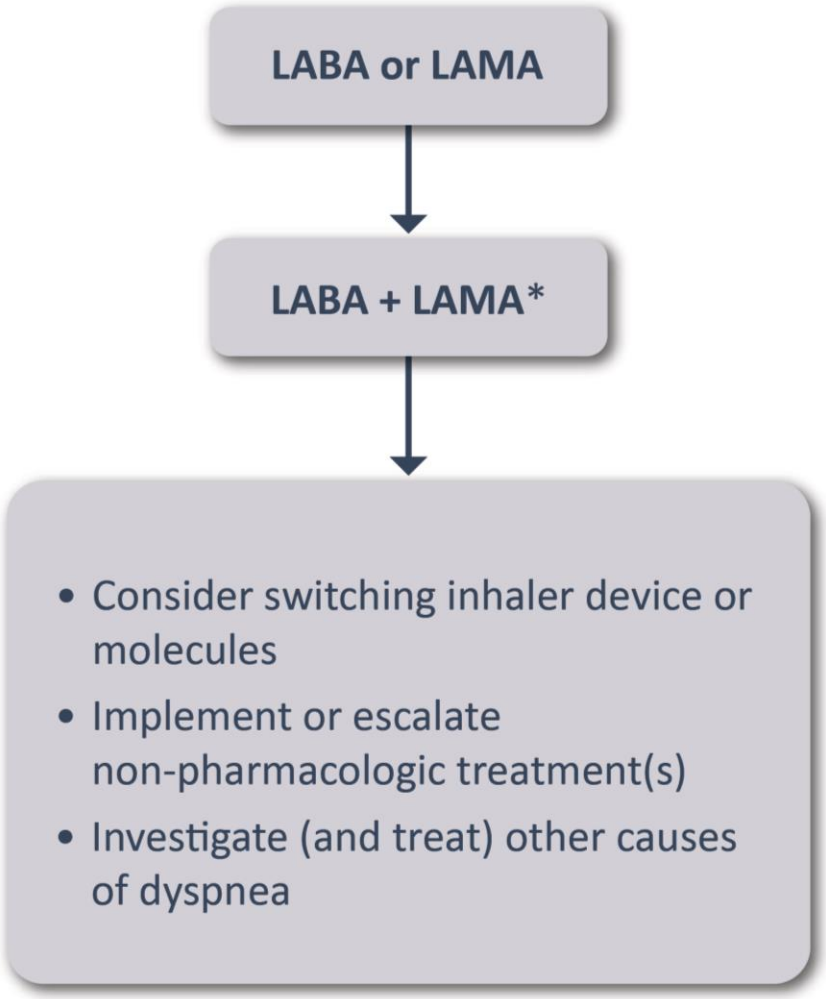
Management Cycle

Figure 4.3

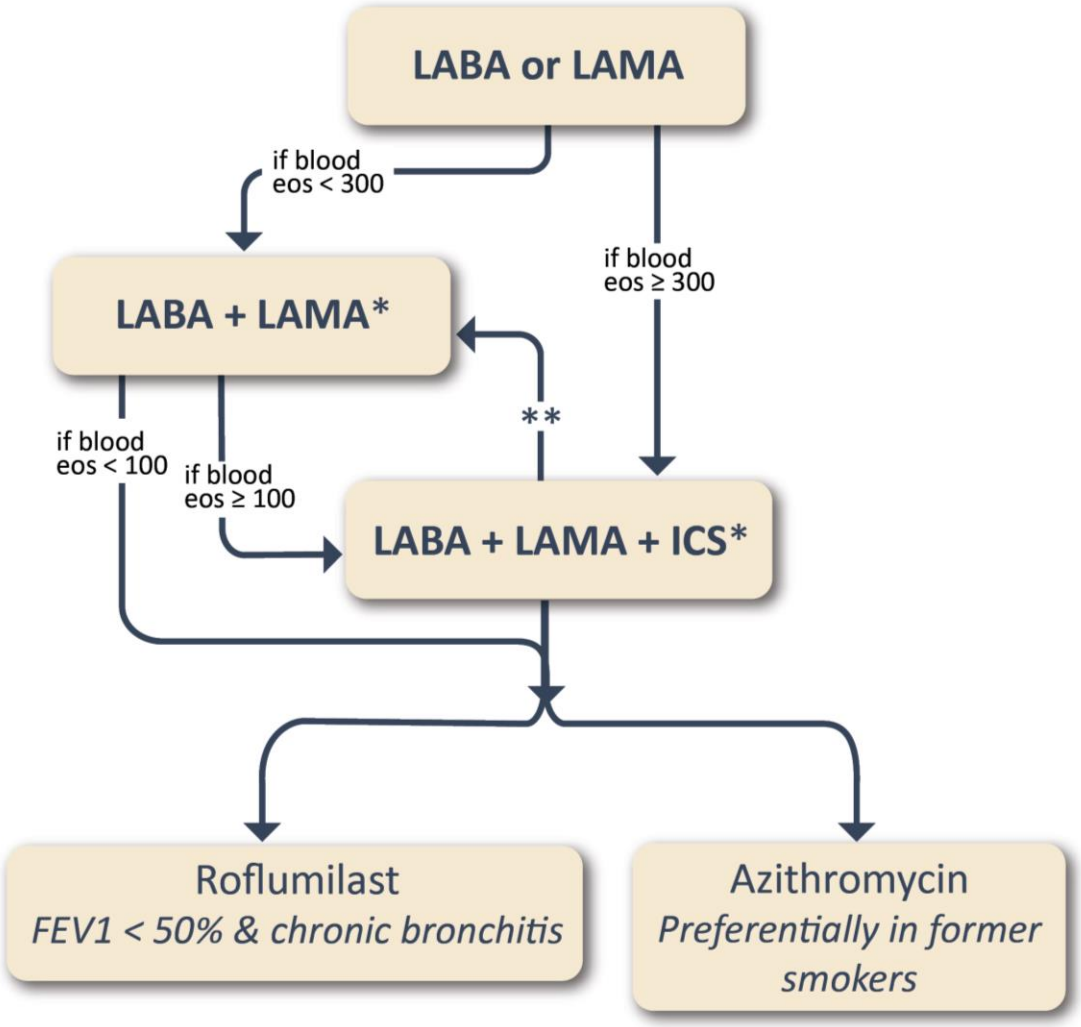


GOLD 2023

DYSPNEA



EXACERBATIONS



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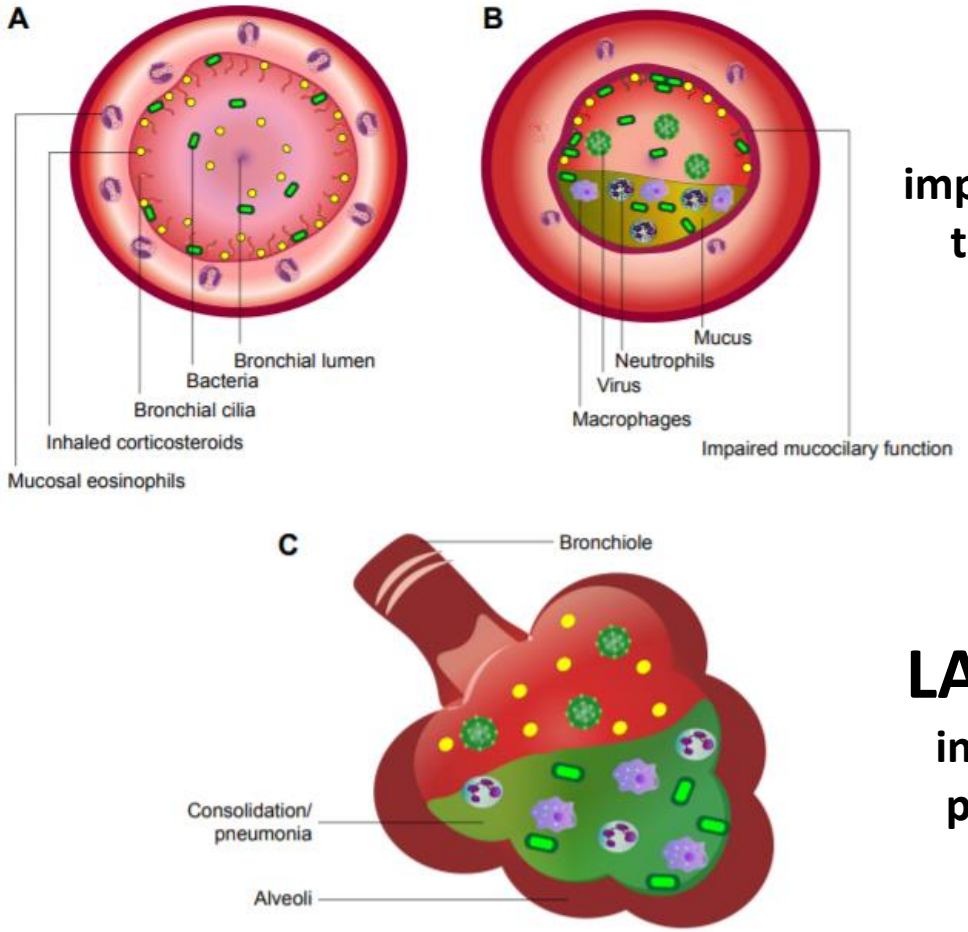
The action of inhaled medication in COPD

ICS: Decrease of AECOPD due to decrease of eosinophilic inflammation

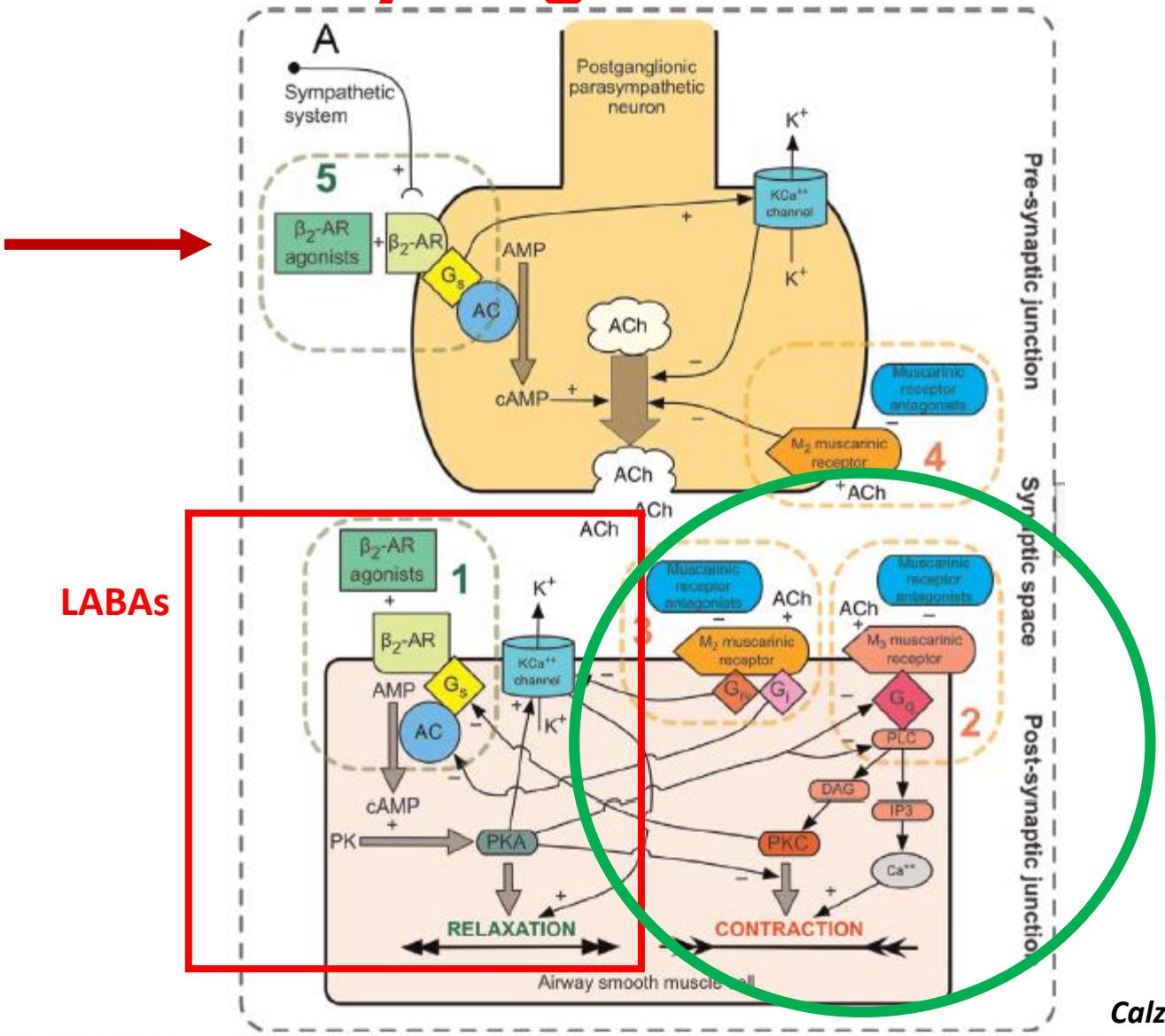


LABA/LAMA: Symptom improvement and decrease of AECOPD through increases in the bronchial diameter

LAMA: anti-inflammatory activity, inhibition of inflammatory cytokine production and decrease of mucus production

Lipworth B et al Int J COPD 2021

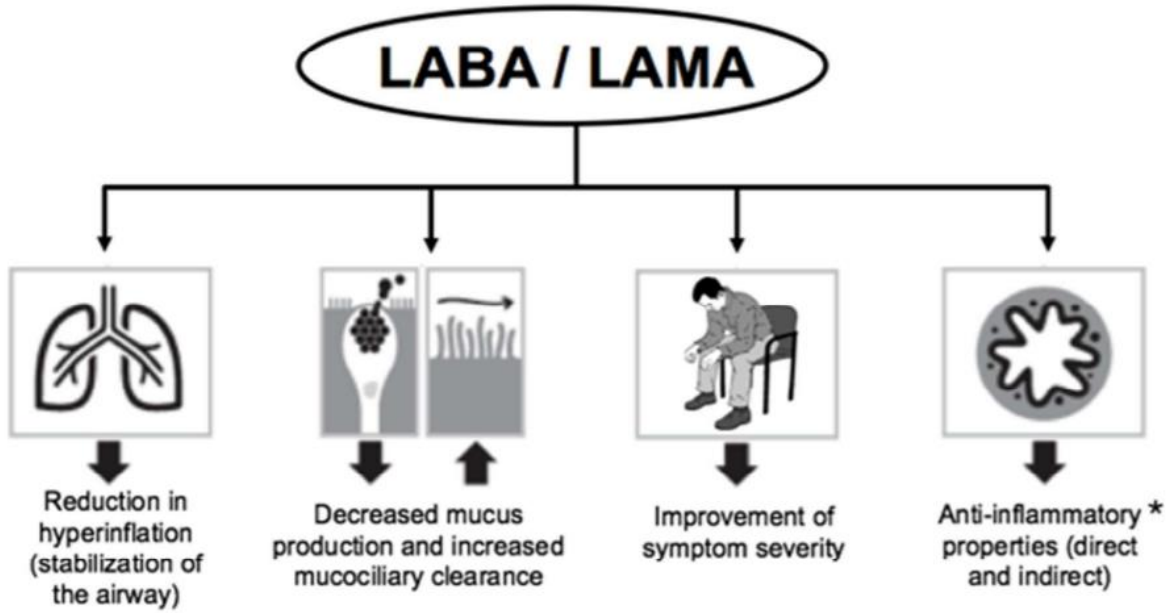
Synergistic effect of LABAs and LAMAs



LABAs

LAMAs

The effect is not only additional but also synergistic



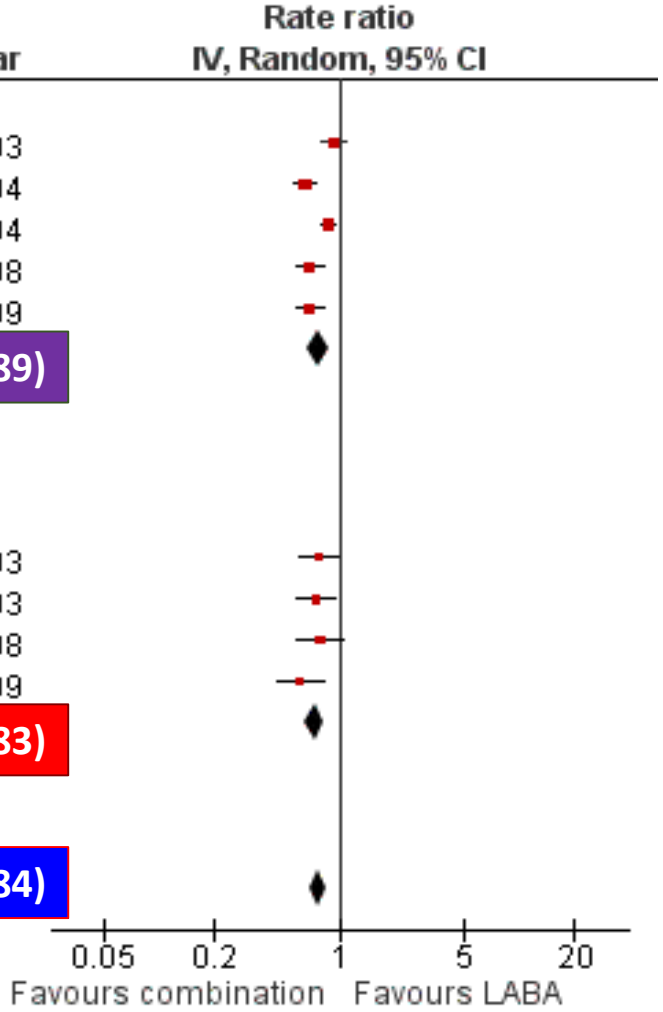
Calzetta L et al EJP 2015

Beeh KM et al AJRCCM 2016

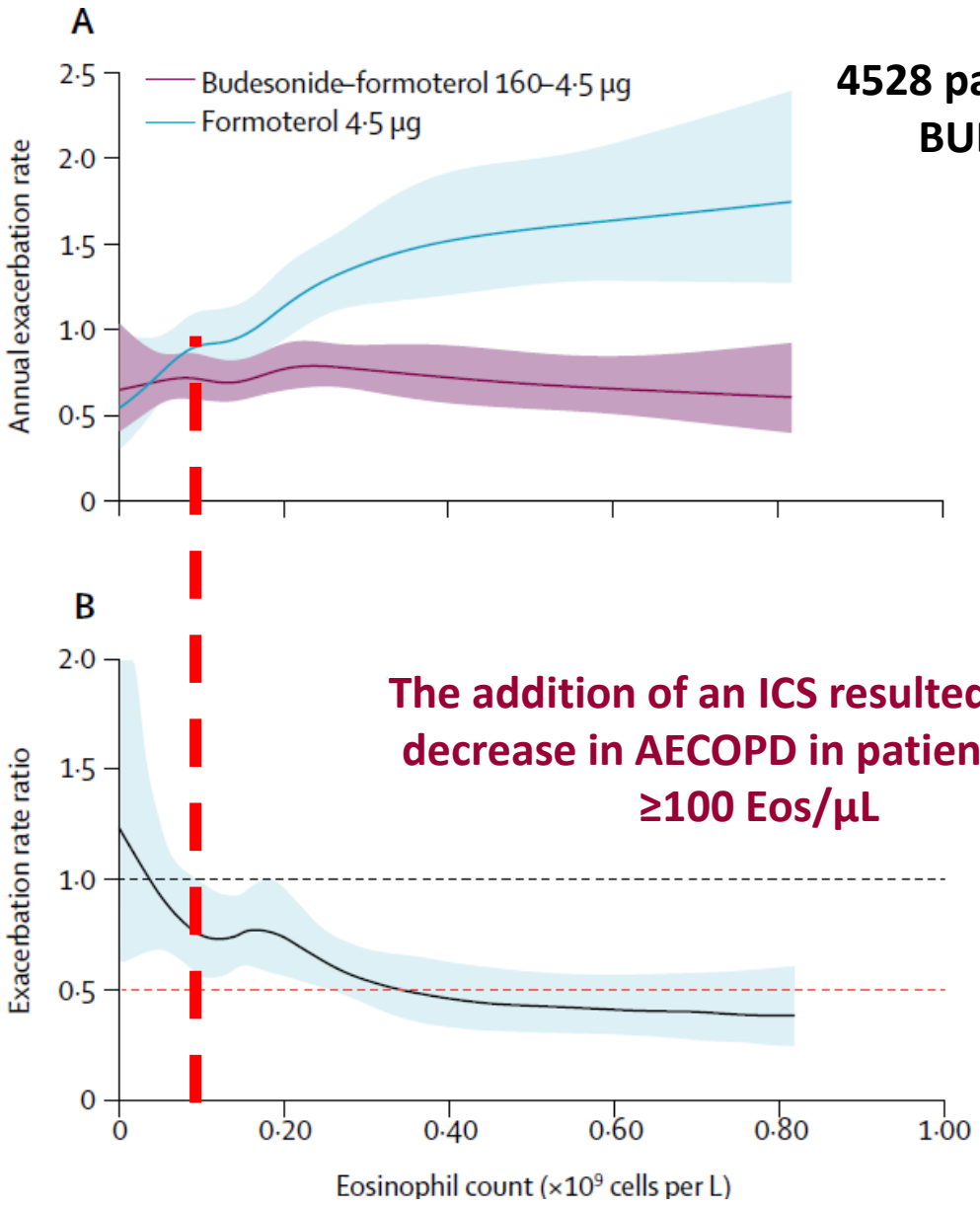
ICS in COPD

LABA/ICS vs. LABA: AECOPD

Study or Subgroup	log[Rate ratio]	SE	Weight	Rate ratio IV, Random, 95% CI	Year
1.1.1 Fluticasone/salmeterol					
TRISTAN	-0.07	0.0734	13.4%	0.93 [0.81, 1.08]	2003
Kardos 2007	-0.4308	0.073	13.5%	0.65 [0.56, 0.75]	2004
TORCH	-0.13	0.044	16.0%	0.88 [0.81, 0.96]	2004
Ferguson 2008	-0.3638	0.091	11.8%	0.70 [0.58, 0.83]	2008
Anzueto 2009	-0.3624	0.091	11.8%	0.70 [0.58, 0.83]	2009
Subtotal (95% CI)			**66.6%**	**HR 0.77 (0.66 to 0.89)**	
Heterogeneity: Tau² = 0.02; Chi² = 21.64, df = 4 (P = 0.0002);					
Test for overall effect: Z = 3.56 (P = 0.0004)					
1.1.2 Budesonide/formoterol					
Szafranski 2003	-0.26	0.125	9.1%	0.77 [0.60, 0.99]	2003
Calverley 2003	-0.294	0.12	9.4%	0.75 [0.59, 0.94]	2003
Tashkin 2008	-0.2357	0.15	7.5%	0.79 [0.59, 1.06]	2008
Rennard 2009	-0.4943	0.15	7.5%	0.61 [0.45, 0.82]	2009
Subtotal (95% CI)			**33.4%**	**HR 0.73 (0.64 to 0.83)**	
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² =					
Test for overall effect: Z = 4.66 (P < 0.00001)					
Total (95% CI)			**100.0%**	**HR 0.76 (0.68 to 0.84)**	
Heterogeneity: Tau² = 0.02; Chi² = 25.18, df = 8 (P = 0.001); I² = 68%					
Test for overall effect: Z = 5.22 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%					



Nannini LJ, Cochrane Library 2012



4528 patients from 3 RCT
BUD/FOR vs FOR

The addition of an ICS resulted in 25% decrease in AECOPD in patients with ≥100 Eos/µL

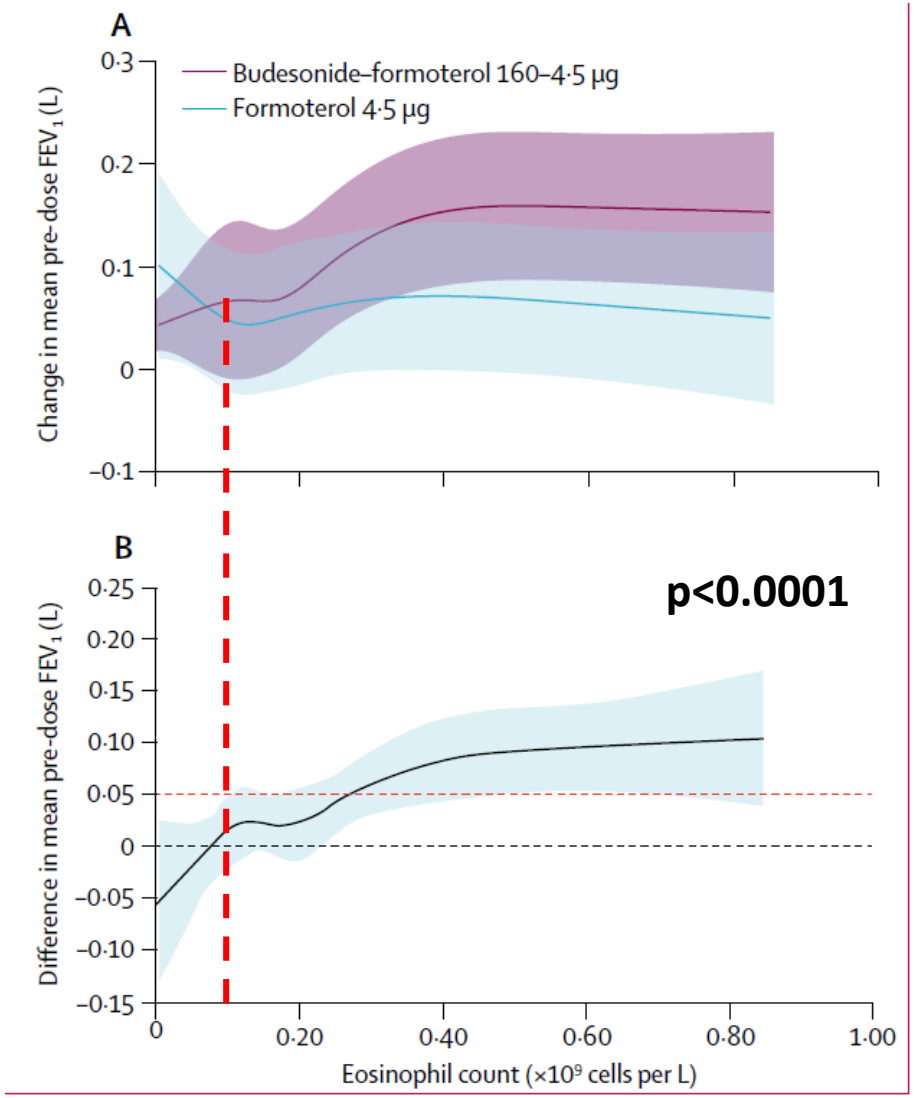
	Mean peripheral blood eosinophil count (× 10^9 cells per L)
Non-significant 25% increase to 22% reduction (rate ratio 0·78–1·25)	0·01–0·09
25% reduction* (rate ratio 0·75)	0·10–0·19
26–50% reduction (rate ratio 0·50–0·74)	0·20–0·34
51–60% reduction (rate ratio 0·40–0·49)	0·35–0·63

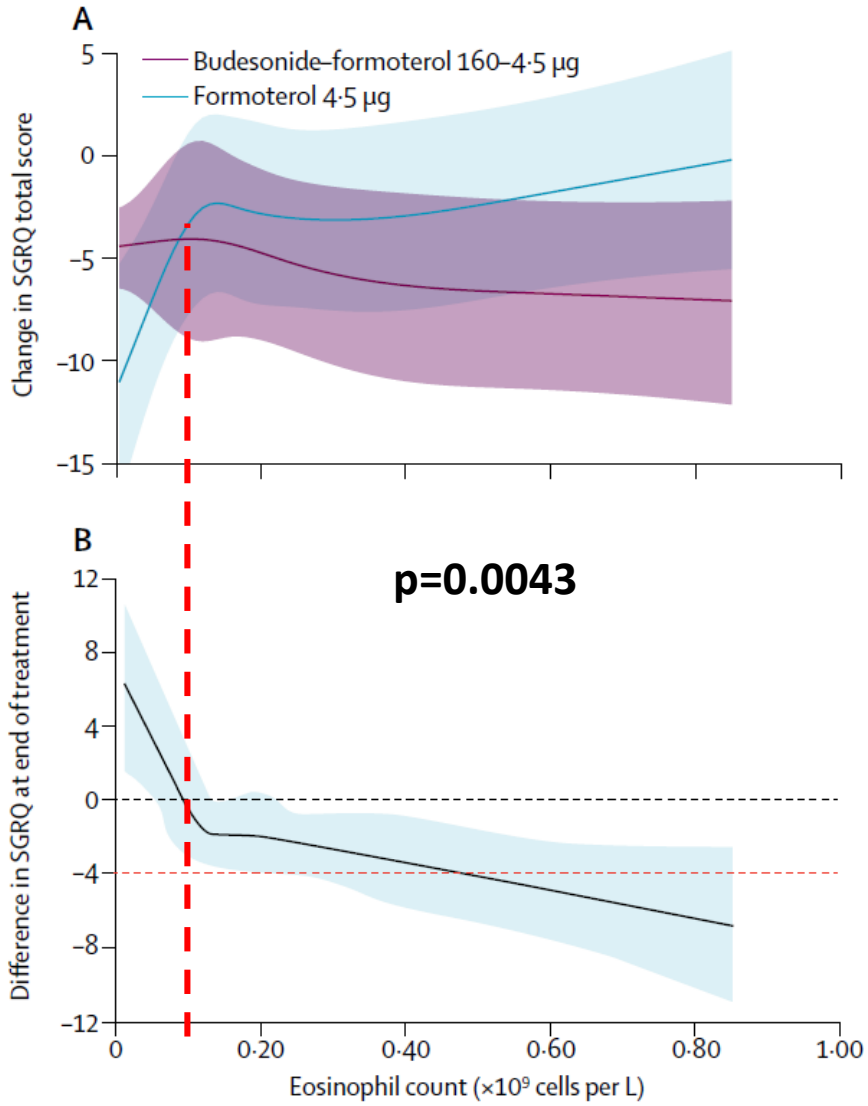
Budesonide–formoterol 160–4·5 µg was administered by pressurised metered-dose inhaler (two inhalations). Formoterol 4·5 µg was administered by dry powder inhaler (two inhalations). *Mean reduction for $0{\cdot}10 \times 10^9$–$0{\cdot}19 \times 10^9$ cells per L.

Table 2: Exacerbation rate reduction treatment effect of budesonide–formoterol 160–4·5 µg as compared with formoterol 4·5 µg, according to eosinophil count

Bafadhel M et al Lancet Resp Med 2018

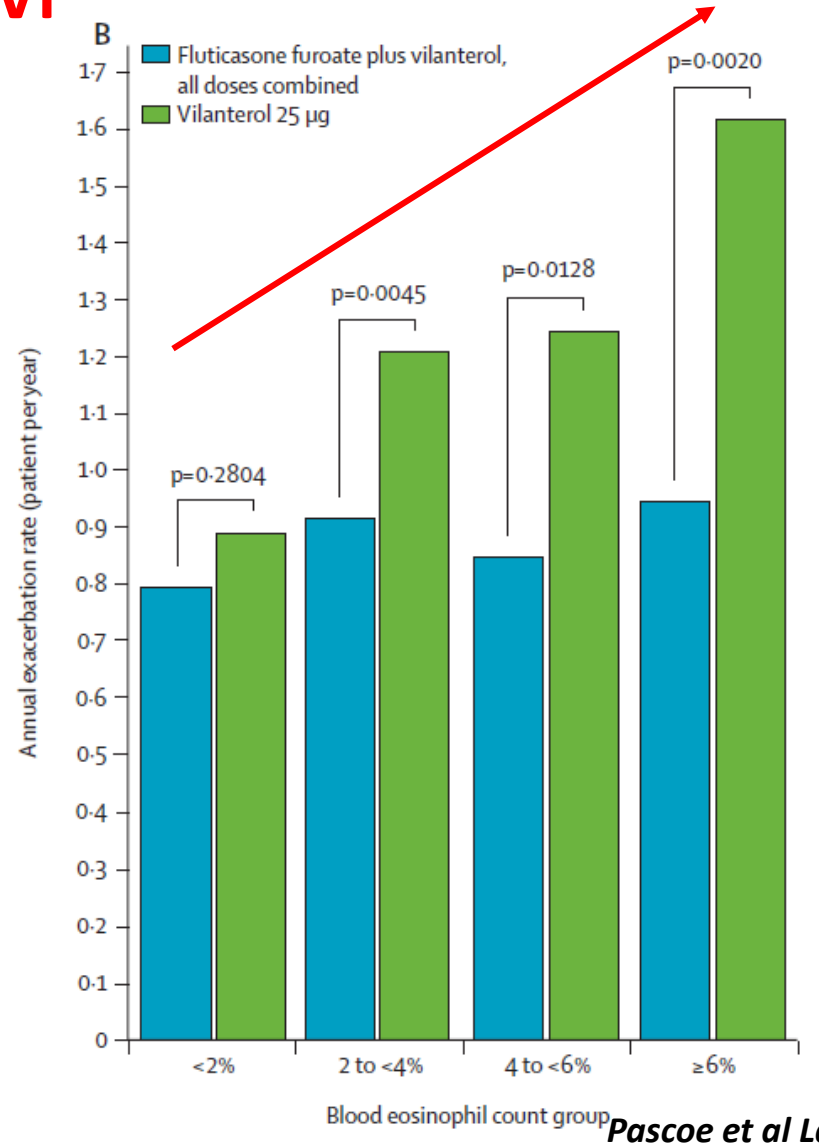
4528 patients from 3 RCT
BUD/FOR vs FOR





Bafadhel M et al Lancet Resp Med 2018

Patients with blood Eos ≥2% had lower risk for AECOPD when treated with FF/Vi vs Vi



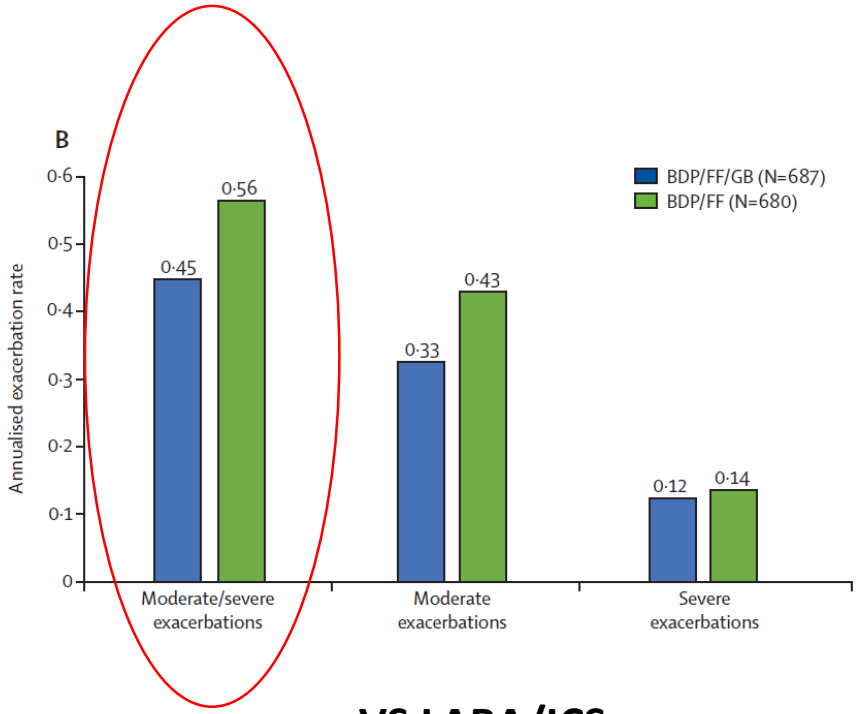
Pascoe et al Lancet Resp Med 2015

Triple therapy and decrease of AECOPD

- FEV_1< 50% pred
- 1 moderate/severe AECOPD during the last year
- CAT score ≥10

TRILOGY

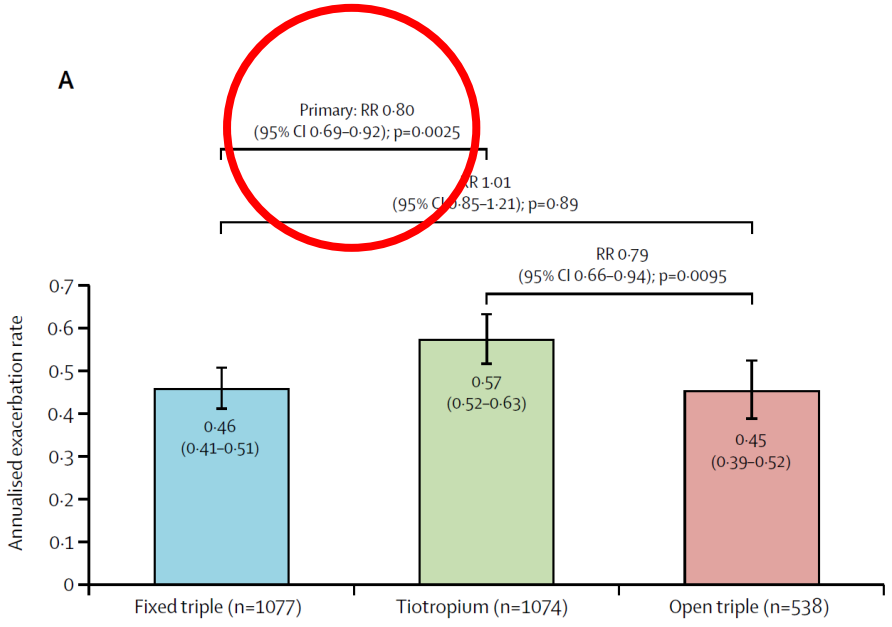
-23%



VS LABA/ICS

TRINITY

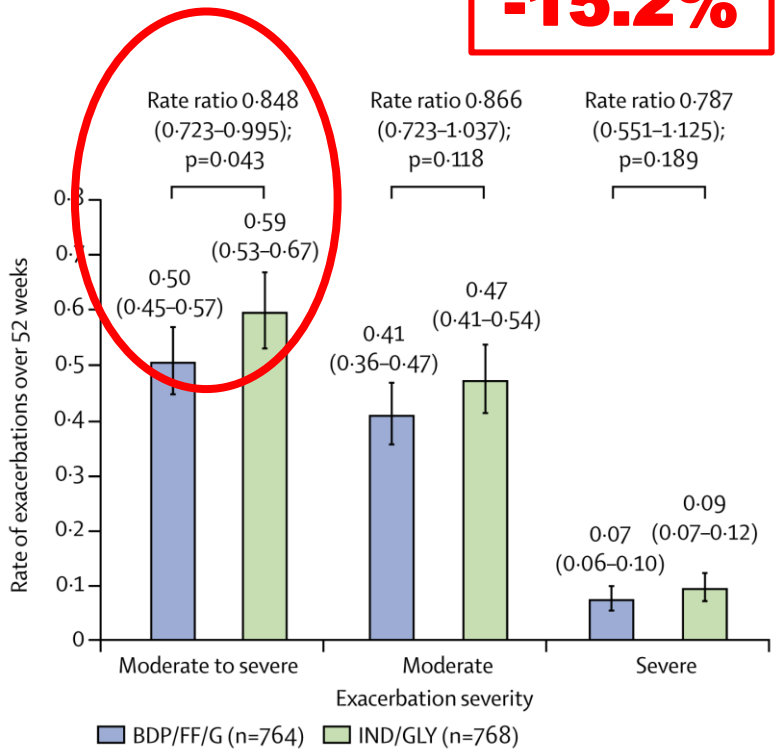
-20%



VS LAMA

TRIBUTE

-15.2%

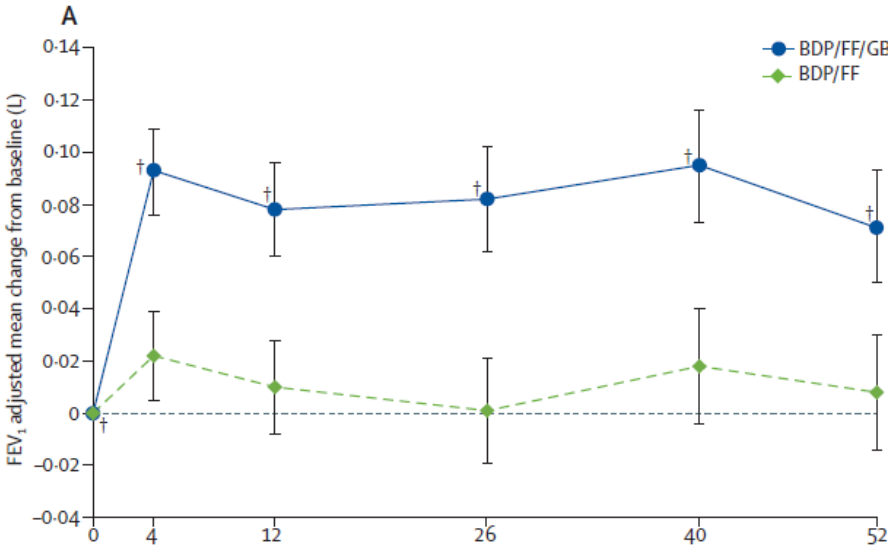


VS LABA/LAMA

Singh D, et al. Lancet 2016
Vestbo J, et al. Lancet 2017
Papi A, et al. Lancet 2018

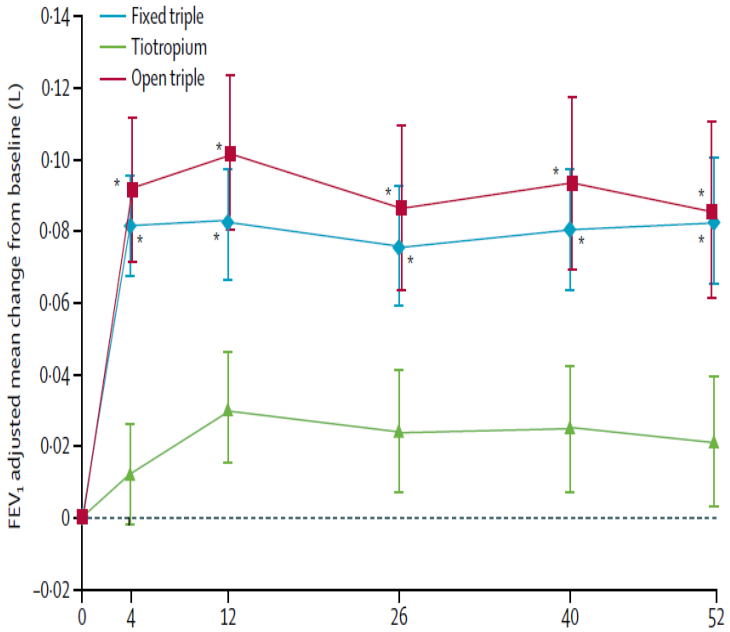
Triple therapy and respiratory function improvement

TRILOGY



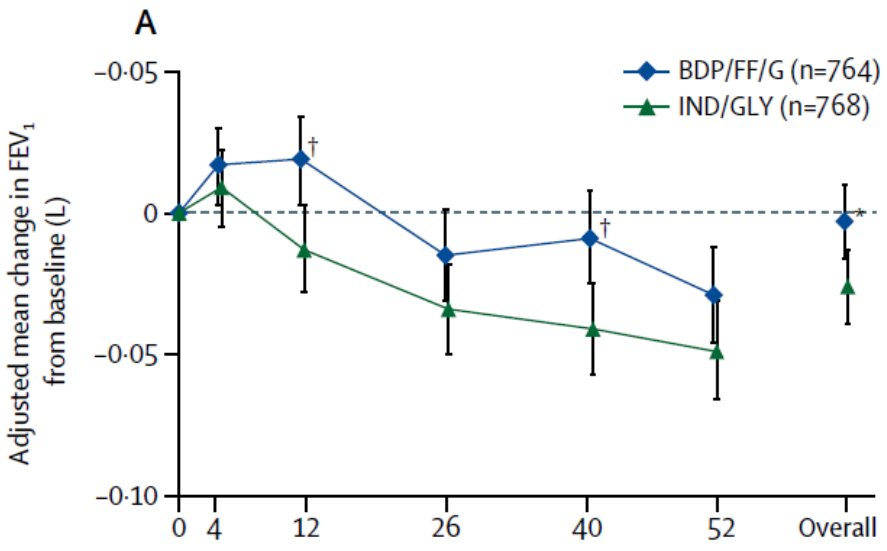
VS LABA/ICS

TRINITY



VS LAMA

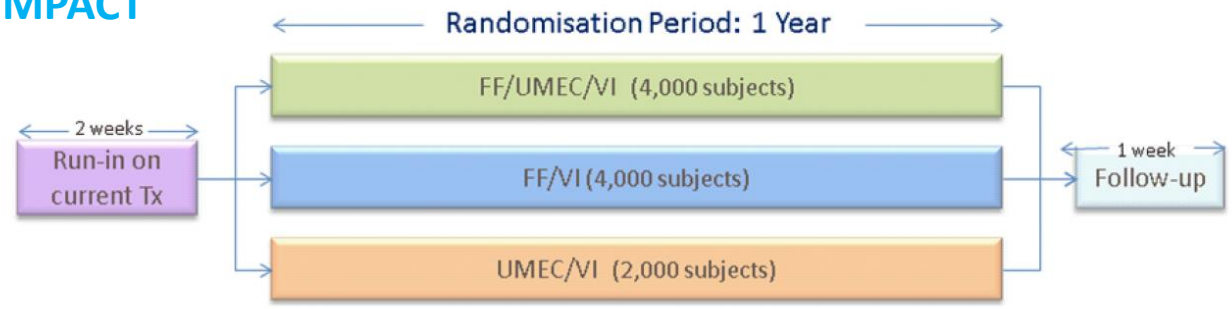
TRIBUTE



VS LABA/LAMA

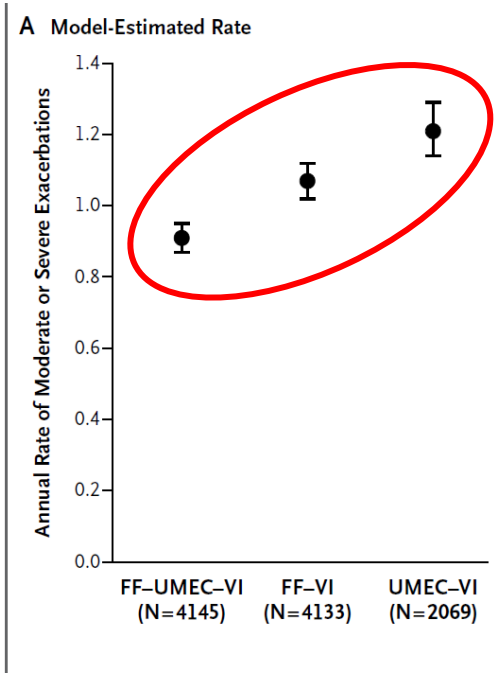
Singh D, et al. Lancet 2016
Vestbo J, et al. Lancet 2017
Papi A, et al. Lancet 2018

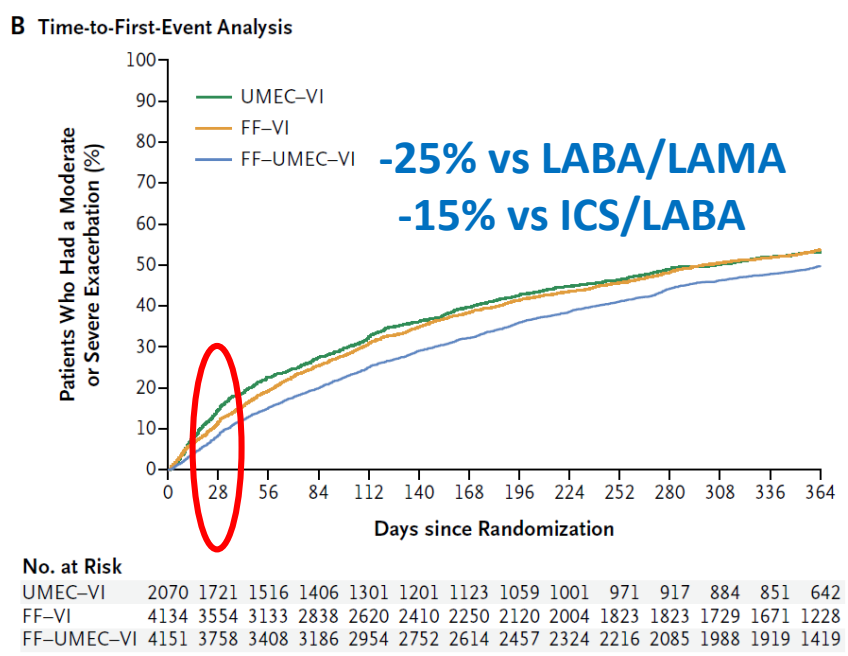
IMPACT



Screen follow-up	V2	V3	V4	V5	V6	V7 +7days
2-week run-in	0	4wk	16wk	28wk	40wk	52wk

Randomization

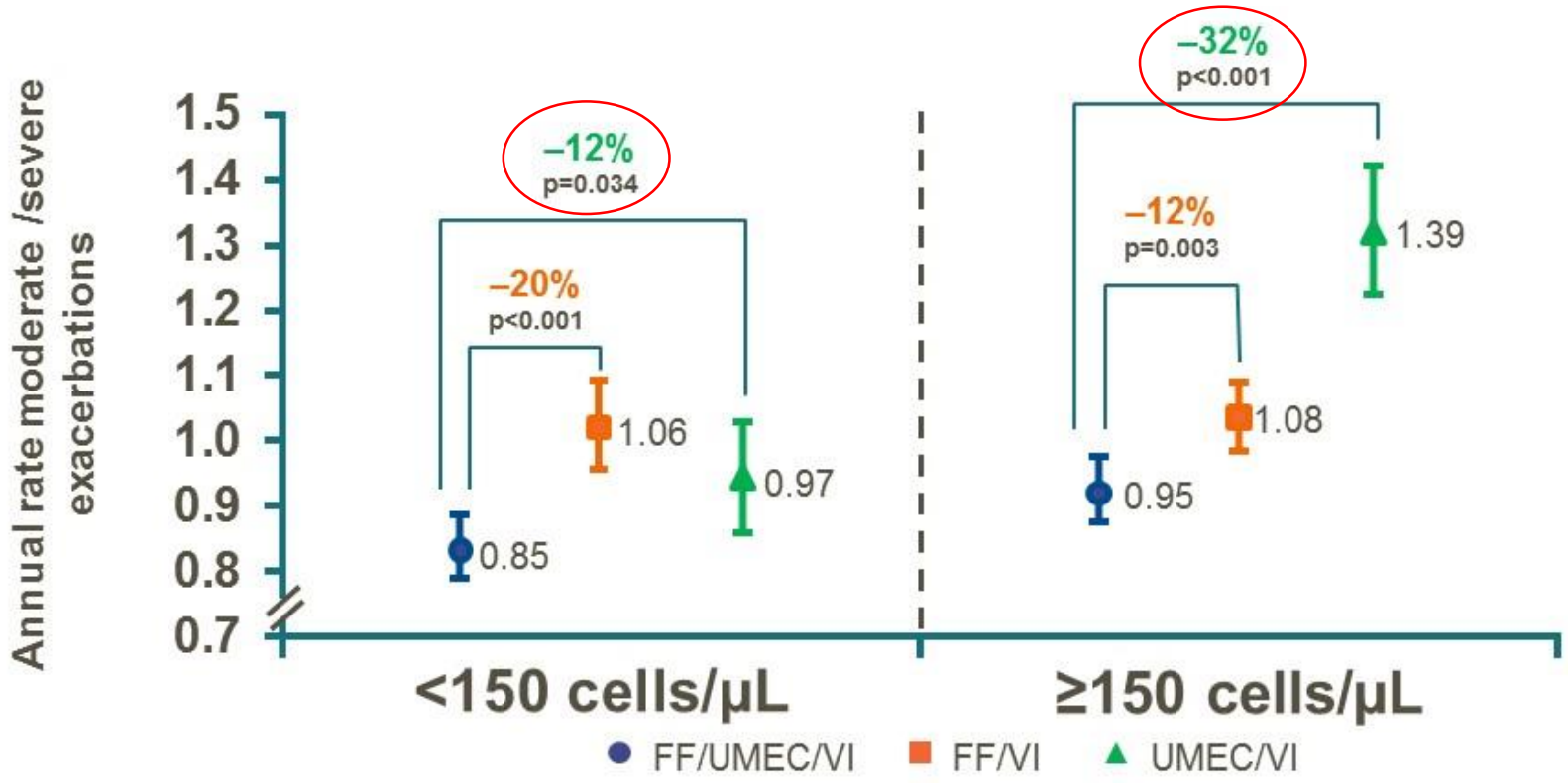




No. at Risk

UMEC–VI	2070	1721	1516	1406	1301	1201	1123	1059	1001	971	917	884	851	642
FF–VI	4134	3554	3133	2838	2620	2410	2250	2120	2004	1823	1823	1729	1671	1228
FF–UMEC–VI	4151	3758	3408	3186	2954	2752	2614	2457	2324	2216	2085	1988	1919	1419

Lipson DA et al. NEJM 2018

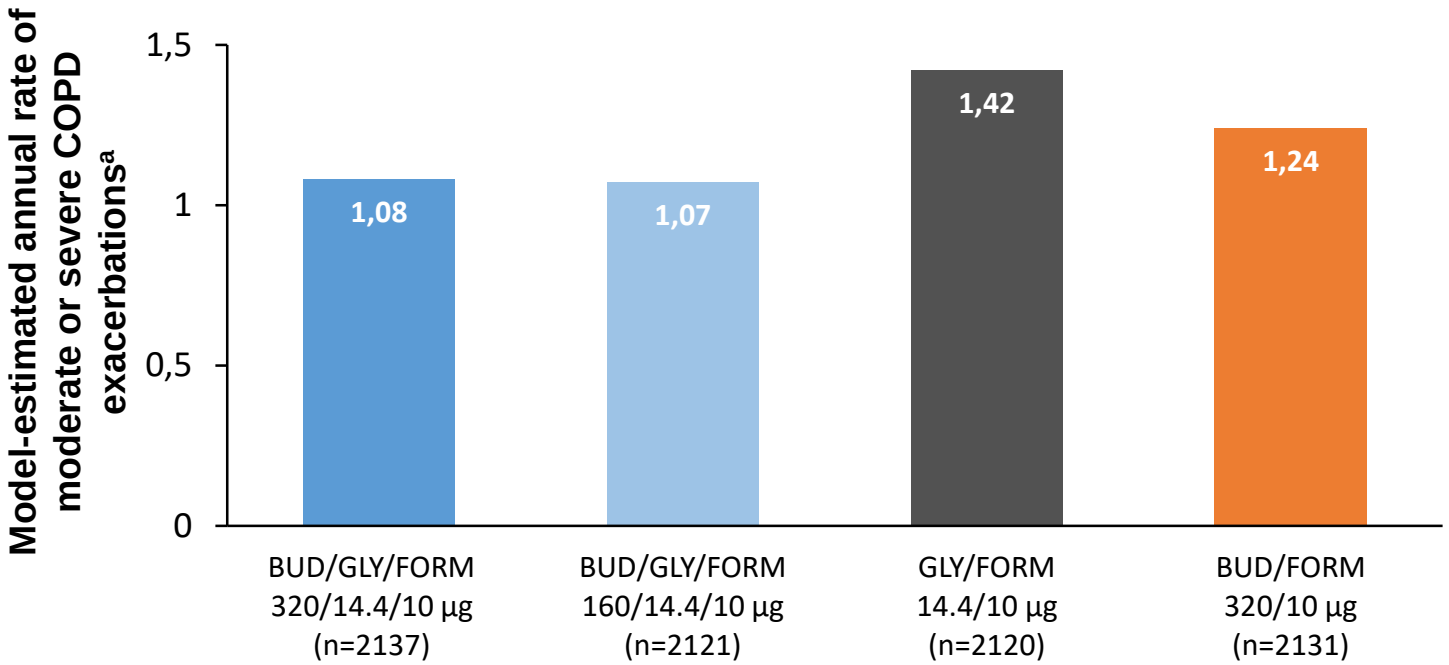


Mortality

-42% vs LABA/LAMA

Lipson DA et al. NEJM 2018

Triple therapy decreases moderate/severe AECOPD



BUD/GLY/FORM 320/14.4/10 µg
Έδειξε:

24%

Decrease in annual rate of AECOPD vs. LAMA/LABA

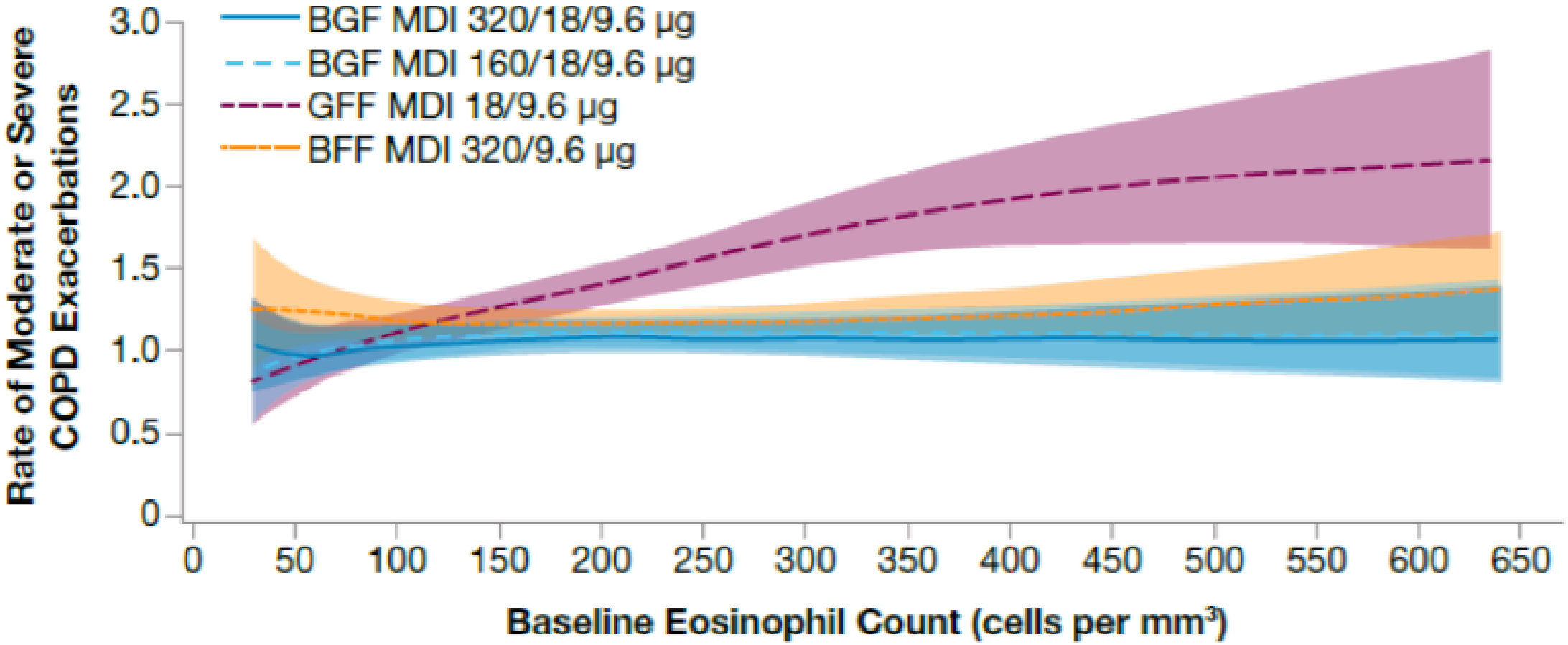
13%

Decrease in the annual rate of AECOPD vs. ICS/LABA

320 µg	**RR: 0.76 95% CI: 0.69 to 0.83 p<0.001 NNT[b] (95% CI)=3 (3 to 5)[2]**	**RR: 0.87 95% CI: 0.79 to 0.95 p=0.003 NNT[b] (95% CI)=7 (4 to 18)[2]**
160 µg	RR: 0.75 95% CI: 0.69 to 0.83 p<0.001	RR: 0.86 95% CI: 0.79 to 0.95 p=0.002

Rabe KF et al NEJM 2020

Decrease in AECOPD according to the number of blood eosinophils



Rabe KF et al NEJM 2020

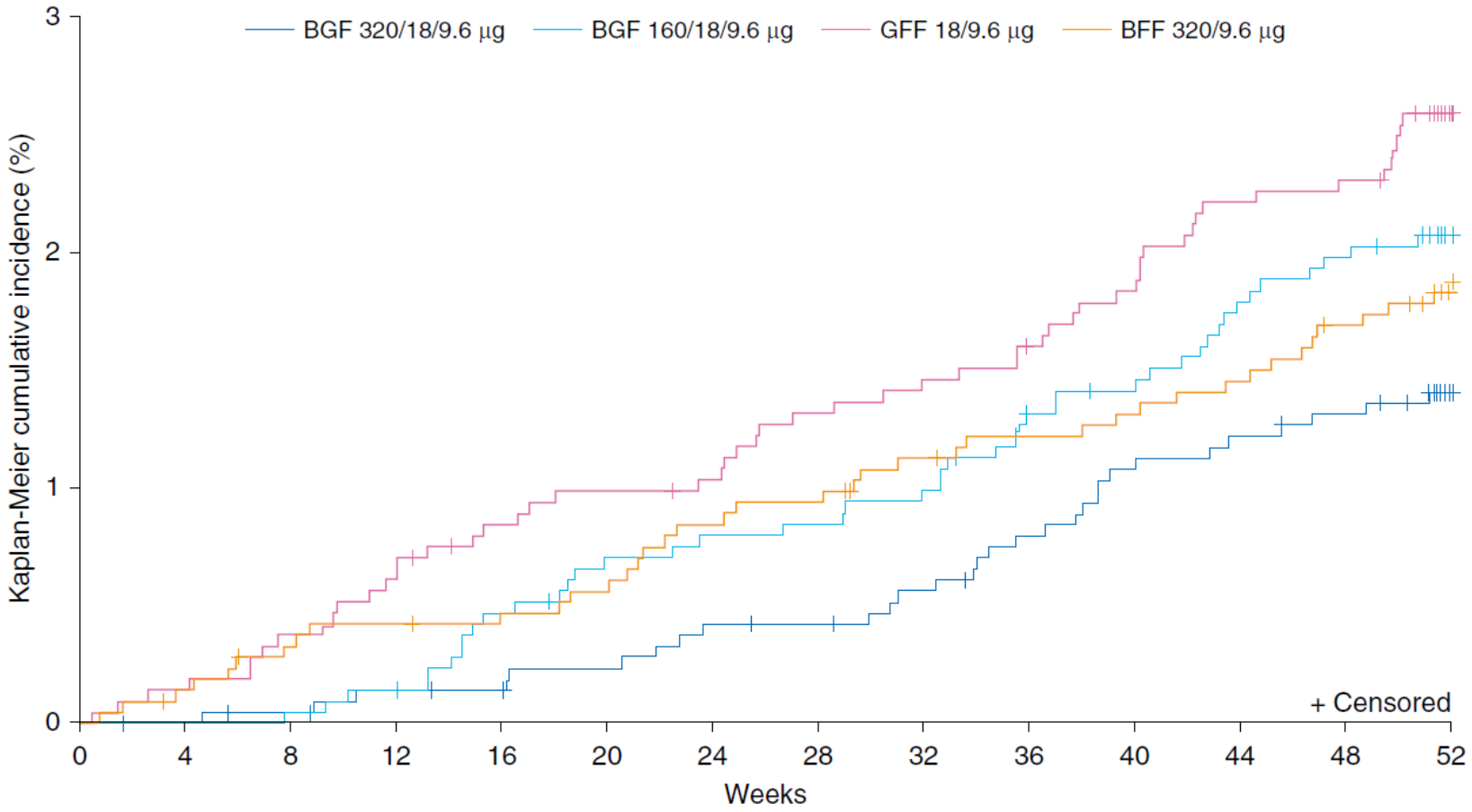
Triple therapy BUD 320/GLY/FORM *decreases the risk of death (all cause mortality) vs. LAMA/LABA*

49% decrease vs LABA/LAMA

HR: 0.51; 95% CI: 0.33 -0.80;
unadjusted p=0.0035

NNT = 80 vs. LAMA/LABA
(95% CI: 58 to 198)

28% decrease vs. ICS/LABA
HR: 0.72; 95% CI: 0.44 to 1.16; p=0.1721



Martinez J. M et al AJRCCM 2021

Adverse effects of ICS

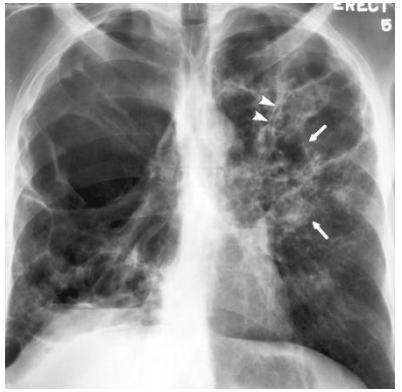
Oral candidiasis

Hoarseness

Bruises

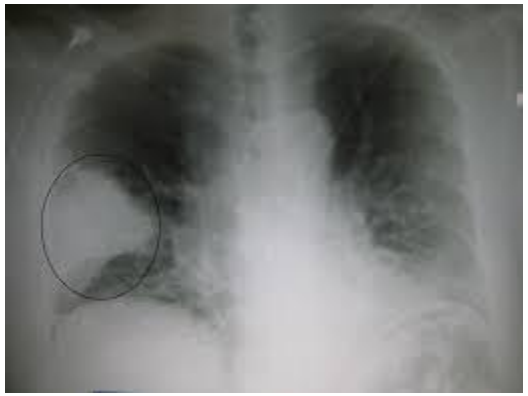
Osteoporosis

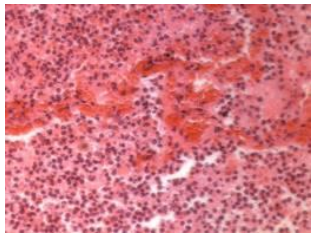
Cataract

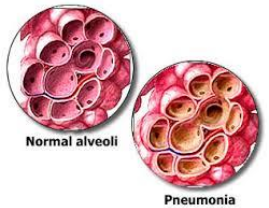


Mycobacterial infection

Pneumonia

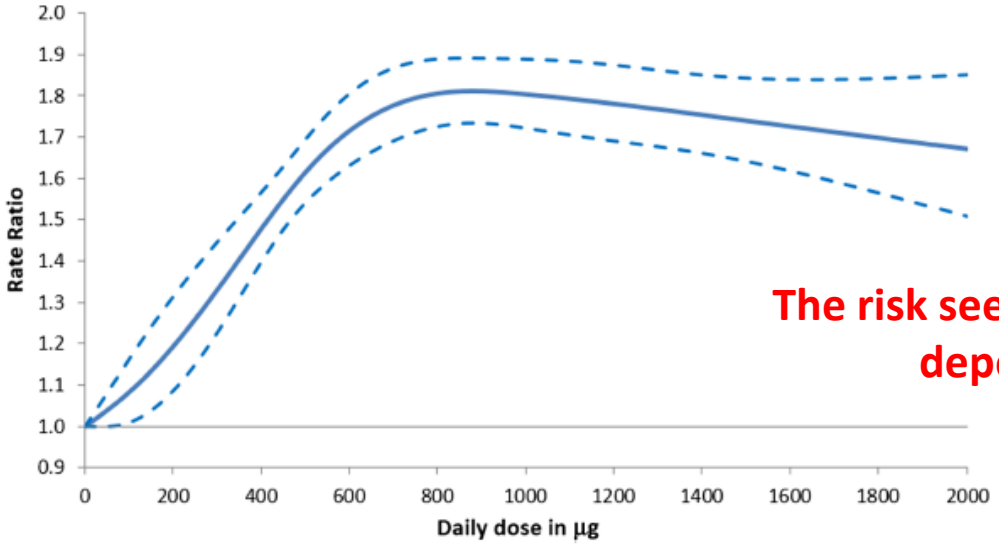






Inhaled Corticosteroids Cause Pneumonia . . . or Do They?

Woodhead M, AJRCCM 2007 (Editorial)



The risk seems to be dose dependent

Suissa S et al Thorax 2013

Rik factors for pneumonia in COPD patients receiving ICS

- Current smokers
- ≥ 55 years of age
- Frequent exacerbations
- Previous history of pneumonia
- BMI<25kg/m^2
- Severe dyspnea (mMRC)
- Severe airway obstruction

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Factors to Consider when Initiating ICS Treatment

Figure 3.1

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

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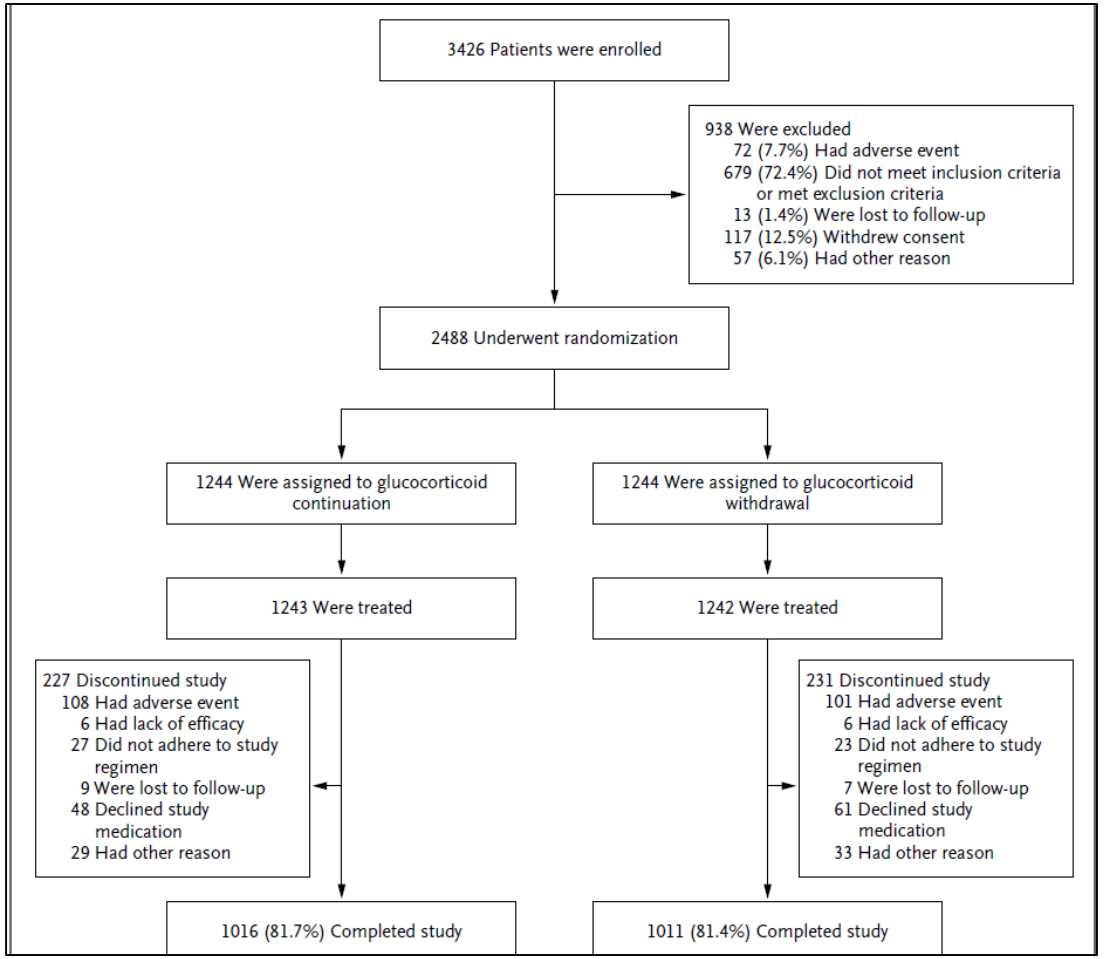
Can we discontinue the use of ICS?



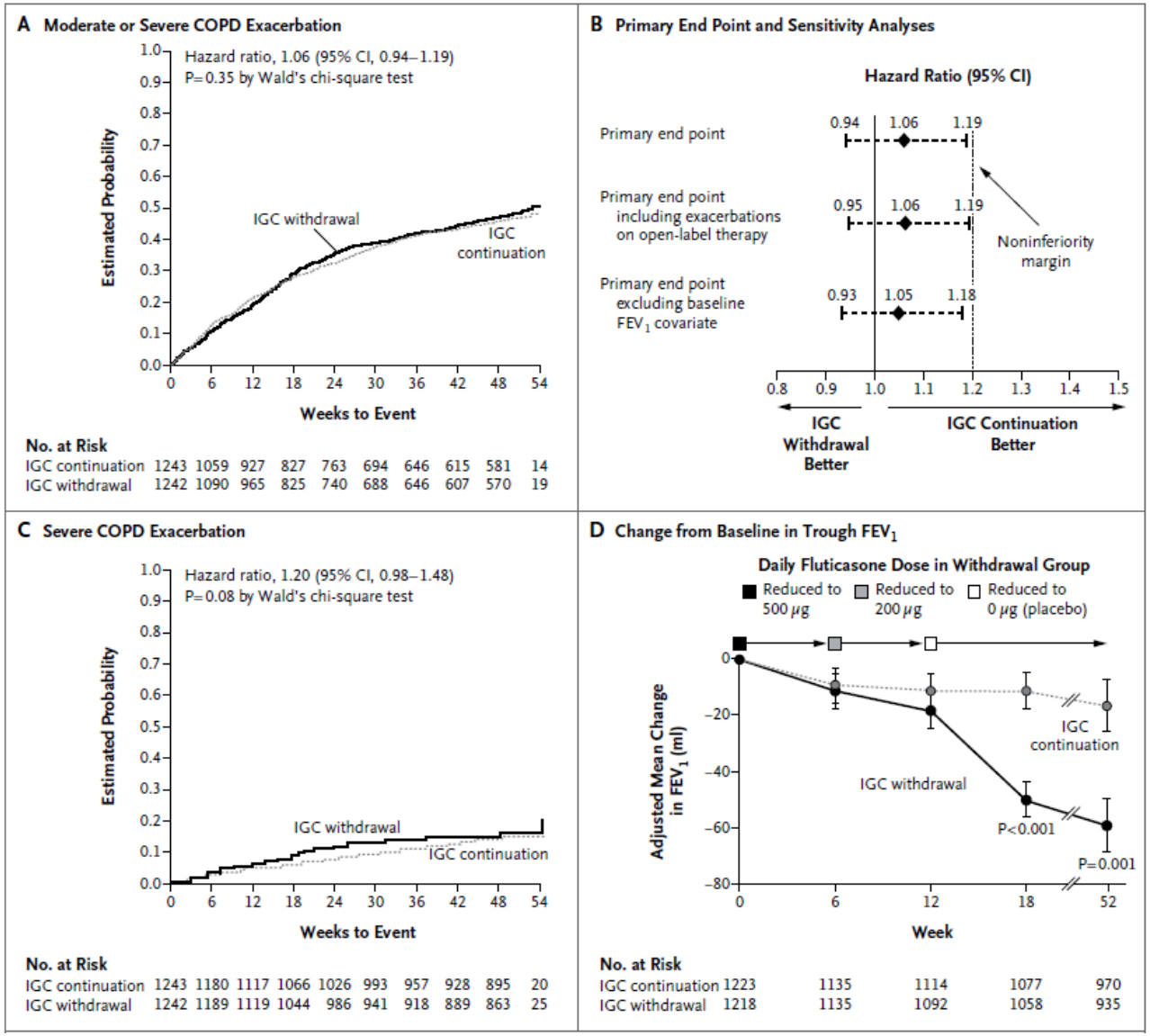
Inclusion criteria

- **Outpatients of either sex**
- **aged ≥ 40 years**
- **diagnosis of COPD (post bronchodilator FEV1 < 50% of predicted (and FEV1 / FVC < 70%)**
- **documented history of exacerbations**
- **smoking history >10pys**

6week run in period
Treatment:
Tiotropium 18μg x 1
Salmeterol 50μg x 2
Fluticasone Propionate 500μg x 2

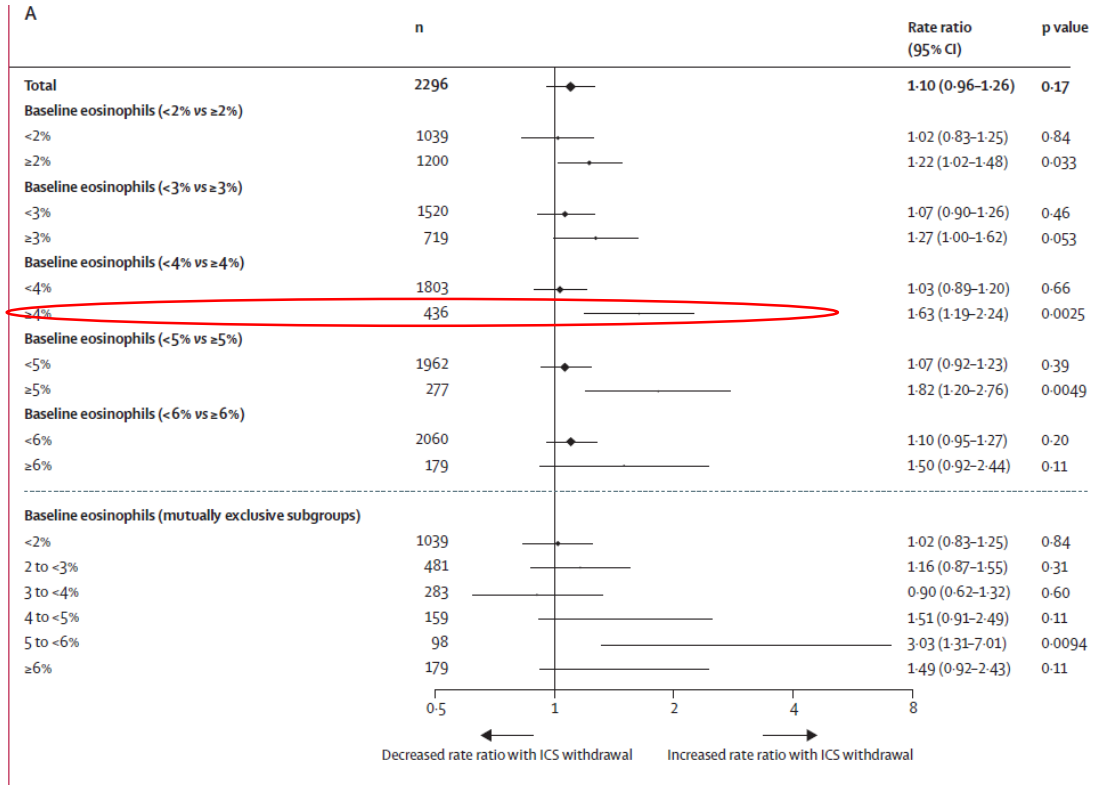
Magnussen H et al NEJM 2014

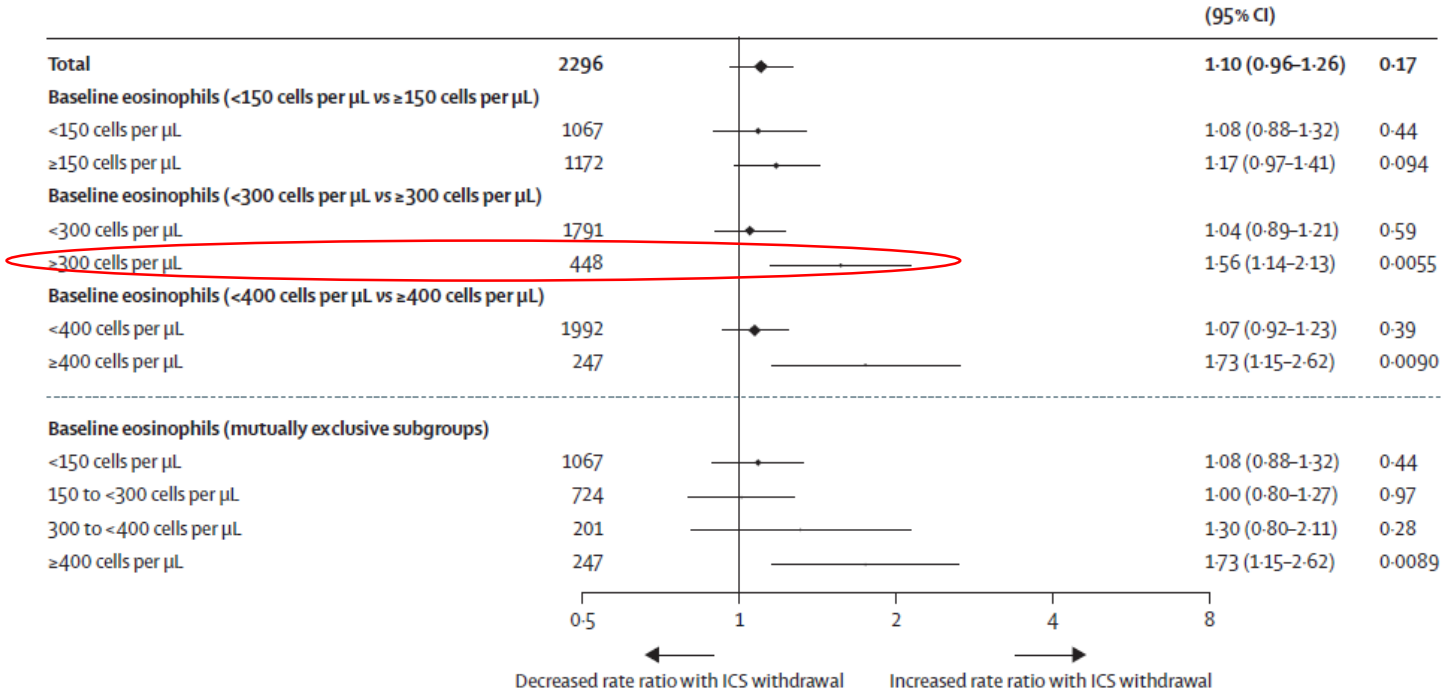
Can we discontinue the use of ICS?



Margnussen H et al NEJM 2014

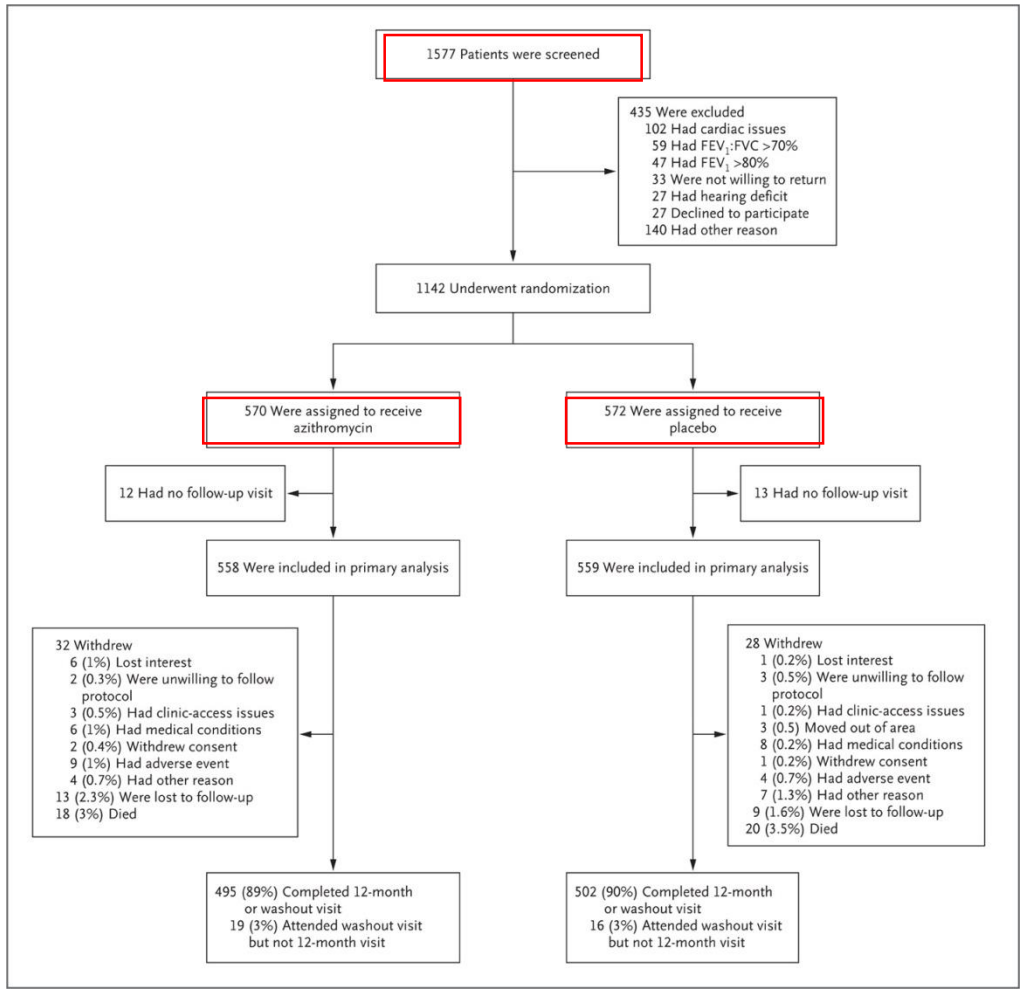
Blood Eos is a potential biomarker of response to ICS in COPD

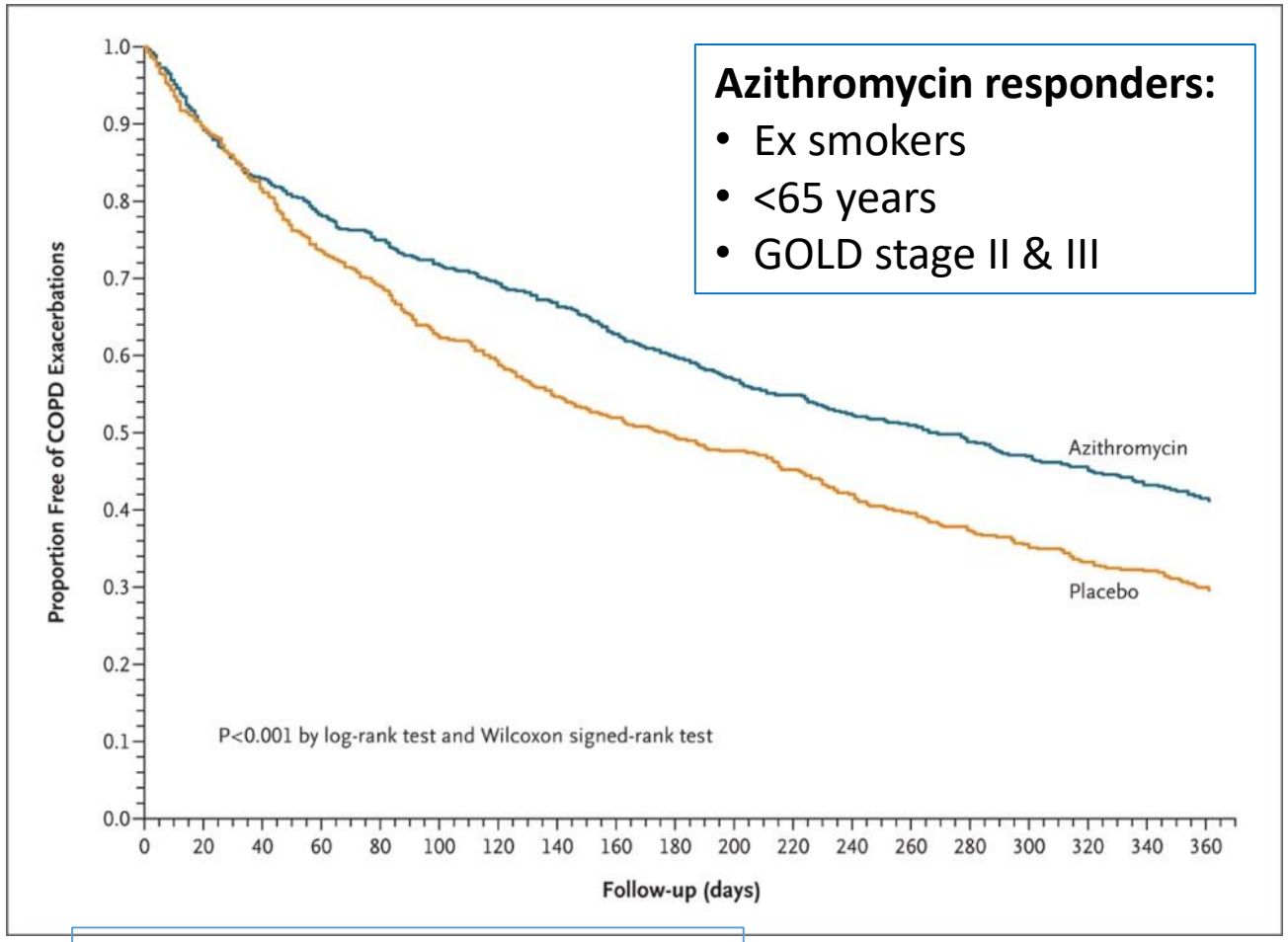




Watz et al Lancet Resp Med 2016

Azithromycin in COPD





Azithromycin responders:

- Ex smokers
- <65 years
- GOLD stage II & III

Adverse effects

Hearing problems
Increase of bacterial resistance
Increase of QTc

Albert RK et al. N Engl J Med 2011

The effect of macrolides in AECOPD

Respiratory Medicine (2013) xx, 1–12

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Preventing COPD exacerbations with macrolides: A review and budget impact analysis

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[b] Respiratory Division, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

Received 22 June 2012; accepted 24 December 2012

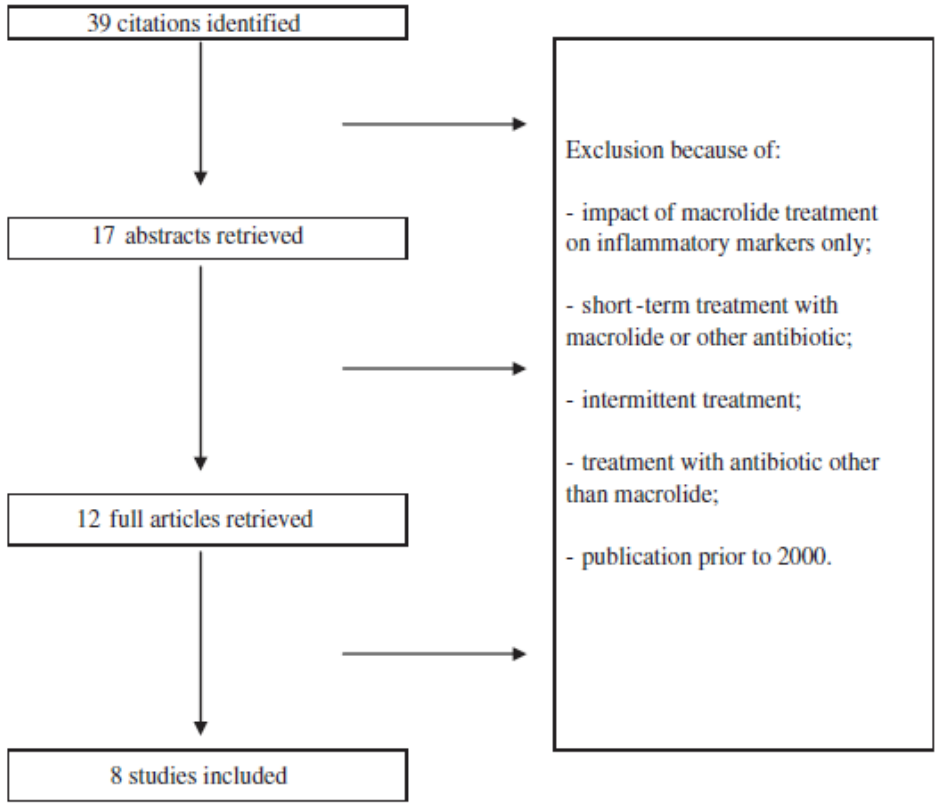


Figure 1 Flow chart of literature search.

Erythromycin	**(3 studies)**
Azithomycin	**(3 studies)**
Clarythomycin	**(2 studies)**

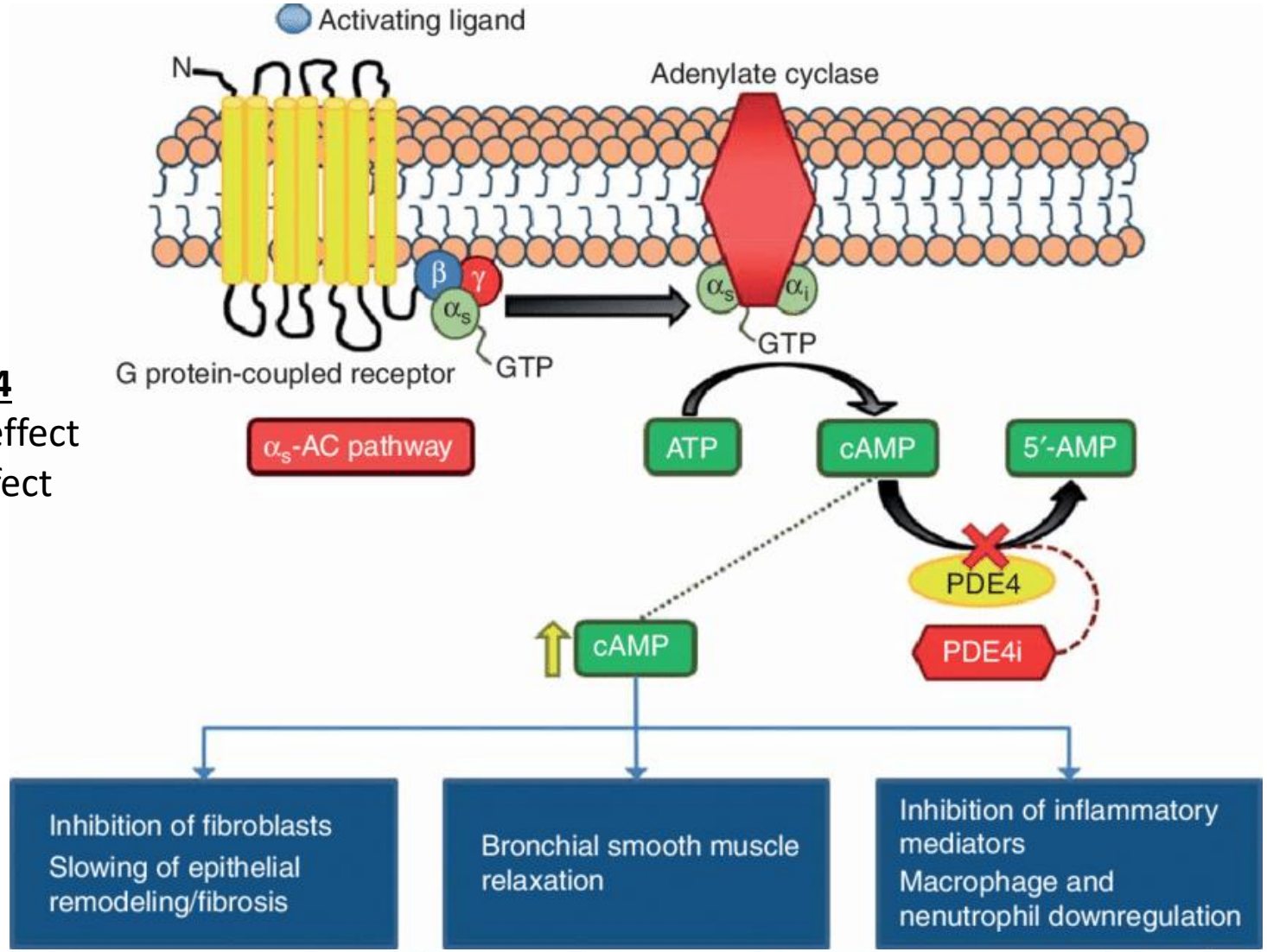
The use of macrolides in COPD patients decreases AECOPD and the health care cost

Simoens S et al Resp Med 2013

PDE4 in COPD

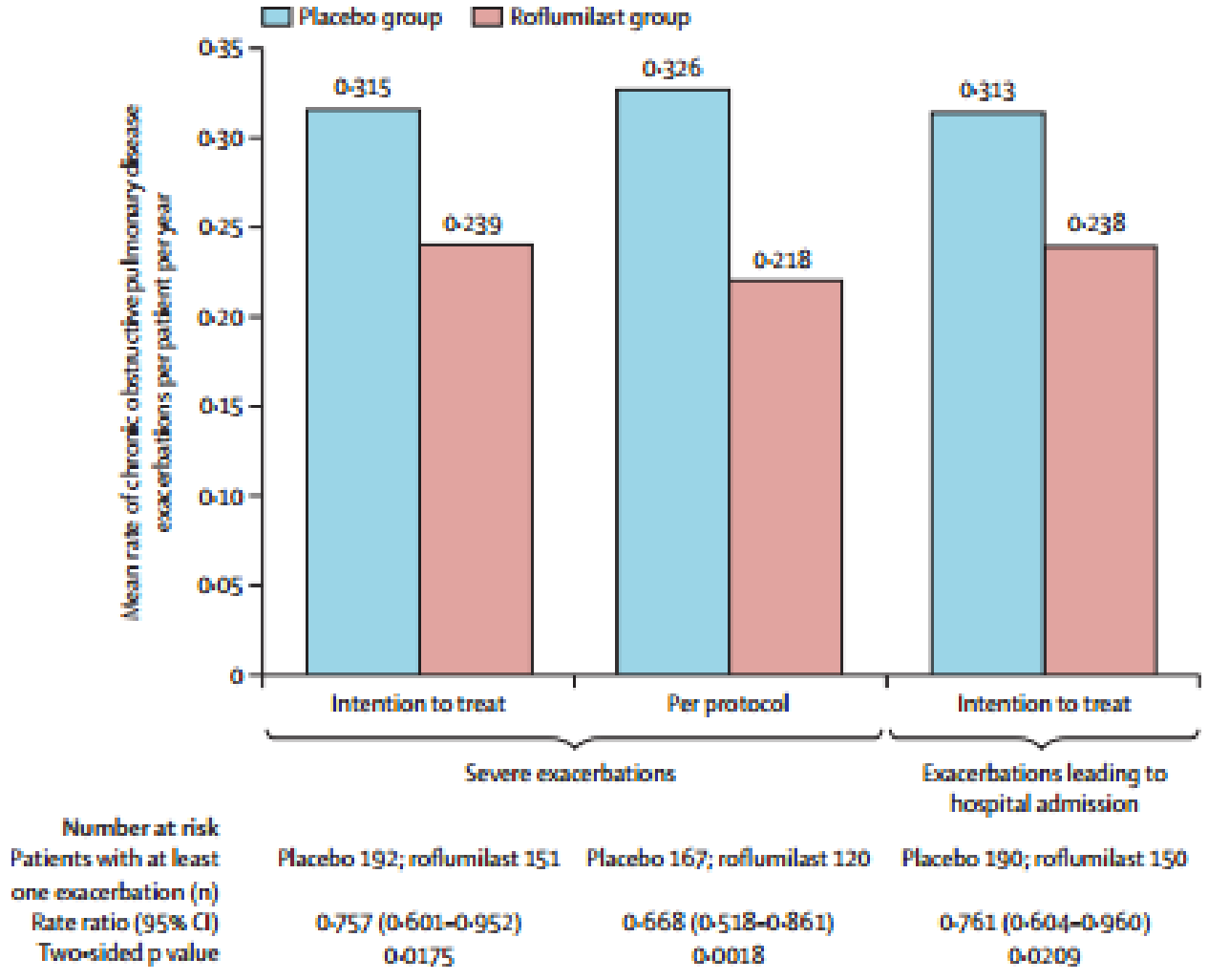
Inhibition of PDE4

- Antiinflammatory effect
- Bronchodilation effect



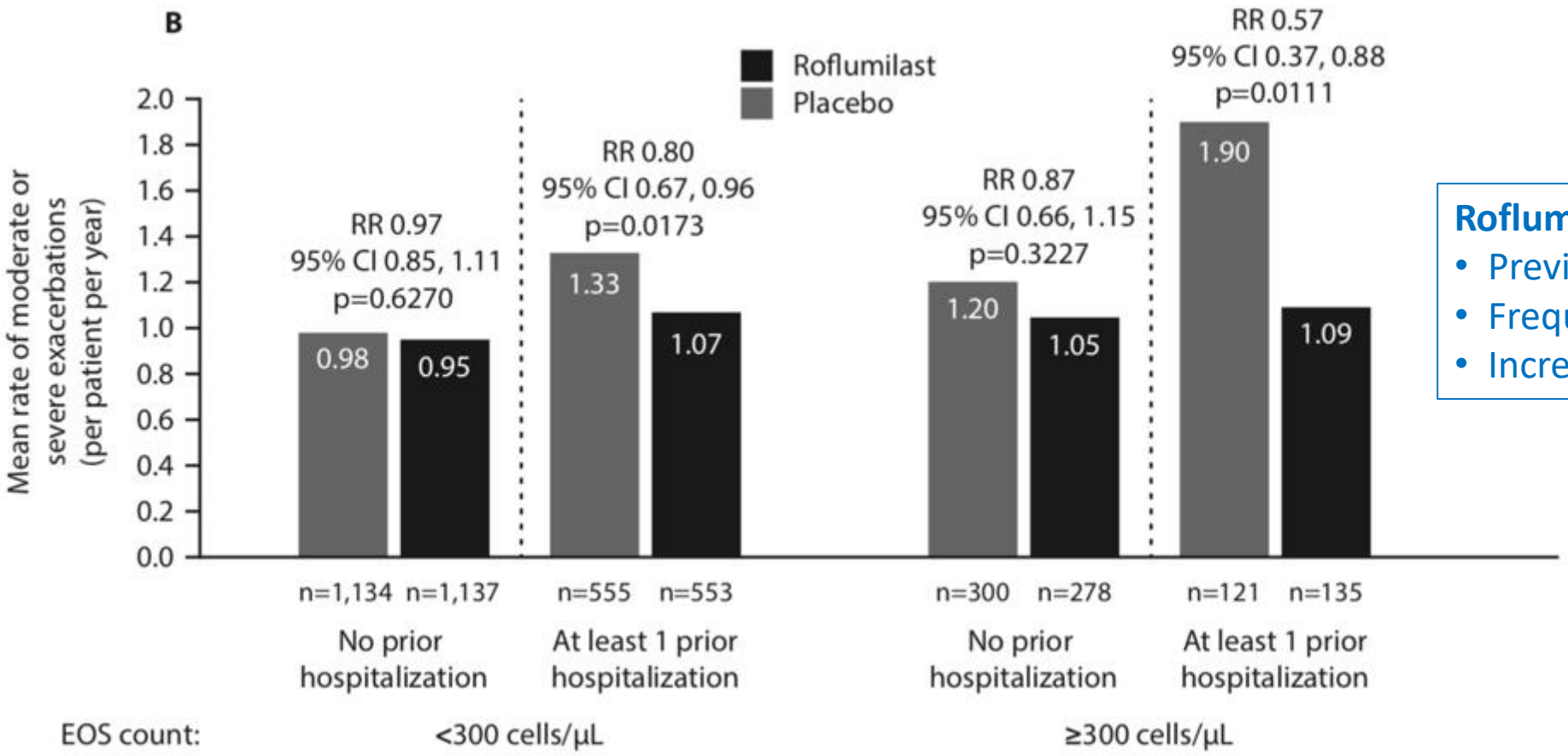
Role: increase of the levels of cAMP

Roflumilast decreases AECOPD in patients with chronic bronchitis



Martinez FJ et al, Lancet 2015

Roflumilast in COPD patients



Roflumilast responders:

- Previous hospitalization of AECOPD
- Frequent exacerbations
- Increased blood Eo

Martinez FJ et al., AJRCCM 2018

Palliative care, end of life and Hospice Care in COPD

Aim: to relive symptoms and support of the patient and caregivers

Palliative Care, End of Life and Hospice Care in COPD

Table 3.9

- Opiates, neuromuscular electrical stimulation (NMES), oxygen and fans blowing air on to the face can relieve breathlessness. **(Evidence C)**
- In malnourished patients, nutritional supplementation may improve respiratory muscle strength and overall health status **(Evidence B)** **+Vit C, Vit E, Zinc, Selenium**
- Fatigue can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions **(Evidence B)**

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AECOPD

An exacerbation of chronic obstructive pulmonary disease (ECOPD) is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in < 14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways

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- They are characterized by deterioration of symptoms and pulmonary function
- They are related to increased morbidity and mortality and high economic cost
- They accelerate disease progression
- In most cases they are related to viral and bacterial infections

Dickson R et al Lancet 2014

Differential diagnosis includes

- Acute coronary syndrome
- Deterioration of congestive heart failure
- Pulmonary embolism
- Pneumonia
- Pneumothorax
- Overdose of sedative medication

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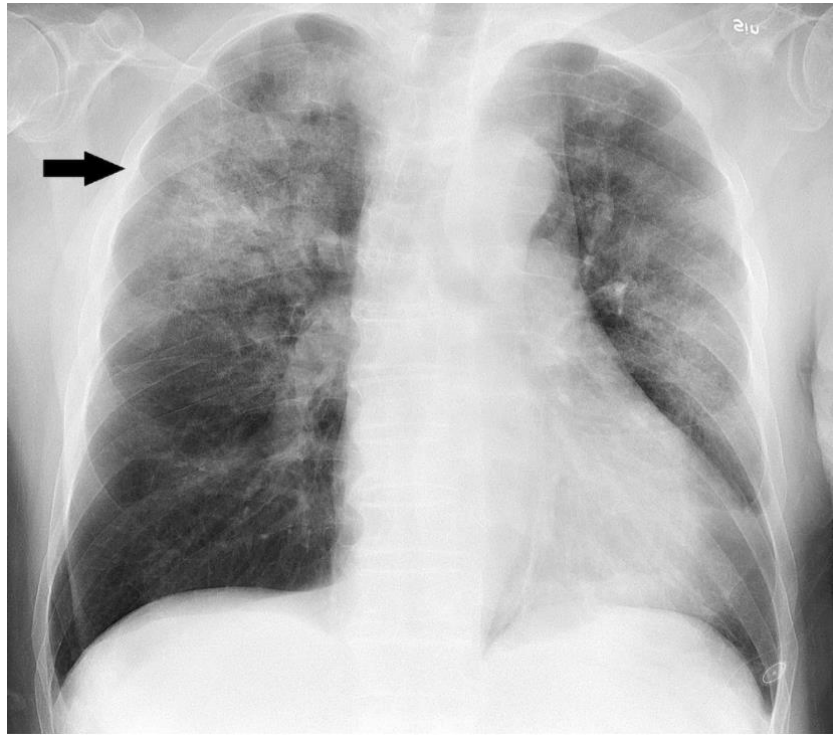
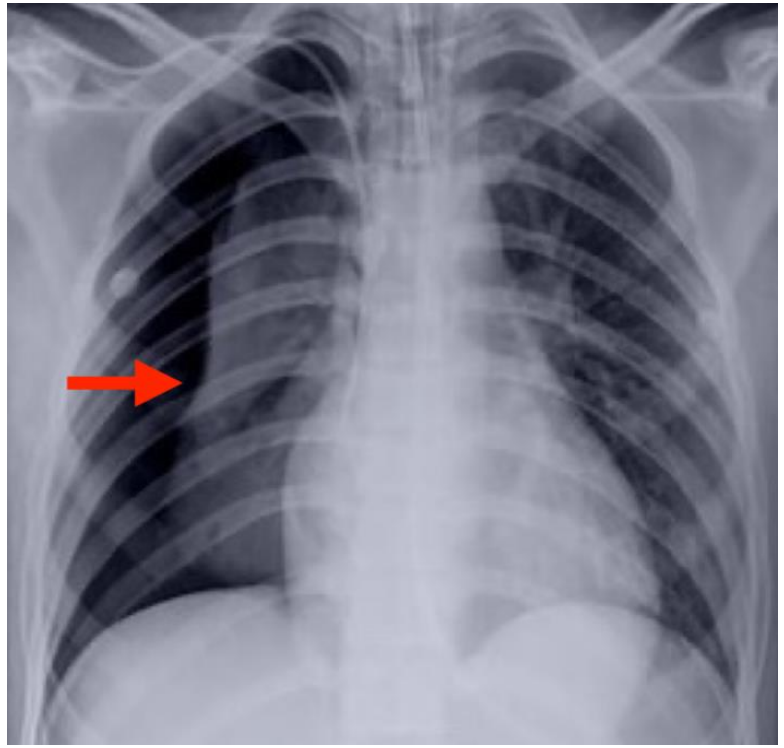
CXR during AECOPD

- It is necessary for differential diagnosis

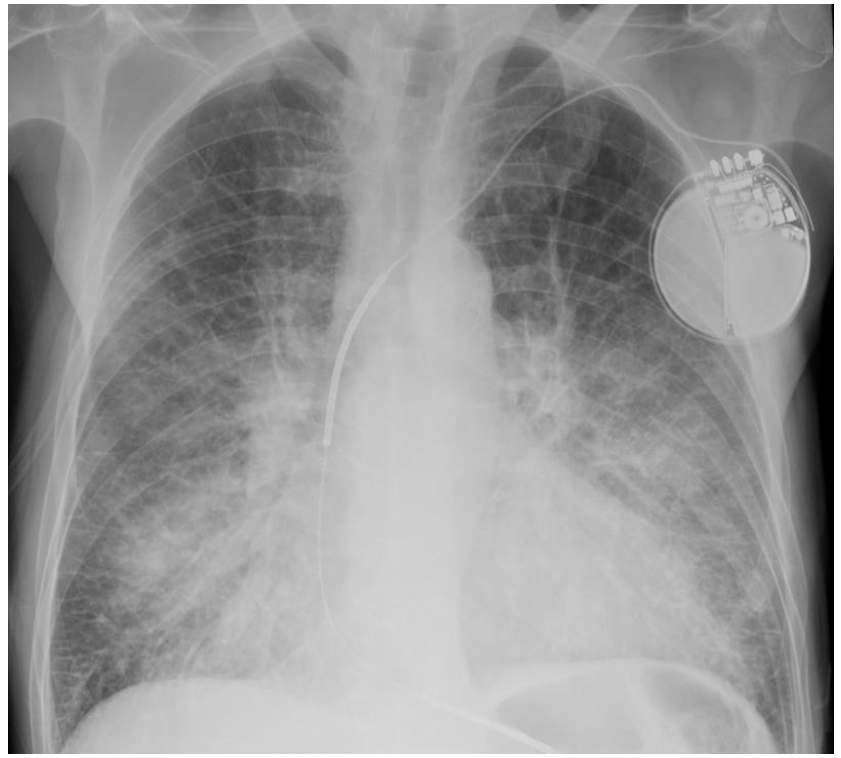
Pneumonia



Pneumothorax



Acute pulmonary edema



Main Pathogens in AECOPD

Table 2 Microbial pathogens in exacerbations of COPD

Pathogen class	Proportion of exacerbations	Specific species	Proportion of class of pathogens
Bacteria	40%–50%	Nontypeable *Haemophilus influenzae*	30%–50%
		Streptococcus pneumoniae	15%–20%
		Moraxella catarrhalis	15%–20%
		Pseudomonas spp. and *Enterobacteriaceae*	Isolated in very severe COPD, concomitant bronchiectasis, recurrent exacerbations
		Haemophilus parainfluenzae	Isolated frequently, pathogenic significance undefined
		Haemophilus hemolyticus	Isolated frequently, pathogenic significance undefined
		Staphylococcus aureus	Isolated infrequently, pathogenic significance undefined
Viruses	30%–40%	*Rhinovirus*	40%–50%
		Parainfluenza	10%–20%
		Influenza	10%–20%
		RSV	10%–20%
		Coronavirus	10%–20%
		Adenovirus	5%–10%
Atypical bacteria	5%–10%	*Chlamydia pneumoniae*	90%–95%
		Mycoplasma pneumoniae	5%–10%

Siddiqi A et al Int J COPD 2008

Severity of AECOPD

COPD Patient with Suspected Exacerbation

Confirm ECOPD Diagnosis and Episode Severity

Severity	Variable thresholds to determine severity
Mild (default)	• Dyspnea VAS < 5 • RR < 24 breaths/min • HR < 95 bpm • Resting SaO_2 ≥ 92% breathing ambient air (or patient's usual oxygen prescription) AND change ≤ 3% (when known) • CRP < 10 mg/L (if obtained)
Moderate (meets at least three of five*)	• Dyspnea VAS ≥ 5 • RR ≥ 24 breaths/min • HR ≥ 95 bpm • Resting SaO_2 < 92% breathing ambient air (or patient's usual oxygen prescription) AND/OR change > 3% (when known) • CRP ≥ 10 mg/L *If obtained, ABG may show hypoxemia (PaO_2 ≤ 60 mmHg) and/or hypercapnia ($PaCO_2$ > 45 mmHg) but no acidosis
Severe	• Dyspnea, RR, HR, SaO_2 and CRP same as moderate • ABG show new onset/worsening hypercapnia and acidosis ($PaCO_2$ > 45 mmHg and pH <7.35)

Determine etiology:
viral testing, sputum culture, other

Consider Differential Diagnosis

- Heart failure
- Pneumonia
- Pulmonary embolism

- Appropriate testing and treatment

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Targets during AECOPD treatment

- Improvement of arterial blood gases (Hypoxemia and hypercarbia)
- Symptom relief (dyspnea)
- Treatment of inflammation/infection
- Discovering the cause of the AECOPD

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Management of Severe but not Life-threatening Exacerbations*

Table 5.4

- **Assess severity of symptoms, blood gases, chest radiograph**
- **Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements**
- **Bronchodilators:**
  - Increase doses and/or frequency of short-acting bronchodilators
  - Combine short-acting beta$_2$-agonists and anticholinergics
  - Consider use of long-acting bronchodilators when patient becomes stable
  - Use spacers or air-driven nebulizers when appropriate
- **Consider oral corticosteroids**
- **Consider antibiotics (oral) when signs of bacterial infection are present**
- **Consider noninvasive mechanical ventilation (NIV)**
- **At all times:**
  - Monitor fluid balance
  - Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.)

*Local resources need to be considered

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Considerations regarding oxygen supplementation

- Target Sat: 88-92%
- Obtain serial blood gas measurements ([HCO_3^-] and pH can also be monitored in venous blood)
- Venturi masks are important for the administration of oxygen supplementation

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Bronchodilators

- Rapid onset-short acting bronchodilators
  - Salbutamol (onset 5min)
  - Ipratropium Bromide (onset 15min)
  - Salbutamol/ipratropium combination

Administer every hour or more frequently according to the patients needs

- Use spacers or nebulizers (similar efficacy)
  - In the ER usually nebulizers with oxygen!!!!

Methylxanthines (theophiline, aminophylline) are not recommended due to limited effectiveness and many adverse events

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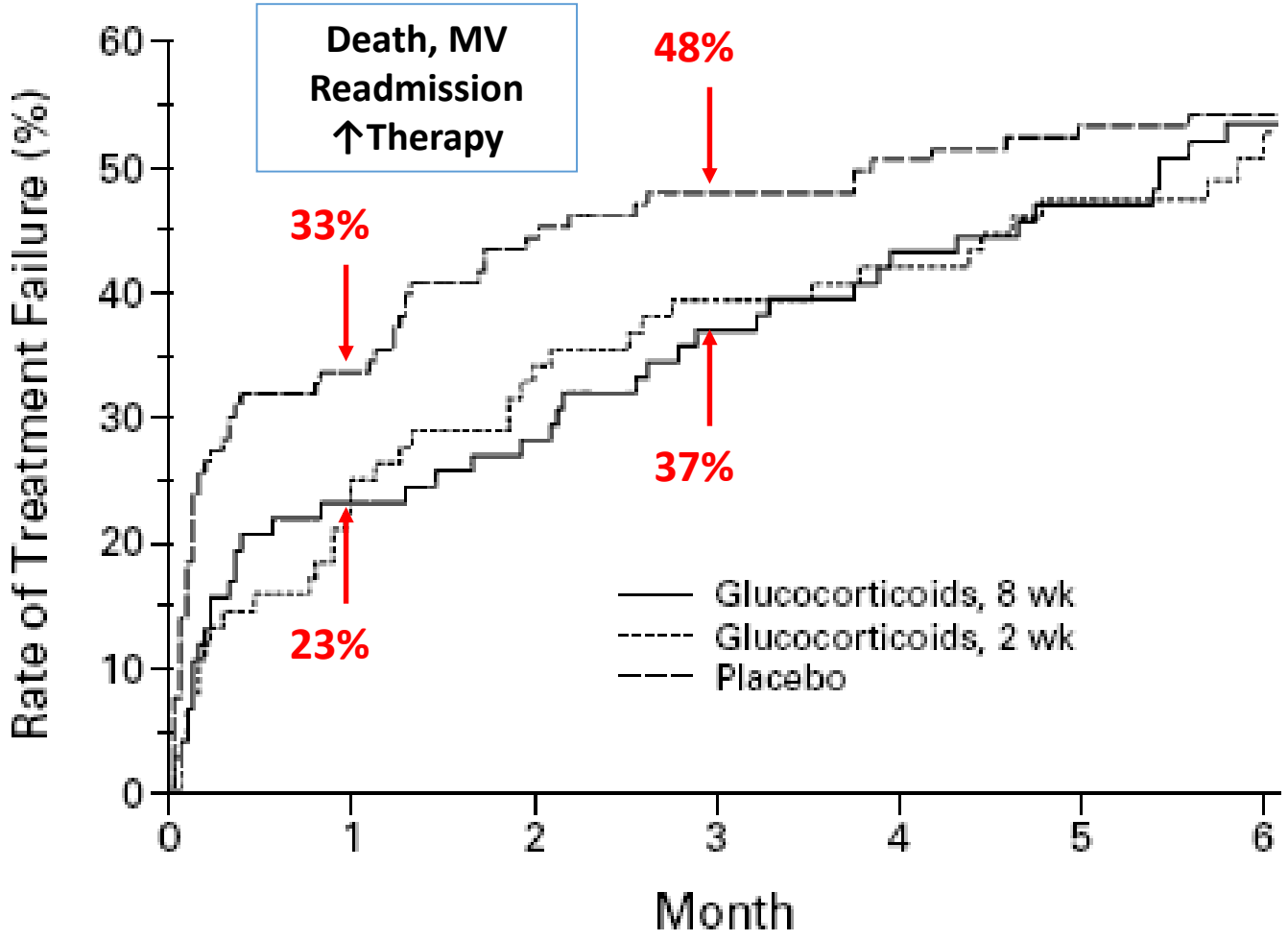
Corticosteroids

EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DENNIS E. NIEWOEHNER, M.D., MARCIA L. ERBLAND, M.D., ROBERT H. DEUPREE, PH.D., DOROTHEA COLLINS, SC.D., NICHOLAS J. GROSS, M.D., PH.D., RICHARD W. LIGHT, M.D., PAULA ANDERSON, M.D., AND NANCY A. MORGAN, R.PH., M.B.A., FOR THE DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY GROUP*



Systemic Corticosteroids when used for the treatment of AECOPD decrease significantly the possibility of readmission for ARCOPD during the following 30 days

Criner GJ, et al. Chest 2015

Corticosteroids

Per os or IV **(40mg prednisolone/day for 5 days (Evidence A)**

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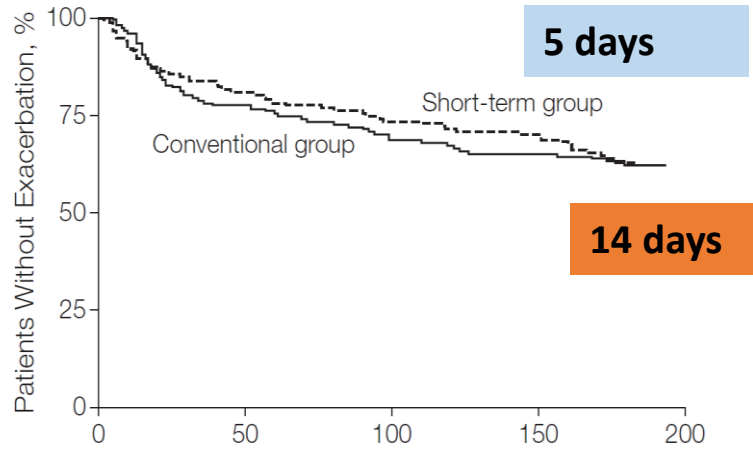
Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease
The REDUCE Randomized Clinical Trial

314 patients with AECOPD

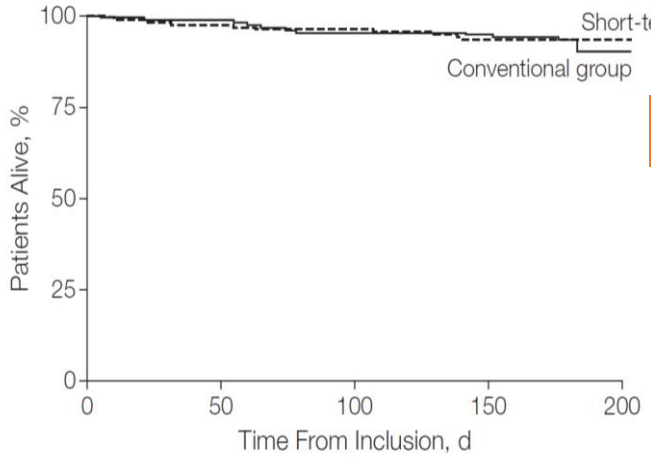
- 40 mg prednisone (iv on day 1 and then per os)
- Duration of treatment 5 days vs 14 days
- Primary outcome:
  - Time to next exacerbation in the next 180 days



5 days

14 days

AECOPD



5 days

14 days

Survival

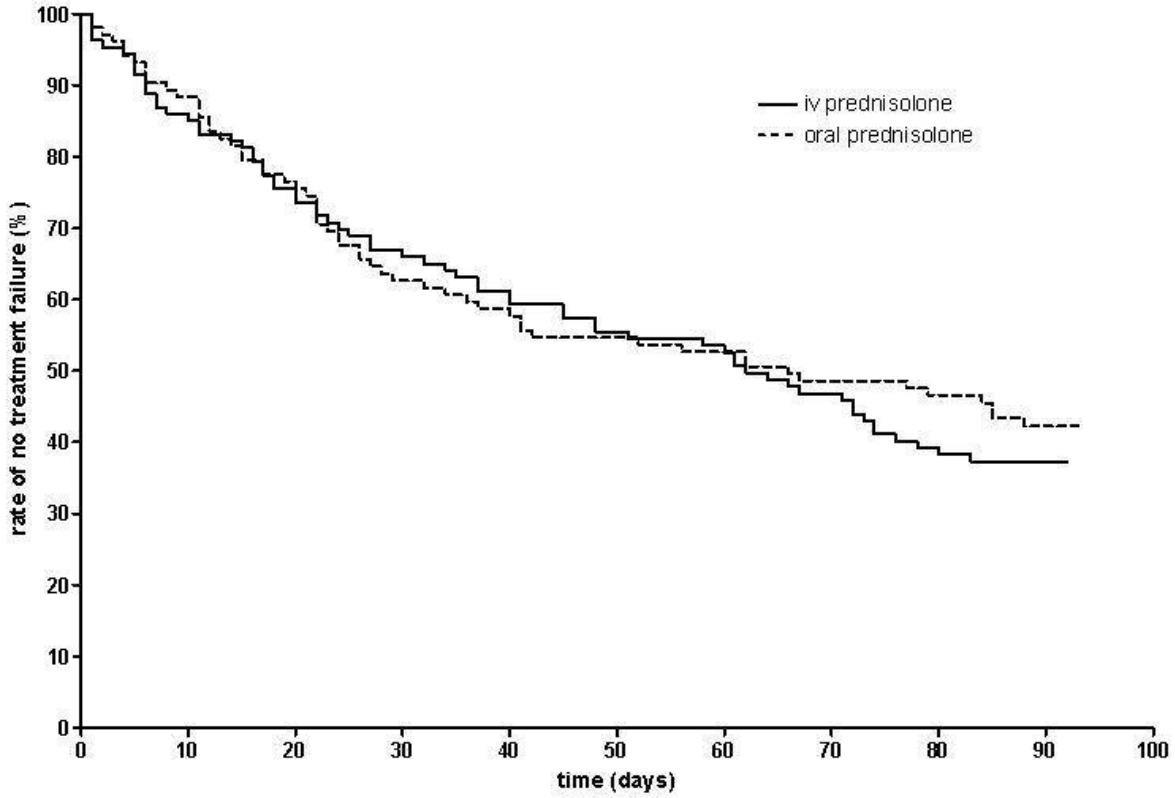
Leuppi JD,et al. *JAMA* 2013

Corticosteroids, IV ή per os;

Oral or IV Prednisolone in the Treatment of COPD Exacerbations*: A Randomized, Controlled, Double-blind Study

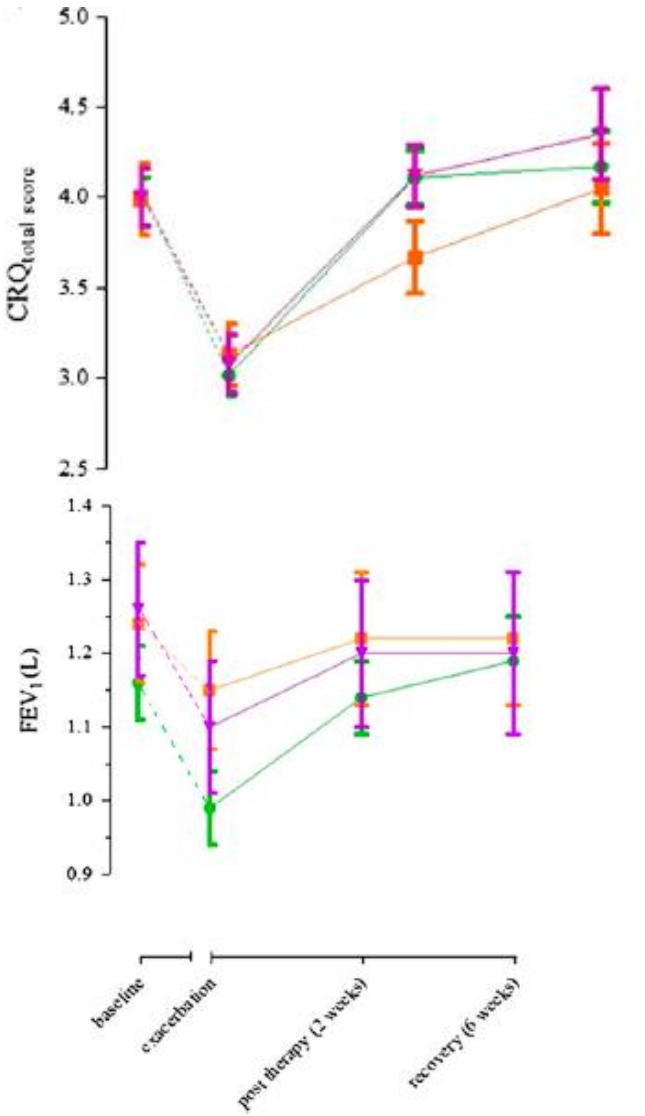
Ynze P. de Jong, Steven M. Uil, Hans P. Grotjohan, Dirkje S. Postma, Huib A.M. Kerstjens and Jan W.K. van den Berg

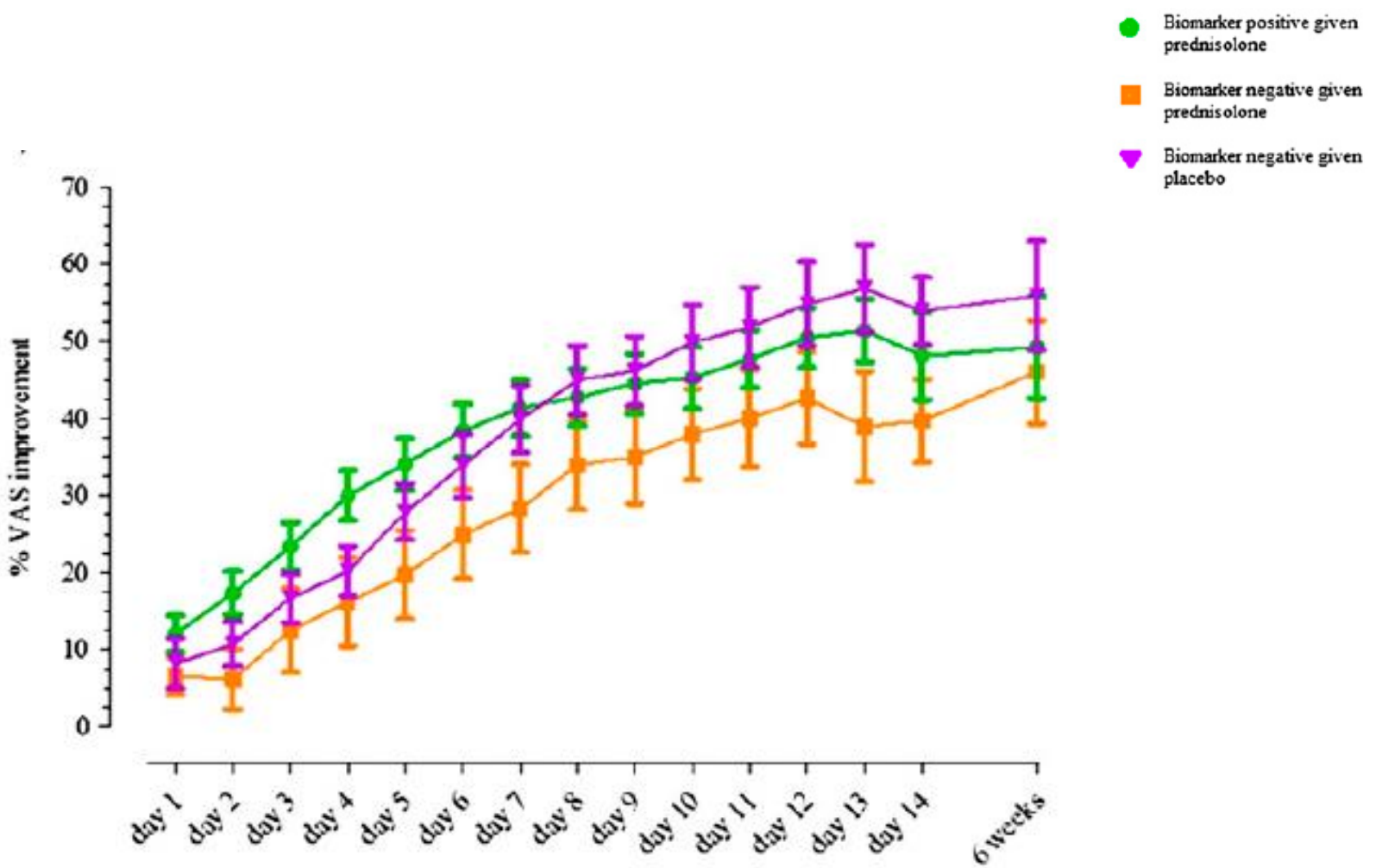
p=0.6



de Jong YP et al, Chest 2007

Do all exacerbations need corticosteroids?





Baffadel M et al. *AJRCCM 2012*

Antibiotics (per os or IV) when sings of bacterial infection are present

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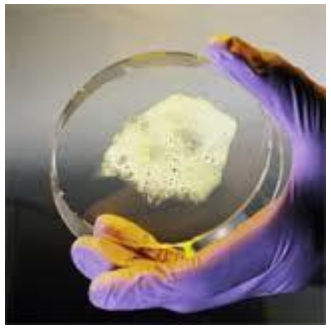
Detection of bacterial causes during AECOPD



30% in sputum cultures

50% in bronchial secretion cultures

70% in bronchial secretion in patients who require mechanical ventilation

Sapey E et al Thorax 2005

ANTHONISEN Criteria (Ann Intern Med 1987)

(α) increased dyspnea

(β) increased sputum volume

(γ) purulent sputum

Anthonisen NR Ann Int Med 1987

(1) 3 criteria met (Type I Anthonisen) [Evidence B]

(2) 2 criteria met – one of them is purulent sputum (Type II Anthonisen) [Evidence C]

(3) Patient on mechanical ventilation (NIV ή MV) [Evidence B]

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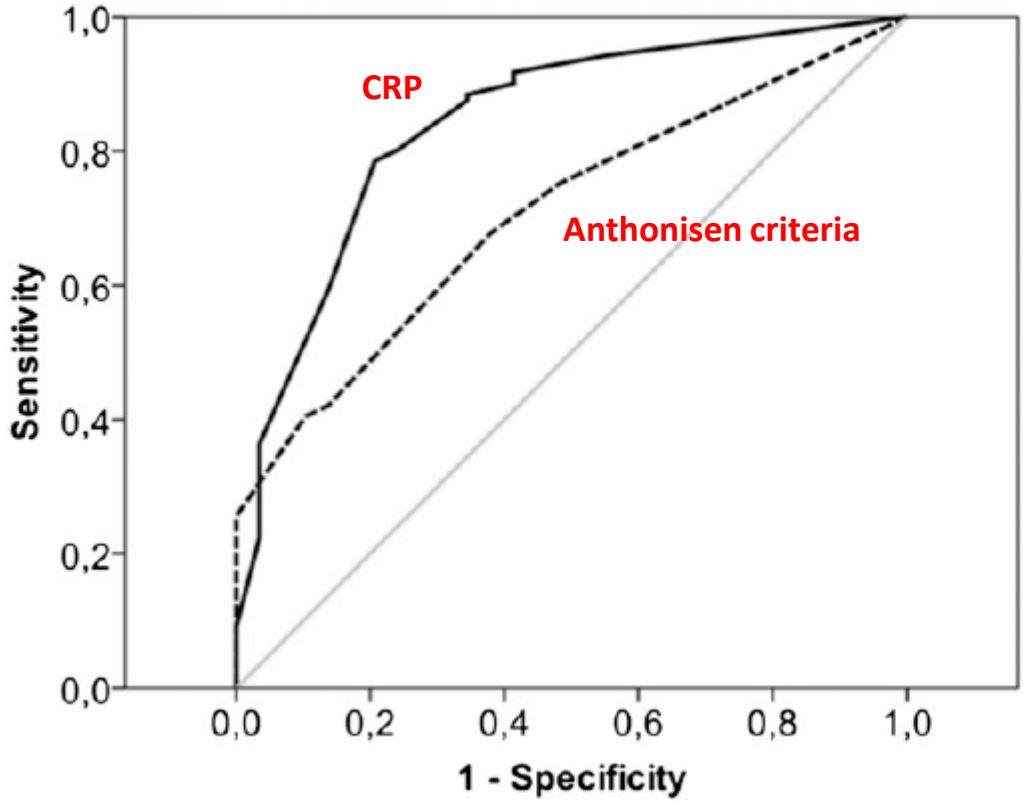
The use of biomarkers during AECOPD

CRP and procalcitonin: recognition of bacterial AECOPD and requirement of antibiotics



***p=0*.033**

Anthonisen criteria
AUC 0.708 (95% CI, 0.616-0.801)

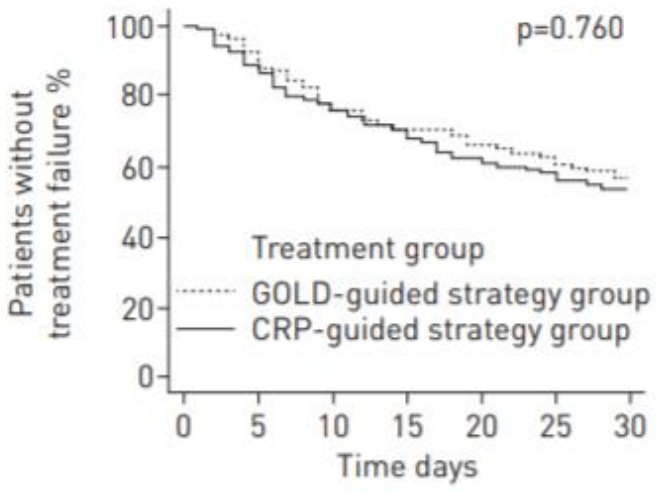
CRP (cut off >40mg/L)
AUC 0.842 (95% CI 0.760-0.924)

Miravitlles M et al Chest 2013

The use of CRP for prescribing antibiotics

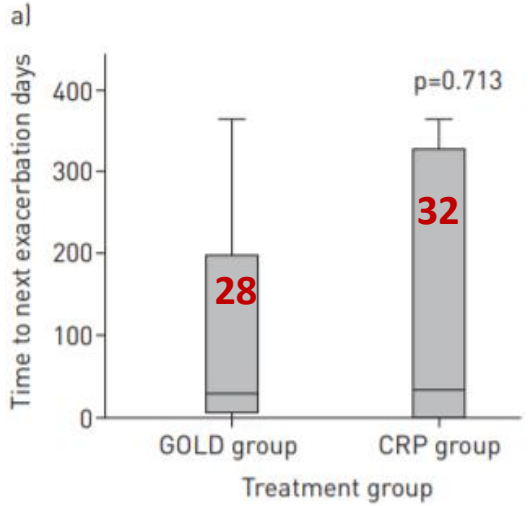
220 patients hospitalized for AECOPD

CRP

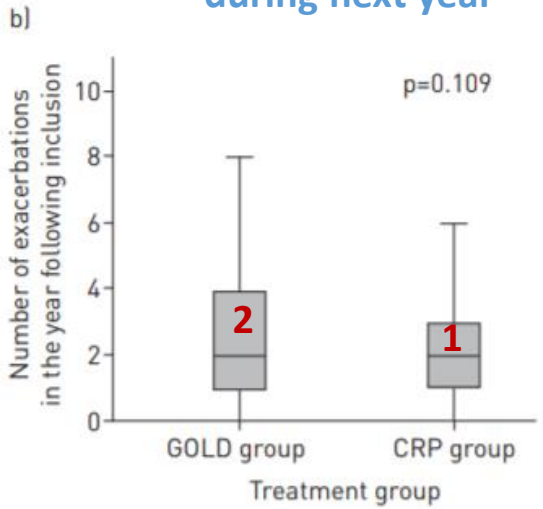


44.5% vs 45.5%

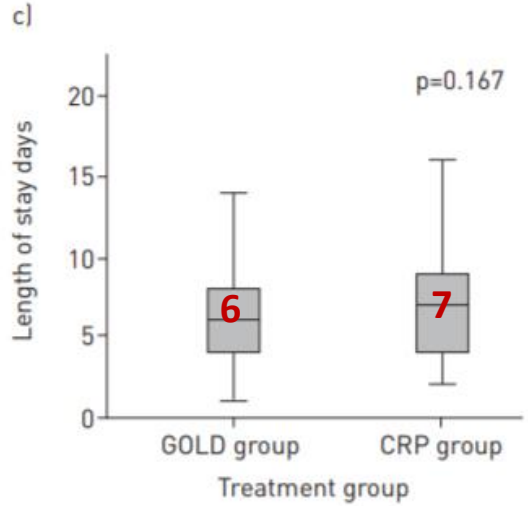
Time to next AECOPD



Number of AECOPD during next year



Hospital stay



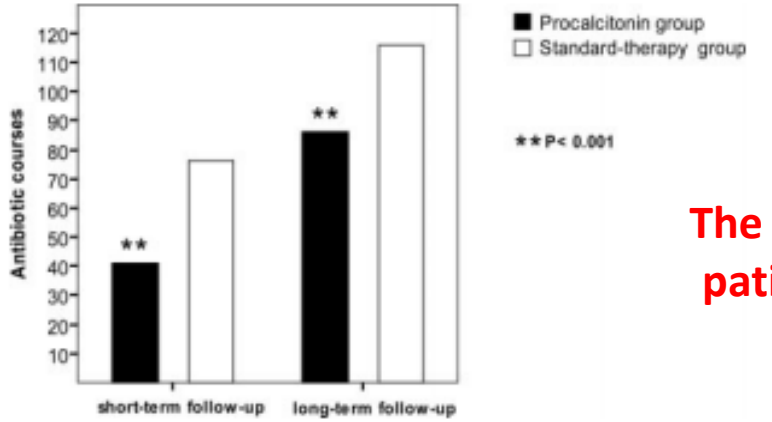
Prescription of antibiotics

CRP vs GOLD : 31.7% vs 46.2%, p=0.028

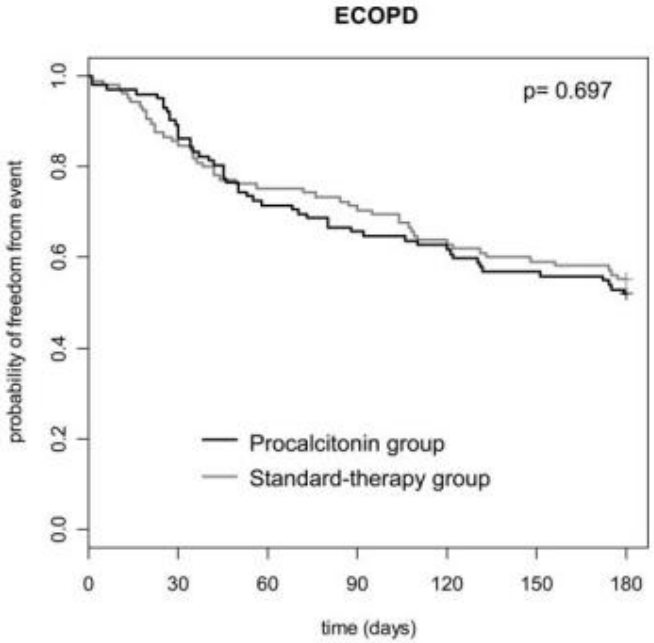
Prins HJ et al ERJ 2019

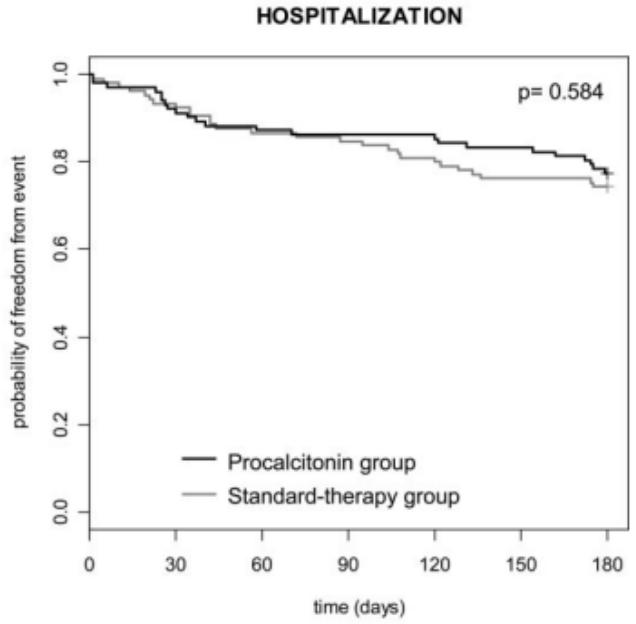
Procalcitonin

A marker of bacterial infection



The use of antibiotics was lower in patients treated according to PCT





Stoltz D et al Chest 2007

Risk factors for P. aeruginosa

Table 1. Risk factors for *Pseudomonas aeruginosa* infection in chronic obstructive pulmonary disease

Reference	Risk factors
Allegra *et al.* [27]	FEV_1 <35%
Eller *et al.* [25]	FEV_1 <35%
	Pretreatment with antibiotics
Miravitlles *et al.* [26]	FEV_1 <50%
Lode *et al.* [28]	FEV_1 <35%
	Use of systemic corticosteroids
	Antibiotics in the previous 3 months
Monsó *et al.* [29]	Low FEV_1
	Use of oral corticosteroids
	Antibiotics in the previous 3 months
	Protective effect of anti-influenza vaccine
García-Vidal *et al.* [30]	Use of systemic corticosteroids
	Poor BODE index
	Hospital admissions in the previous year
	Previous isolation of *P. aeruginosa*
Gallego *et al.* [31]	Presence and extension of bronchiectasis
	Previous exposure to antibiotics

Patients with

- ✓ **Severe and very severe obstruction**
- ✓ **Recent use of antibiotics**
- ✓ **Recent use of systemic CS**
- ✓ **Previous detection of *P aeruginosa***

Miravitlles M et al Cur Opin 2015

Antibiotic choices during AECOPD

The choice of the antibiotic should be based on the local bacterial resistance pattern.

Initial empirical treatment usually includes:

- aminopenicillin with clavulanic acid,
- macrolide, tetracycline
- quinolone (in selected patients)

Antibiotic treatment effective against Gram – bacteria should be administered in patients with:

- frequent exacerbations
- severe airflow obstruction
- exacerbations requiring mechanical ventilation
- Previous detection of Gram - bacteria or resistant pathogens

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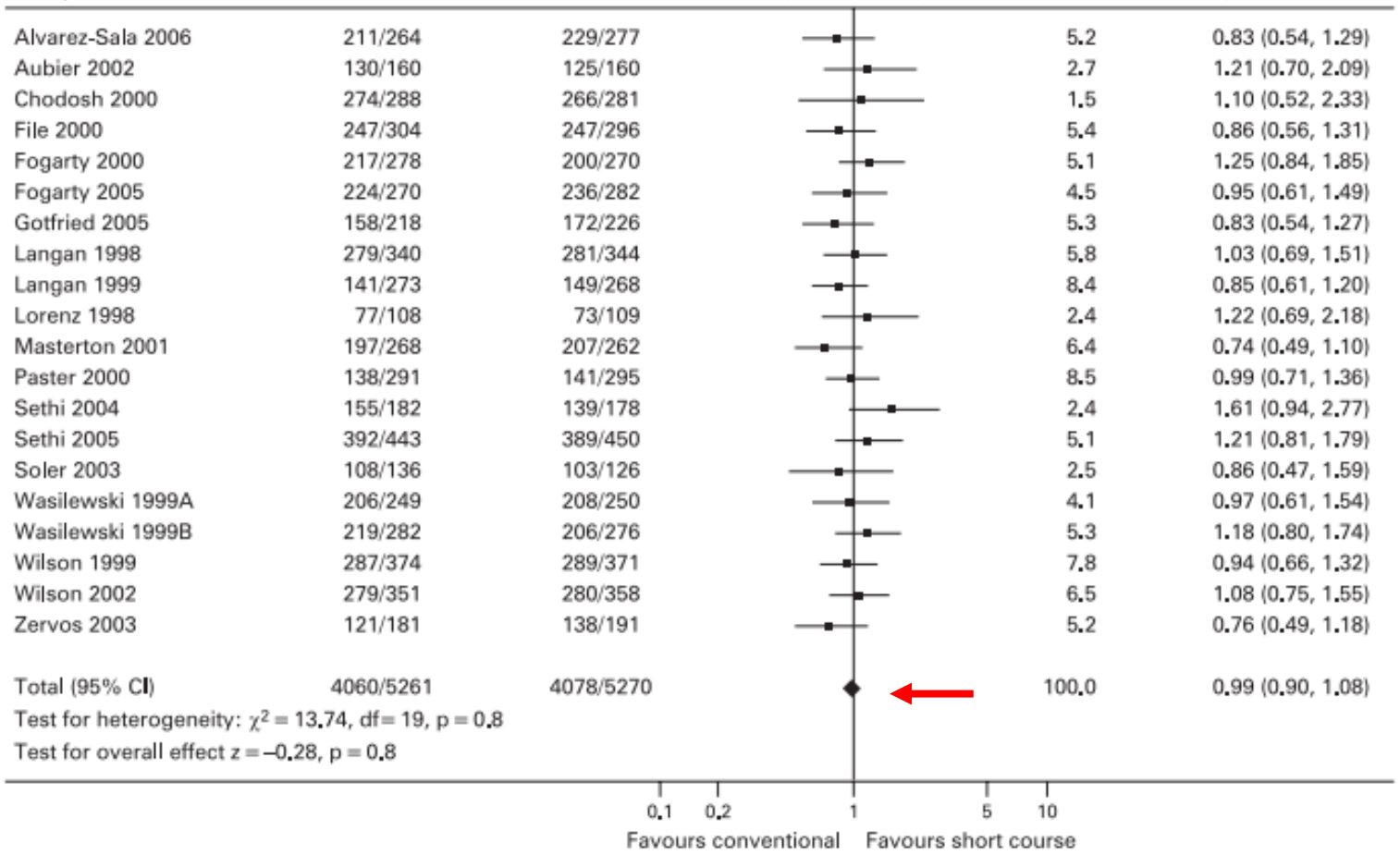
Duration of antibiotic treatment during AECOPD

≤ 5 days > 5 days

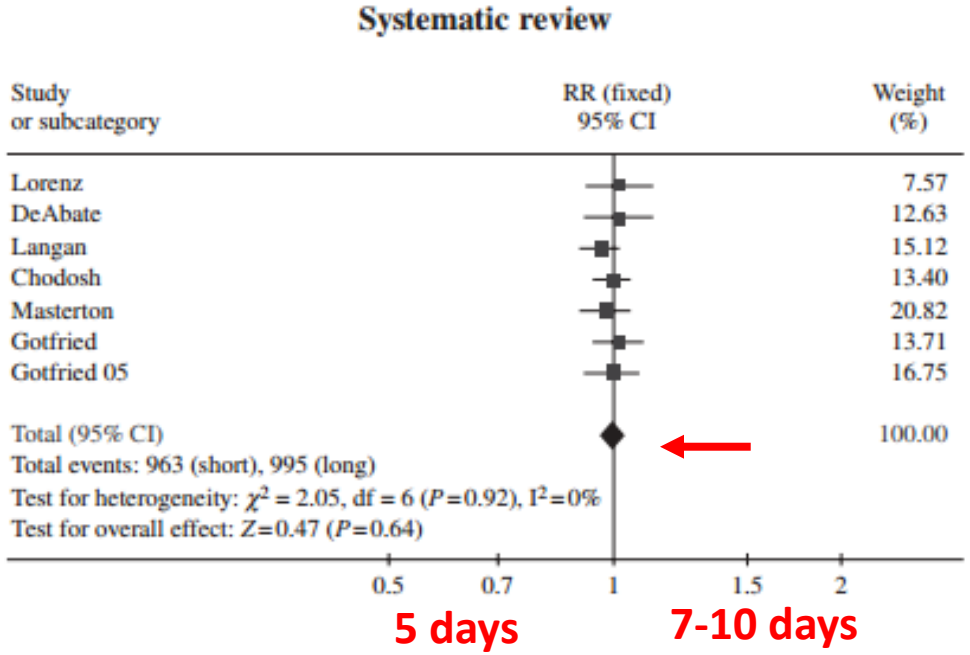
Study	Short course n/N	Conventional course n/N	OR (95% CI fixed)	Weight %	OR (95% CI fixed)
Alvarez-Sala 2006	211/264	229/277		5.2	0.83 (0.54, 1.29)
Aubier 2002	130/160	125/160		2.7	1.21 (0.70, 2.09)
Chodosh 2000	274/288	266/281		1.5	1.10 (0.52, 2.33)
File 2000	247/304	247/296		5.4	0.86 (0.56, 1.31)
Fogarty 2000	217/278	200/270		5.1	1.25 (0.84, 1.85)
Fogarty 2005	224/270	236/282		4.5	0.95 (0.61, 1.49)
Gotfried 2005	158/218	172/226		5.3	0.83 (0.54, 1.27)
Langan 1998	279/340	281/344		5.8	1.03 (0.69, 1.51)
Langan 1999	141/273	149/268		8.4	0.85 (0.61, 1.20)
Lorenz 1998	77/108	73/109		2.4	1.22 (0.69, 2.18)
Masterton 2001	197/268	207/262		6.4	0.74 (0.49, 1.10)
Paster 2000	138/291	141/295		8.5	0.99 (0.71, 1.36)
Sethi 2004	155/182	139/178		2.4	1.61 (0.94, 2.77)
Sethi 2005	392/443	389/450		5.1	1.21 (0.81, 1.79)
Soler 2003	108/136	103/126		2.5	0.86 (0.47, 1.59)
Wasilewski 1999A	206/249	208/250		4.1	0.97 (0.61, 1.54)
Wasilewski 1999B	219/282	206/276		5.3	1.18 (0.80, 1.74)
Wilson 1999	287/374	289/371		7.8	0.94 (0.66, 1.32)
Wilson 2002	279/351	280/358		6.5	1.08 (0.75, 1.55)
Zervos 2003	121/181	138/191		5.2	0.76 (0.49, 1.18)
Total (95% CI)	4060/5261	4078/5270		100.0	0.99 (0.90, 1.08)
Test for heterogeneity: $\chi^2 = 13.74$, df = 19, p = 0.8					
Test for overall effect z = –0.28, p = 0.8					



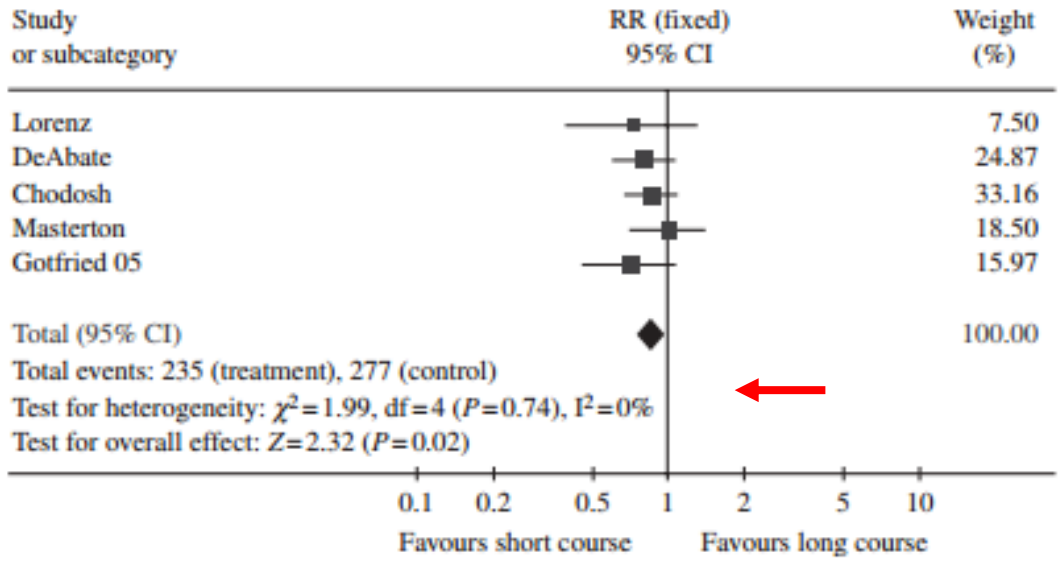
Moussaoui RE et al. Thorax 2008

Duration of antibiotic treatment during AECOPD

Efficacy



Adverse events



Falagas ME et al J Antim Chem 2008

NIV

Indications:

- ✓ Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing (use of respiratory accessory muscles, paradoxical motion of the abdomen or retraction of the intercostal spaces)
- ✓ Respiratory acidosis (PCO_2 >6kPa or 45 mmHg and pH ≤ 7.35)
- ✓ Persistent hypoxemia despite supplemental oxygen therapy

Contraindications

- ✓ Respiratory or cardiac arrest
- ✓ Hemodynamic instability (hypotension, arrhythmia, acute coronary infraction)
- ✓ Inability of the patient to co-operate or refusal
- ✓ Increased risk of aspiration
- ✓ Increased respiratory secretions
- ✓ Recent facial or upper abdomen surgery or burns
- ✓ Severe hypoxemia in patients who do not cooperate with NIV

NIV should be the initial mode of ventilation to treat acute respiratory failure in patients hospitalized for acute exacerbations of COPD

Caution!!!!

- ➢ Severe acidosis is not a contraindication for NIV if there is a possibility for immediate intubation in case of failure
- ➢ The use of NIV should not delay intubation if it is necessary

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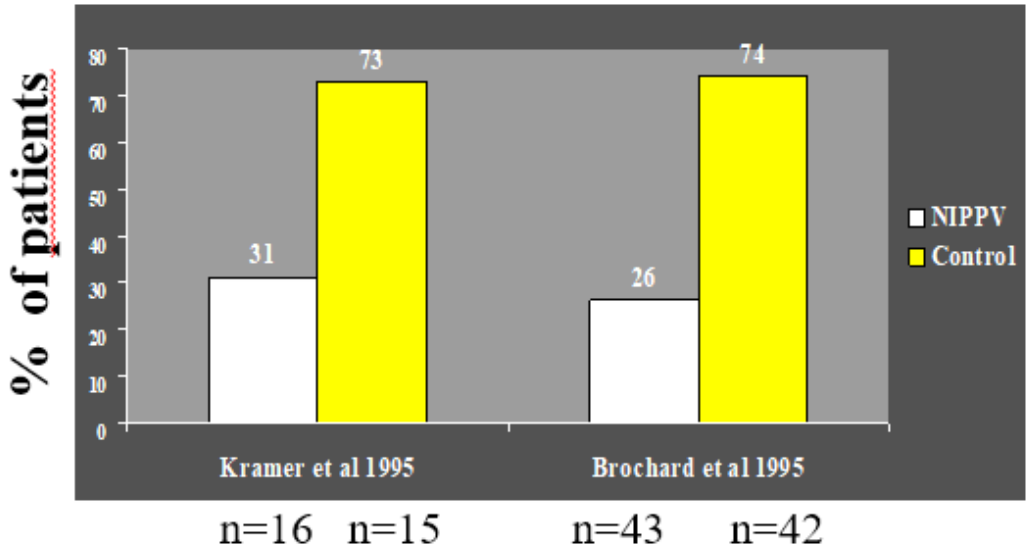
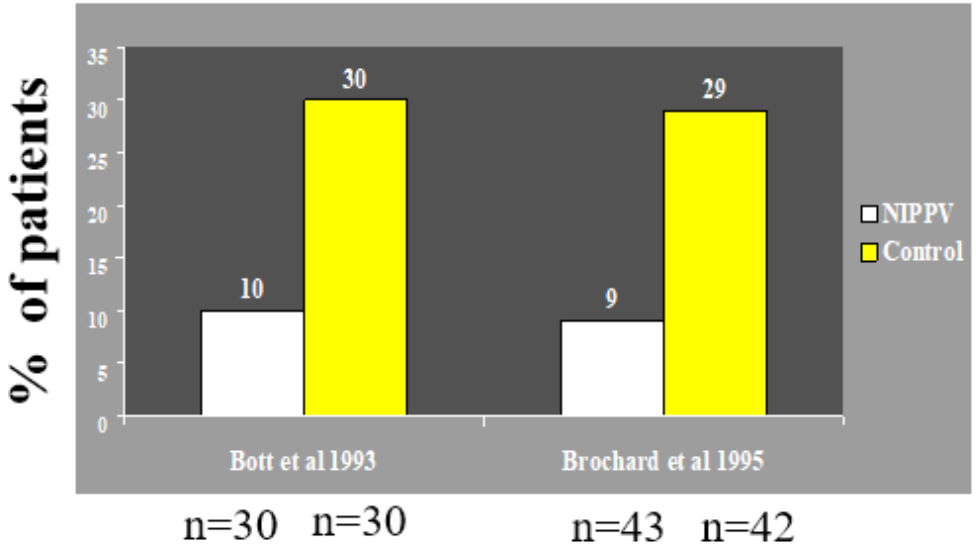
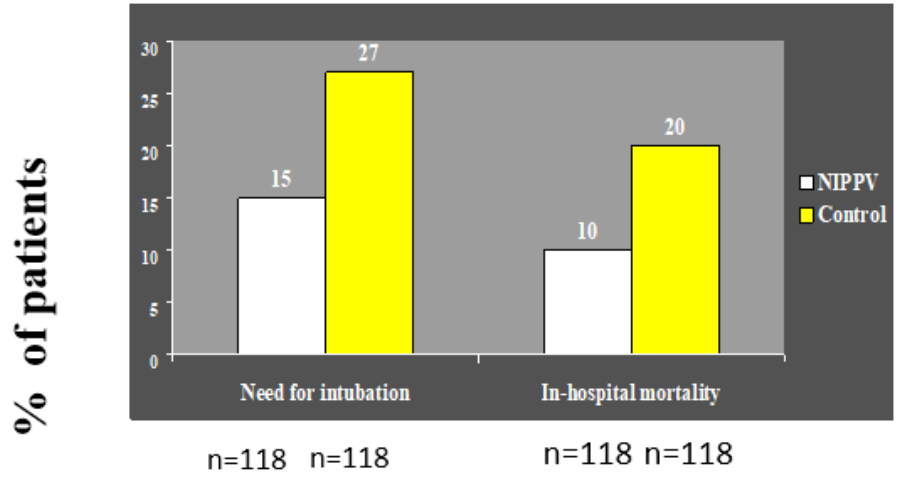
NIV in AECOPD

Intubation



Mortality





Plant PK, et al. Lancet 2000

Nasal High Flow

- High-flow nasal therapy (HFNT) delivers heated and humidified air-oxygen blends via special devices) at rates up to 60 L/min
- It has been associated with decreased respiratory rate and effort, decreased work of breathing, improved gas exchange, improve lung volume and dynamic compliance, transpulmonary pressures and homogeneity
- It improves oxygenation and ventilation, decrease hypercarbia and improve HRQoL in patients with acute hypercapnia during an acute exacerbation, and also in selected patients with stable hypercapnic COPD
- A trial of NIV prior to use of HFNT in patients with COPD and hypercapnic ARF is recommended

Pantazopoulos I et al COPD 2020

Management of AECOPD

Always

- Close follow up of fluid uptakes and diuresis
- LMWH Sc
- Diagnose and treat comorbidities (especially cardiovascular)

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Severe AECOPD: Admission to the ICU

Indications for Respiratory or Medical Intensive Care Unit Admission*

Table 5.6

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (PaO_2 < 5.3 kPa or 40 mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability - need for vasopressors

*Local resources need to be considered.

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When we treat stable and exacerbating COPD

We should

- Take into account the patient's phenotype (personalized therapy)

- Target not only symptoms but also airway and systemic inflammation

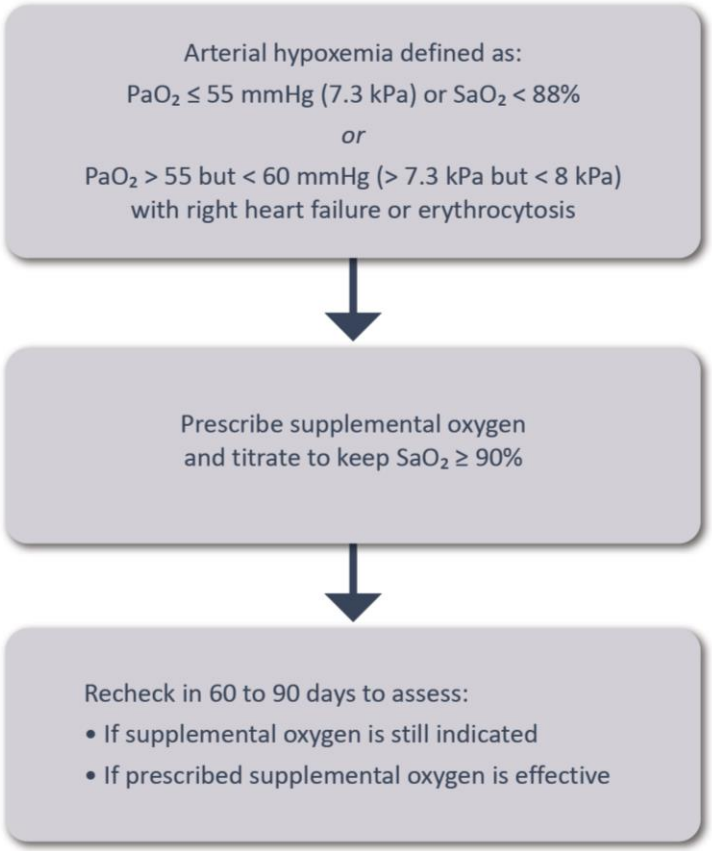
- All (pharmacologic and non pharmacologic) therapeutic interventions should be offered in each COPD patient to improve HRQoL and to increase survival


You don't always need a plan.
Sometimes you just need to...
Breathe,
Trust,
Let Go
and See what happens.

Back up slide

Prescription of Supplemental Oxygen to COPD Patients

Figure 4.5



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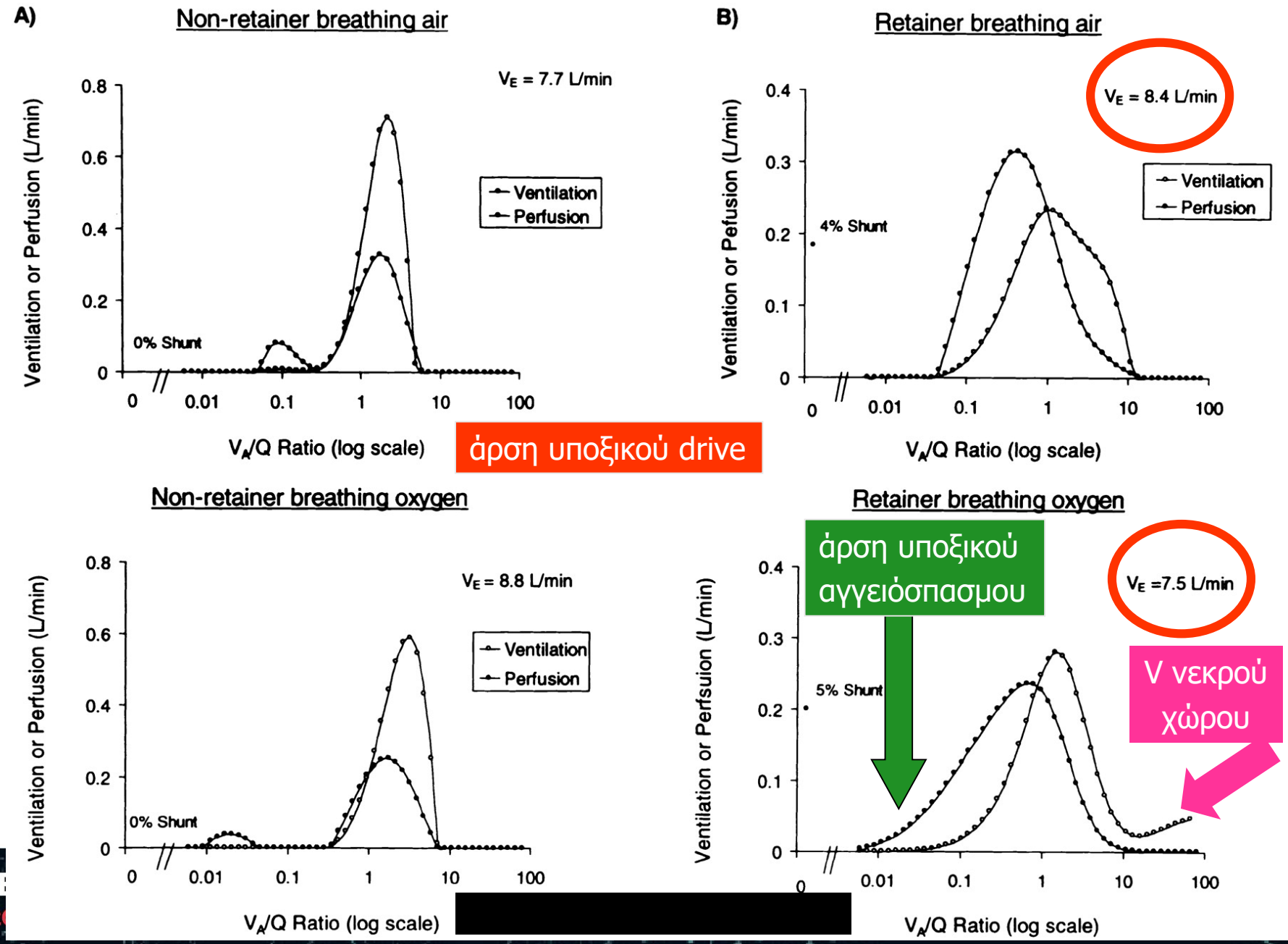
Μηχανισμός υπερκαπνίας λόγω O_2 στη ΧΑΠ



Adverse events of Roflumilast

- Diarrhea
- Nausea
- Loss of appetite
- Weight loss
- Abdominal pain
- Sleep disorders
- Headache

Usually in the beginning of treatment and decrease with time

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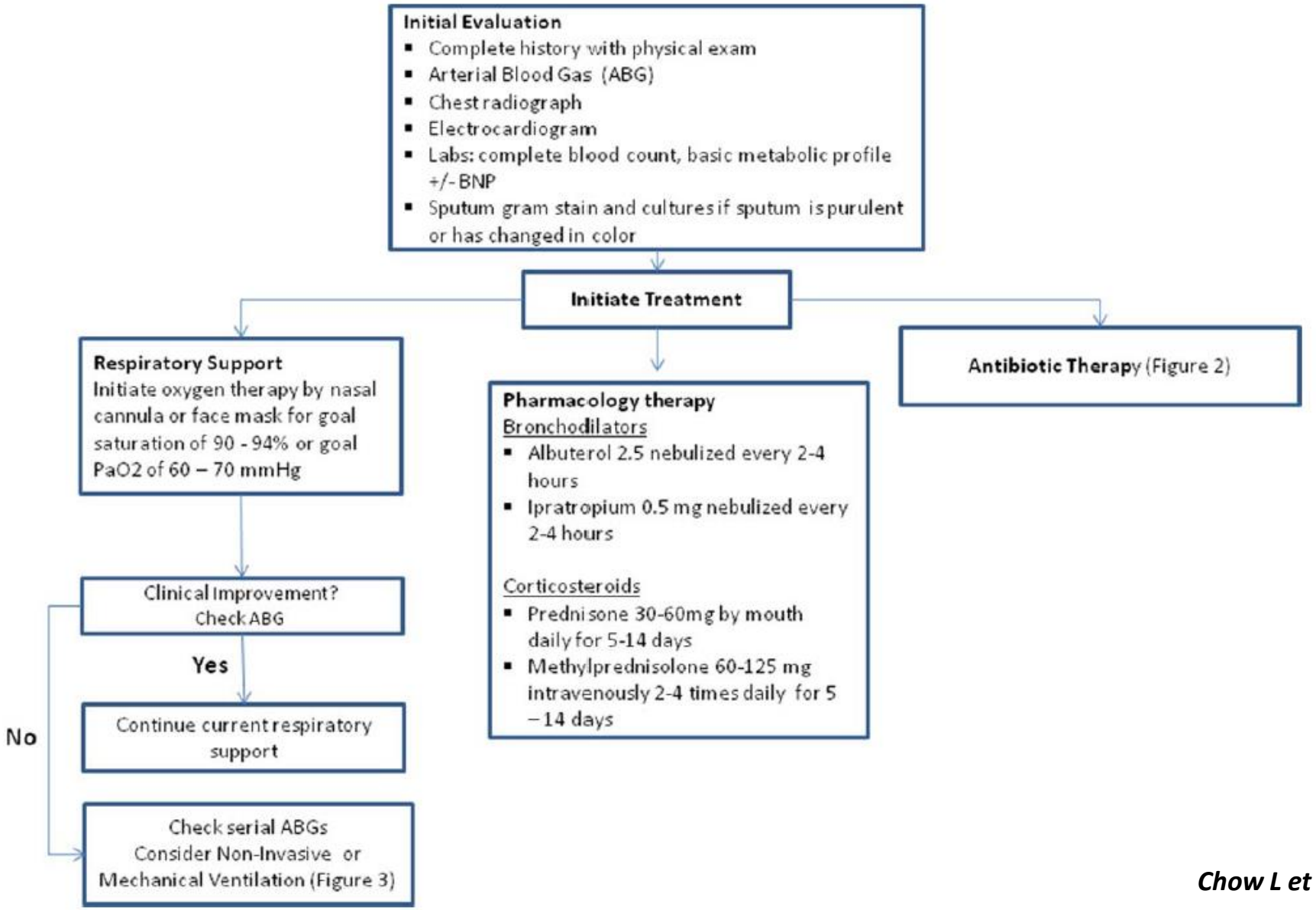


Chow L et al J Hosp Med 2015

Typical initial settings for NIV in AECOPD

Mode: Spontaneous (pressure support)/timed

EPAP: 4–5 cm H_2O

IPAP: 15 cm H_2O (to be increased as tolerated to 20-30 cmH_2O)

with 20 cm H_2O if pH < 7.25

Triggers: Maximum sensitivity

Back up rate: 15 breaths/min

Back up I:E ratio: 1:2

In case of not improvement

Increase IPAP

Change of mask (Air leak)

Increase of EPAP

NIV in AECOPD

Check ventilator

- Check machine and circuit
- Check expiration valve

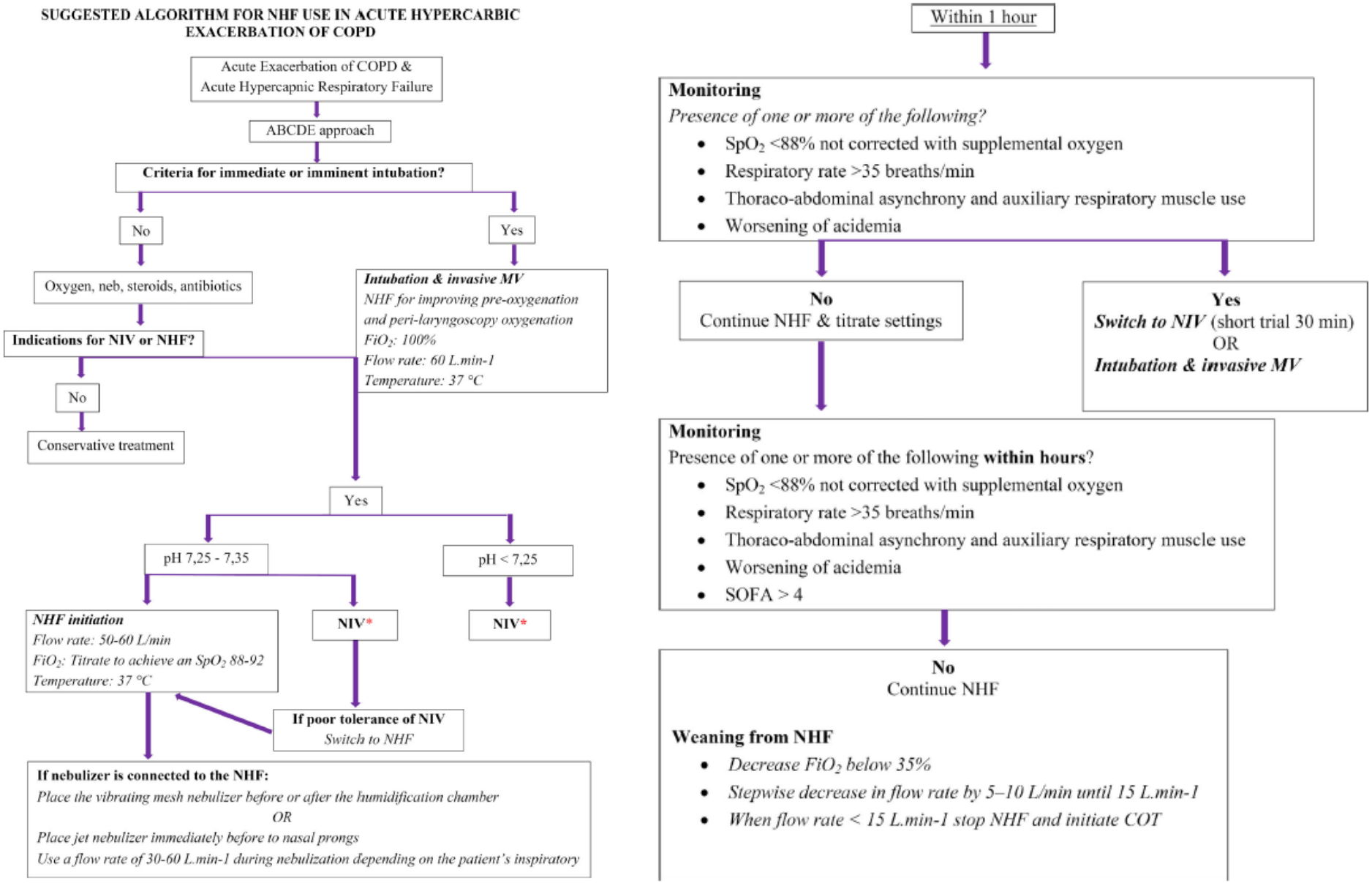
Inform the patient

- What will happened and why
- Oxygen delivery through the circuit or through the mask

Choose the right mask

- Size
- Full-face mask is preferred compared to nasal mask
- Removal of artificial dentures
- Claustrophobia : it decreases as blood gases improve

CM Roberts et al *Clin Med* 2008



Pantazopoulos I et al COPD 2020