UNIVERSITÀ
DEGLI STUDI
DI MILANO

Ospedale Luigi Sacco
AZIENDA OSPEDALIERA - POLO UNIVERSITARIO

La BPCO, le sue Riacutizzazioni, la graduale evoluzione a Insufficienza Respiratoria. Il ruolo delle terapie inalatorie

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Dipartimento di Scienze Biomediche e Cliniche
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Conflicts of interest

Dr. Dejan Radovanovic declares having received fees for lecturing from:

- Astra Zeneca
- Boehringer Ingelheim
- Berlin Chemie
- Glaxo Smith Kline
- Menarini Farmaceutici
- Roche

NONE PERCEIVED FOR THE CURRENT LECTURE

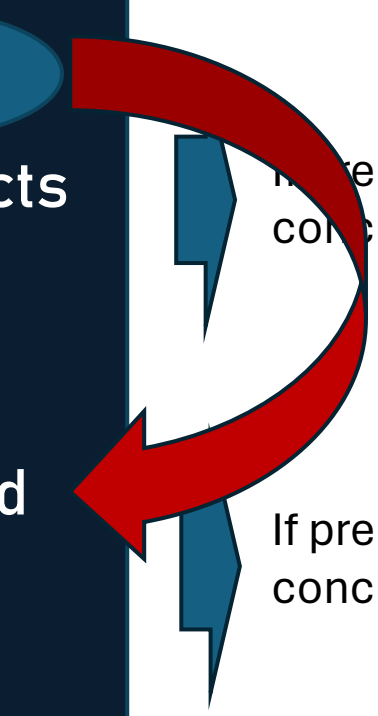
During the war the cargo religion saw airplanes land with lots of good materials, and they want the same thing to happen now. So they've arranged to imitate things like runways, to put fires along the sides of the runways, to make a wooden hut for a man to sit in, with two wooden pieces on his head like headphones and bars of bamboo sticking out like antennas, he's the controller and they wait for the airplanes to land."

Richard Feynman

Will the sun rise tomorrow?

DEDUCTIVE THINKING
Hypothesis driven → supporting or refuting facts

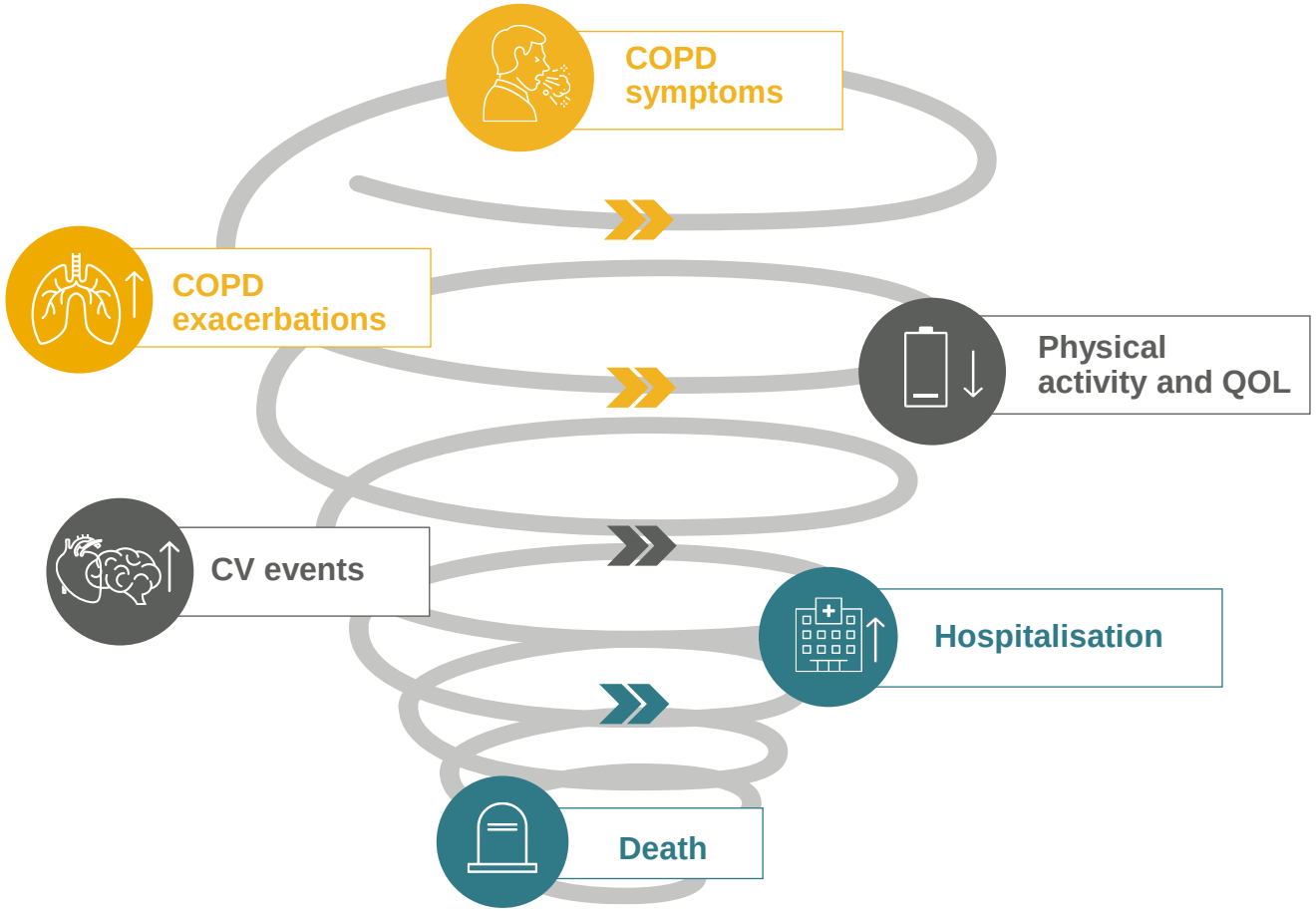
INDUCTIVE THINKING
Experience + knowledge
(presentation based model) → hypothesis and diagnosis



If premises are true
conclusions MUST be true

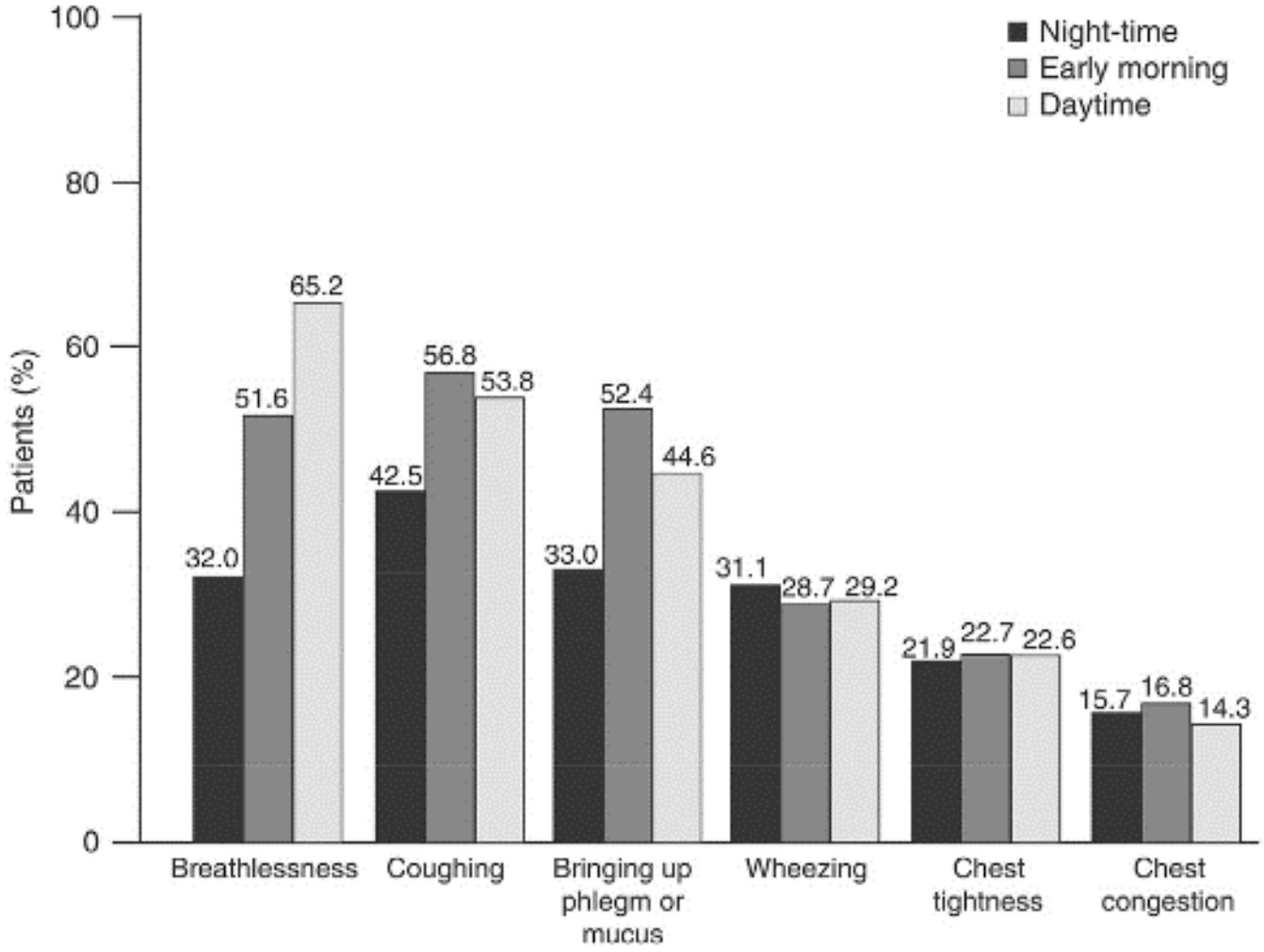
If premises are true
conclusions ARE PROBABLY true

Patients with COPD face increased risk of lung and heart events that could potentially lead to premature death



COPD patients, despite treatment,
are in need

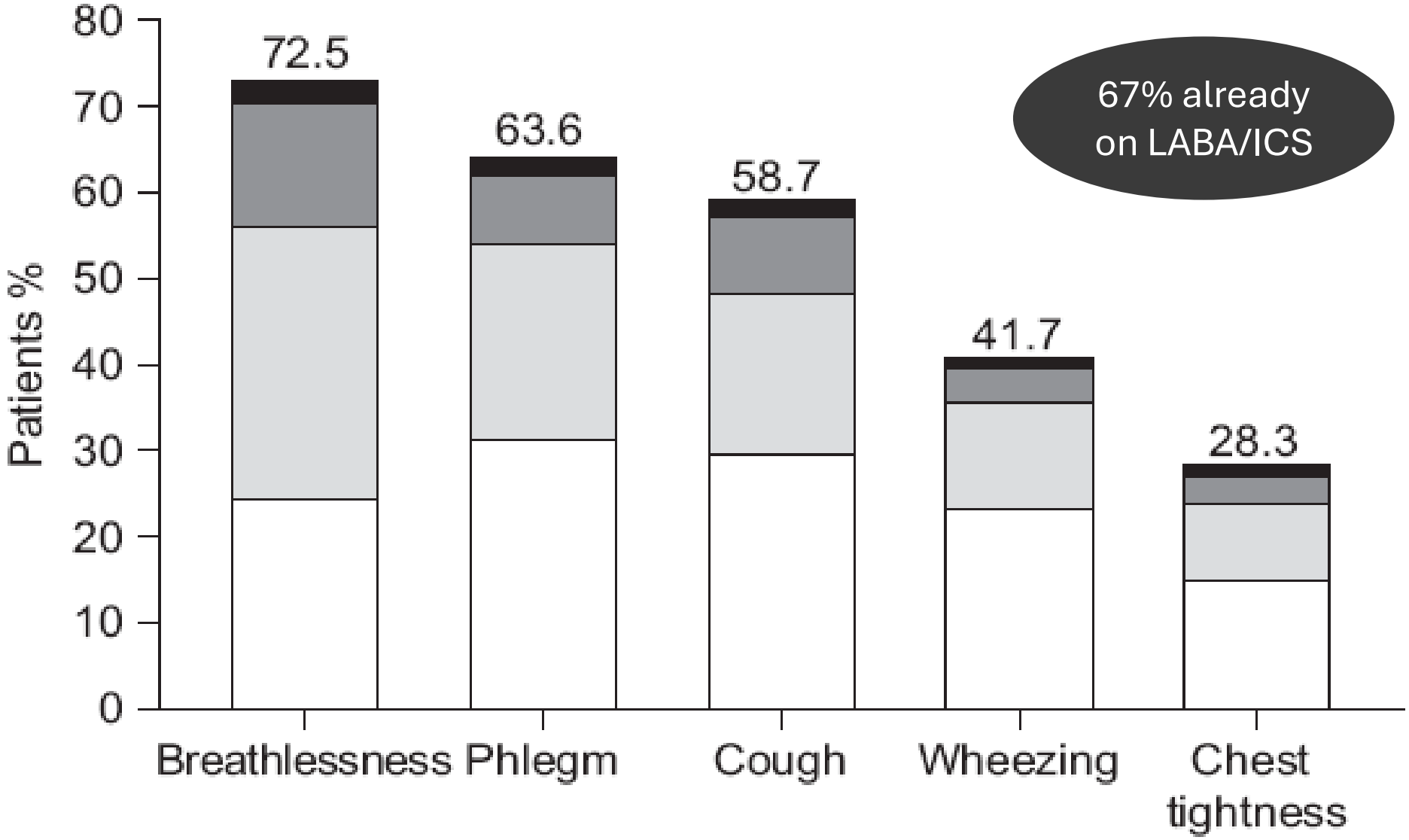
Reported symptoms despite ongoing treatment



COPD severity, n (%)	
GOLD group I (mild)	63 (8.7)
GOLD group II (moderate)	265 (36.5)
GOLD group III (severe)	261 (35.9)
GOLD group IV (very severe)	73 (10.0)

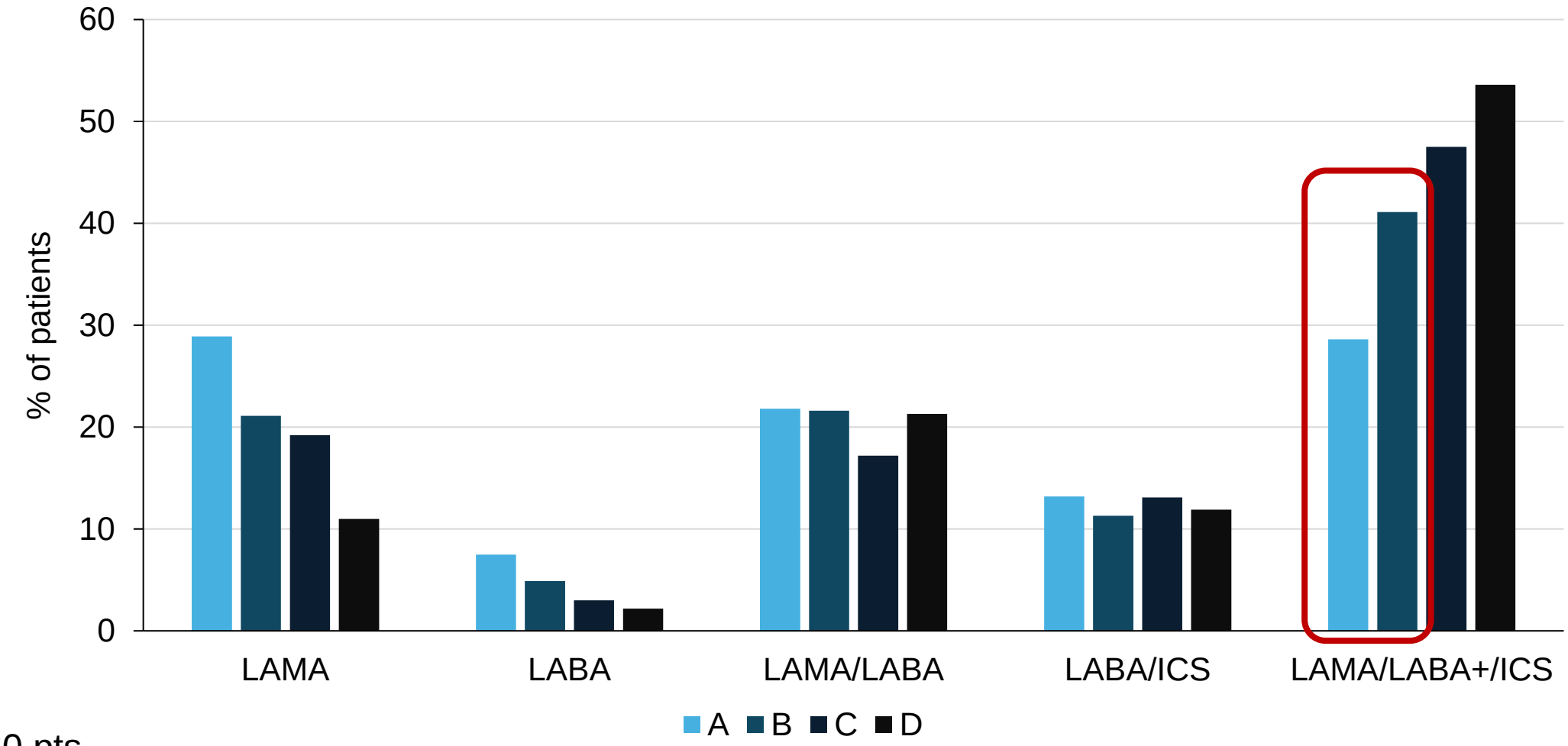
COPD medication, n (%)[a]	
LABAs + LAMAs + ICS	355 (48.8)
LABAs + ICS	100 (13.8)
LABAs + LAMAs	70 (9.6)
LABAs alone	66 (9.1)
LAMAs alone	50 (6.9)

Di Marco F et al. Respir Med 2017 (From Miravitlles M et al. Respir Res 2014)



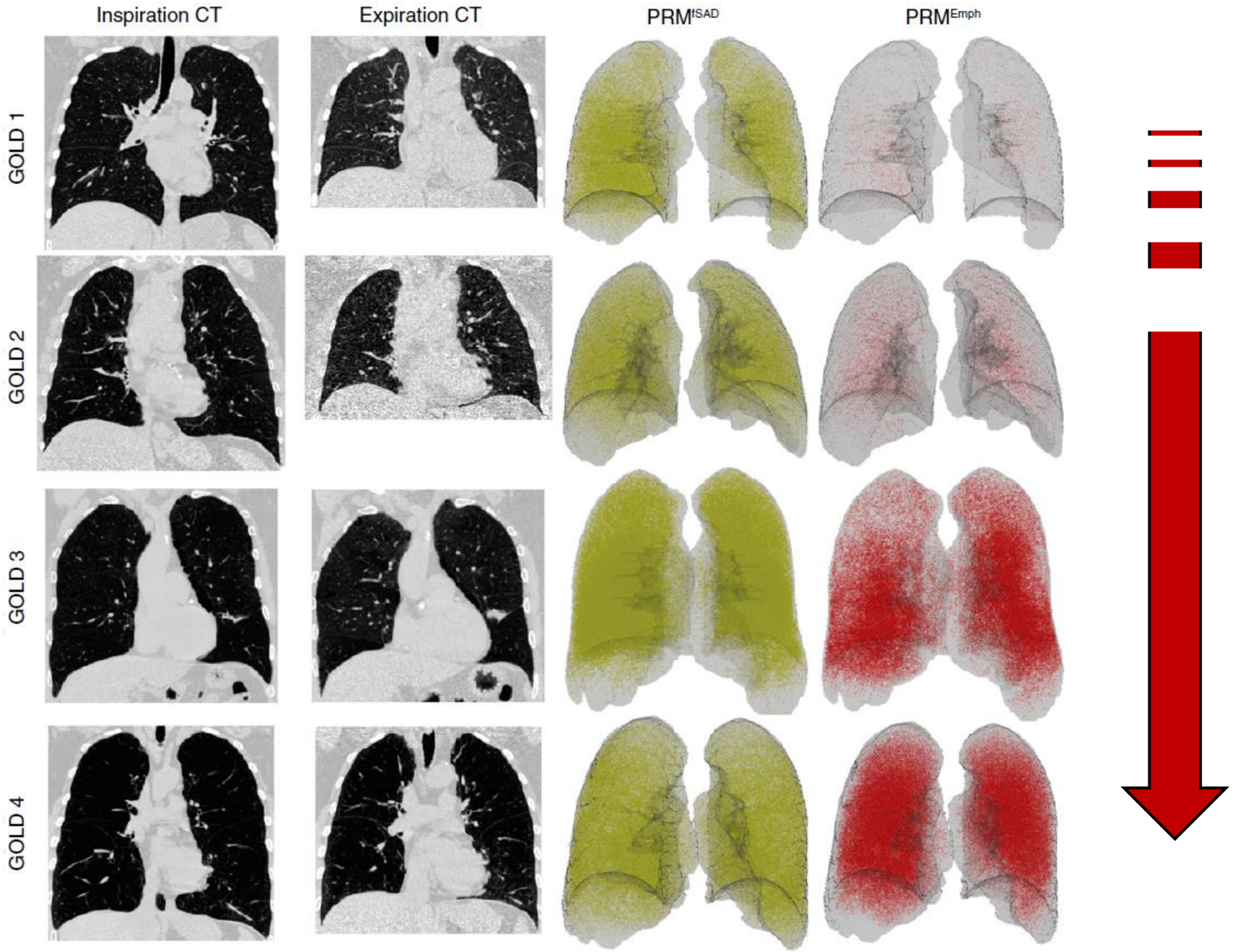
Rennard S et al. ERJ 2002

Prescribing patterns in patients with COPD. Data from the GULP study

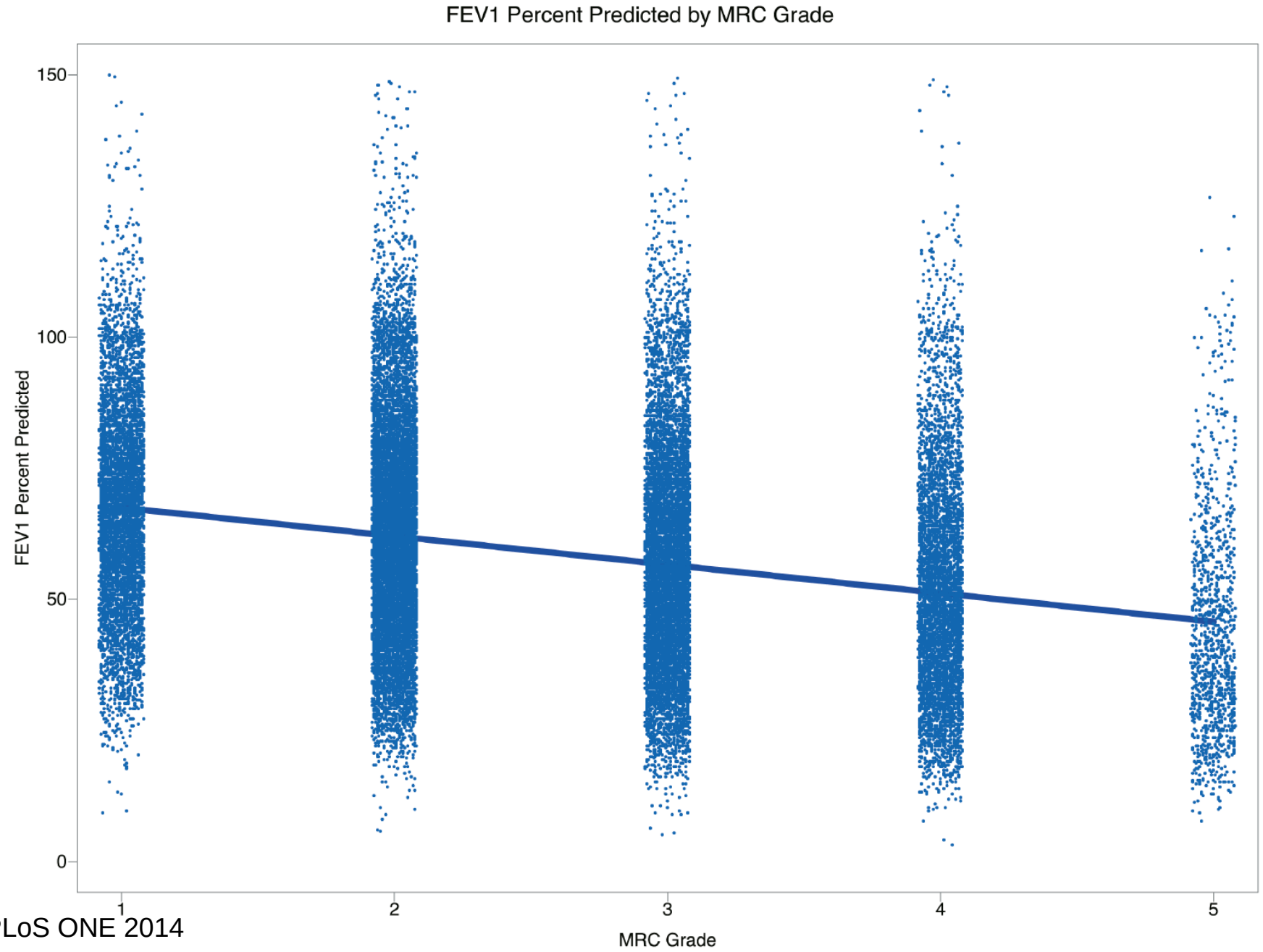


n = 1360 pts
32% ≥ 2 AECOPD previous 12 mo

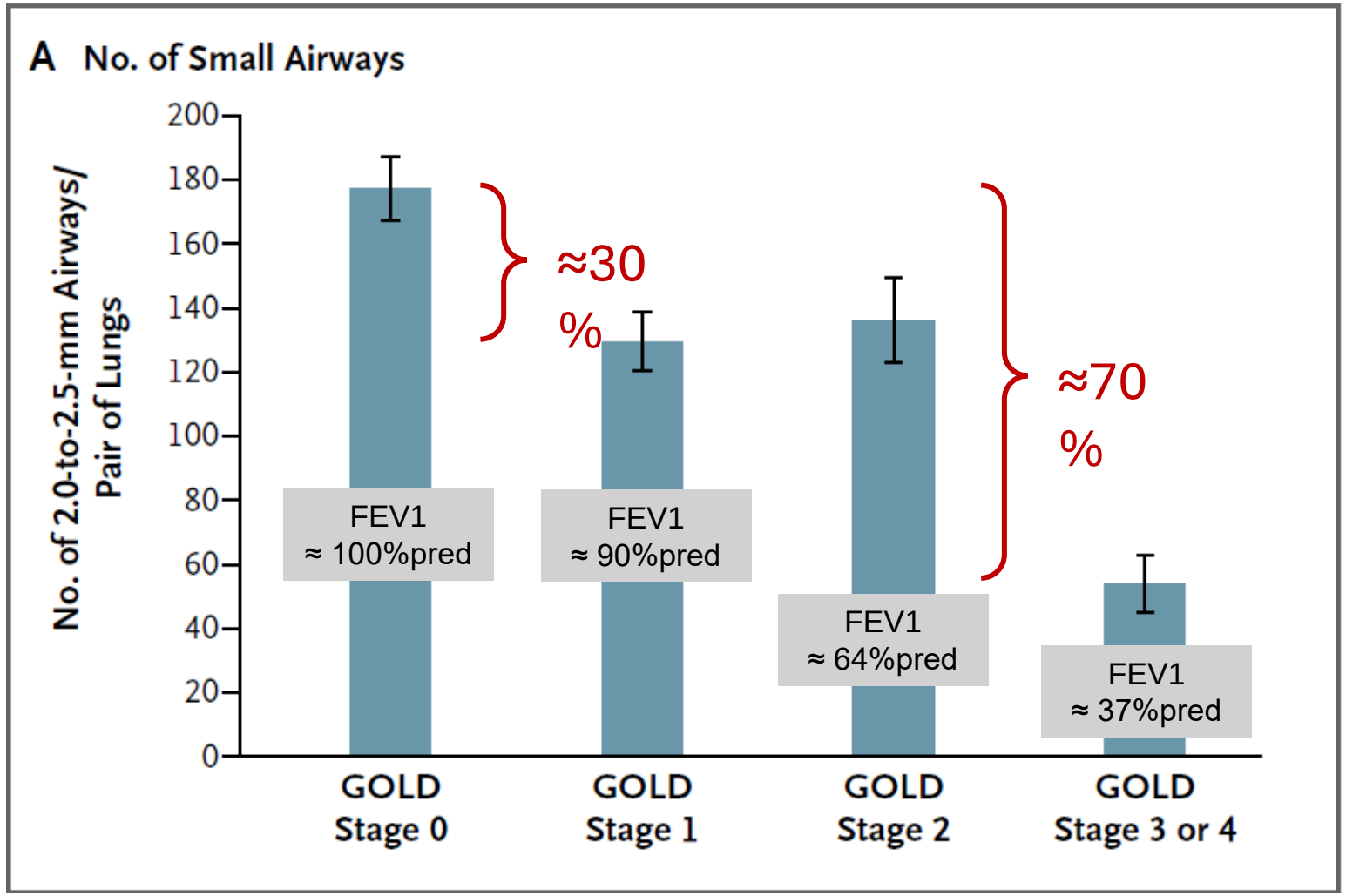
Radovanovic D et al. COPD 2019



Bhatt S et al.
Am J Respir Crit Care Med 2016

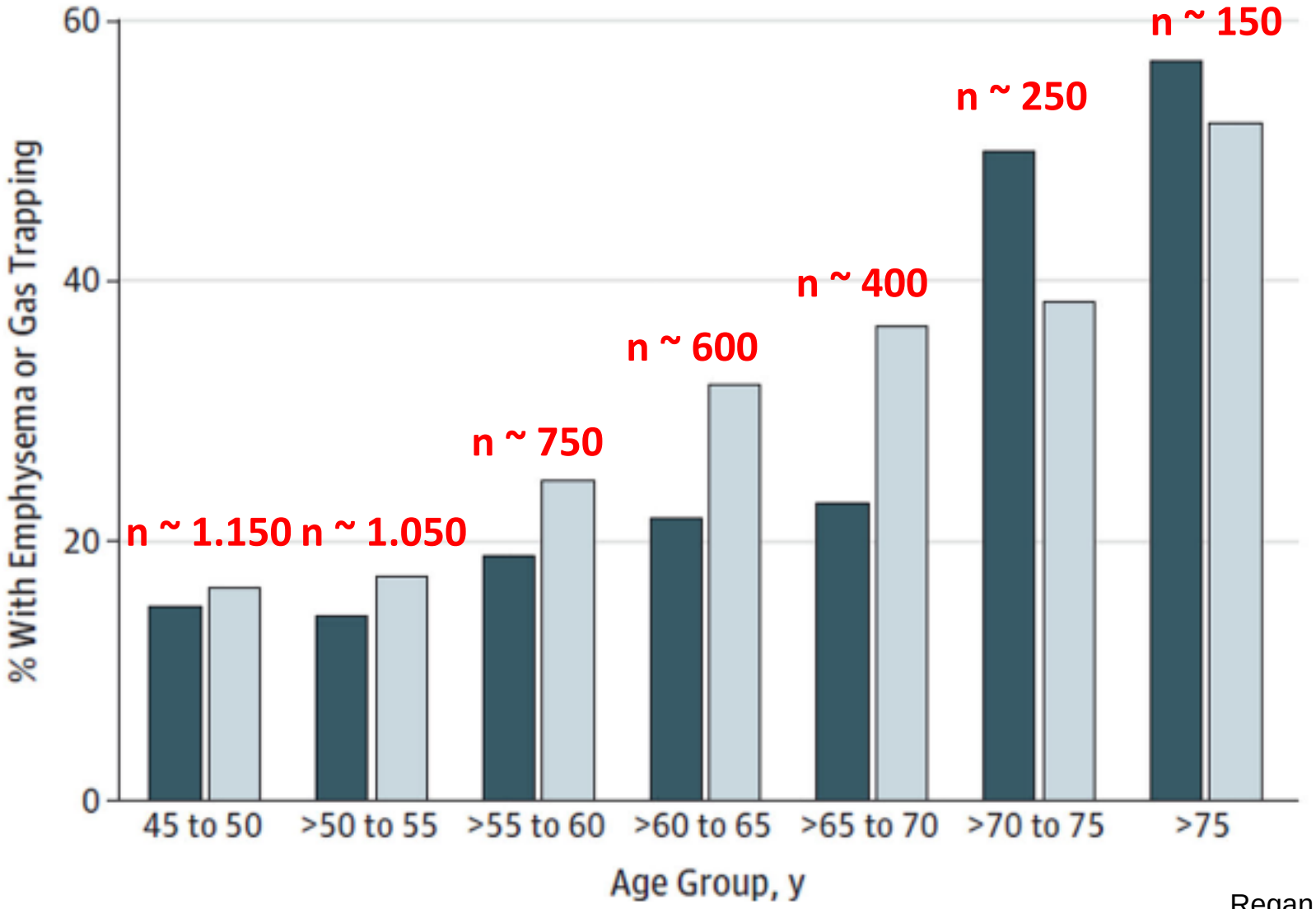


Mullerova H et al. PLoS ONE 2014

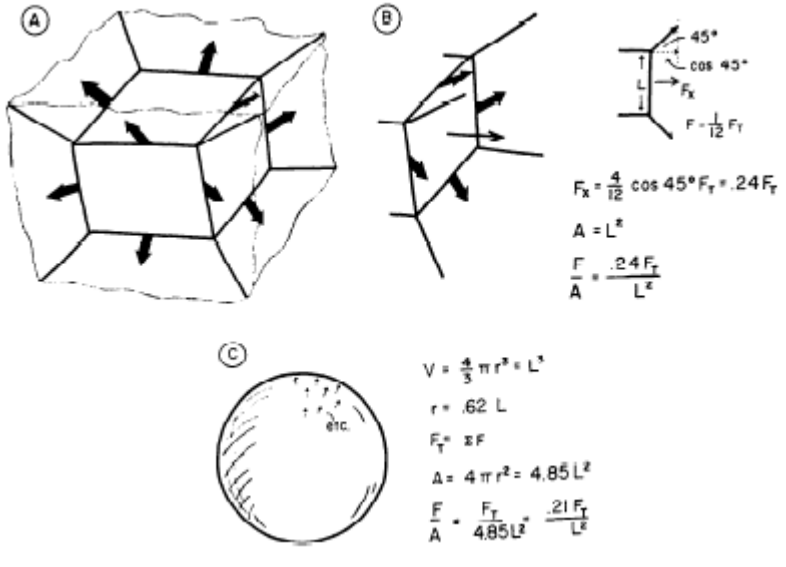


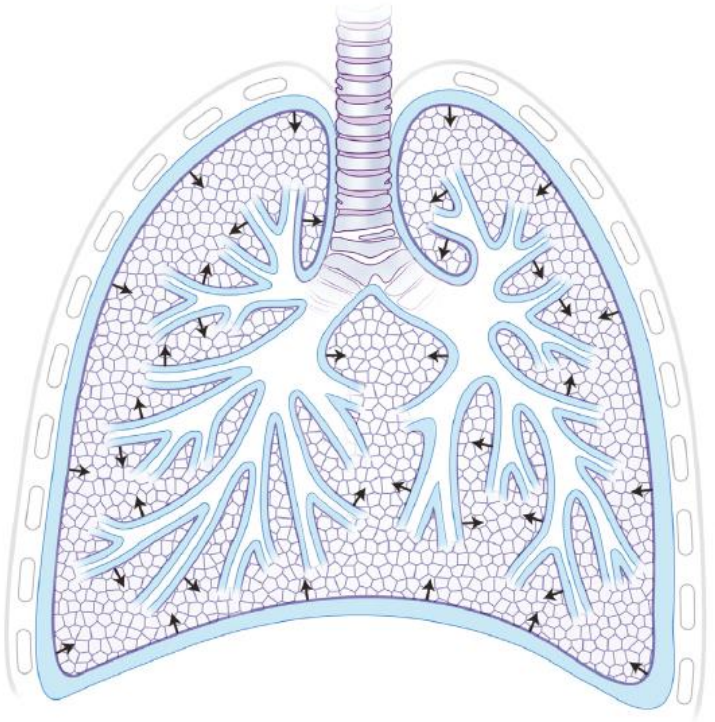
McDonough JE et al. N Engl J Med 2011

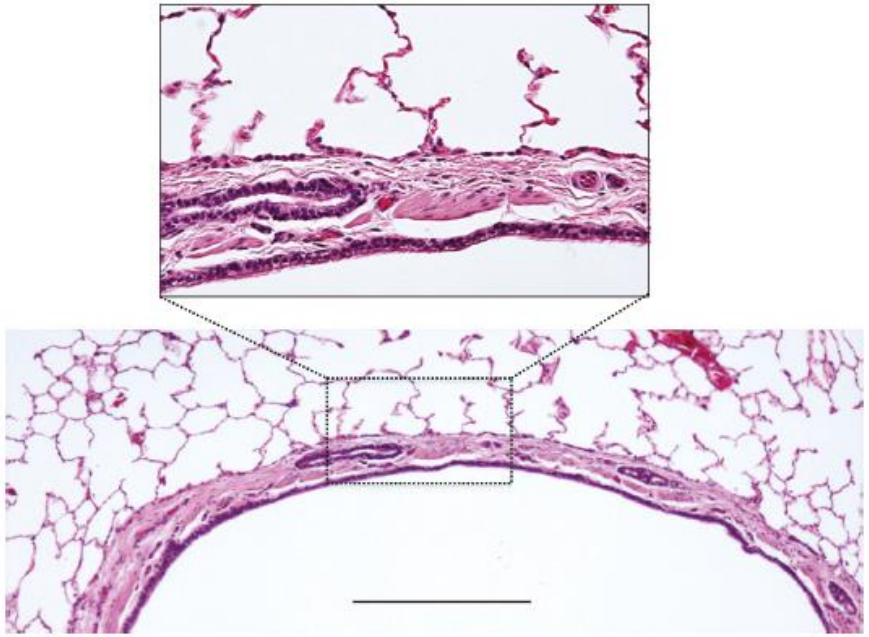
Static volume abnormalities in smokers with normal spirometry



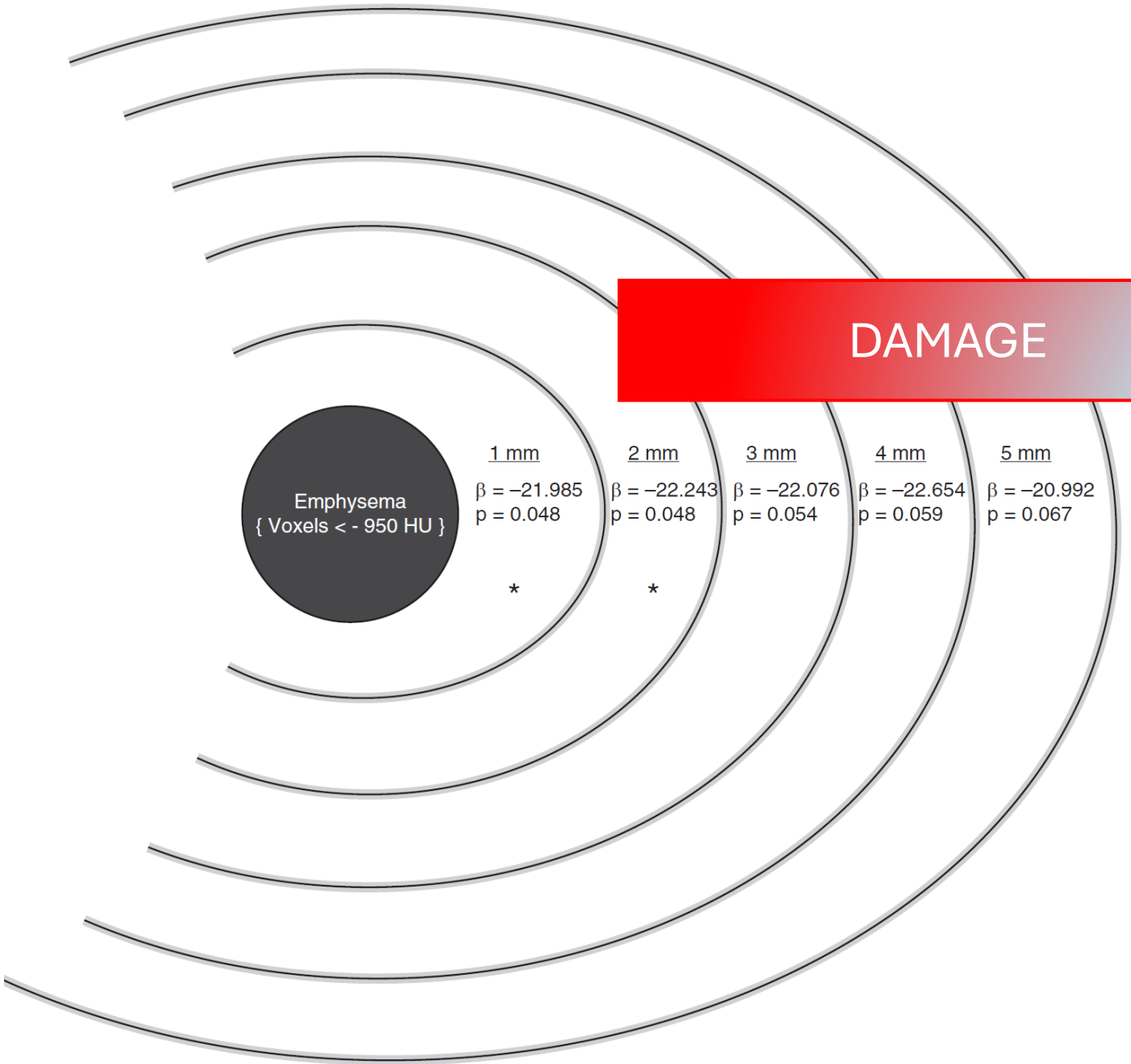
Regan EA et al. JAMA Int Med 2015



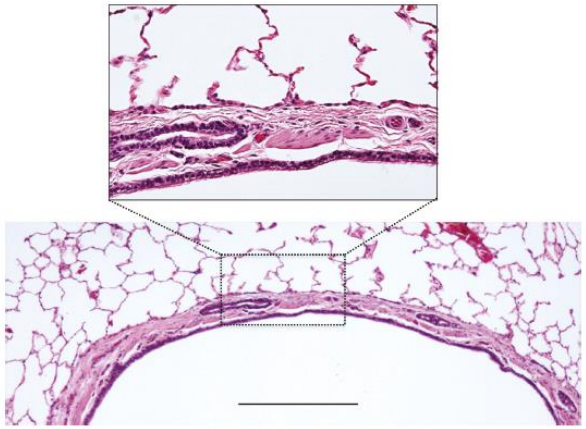


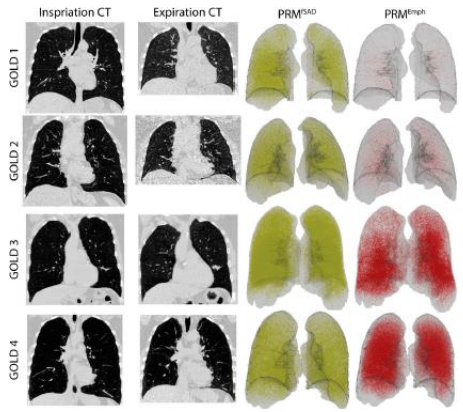


Mead J. JAP 1970
Parè & Mitzner.
Comprehensive Physiology 2012

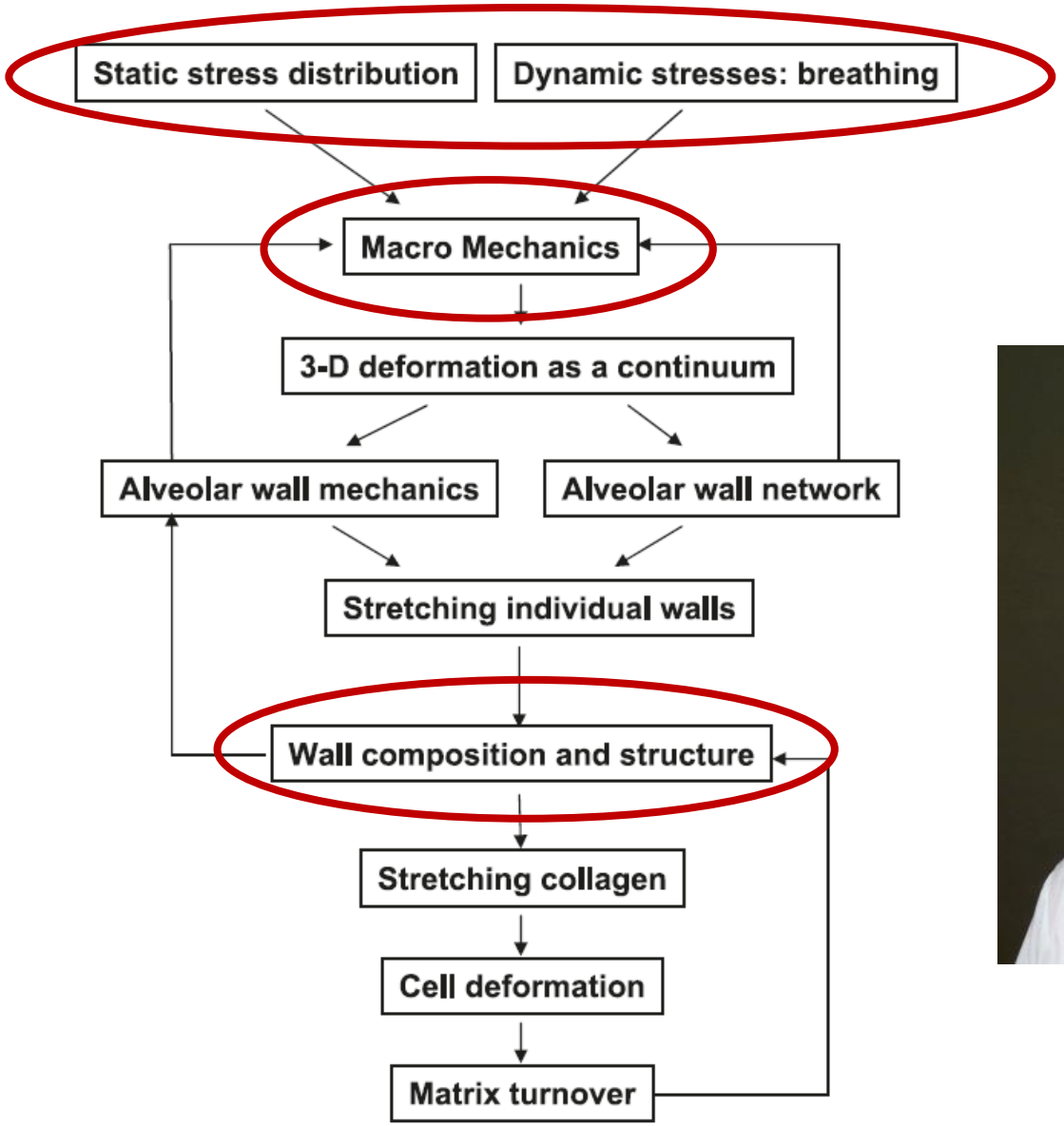


DAMAGE

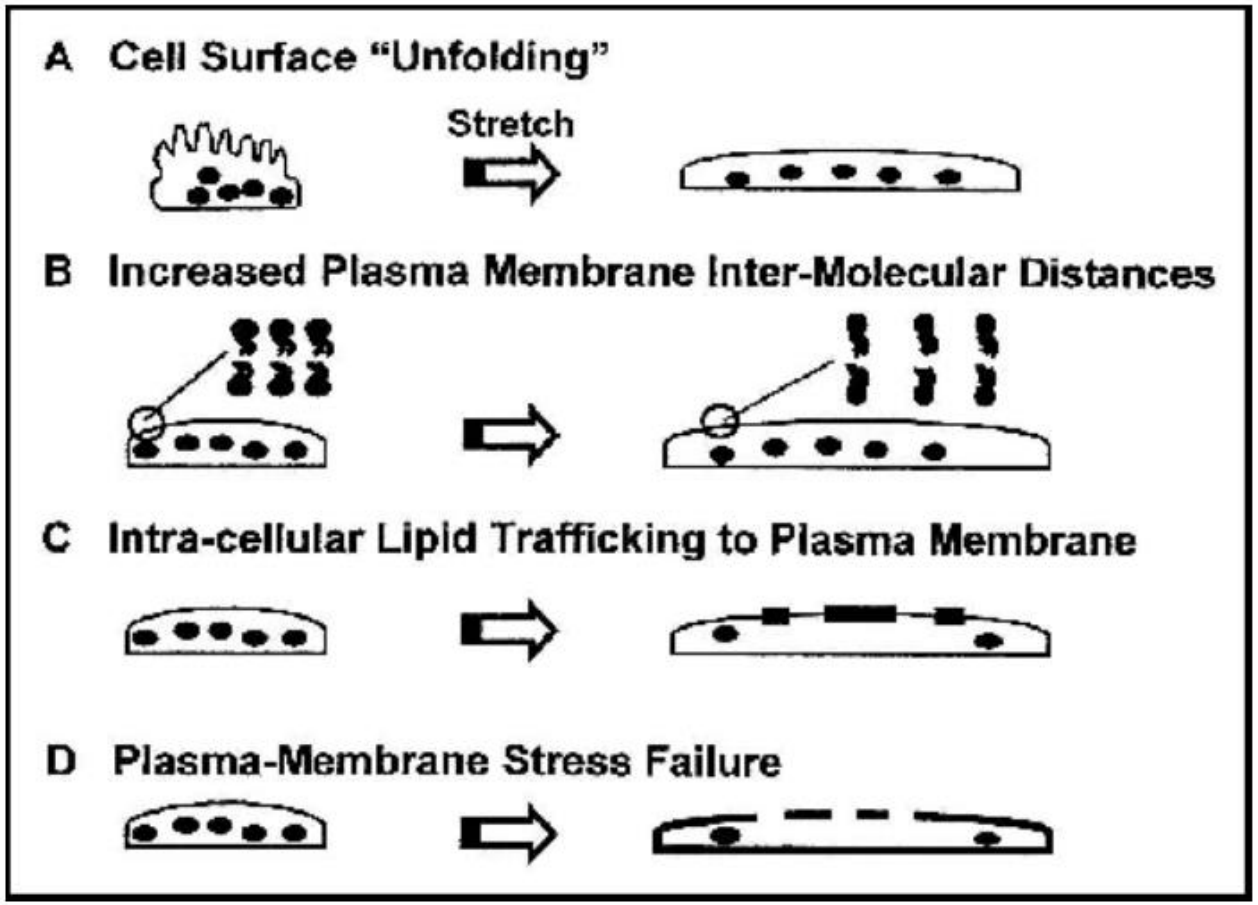


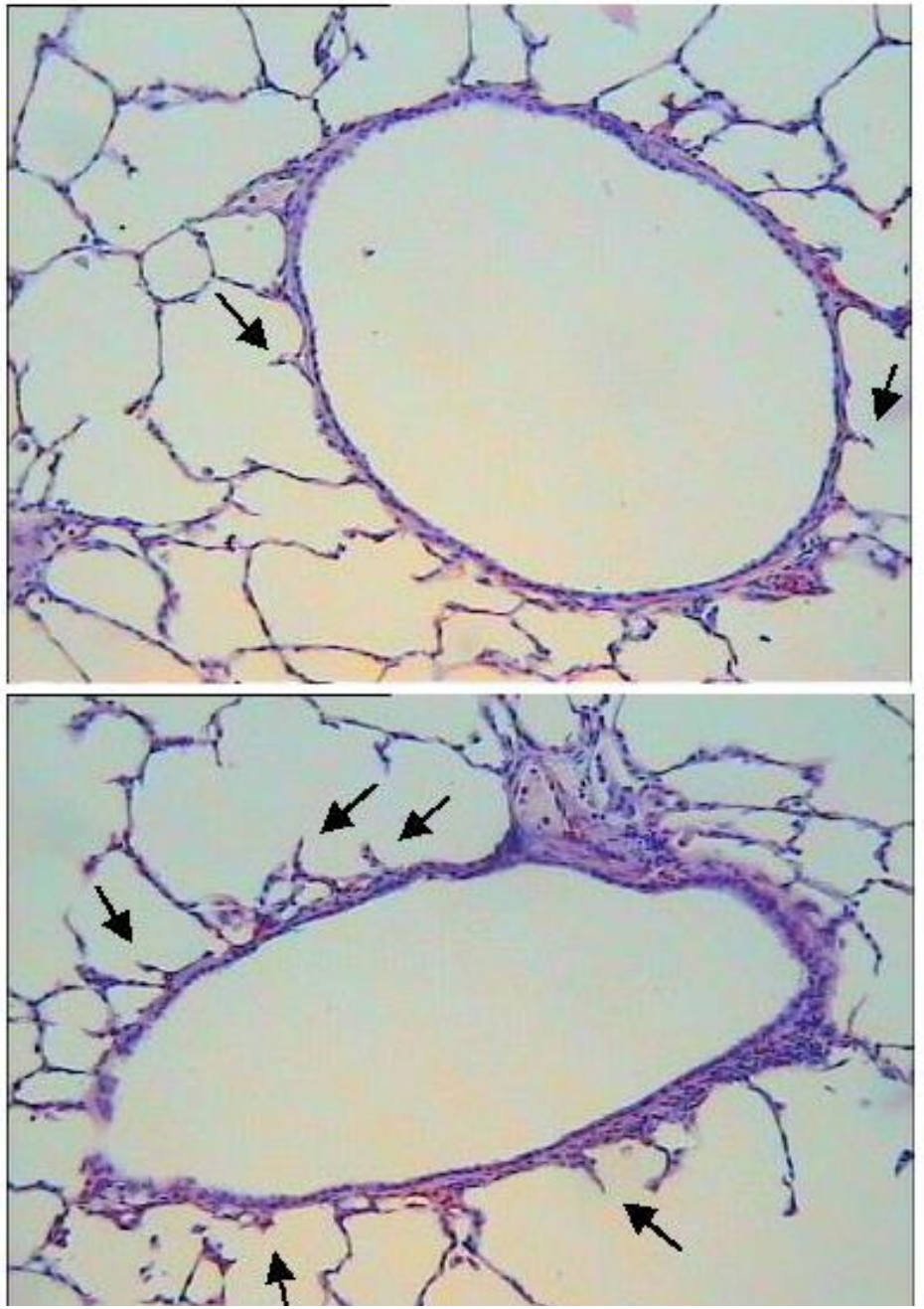


Bhatt SP et al. AJRCCM 2017

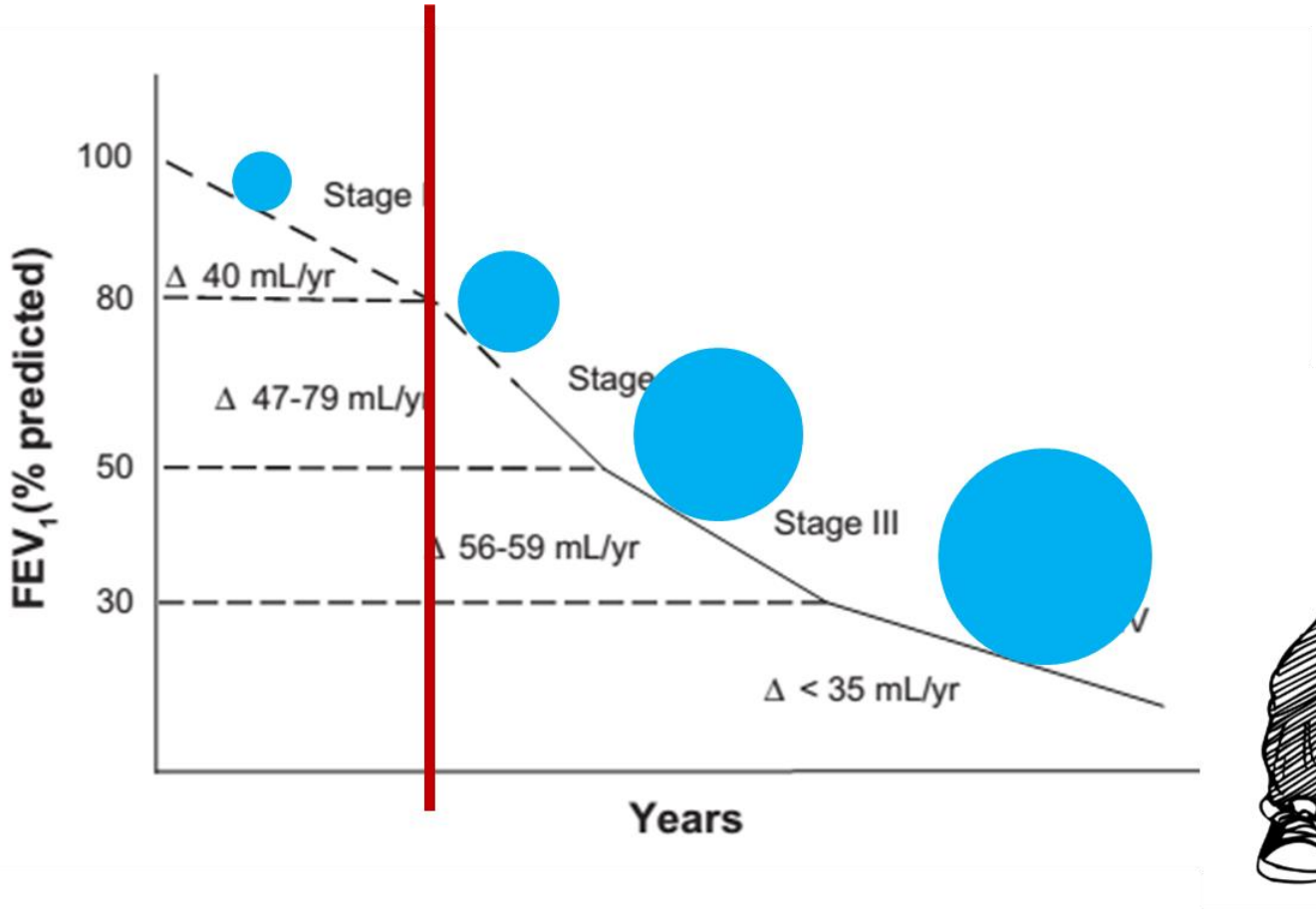


Suki B et al. J Appl Physiol 2005



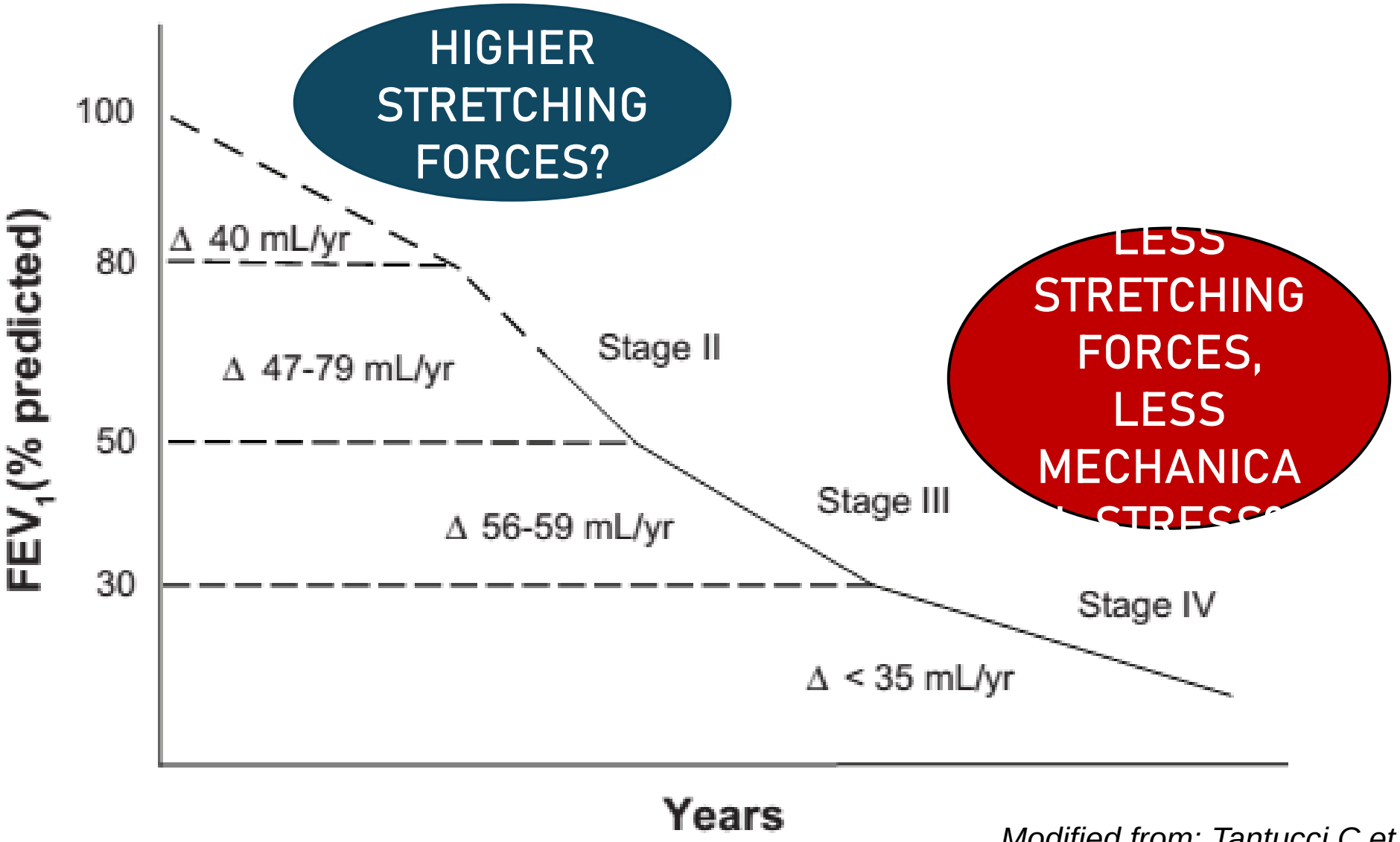


Vlahakis NE & Hubmair RD. Curr Opin Crit Care 2 Courtesy of Prof. Pecchiari, University

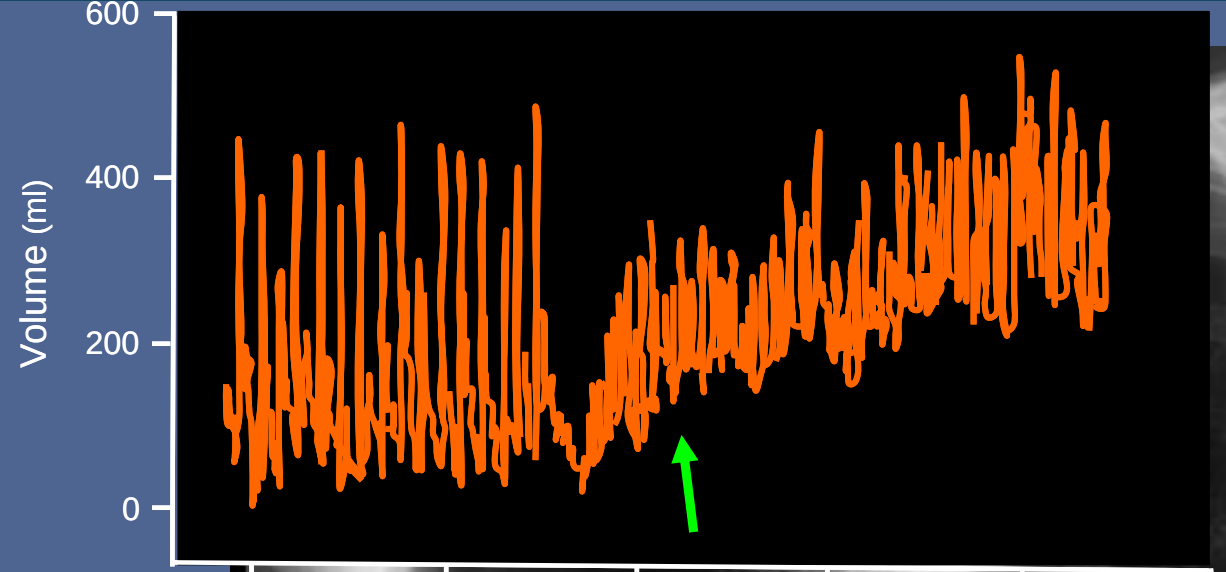


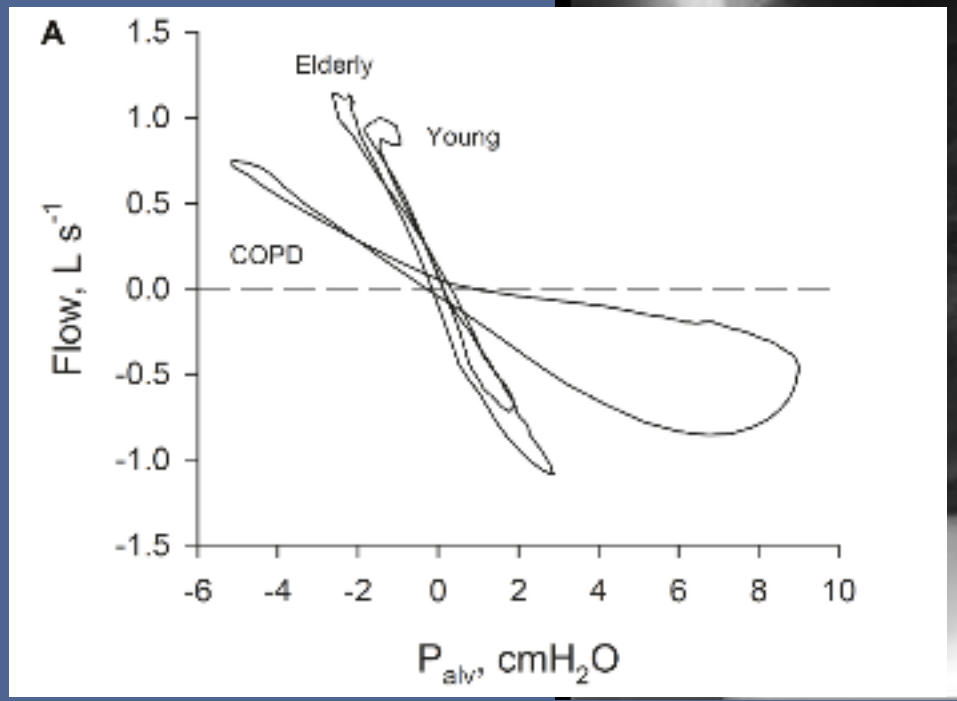
Modified from: Tantucci C et al, Int J COPD 2012

…lung vanishes

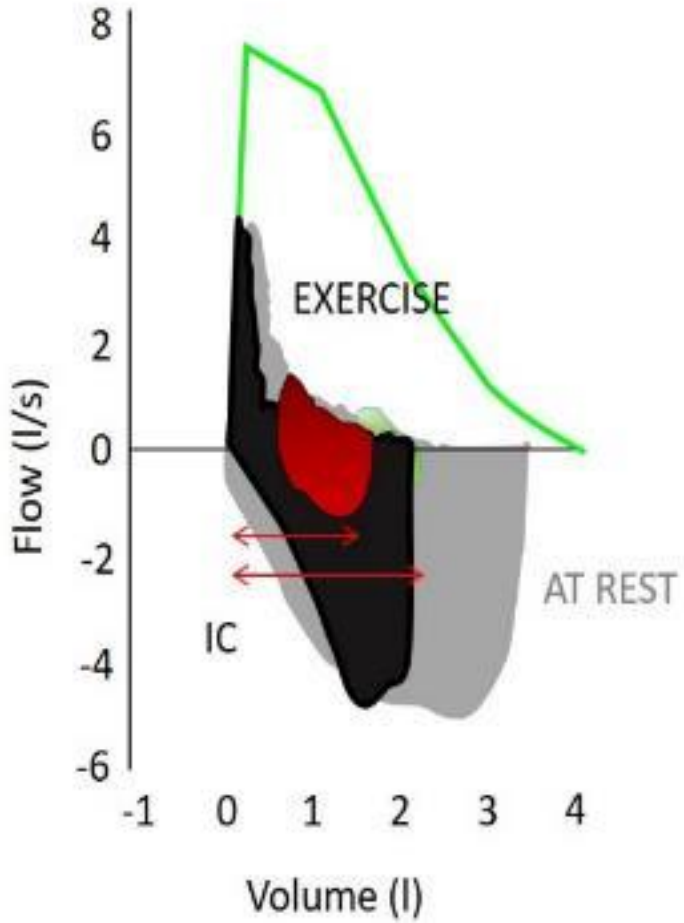


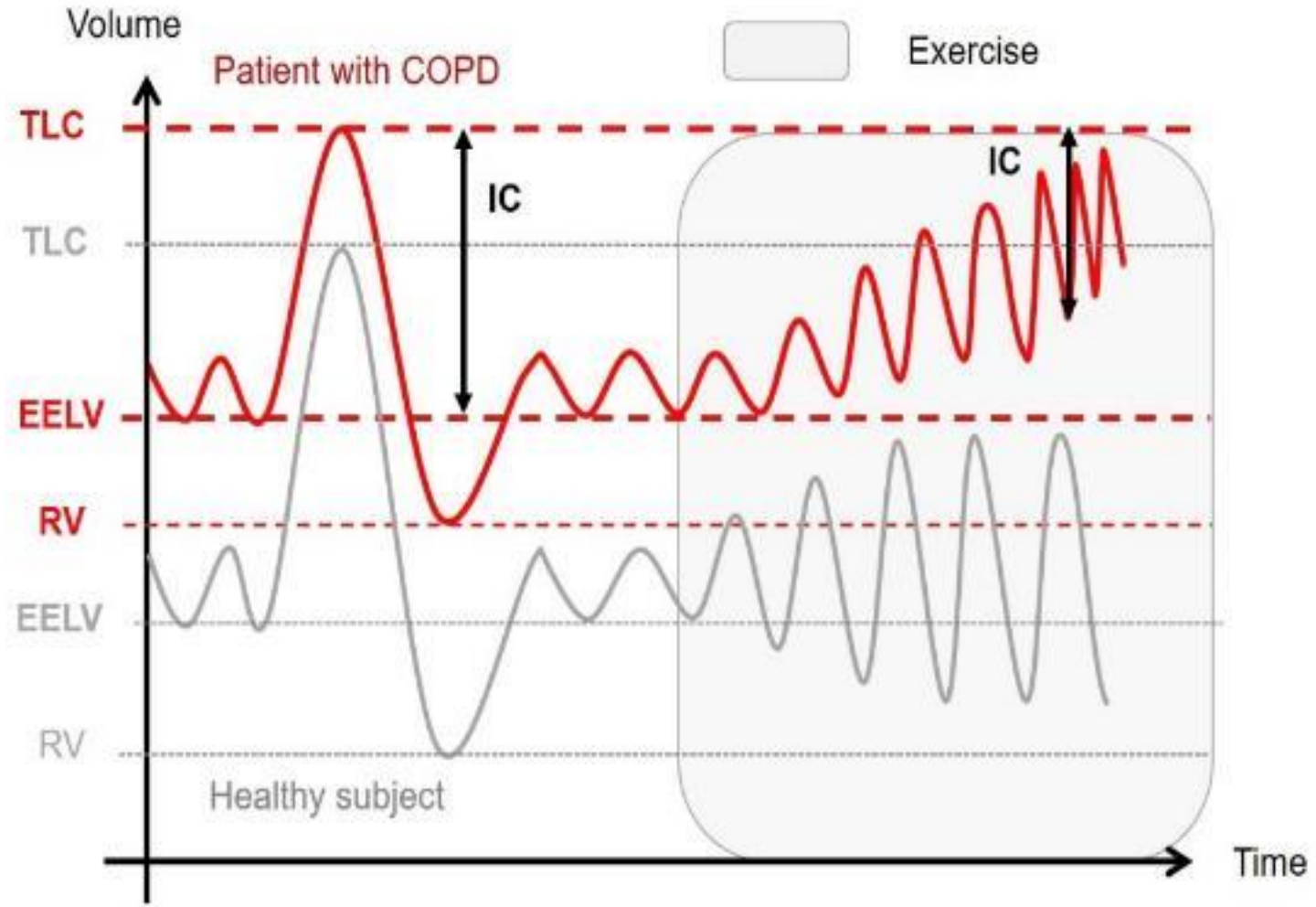
Modified from: Tantucci C et al. Int J COPD 2012





Radovanovic D et al. Front Physiol 2018
Parthasarathy S et al. J Appl Physiol 2007

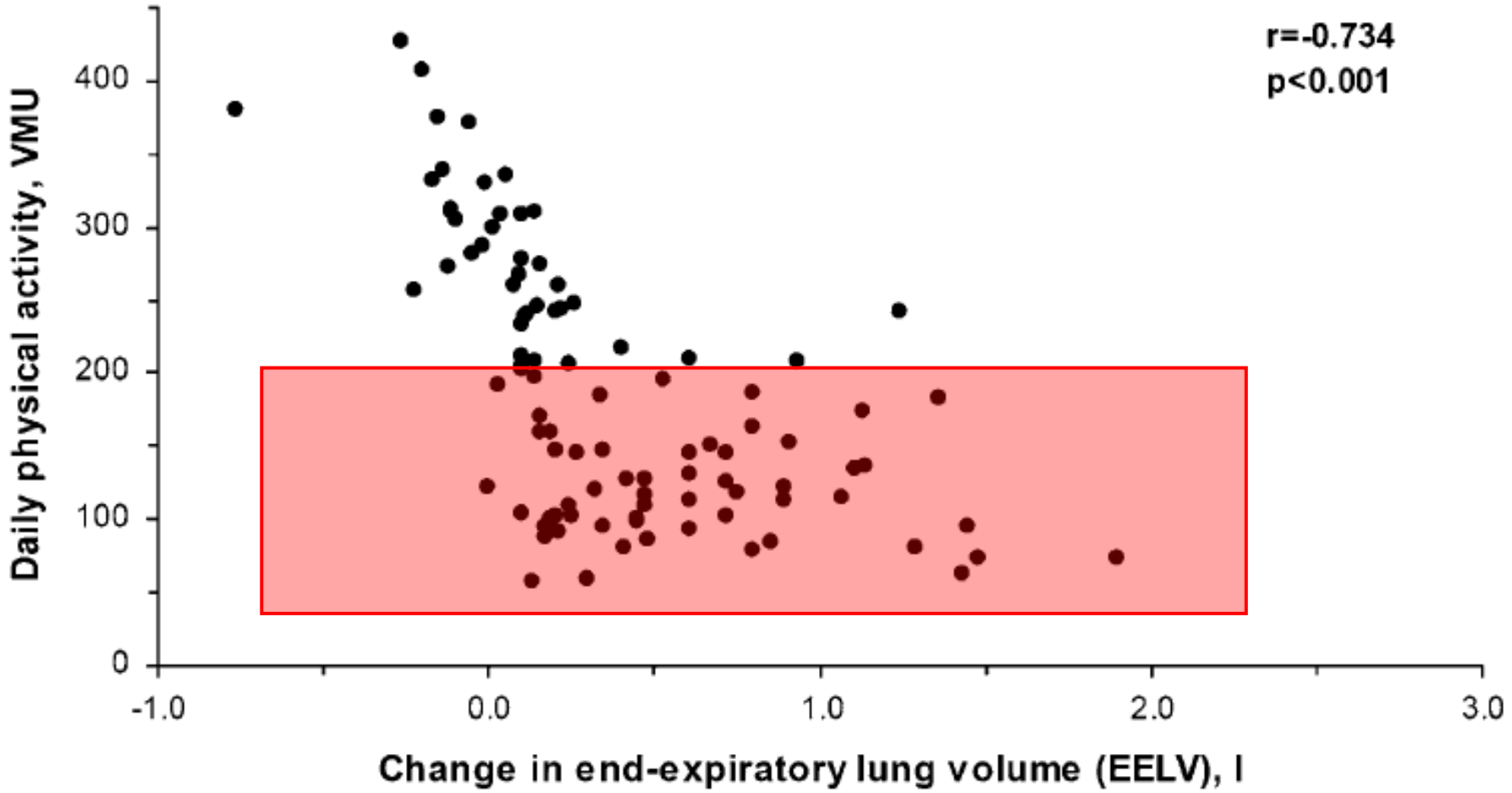




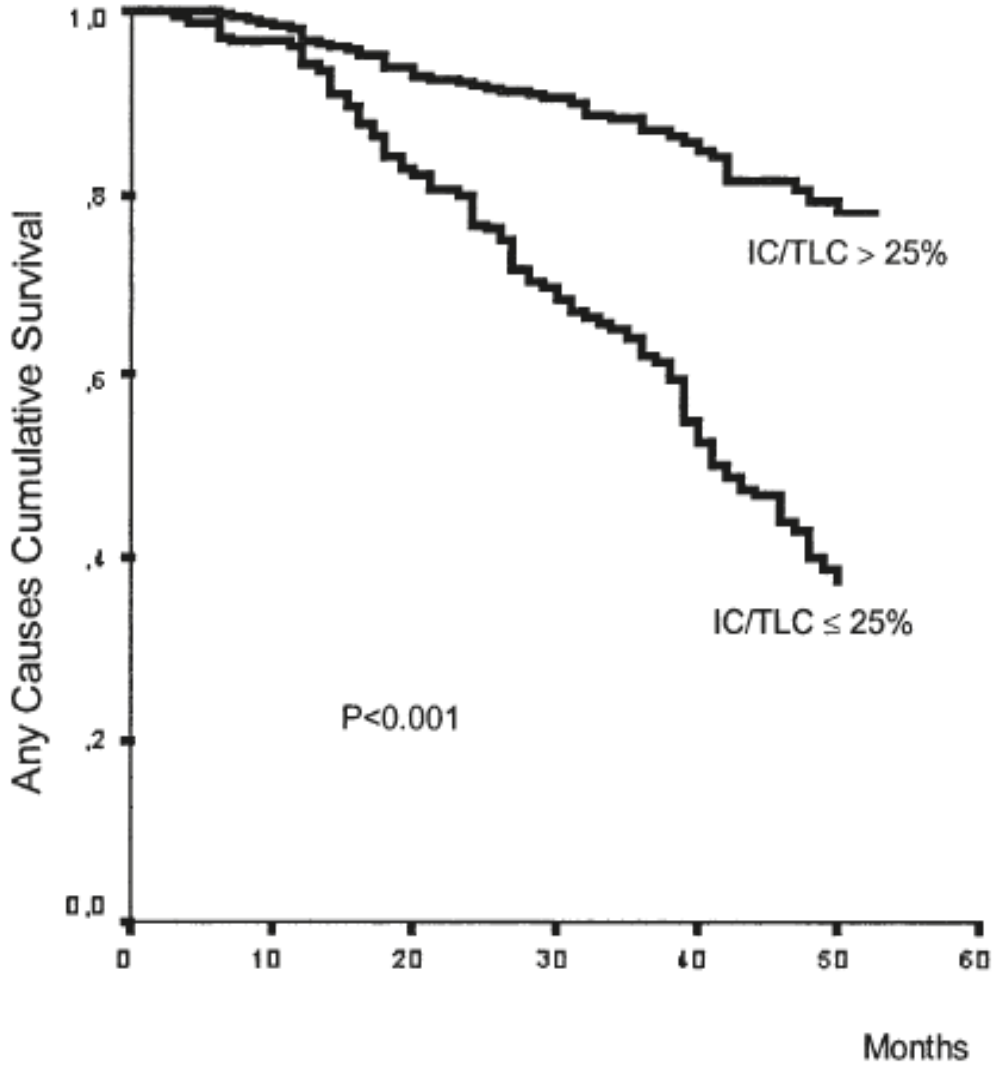
Danzo F et al. Submitted

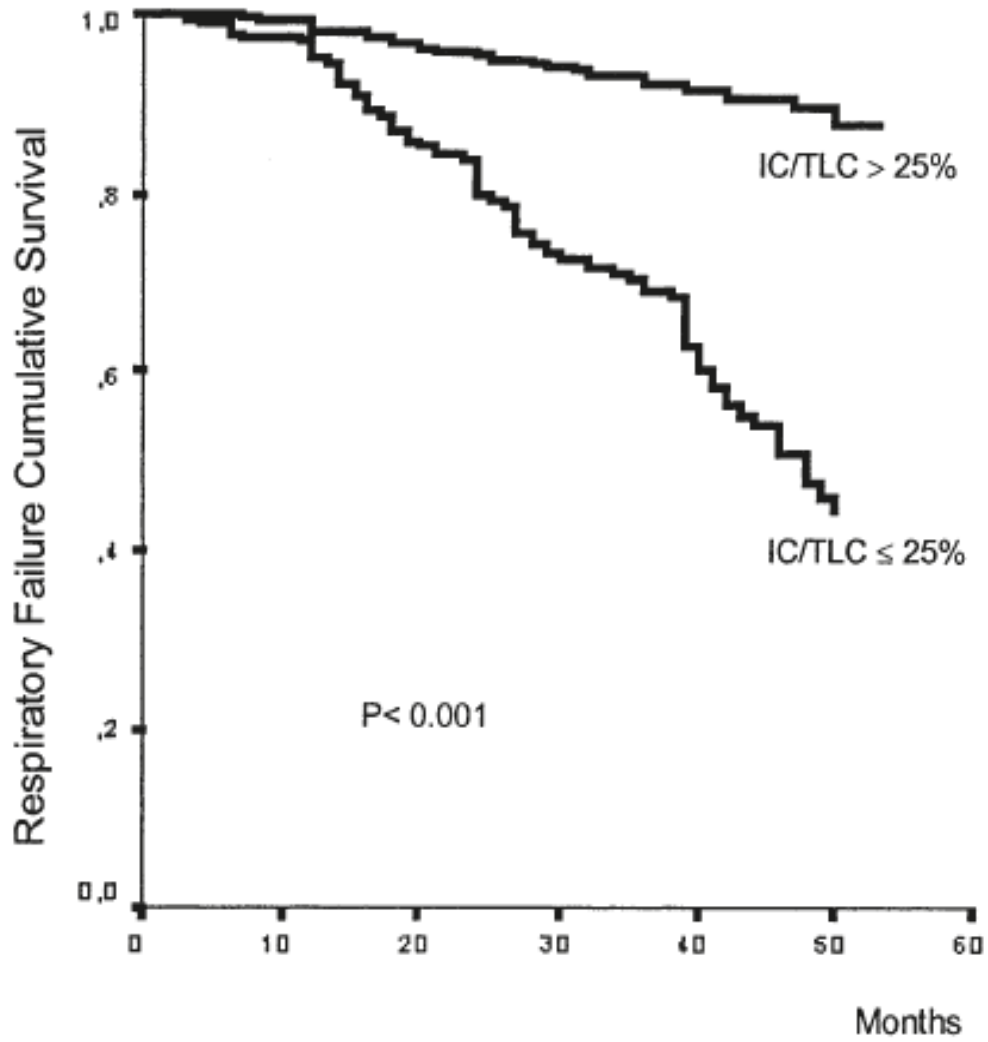
Daily Physical Activity in Patients with Chronic Obstructive Pulmonary Disease Is Mainly Associated with Dynamic Hyperinflation

Francisco Garcia-Rio[1], Vanesa Lores[1], Olga Mediano[2], Blas Rojo[2], Angel Hernanz[3], Eduardo López-Collazo[4], and Rodolfo Alvarez-Sala[1]



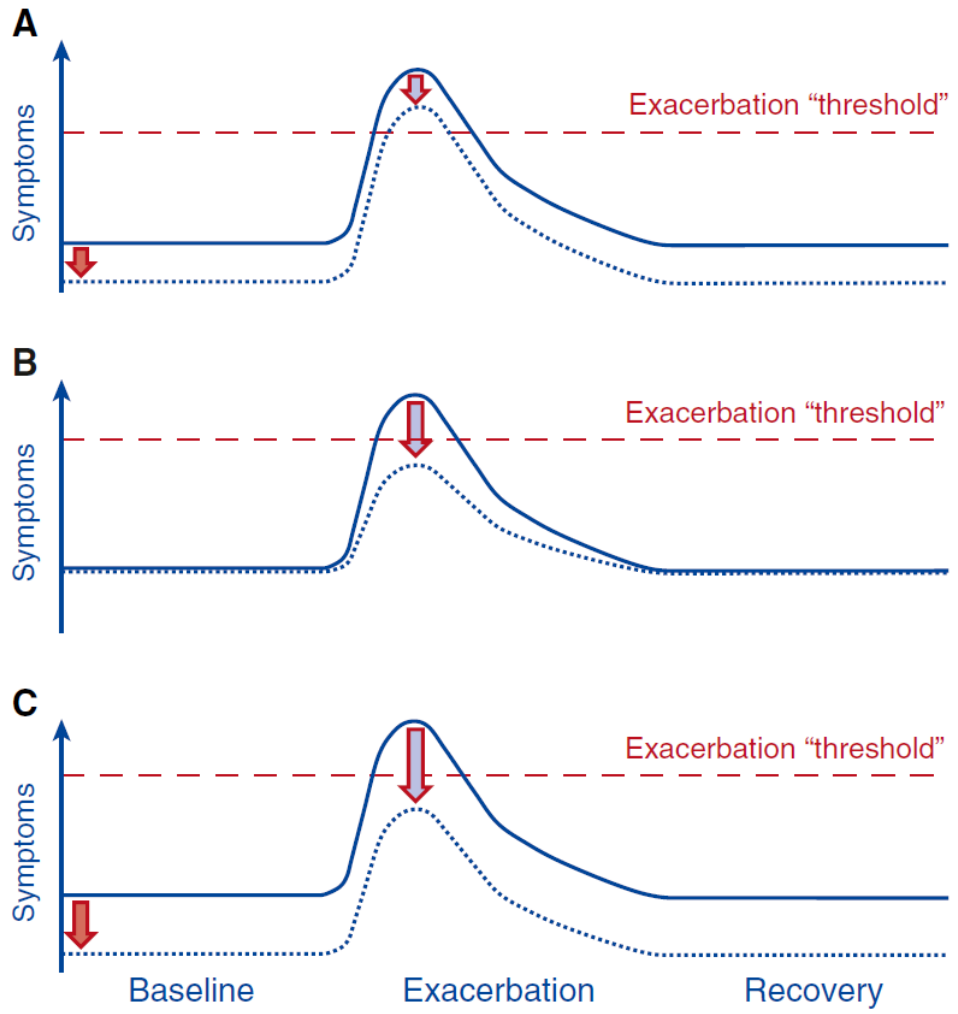
Garcia Rio F et al. Am J Respir Crit Care Med 2009





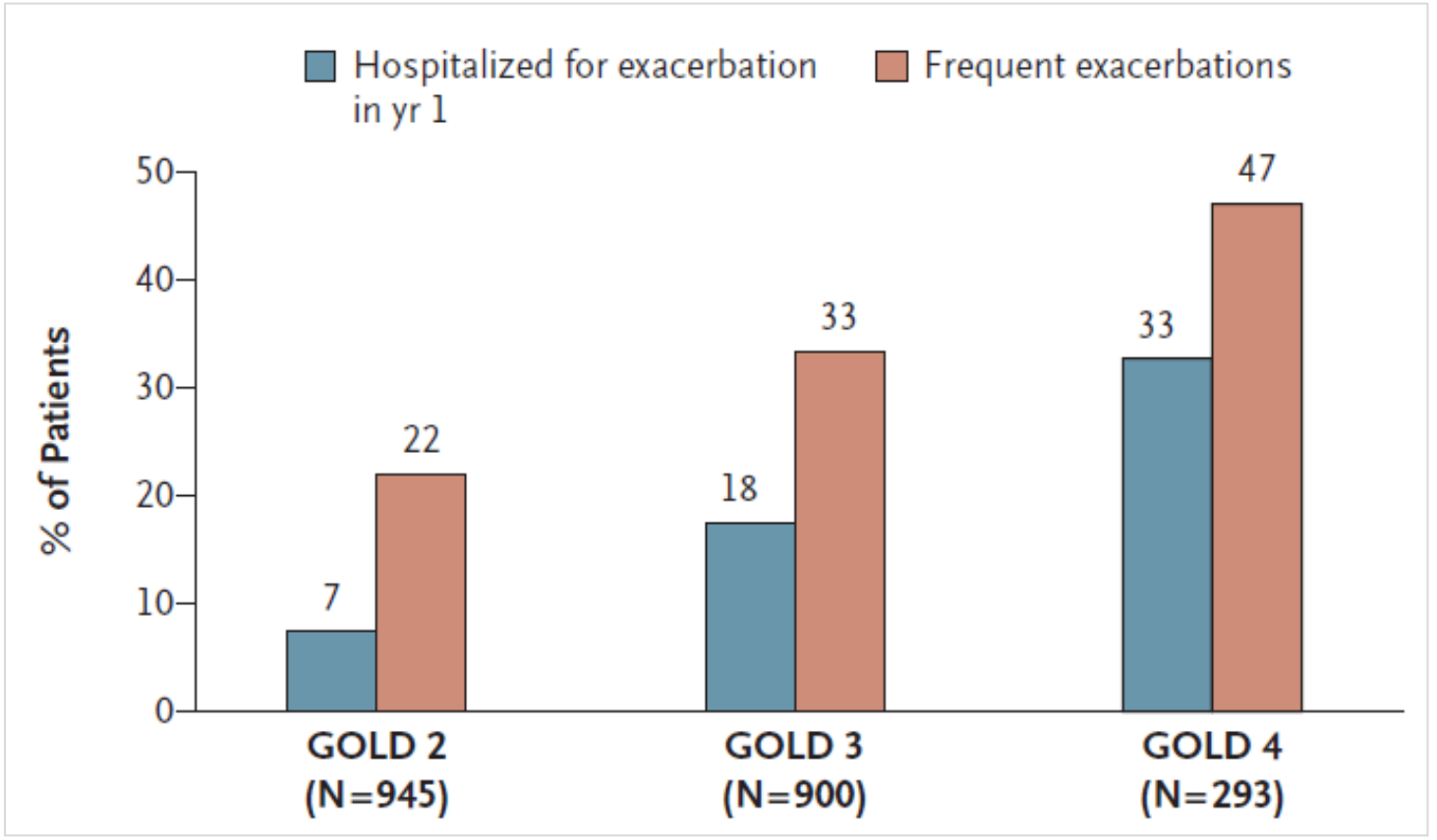
Casanova C et al. Am J Respir Crit Care Med 2005

In search for the ideal bronchodilator for COPD exacerbations

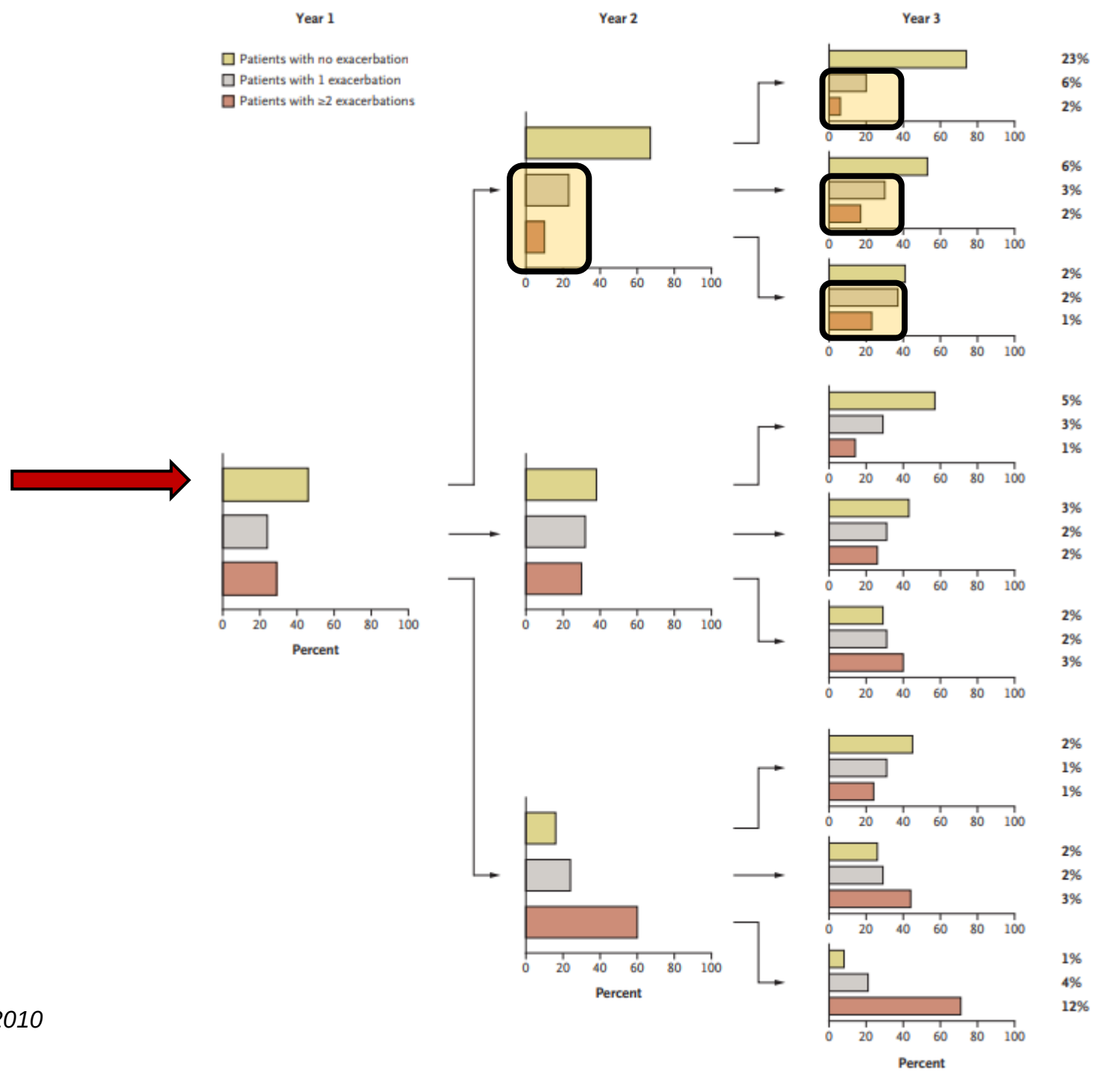


Adapted from Beeh K. AJRCCM 2017;2.

Eclipse study
2138 patients

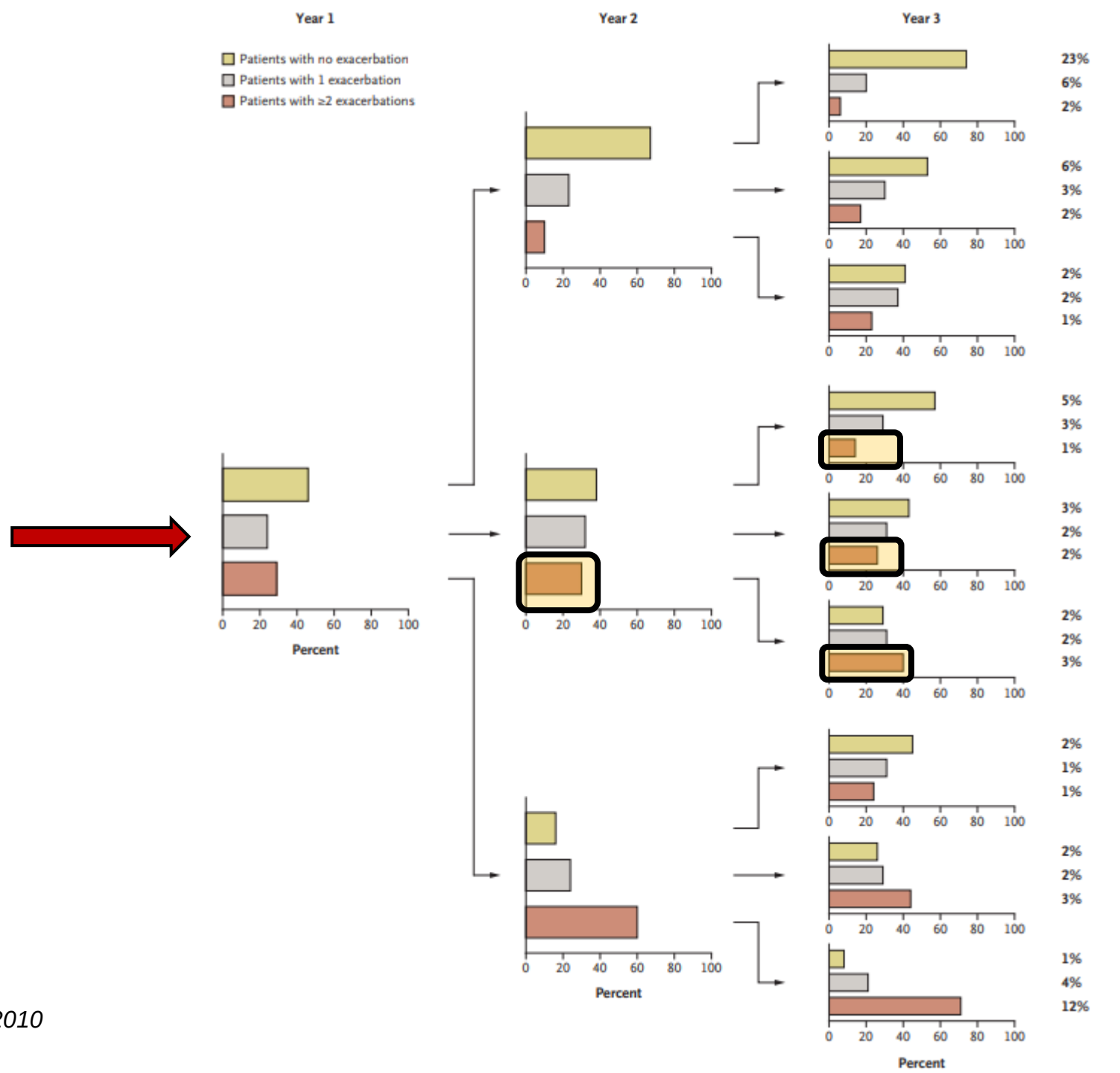


Hurst et al. N Engl J Med 2010



35% of NON exacerbating patients will experience at least 1 ex. in 3 years

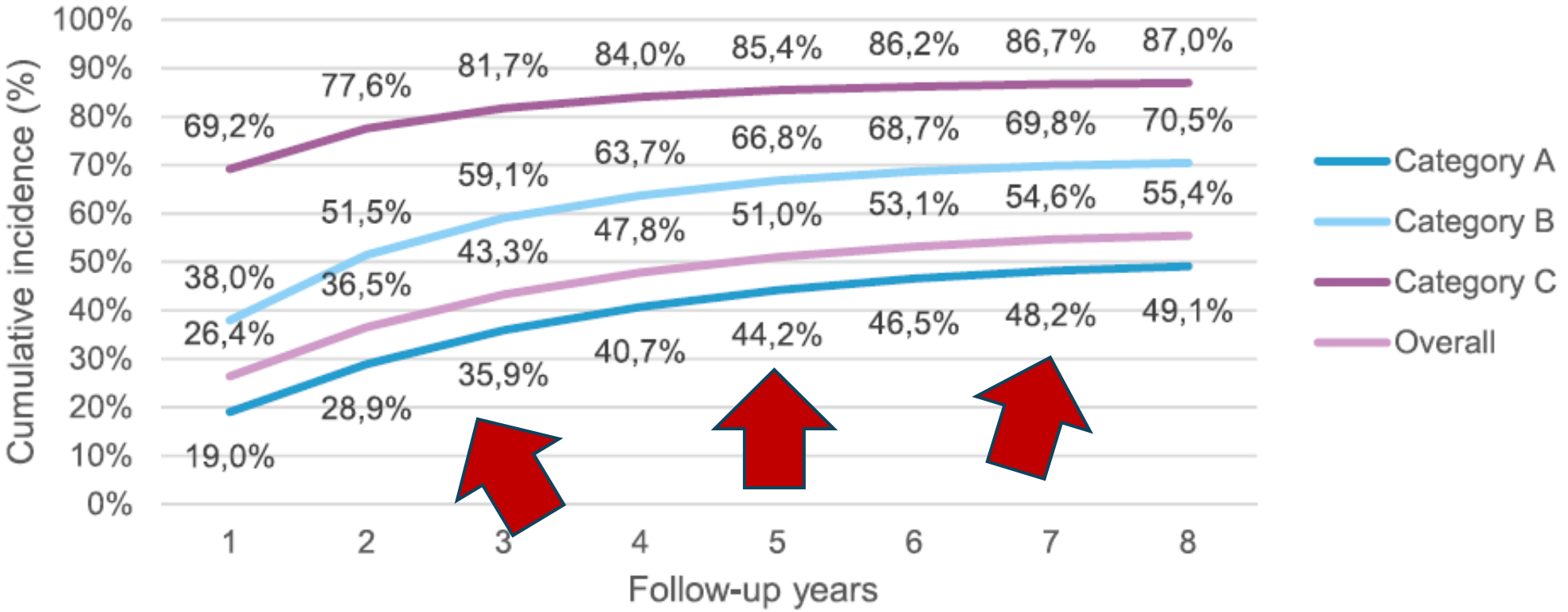
Hurst et al. N Engl J Med 2010



25% of low risk patients will experience ≥ 2 ex. in 3 years

Hurst et al. N Engl J Med 2010

Cumulative incidence of COPD exacerbations
Significant risk also in patients without exacerbations at baseline



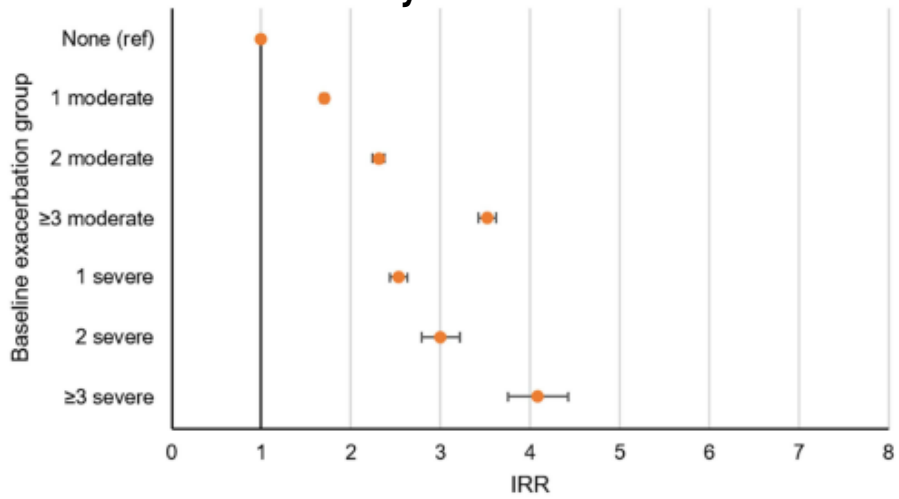
No exacerbations in previous year

› 250000 COPD patients

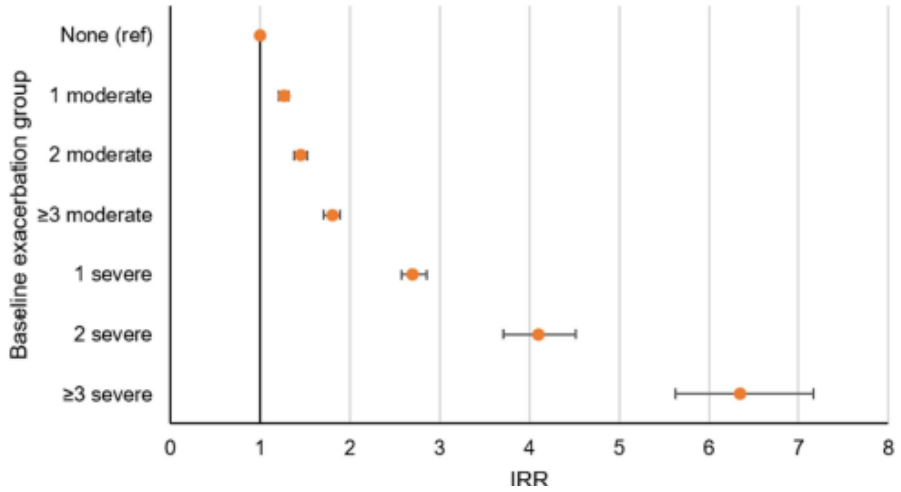
Vogelmeier CF et al. Int J COPD 2021

Any AECOPD frequency and severity are associated with future risk of AECOPD and mortality

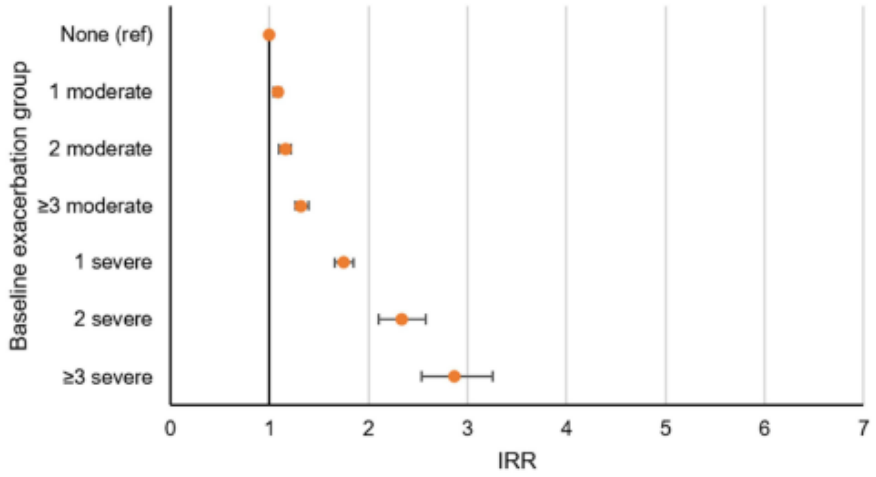
Any exacerbation



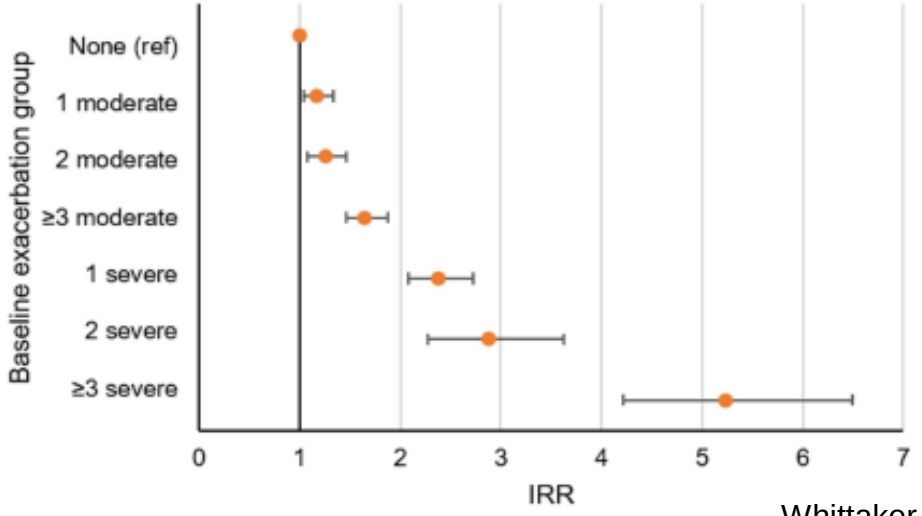
Severe exacerbations



All cause mortality

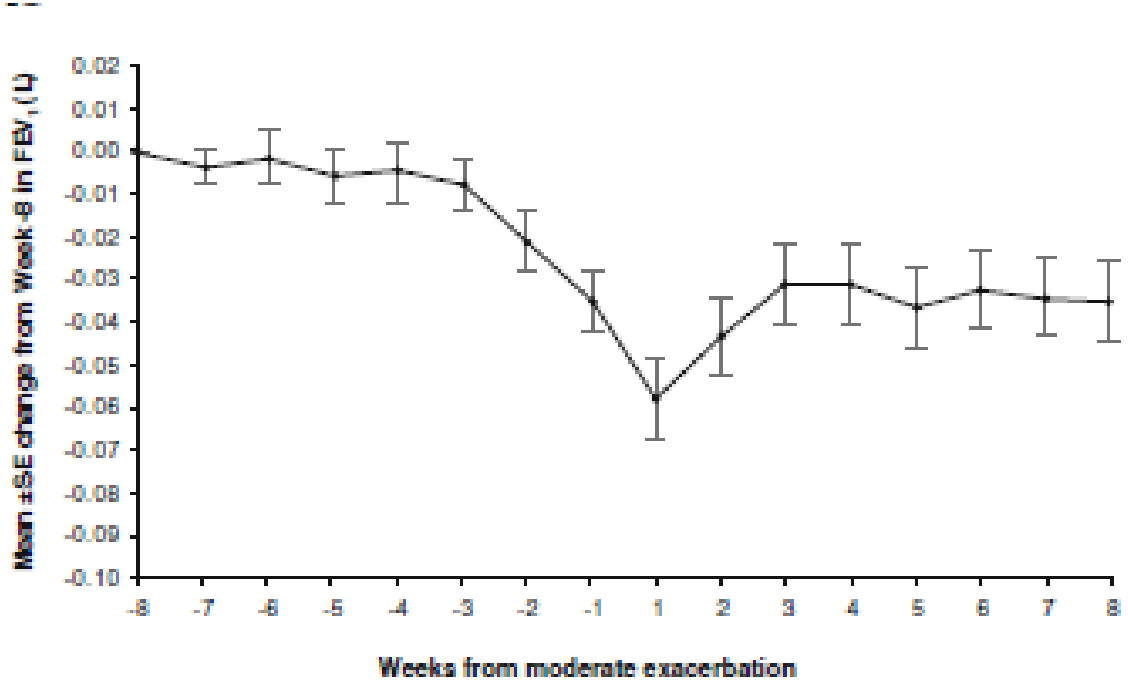


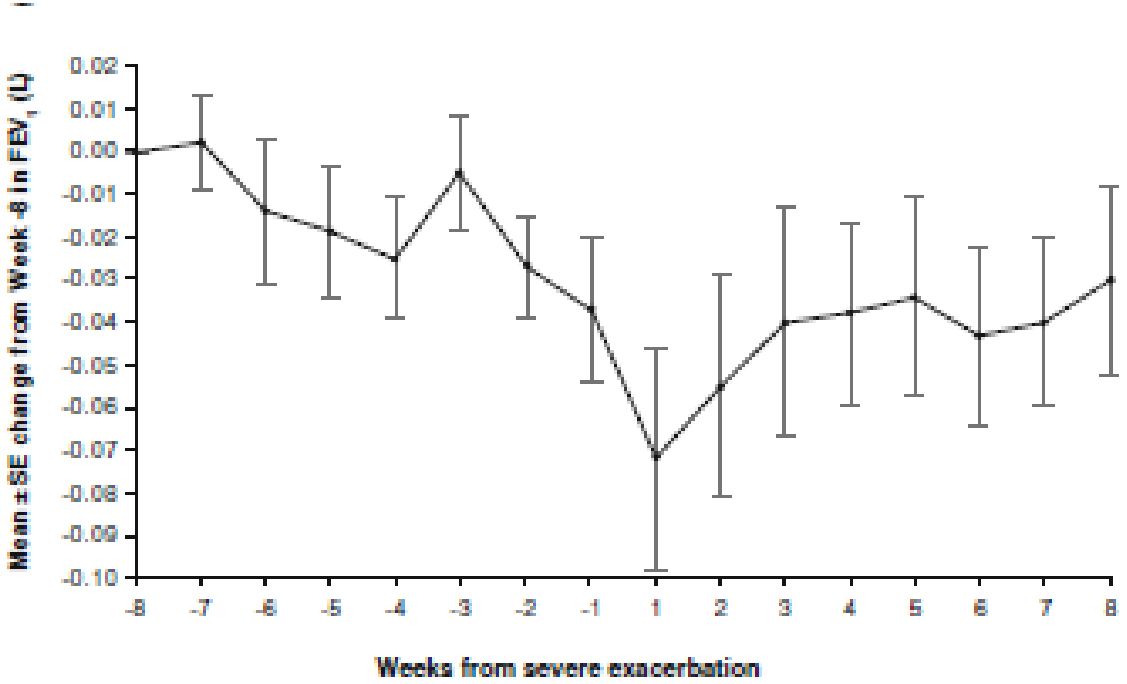
COPD related mortality



Whittaker H et al. Int J COPD 2022

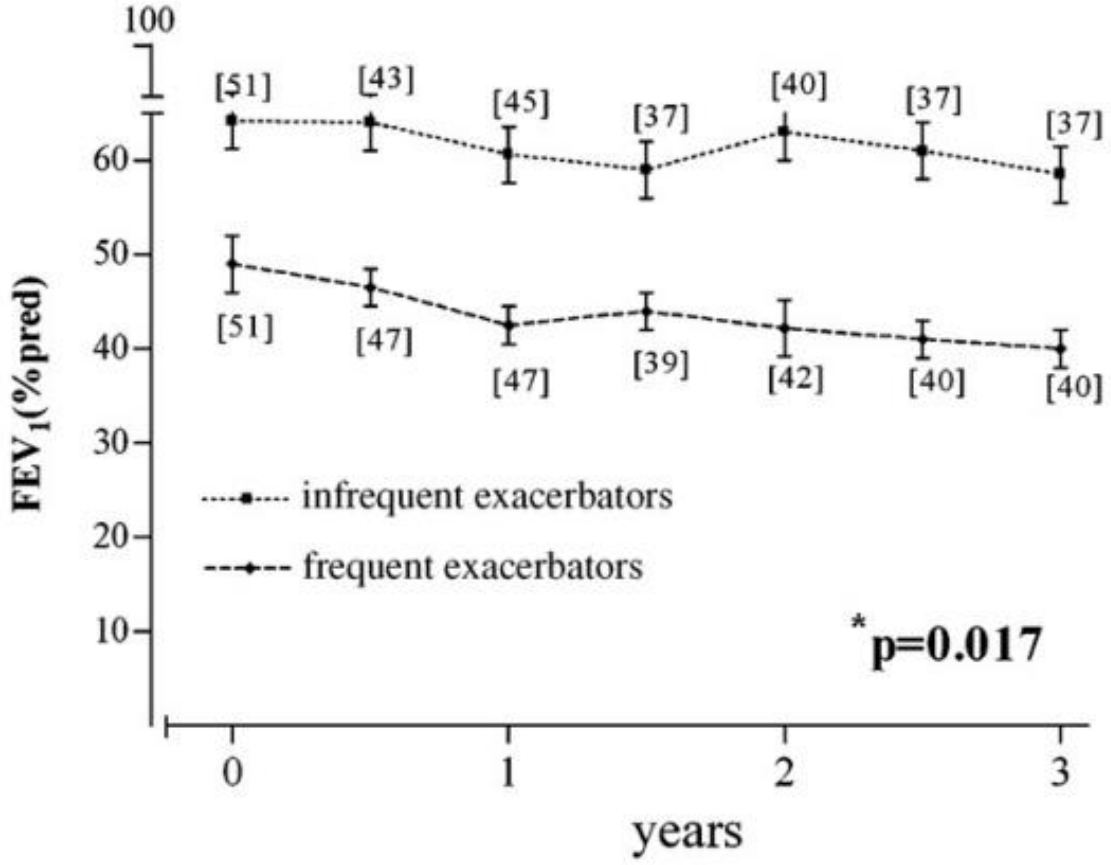
Lung function changes during COPD exacerbations





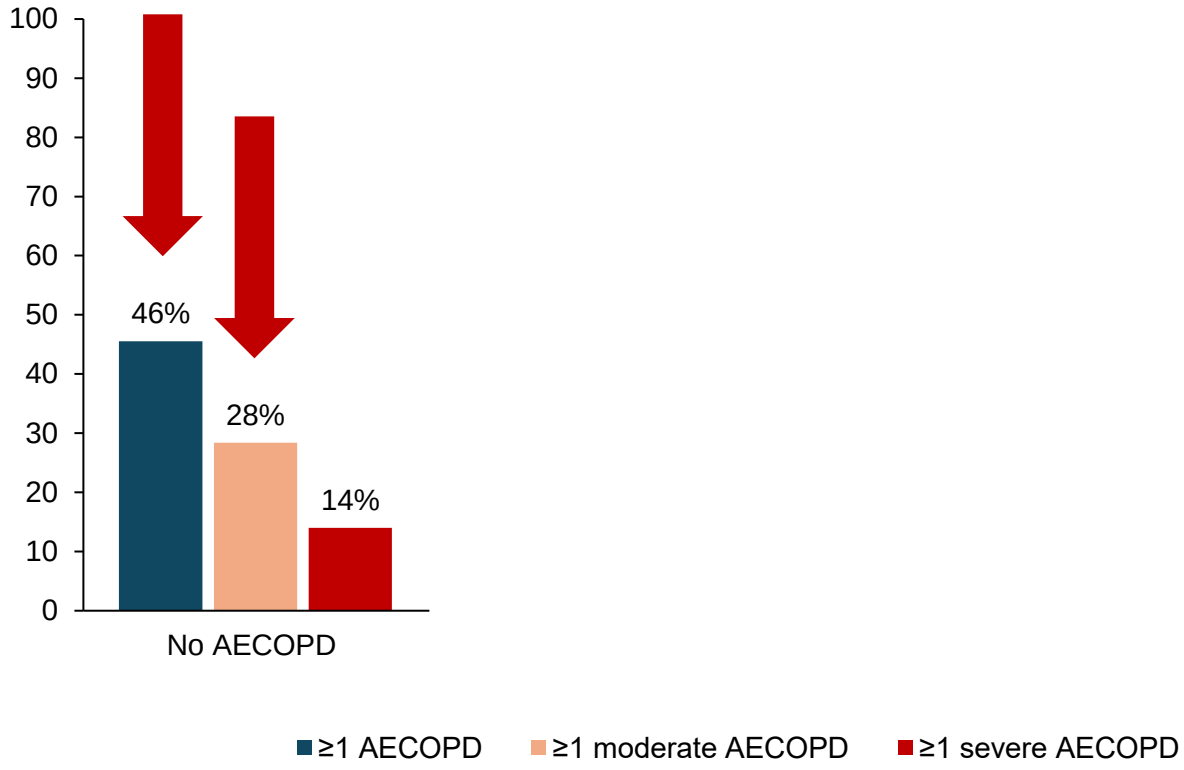
Watz et al. Respir Res 2018

Impact of exacerbations on lung function decline



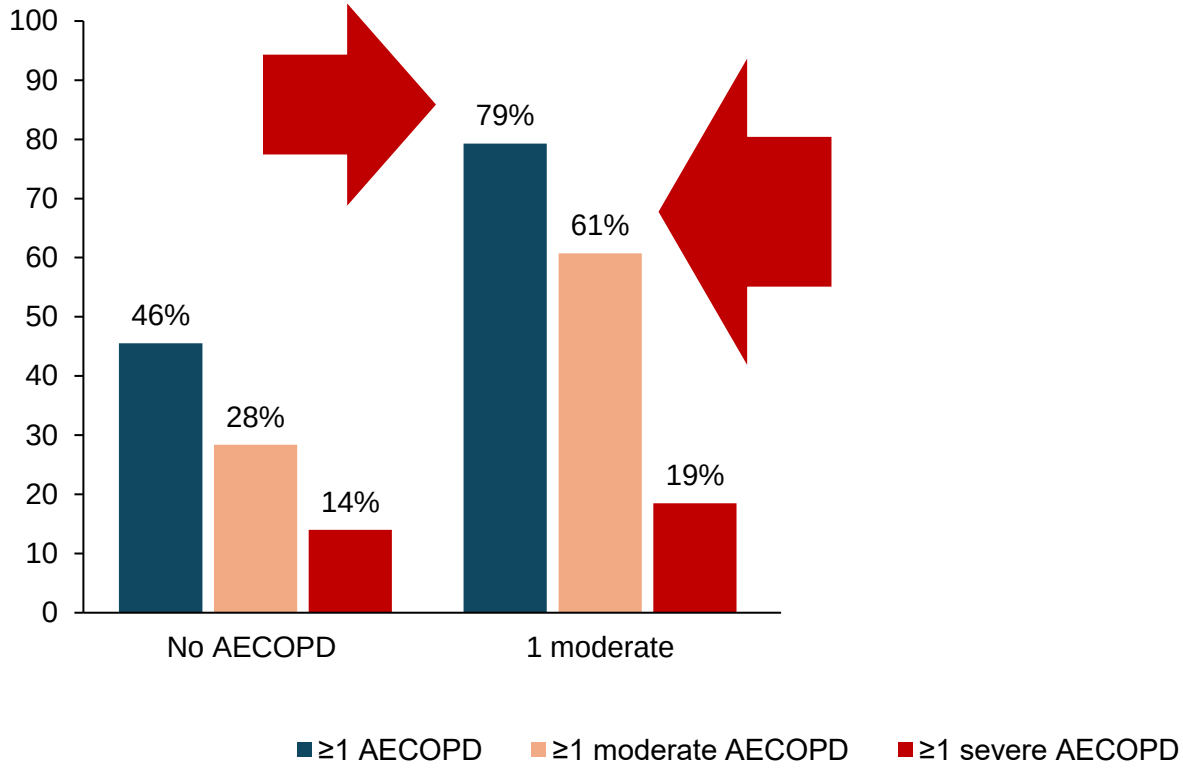
Makris D et al. Respir Med 2006

Real world exacerbation risk in patients with COPD – Italian real life data



Data from Italian COPD registry
GULP Study
Santus P et al. Int J COPD 2024

Real world exacerbation risk in patients with COPD – Italian real life data



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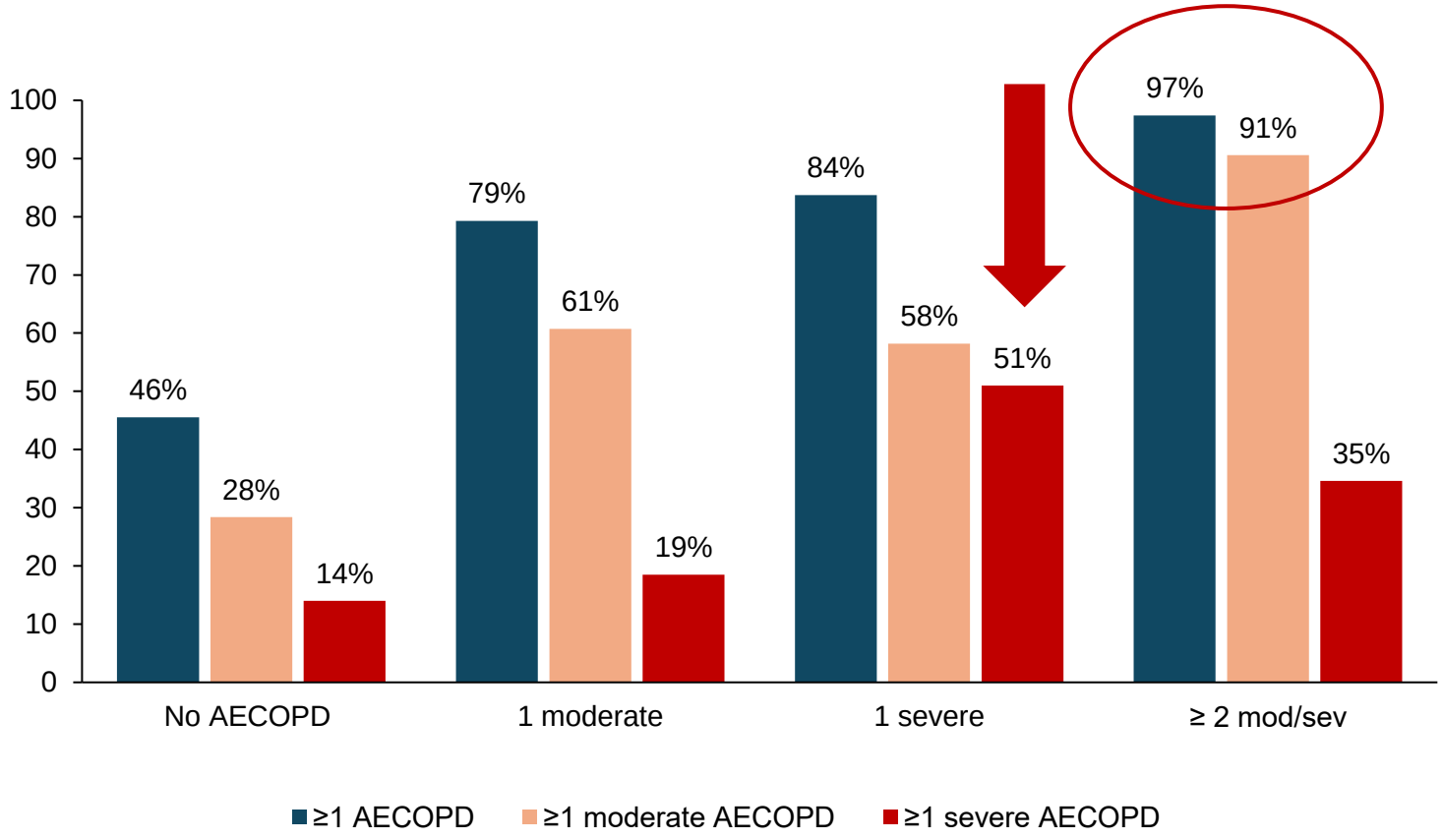

Data from Italian COPD registry
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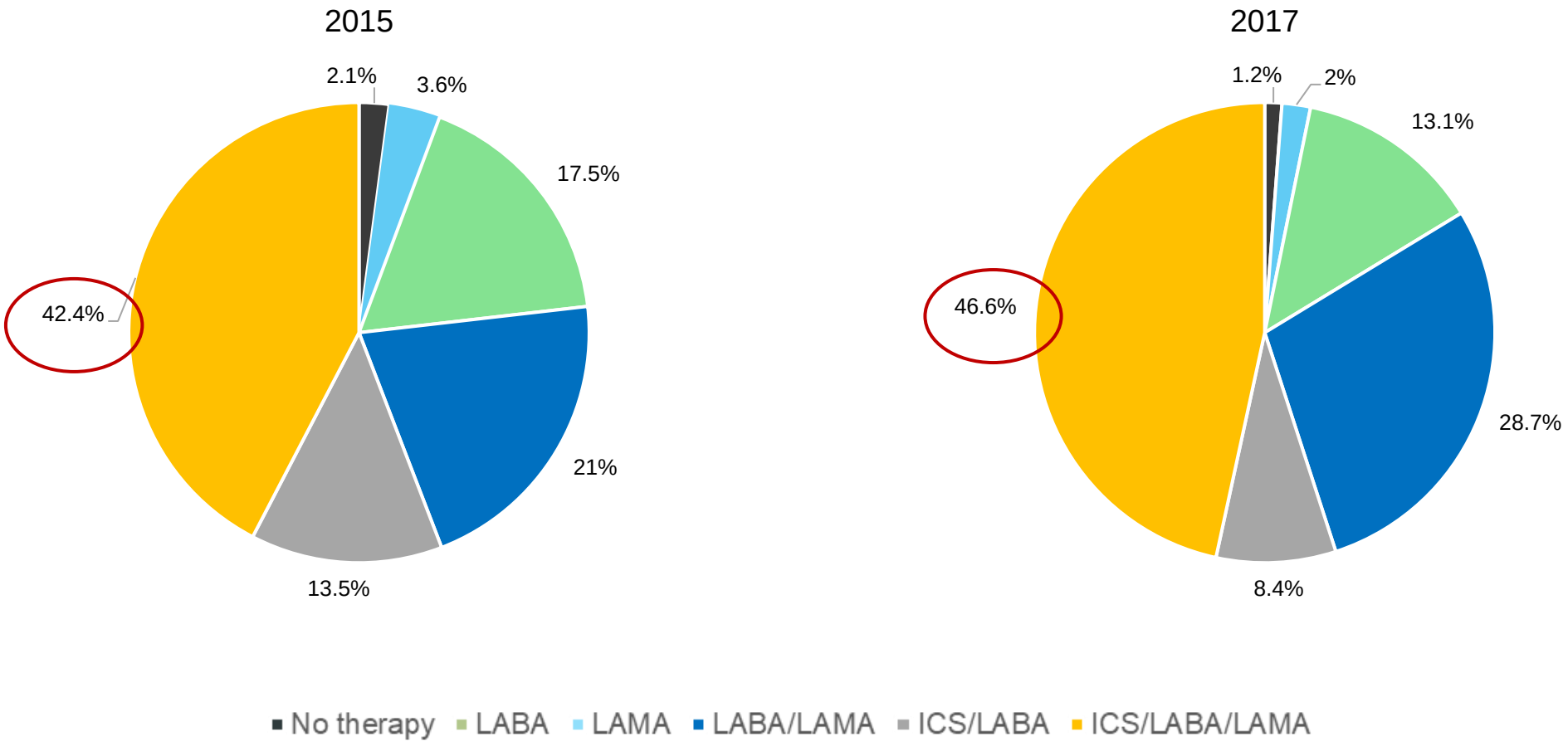
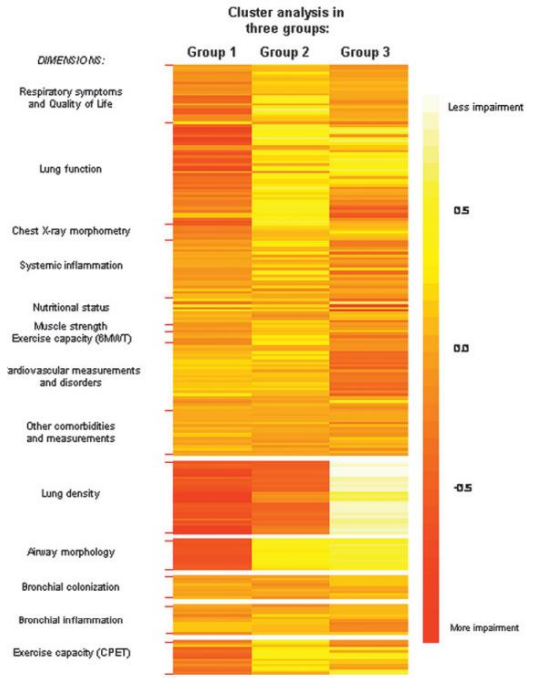


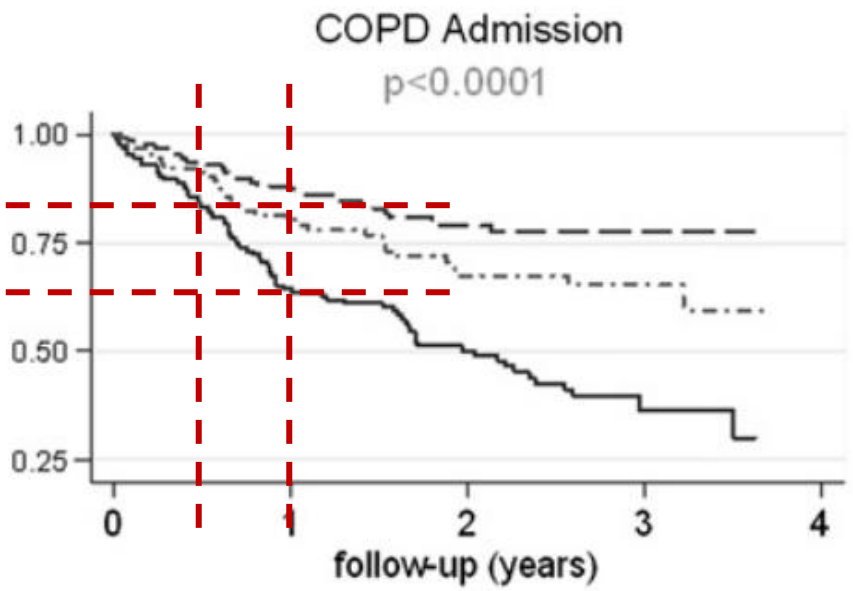
Data from Italian COPD registry
GULP Study
Santus P et al. Int J COPD 2024

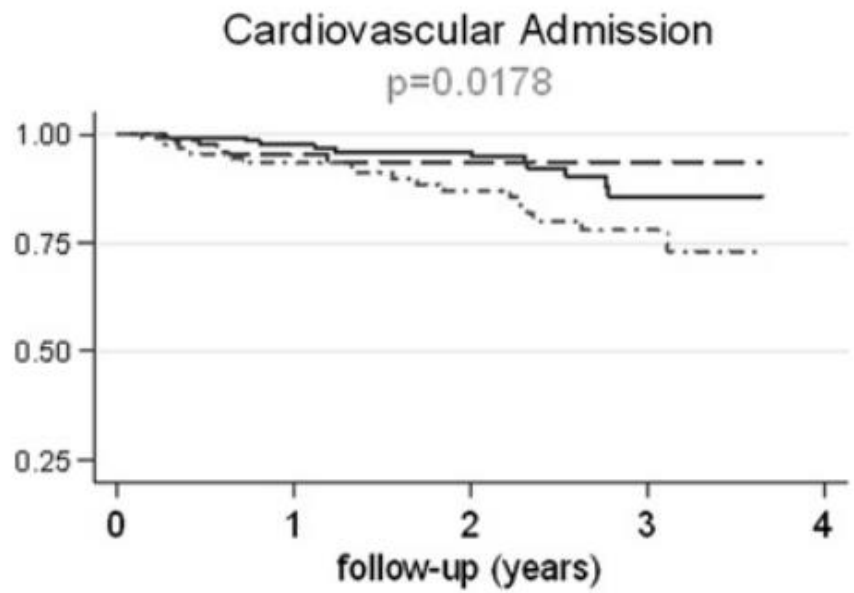
342 patients at their first severe exacerbation



≈ 20%

≈38%

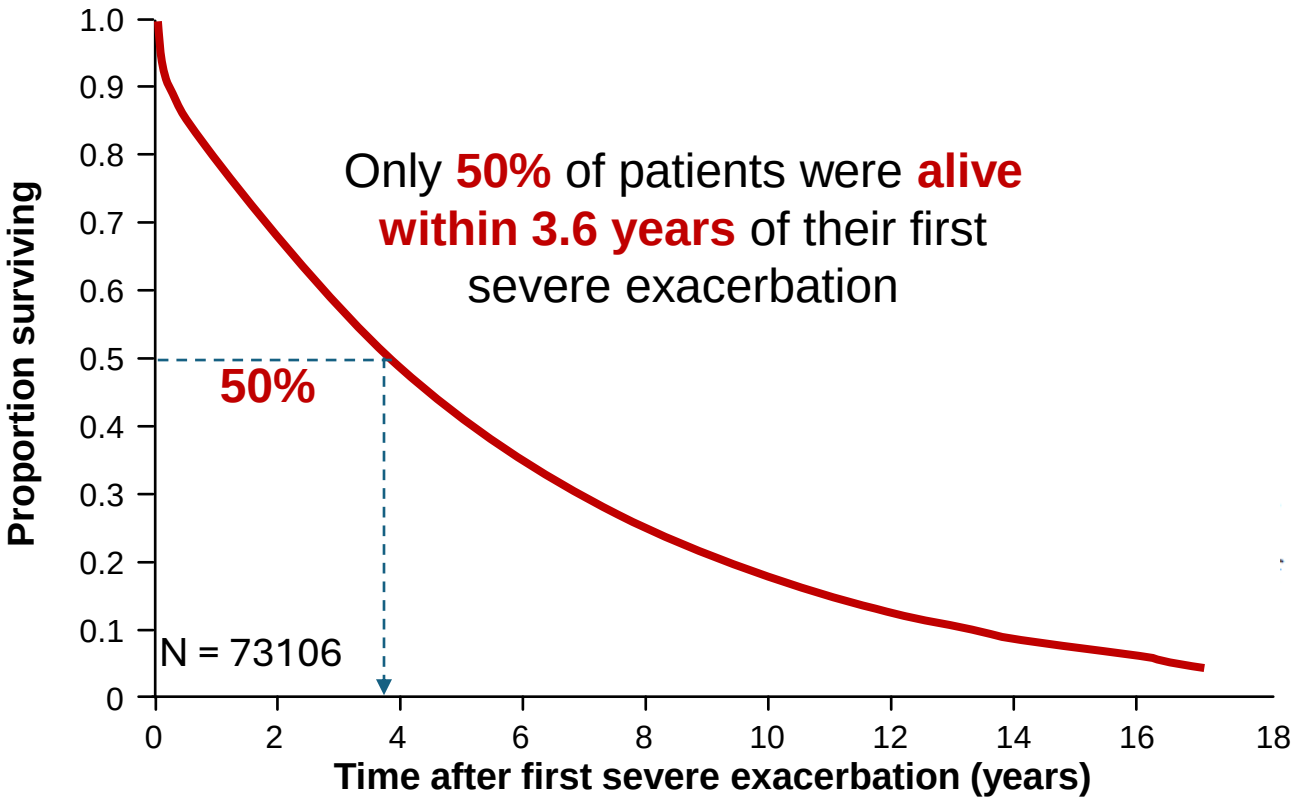


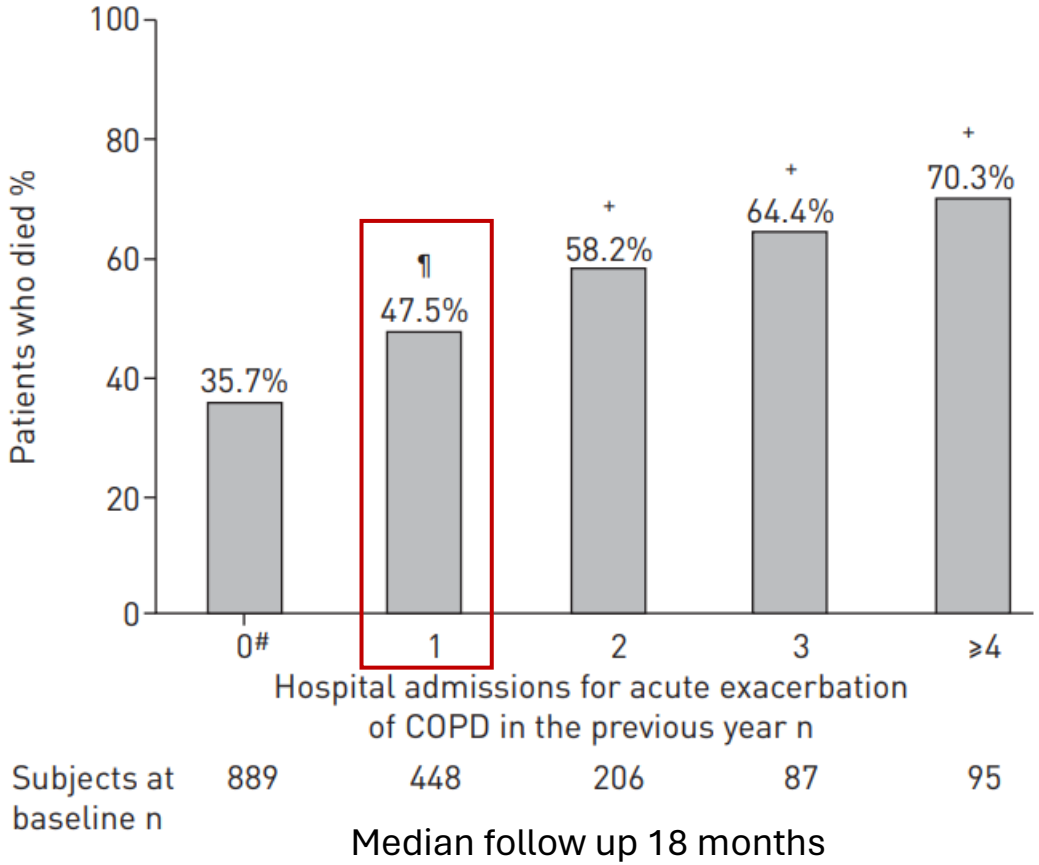


Group 1	Severe obstruction, more emphysema
Group 2	Moderate obstruction
Group 3	Moderate obstruction, more obese, more HF

Garcia-Aymerich J et al. Thorax 2011

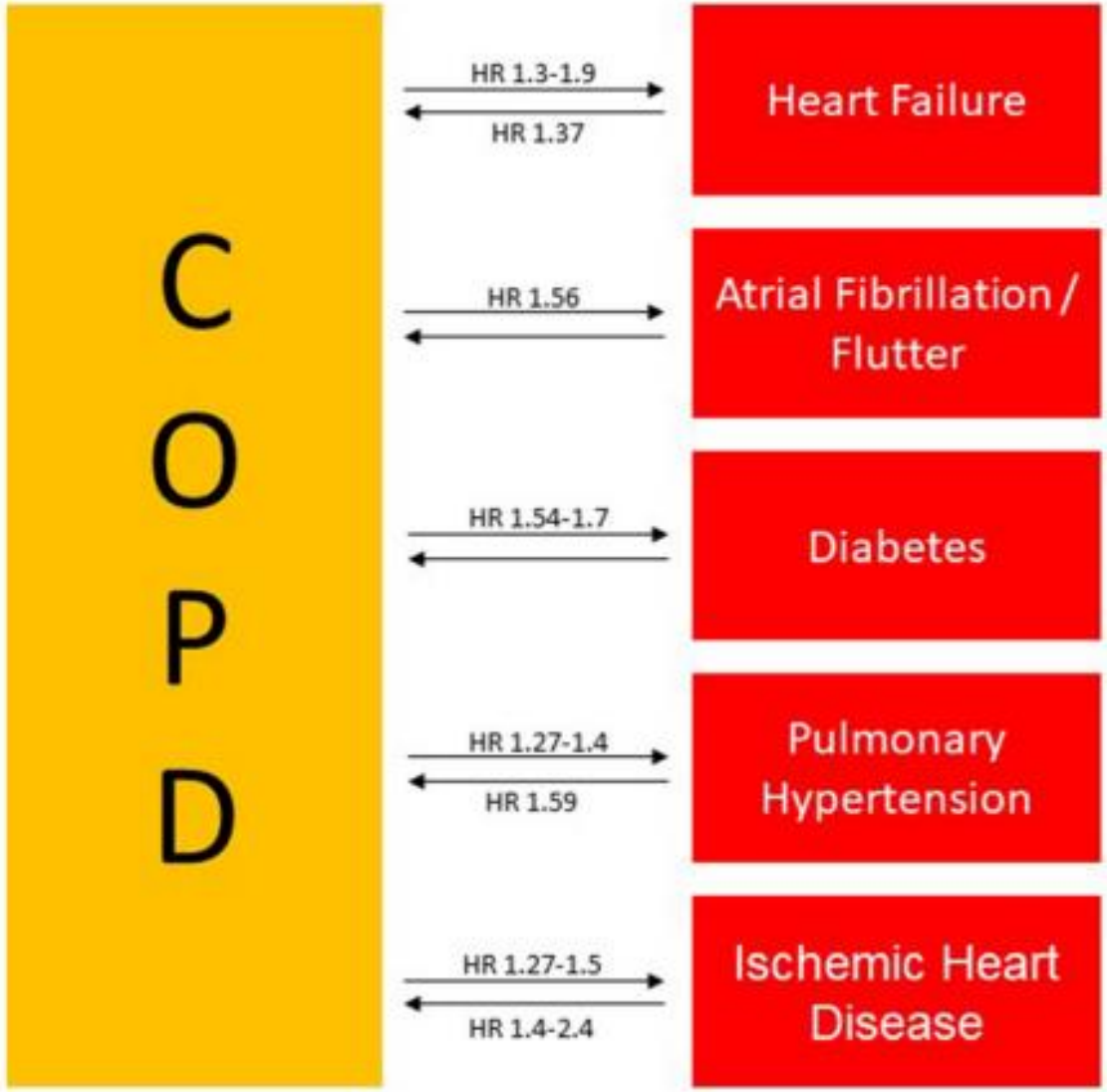
COPD exacerbations and risk of death: high regardless of number of events

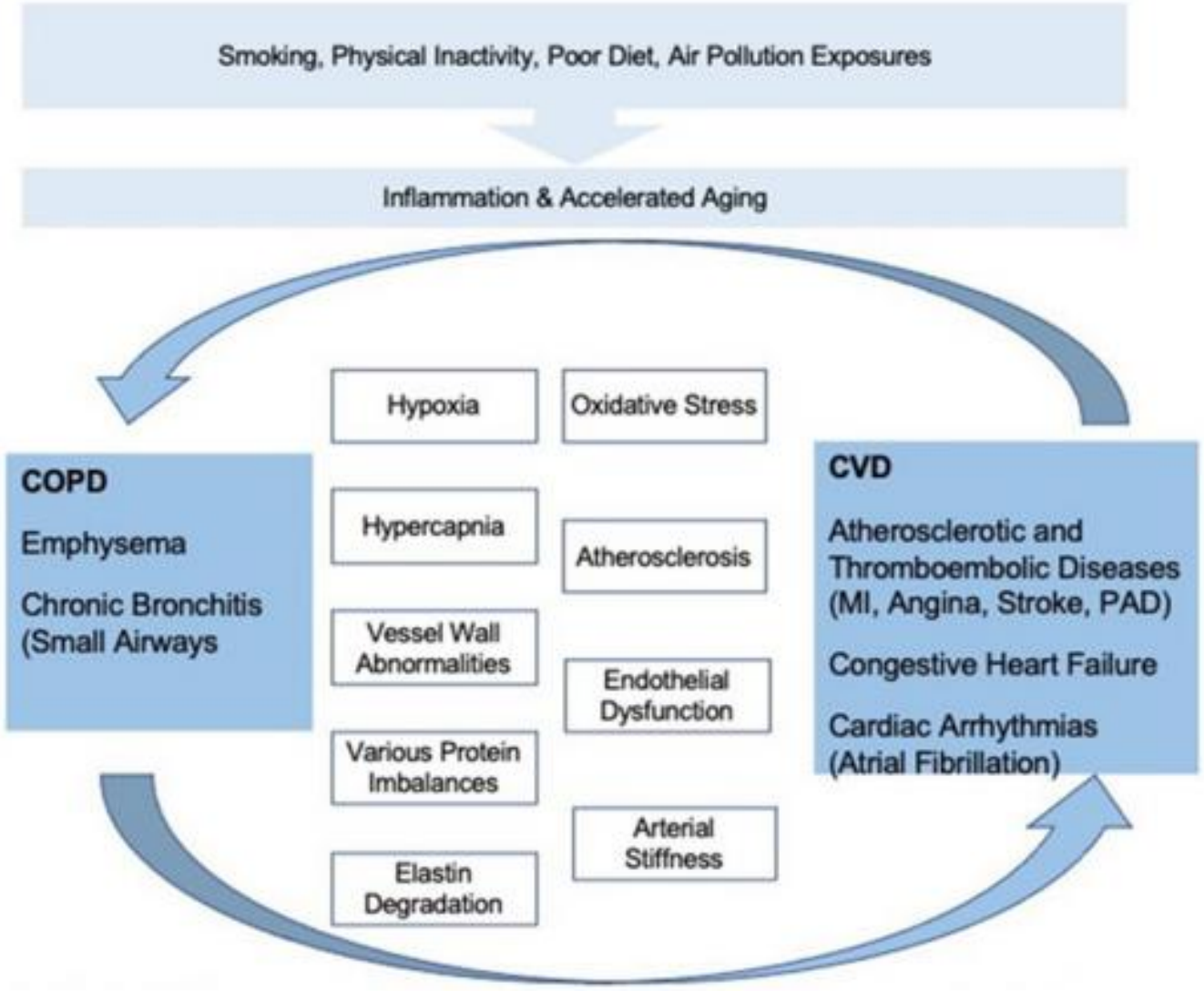




Suissa S et al. Thorax 2012

Piquet J et al. Eur Respir J 2013



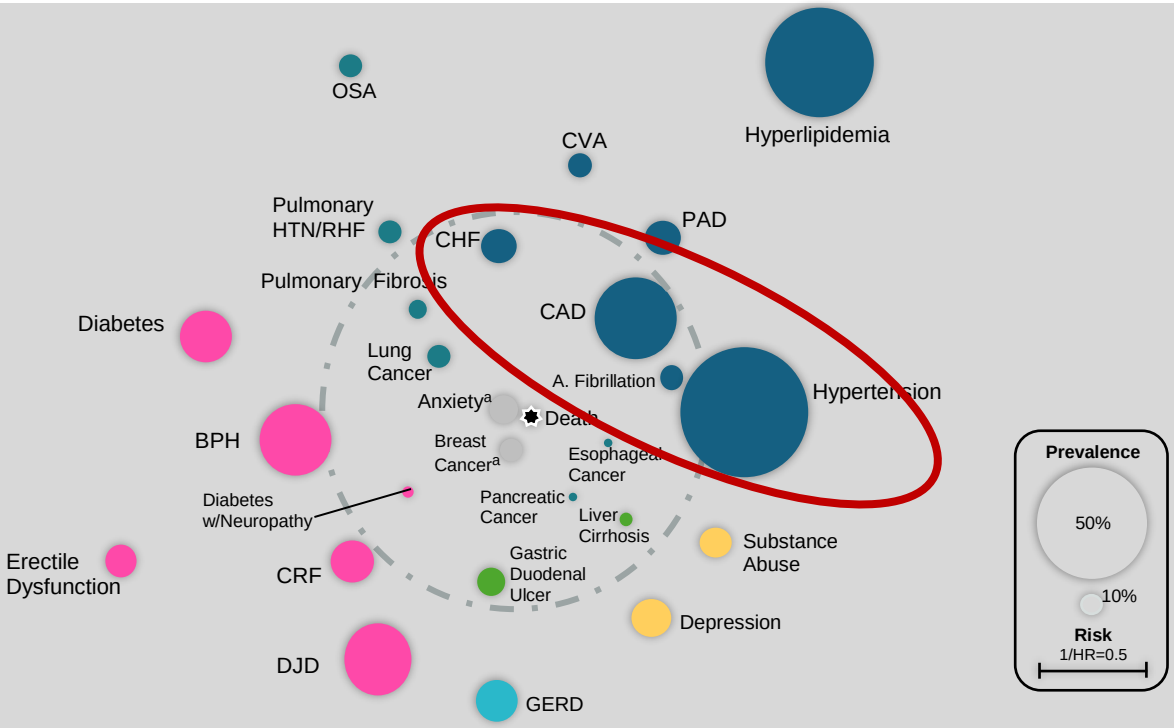


Solidoro P et al. Front Med 2022

COPD Is Associated With Comorbidities that Increase Mortality and Morbidity

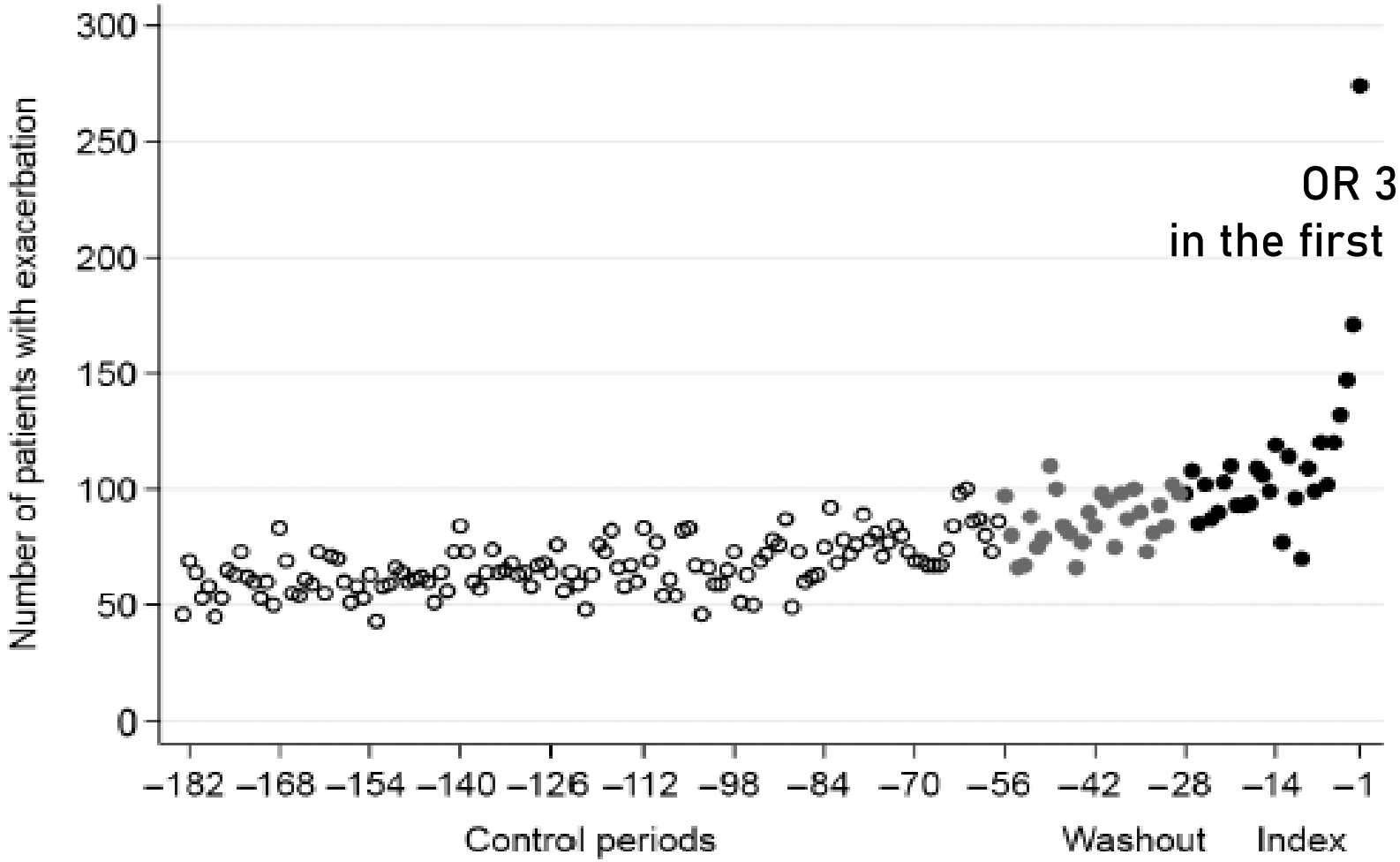
The COPD "Comorbidome"

Cardiovascular diseases are among the **most prevalent of comorbidities** and have one of the strongest associations with **increased risk for death**



Divo M et al. Am J Respir Crit Care Med. 2012

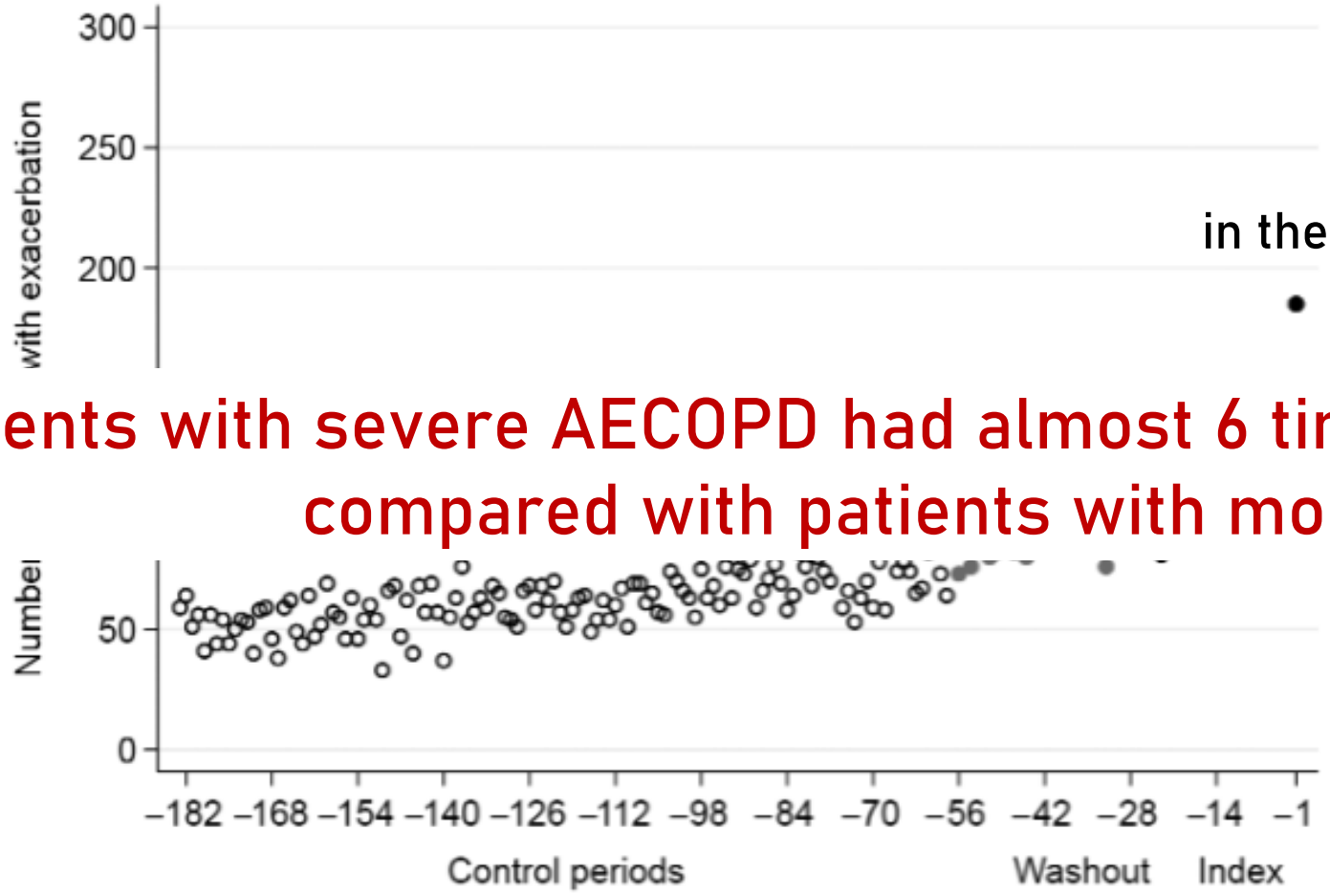
MYOCARDIAL INFARCTION



OR 3.57 (95%CI 3.43-3.71)
in the first 4 weeks following AECOPD

Reilev M et al. Respirology 2019

CARDIOVASCULAR DEATH

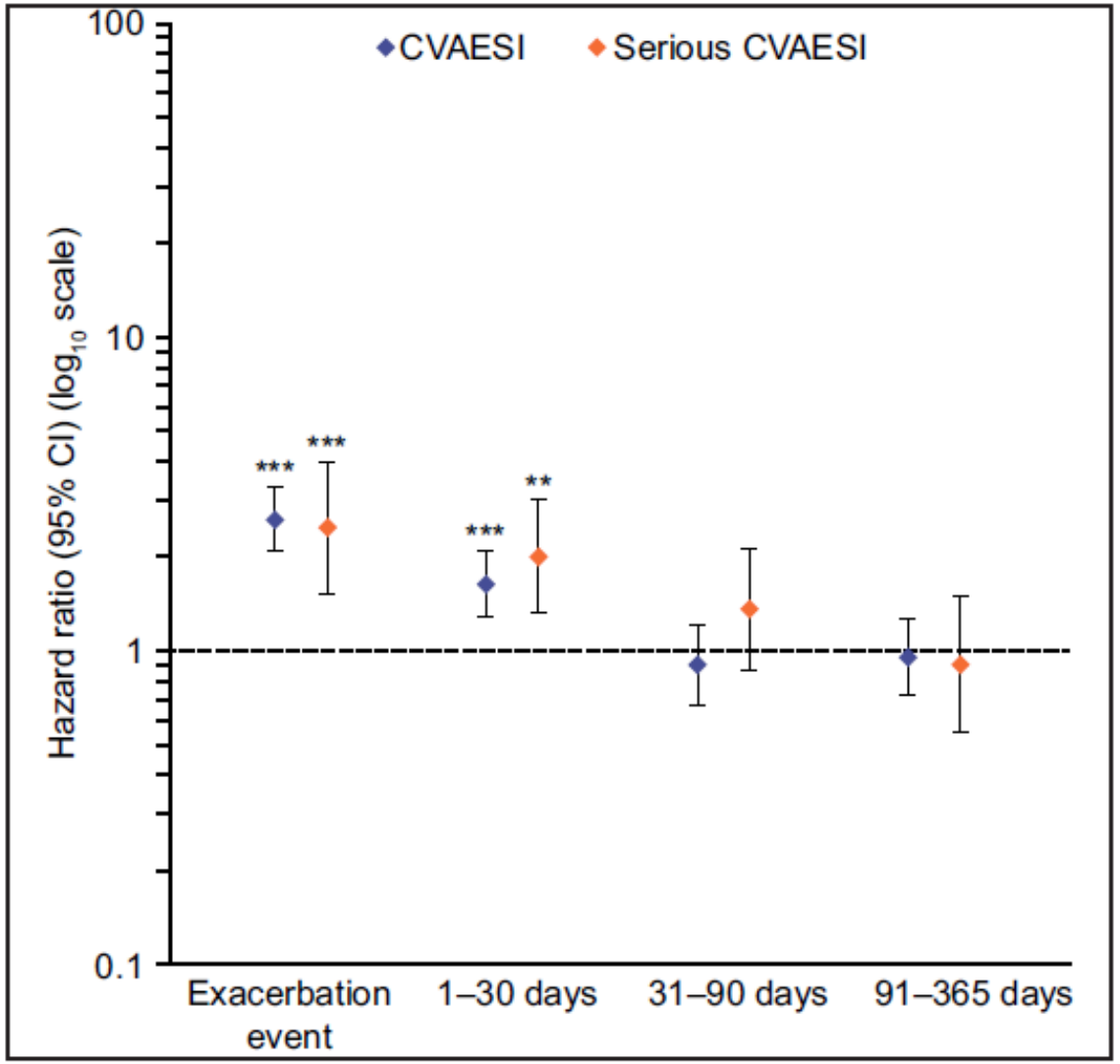


OR 4.33 (95%CI 4.15-4.52)
in the first 4 weeks following AECOPD

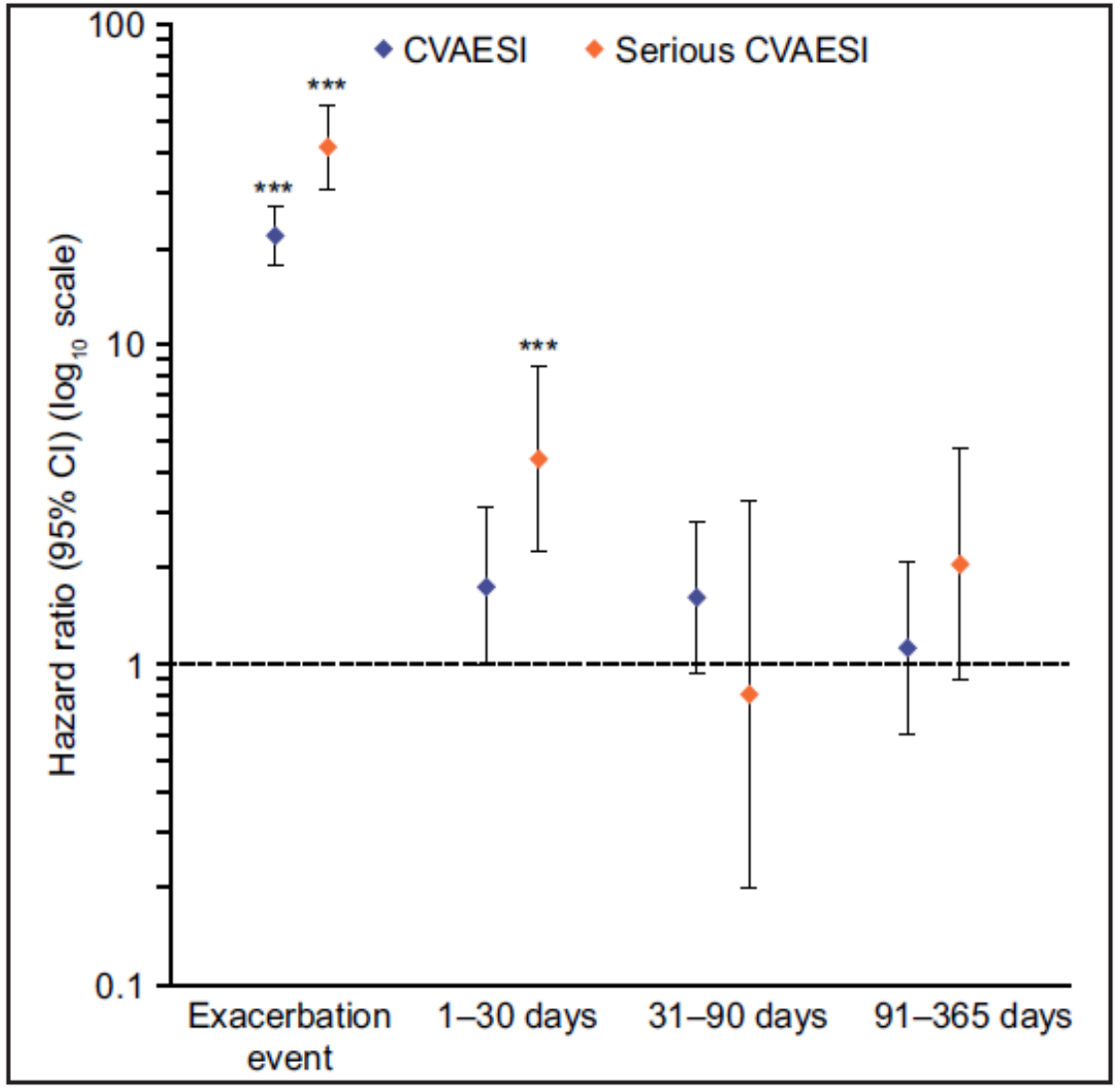
Patients with severe AECOPD had almost 6 times the risk of having MACE compared with patients with moderate AECOPD

Reilev M et al. Respirology 2019

Following a moderate AECOPD



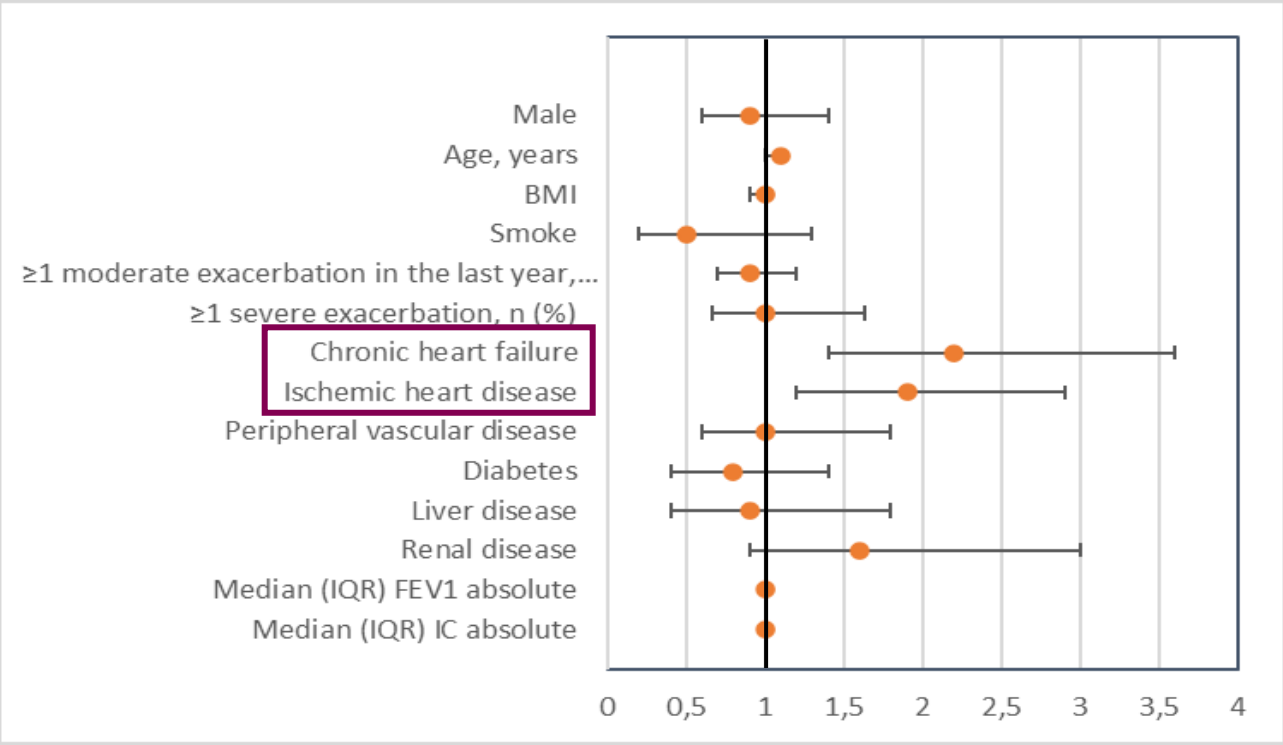
Following a severe AECOPD



Data from IMPACT trial

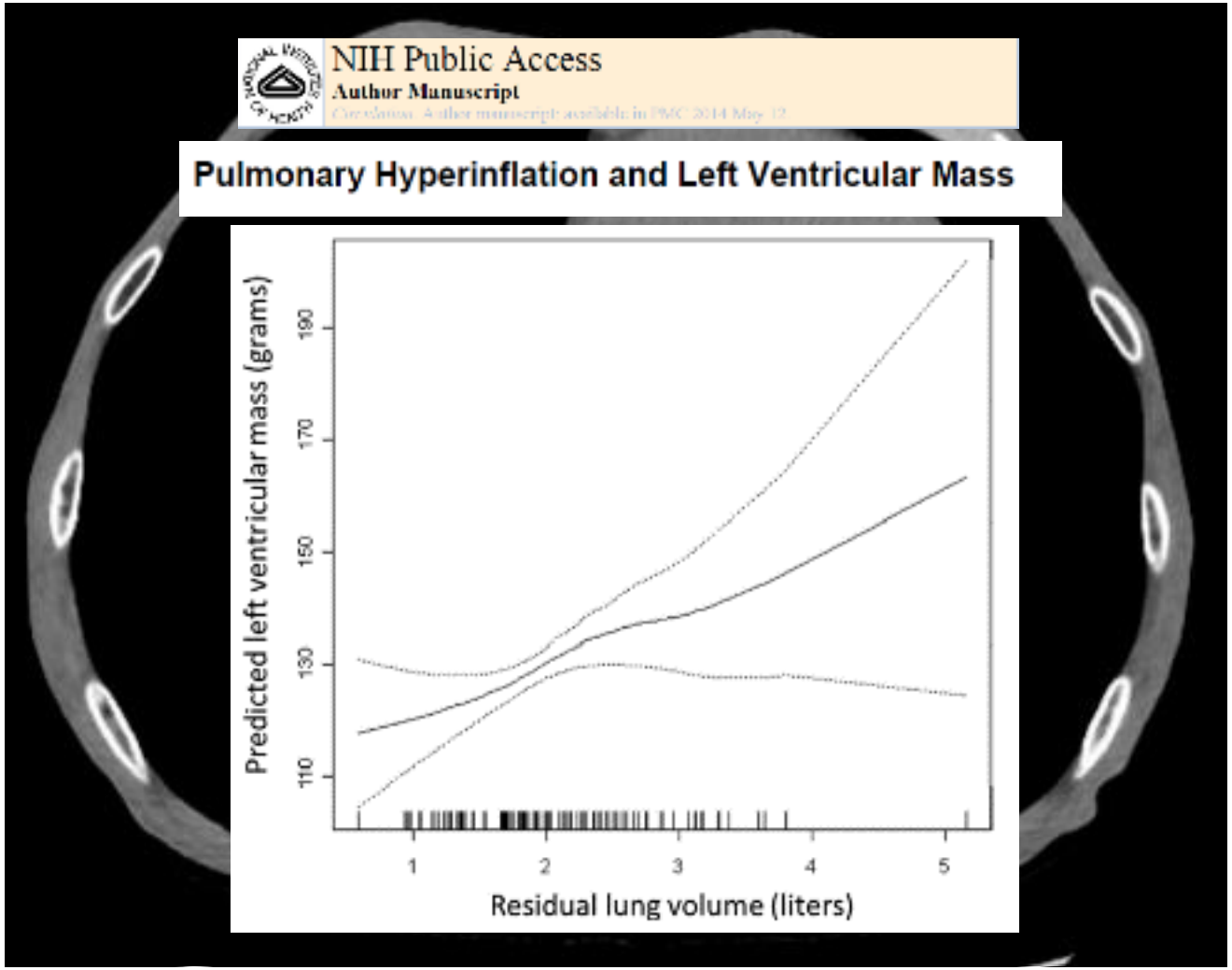
Dransfield et al. J Am Heart Assoc 2022

GULP Study: Relationship between clinical features and mortality in a cohort of COPD patients



Among all described comorbidities, only **chronic heart failure** **and** **ischemic heart disease** were associated with a **statistically significant higher odds ratio (OR) of mortality**

Solidoro et al. Submitted – under review



Smith BM et al. Circulation 2013

Effect of indacaterol on lung deflation improves cardiac performance in hyperinflated COPD patients: an interventional, randomized, double-blind clinical trial

Pierachille Santus[1,2]
Dejan Radovanovic[1,2]
Silvia Di Marco[3]
Vincenzo Valenti[4,5]
Rita Raccanelli[1,2]
Francesco Blasi[6,7]
Stefano Centanni[8,9]
Maurizio Bussotti[3]

Table 4 Cardiac performance after 60 and 180 minutes' treatment with indacaterol or placebo

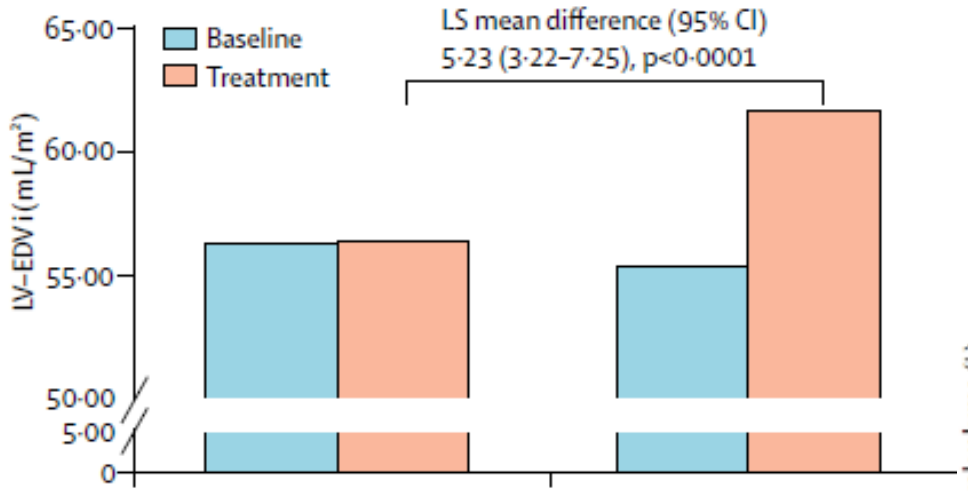
Parameter	Indacaterol			Placebo		
	T0	ΔT60	ΔT180	T0	ΔT60	ΔT180
TAPSE, mm	22.30±3.52	+0.05±1.28*	+0.41±1.07#,*	21.90±3.83	−0.03±1.26	+0.02±3.80
PAPs, mmHg	33.03±8.10	+0.71±5.50	−0.08±7.76	32.78±8.30	+0.77±4.46	+0.24±5.76
DT-TR, msec	207.80±64.90	+9.93±36.31*	+11.90±32.86#,*	206.70±65.84	+2.60±35.90	+3.80±38.90
LVEF, %	61.80±5.25	−0.03±1.90	−0.25±2.20	60.60±6.21	+0.09±2.12	−0.14±2.35
DT-MR, msec	230.18±58.69	+3.98±38.24	+4.33±38.79	228.25±59.33	+1.12±37.52	+1.38±36.81
HR, bpm	71.54±10.60	−1.95±5.30#,*	−2.00±6.10#,*	70.21±9.40	−0.80±1.20	+0.60±1.30

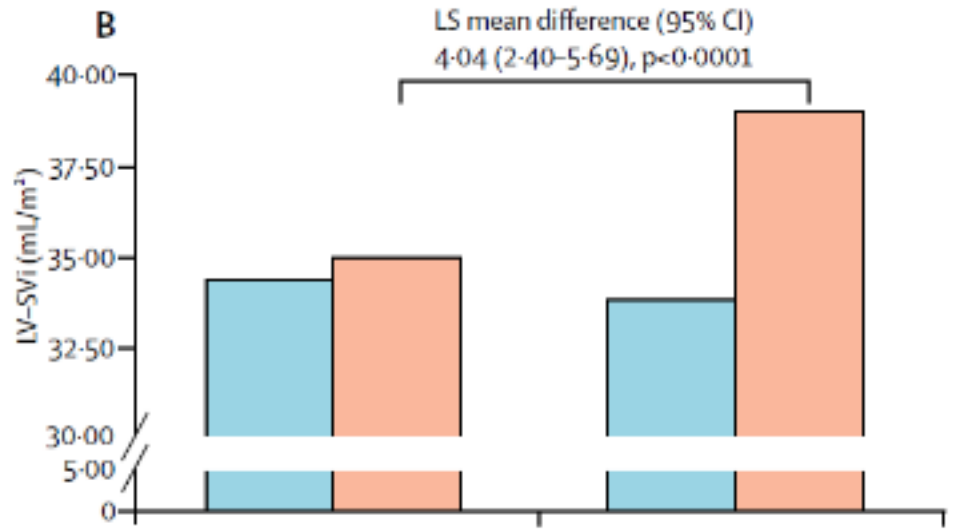
Santus P et al. Int J COPD 2015

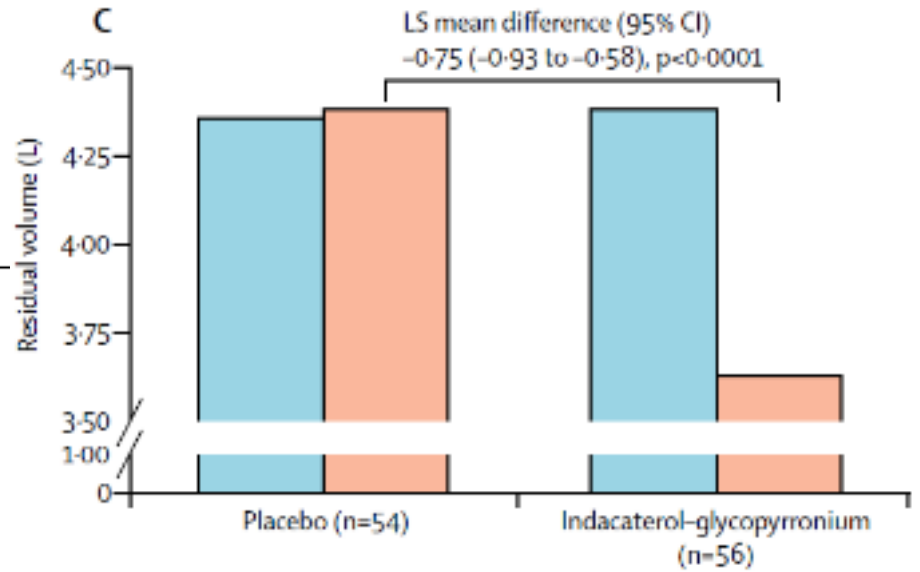
Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial

Jens M Hohlfeld*, Jens Vogel-Claussen*, Heike Biller, Dominik Berliner, Korbinian Berschneider, Hanns-Christian Tillmann, Simone Hiltl, Johann Bauersachs, Tobias Welte

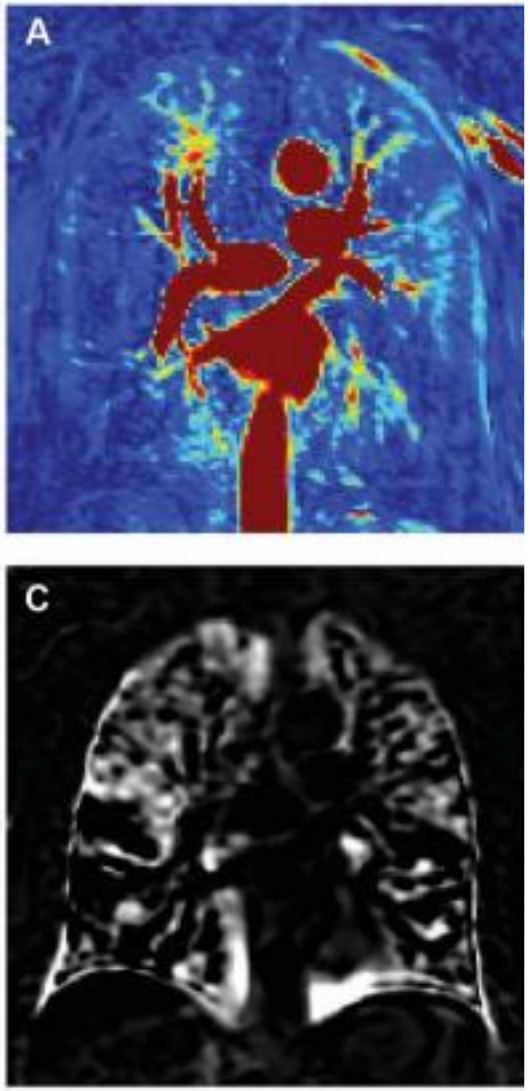
THE LANCET
Respiratory Medicine







Hohfeld JM et al. Lancet Respir Med 2018



Vogel-Claussen J et al. AJRCCM 2019

EMAX -Early MAXimisation of bronchodilation for improving COPD stability

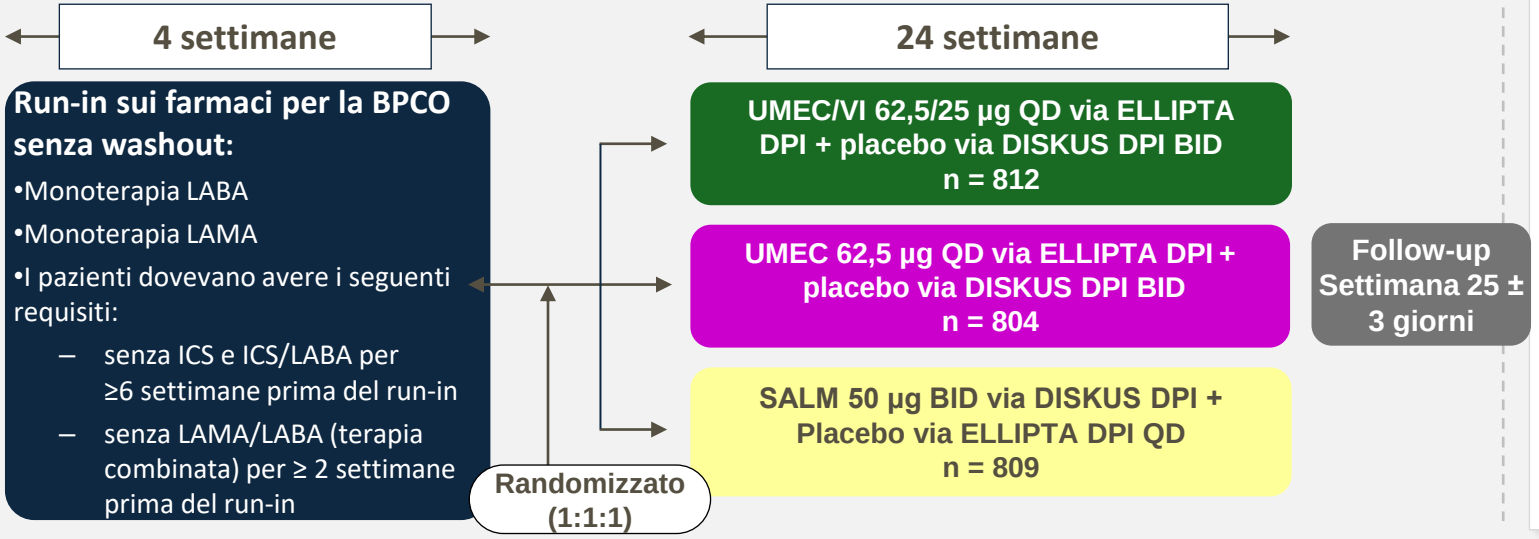
2425 patients

Disegno dello studio di EMAX

Studio muticentrico di 24 settimane, randomizzato, in doppio cieco, double-dummy a gruppi paralleli, in pazienti sintomatici con BPCO

Principali criteri di inclusione:

- ≥40 anni di età
- Fumatore/ex fumatore
- Diagnosi BPCO
- FEV_1/FVC <0,7 pre e post-SAL; **FEV_1 post-SAL, ≥30–≤80%** del predetto
- **Punteggio CAT ≥10**
- **≤1 esacerbazioni** moderate e nessuna esacerbazione grave nell'anno precedente



Endpoint primario:

- Variazione rispetto al basale del **trough FEV_1** alla settimana 24

Principali endpoint II:

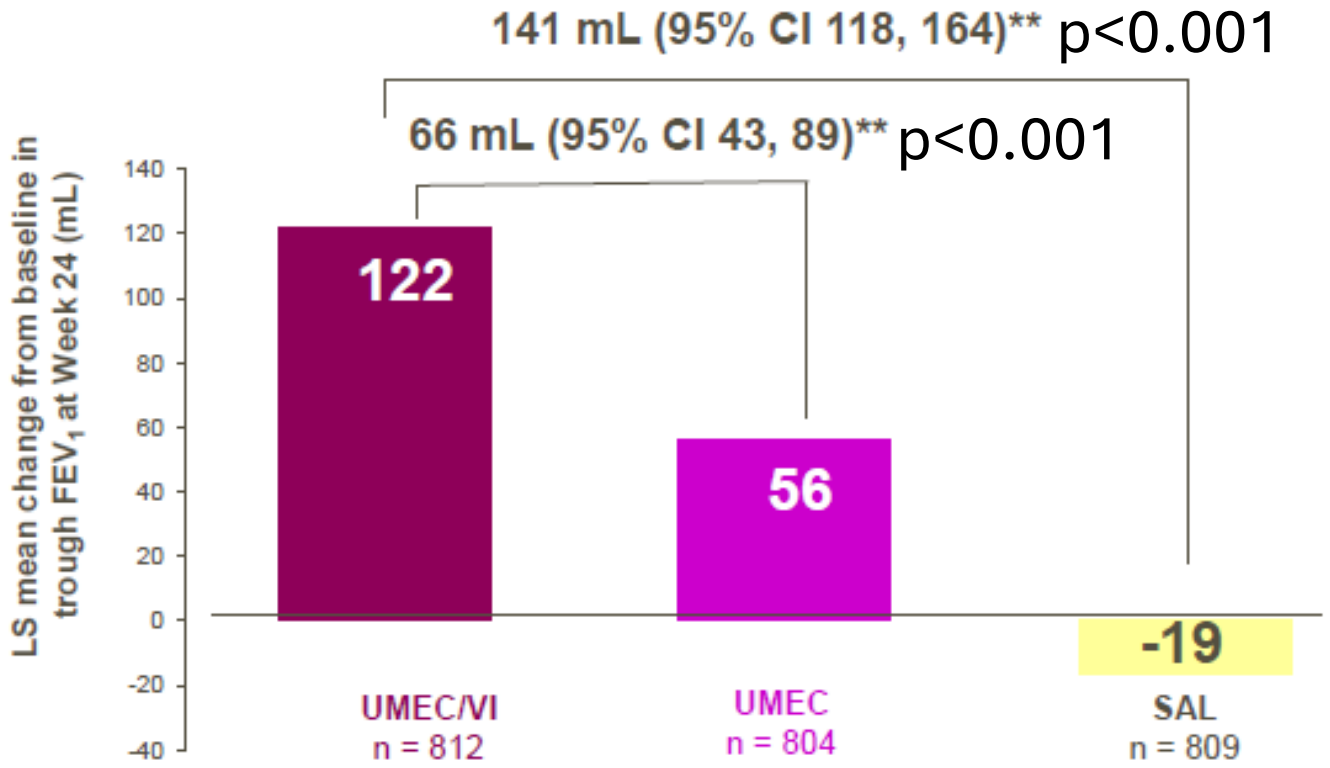
- SAC-**TDI** per dispnea
- Trough FVC, IC in 24 settimane
- Uso di farmaci al bisogno
- Punteggio totale E-RS

*Stratificazione alla randomizzazione, basata sull'uso di broncodilatatori a lunga durata d'azione durante il run-in (0 o 1), paese e sottoinsieme di attività. BID, due volte al giorno; CAT, test di valutazione della BPCO; BPCO, malattia polmonare ostruttiva cronica; DPI, inalatore a polvere secca; E-RS, valutazione dei sintomi respiratori; FEV1, volume espiratorio forzato in 1 secondo; FVC, capacità vitale forzata; IC, capacità inspiratoria; ICS, corticosteroidi inalatori; LABA, β2-agonista a lunga durata d'azione; LAMA, antagonista muscarinico a lunga durata d'azione; QD, una volta al giorno; SAC-TDI, indice di dispnea transizionale autosomministrato al computer; SAL, salmeterolo; UMEC, umeclidinio; VI, vilanterolo.

Maltais F et al. Respir Res 2019

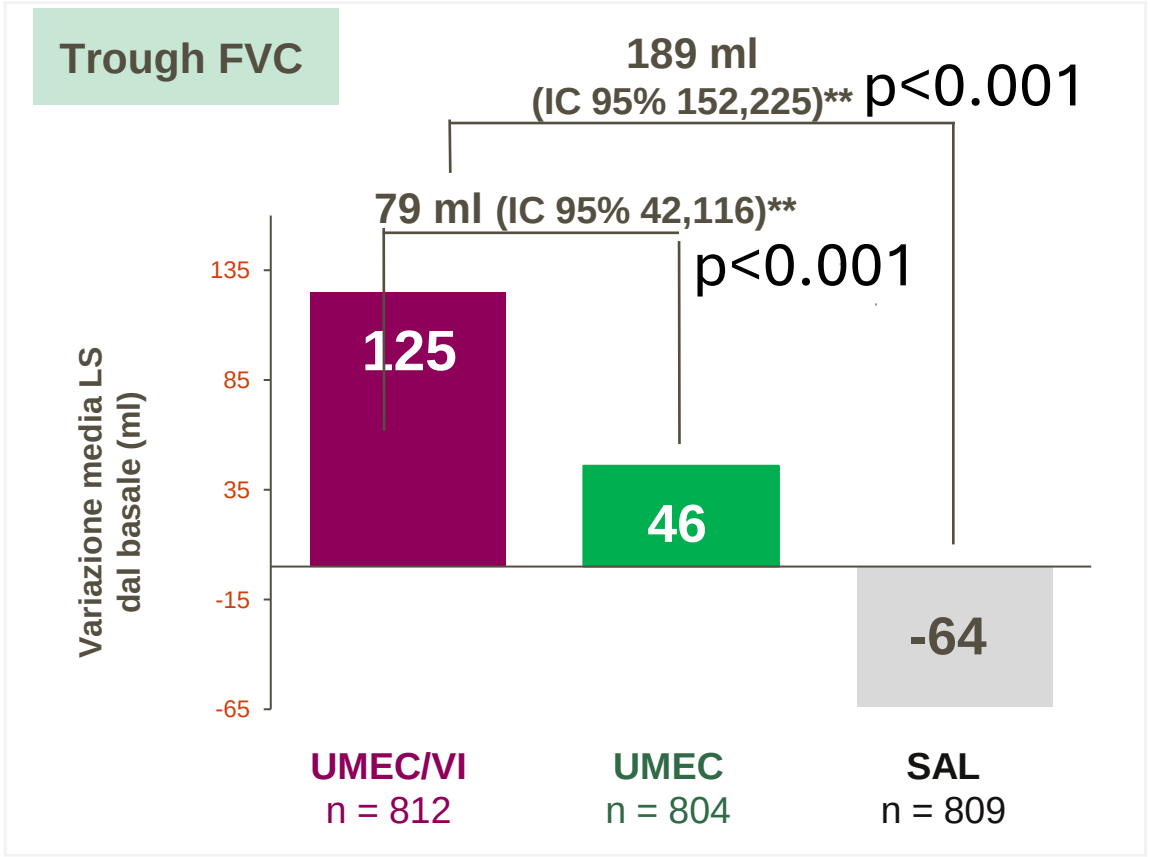
CHANGES IN FEV1 AT WEEK 24

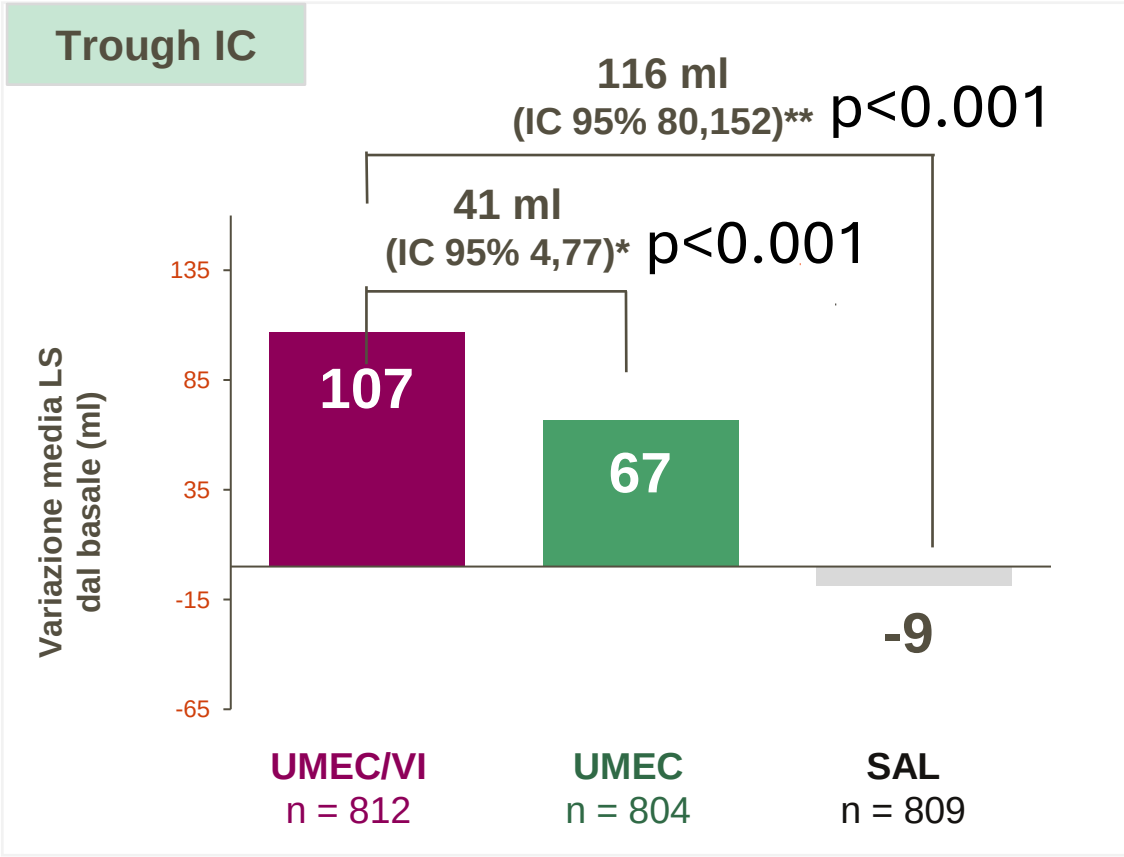
ITT population



Maltais F et al. Respir Res 2019

EFFECT OF DUAL BRONCHODILATION ON HYPERINFLATION

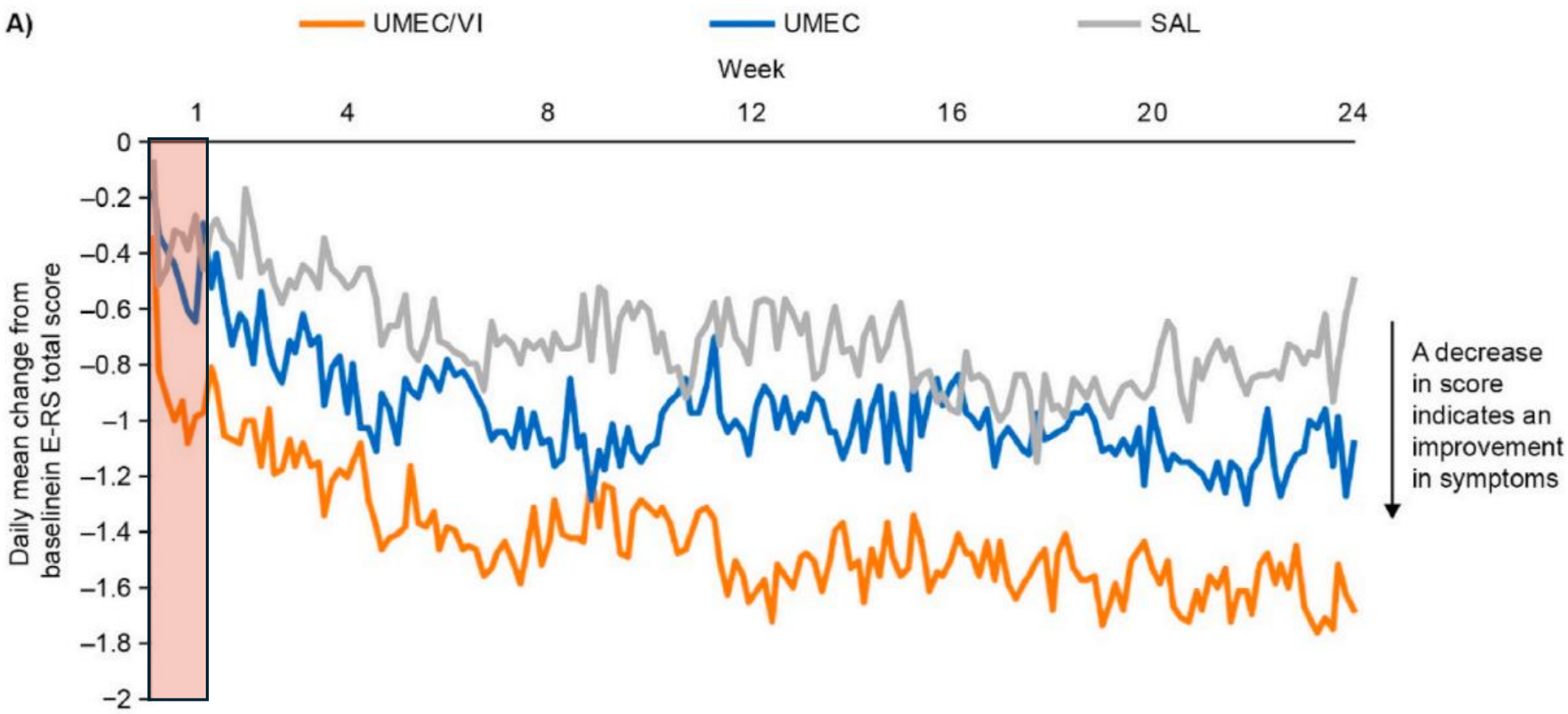




Popolazione ITT
FVC: capacità vitale forzata; IC, capacità inspiratoria; LS, minimi quadrati. $^{**}p < 0,001$; $^{*}p = 0,028$

Maltais F et al, Respir Res 2019

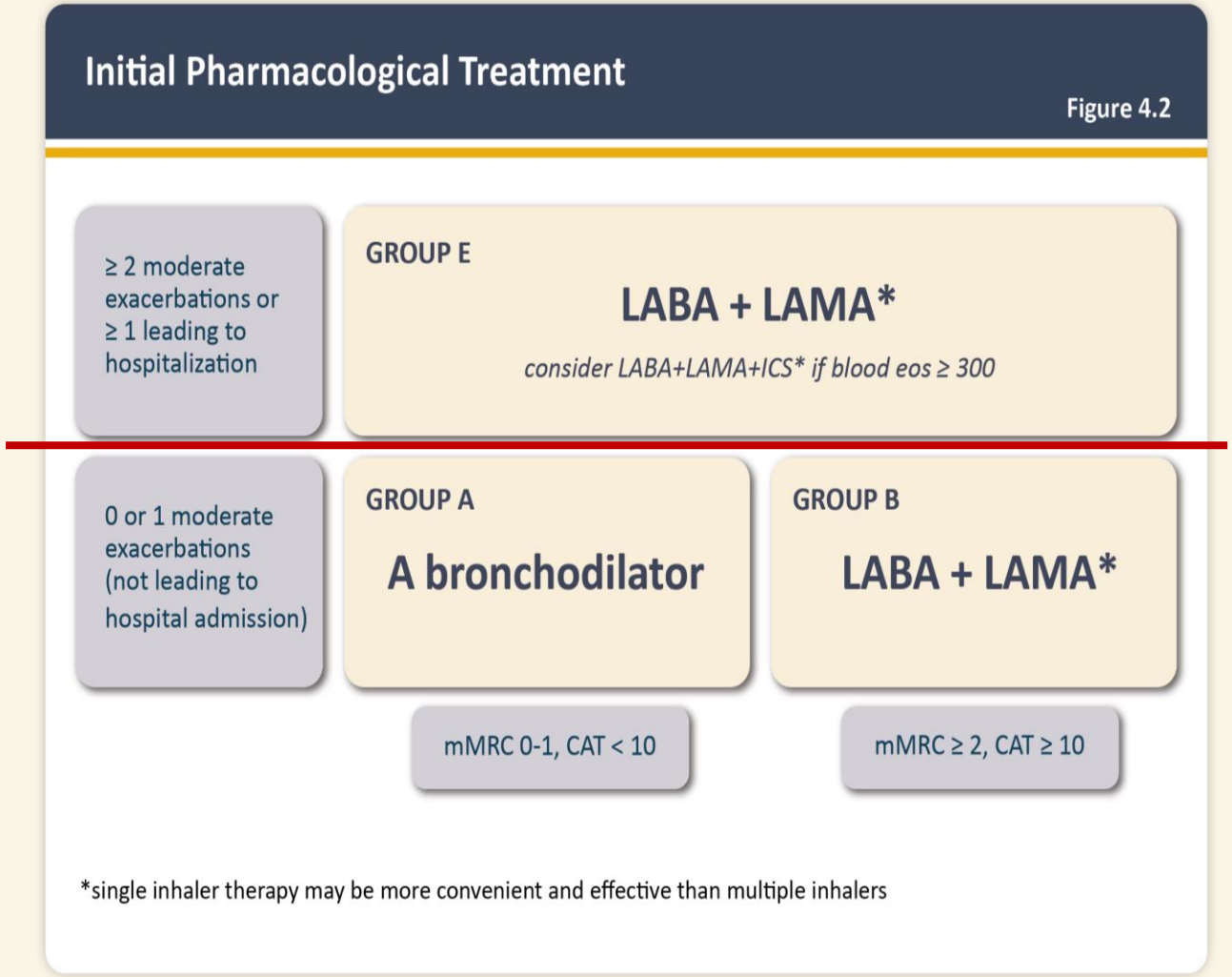
early improvement in symptoms WITH UMEC/VI vs. monotherapy in the EMAX trial



Maltais F et al. Respir Med 2022

GOLD 2023 – Treatment of Stable COPD

2023 REPORT



Note: ICS/LAMA/LABA as initial maintenance therapy is off-label in the EU and other LOCs.

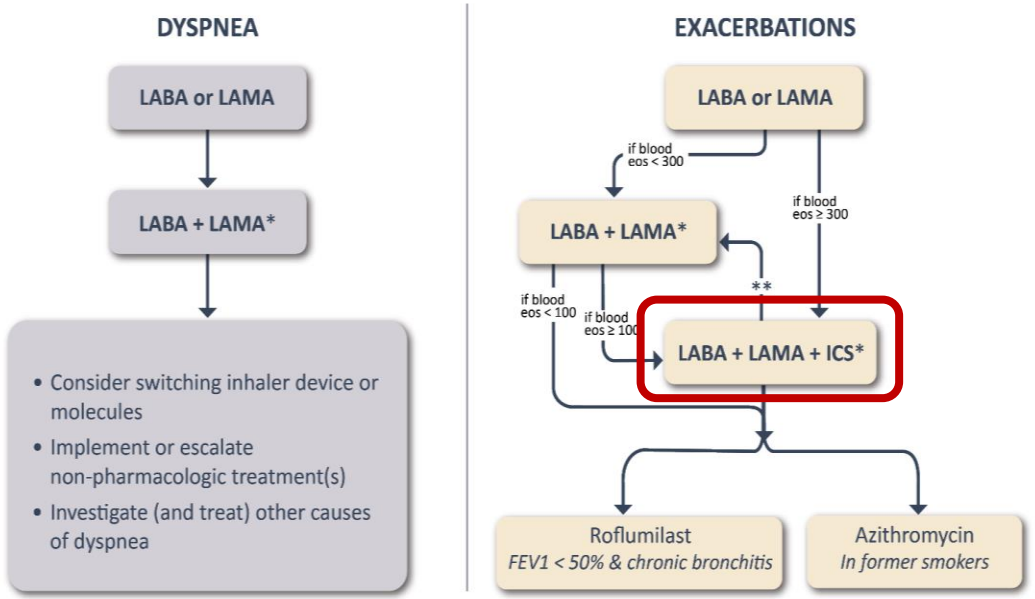
GOLD 2023 – Treatment of Stable COPD

2023 REPORT

Follow-up Pharmacological Treatment

Figure 4.4

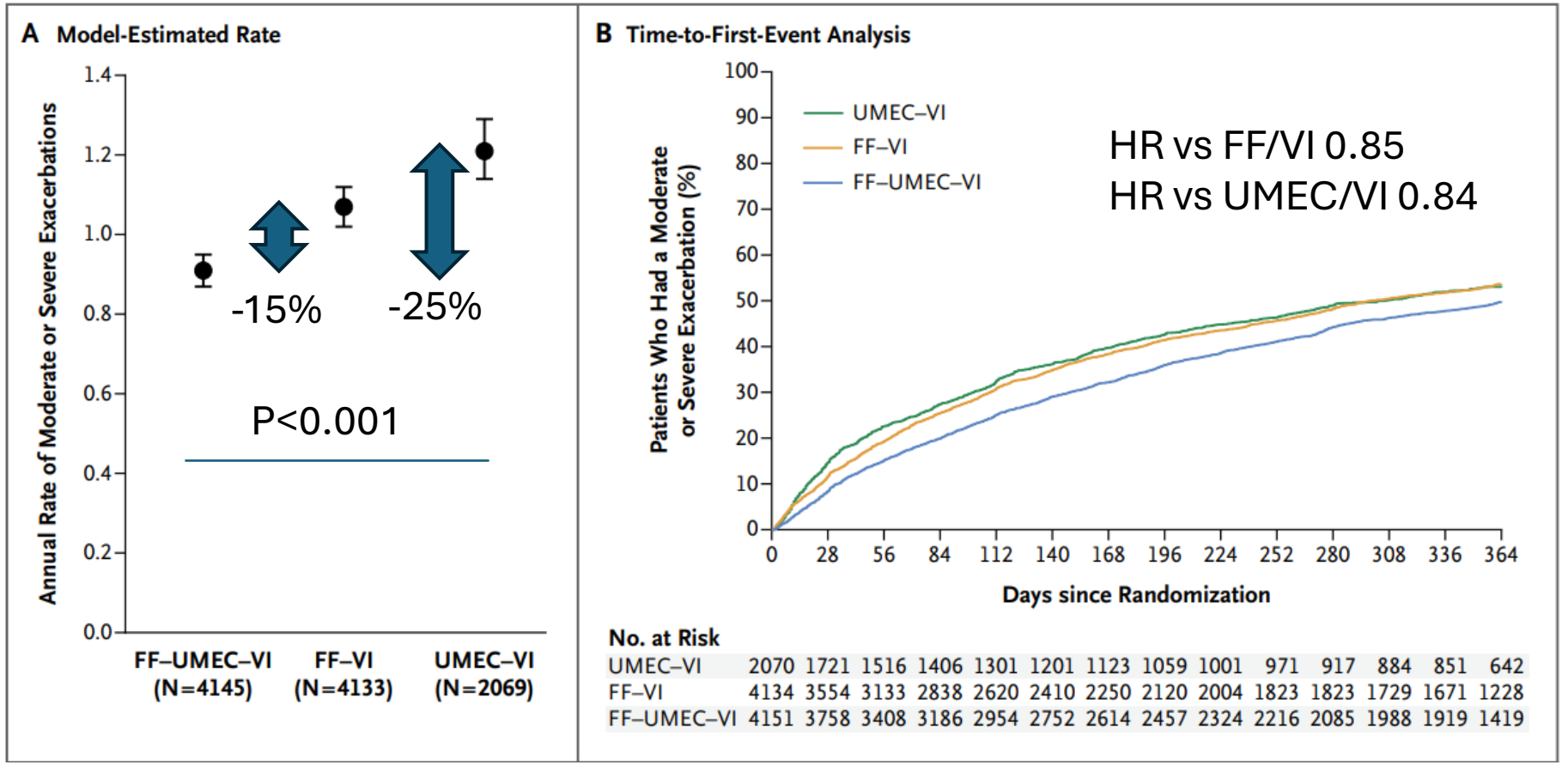
1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers

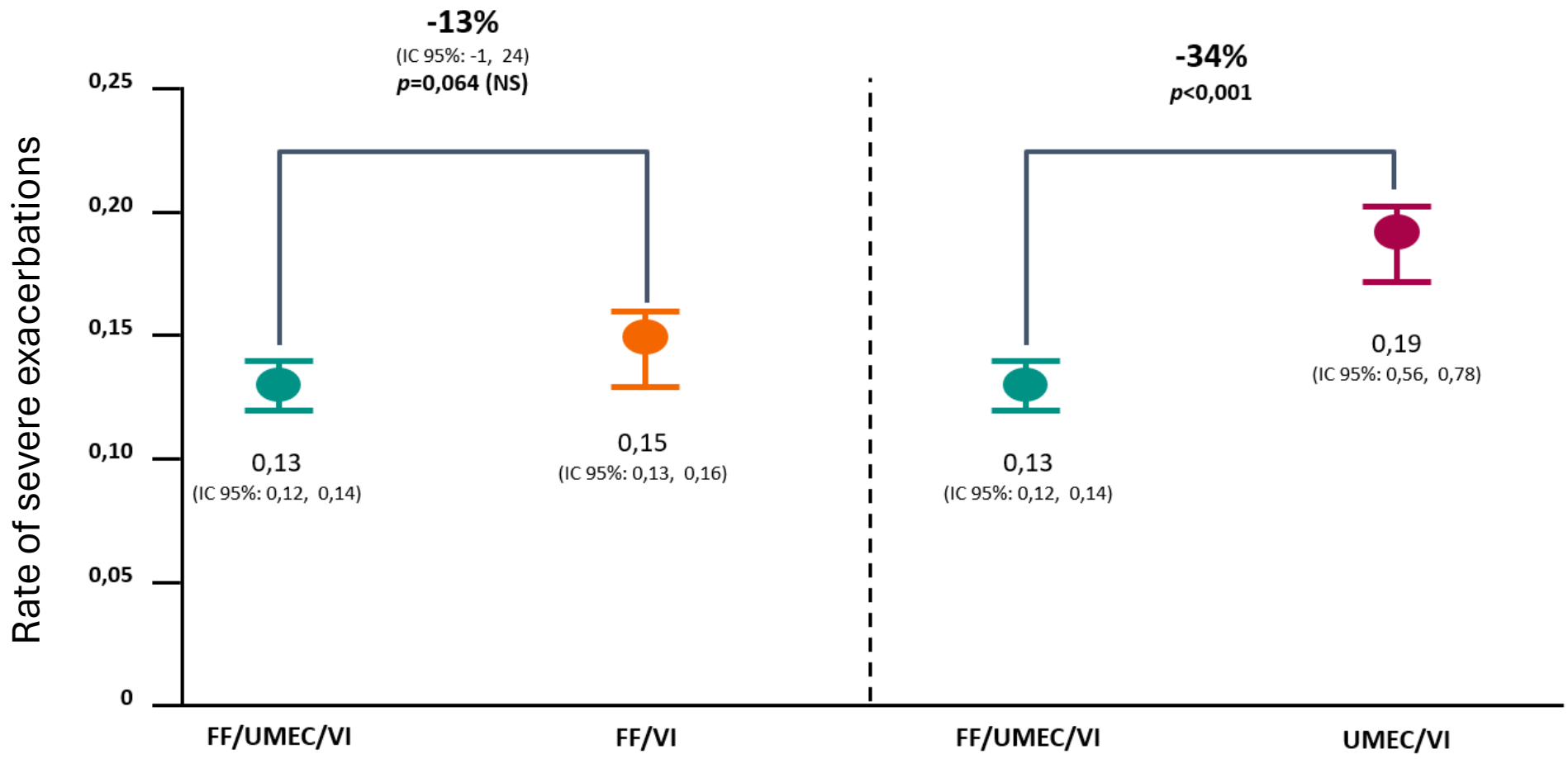
**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

Triple therapy with FF/UMEC/VI efficacy on mod/severe exacerbations



Lipson DA et al. N Eng J Med 2018

Triple therapy with FF/UMEC/VI reduces severe exacerbations



Lipson DA et al. N Eng J Med 2018

GOLD 2023 has strengthened the emphasis on the importance of preventing premature mortality with pharmacotherapy[1]

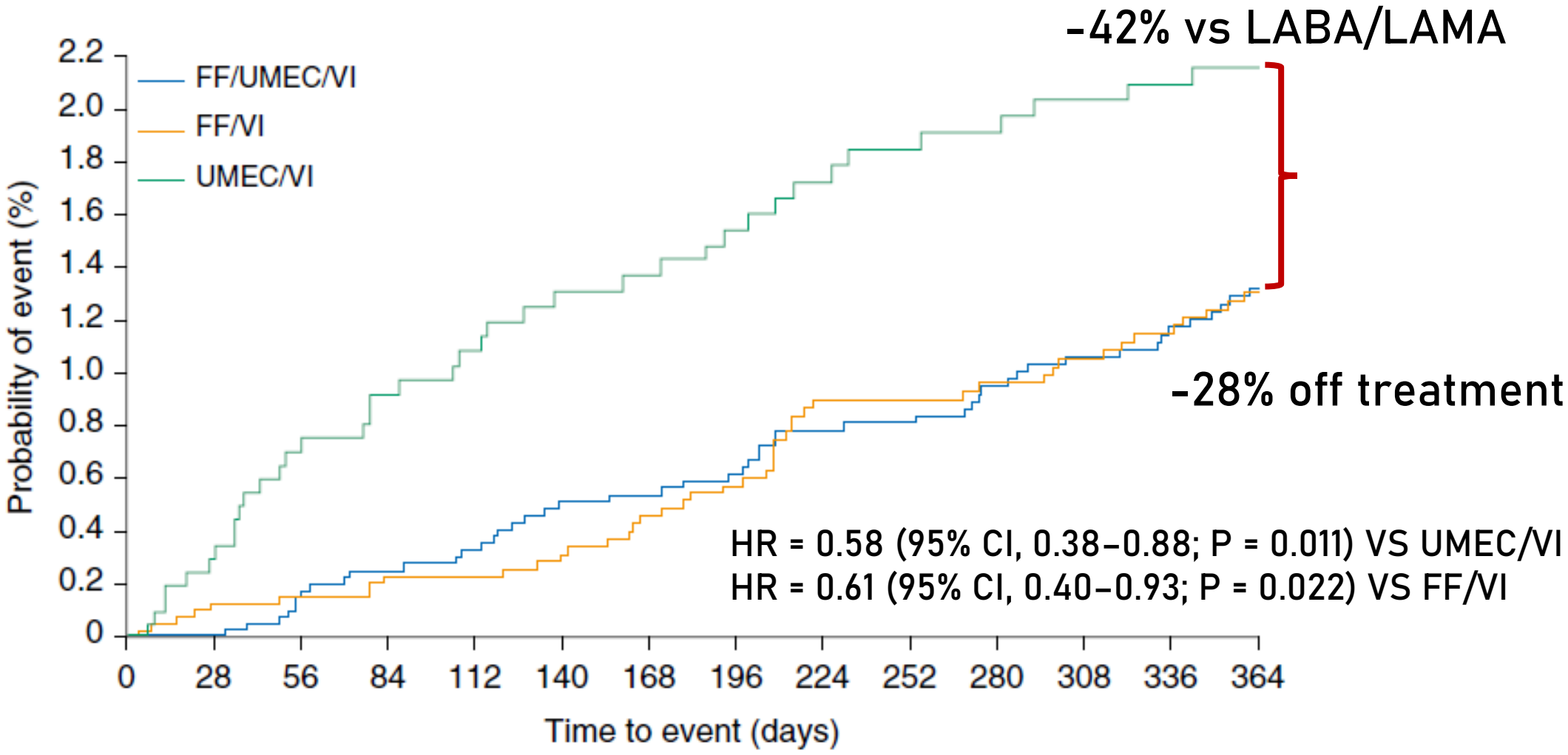
Triple therapy is the **only pharmacotherapy** with evidence supporting a **reduction in mortality** in patients with COPD[1]

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA + LAMA + ICS	Yes	Triple compared with dual LABD relative risk reduction: **IMPACT:** HR 0.72 (95% CI 0.53, 0.99)[2] **ETHOS:** HR 0.51 (95% CI 0.33, 0.80)[3]	Symptomatic people with a history of frequent and/or severe exacerbations

Non-pharmacological options that reduce mortality include smoking cessation, pulmonary rehabilitation, long-term oxygen therapy, non-invasive positive pressure ventilation and lung volume reduction surgery

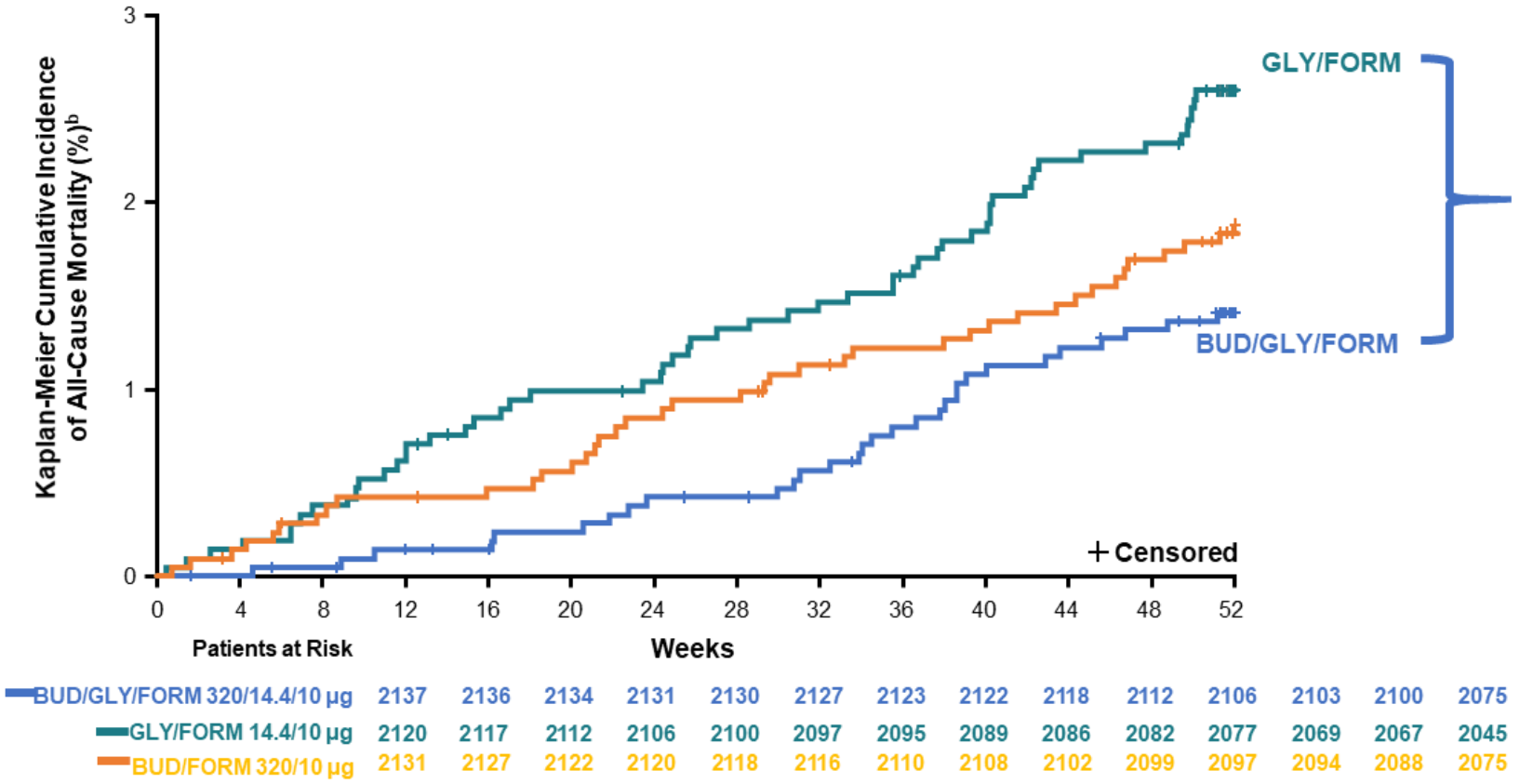
Page 68, Table 3.6

Mortality reduction with triple therapy in IMPACT trial



Lipson DA et al. Am J Respir Crit Care Med 2020

MORTALITY IN THE ETHOS STUDY



Over 52 weeks
BUD/GLY/FORM 320/14.4/10 µg
demonstrated a:

49%

significant reduction vs. LAMA/LABA[c]
HR: 0.51; 95% CI: 0.33 to 0.80;
unadjusted p=0.0035[a]

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

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

Rabe KF et al. N Engl J Med 2020

Riduzione degli eventi fatali con terapia contenenti ICS extrafine nell'analisi aggregata degli studi TRILOGY, TRINITY e TRIBUTE

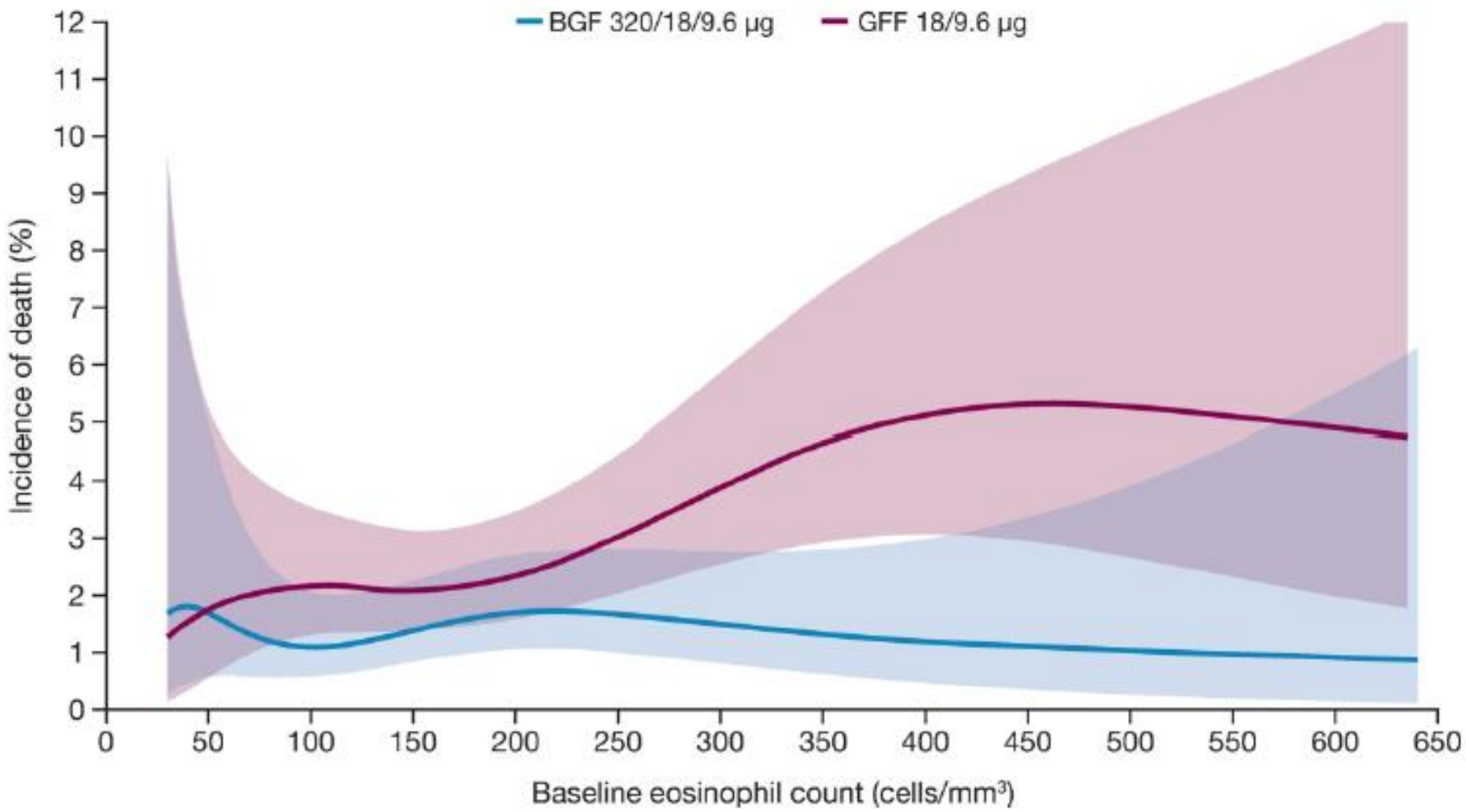
N of patients with events (%)	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GLY (N=1844)	**HR (95% CI) p value**
RESPIRATORY	19 (0.5%)	9 (0.5%)	1.01 (0.45; 2.22) p=0.990
NON - RESPIRATORY	56 (1.5%)	41 (2.2%)	0.65 (0.43; 0.97) p=0.037

Patients (%) with fatal AEs and hazard ratios (HRs) for treatment group comparisons

I trattamenti contenenti ICS sono associati ad un minor tasso di **mortalità non respiratoria** in soggetti con BPCO sintomatica a rischio di riacutizzazioni

Scuri M. et al., American Journal of Respiratory and Critical Care Medicine 2018; 197: A7726

MORTALITY BASED ON EOSINOPHIL COUNT IN ETHOS (TRIPLE vs LABA/LAMA)



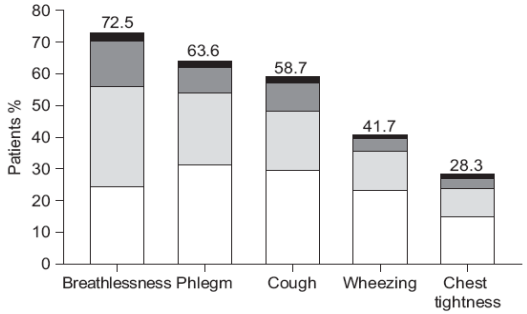
Rabe KF et al. N Engl J Med 2020

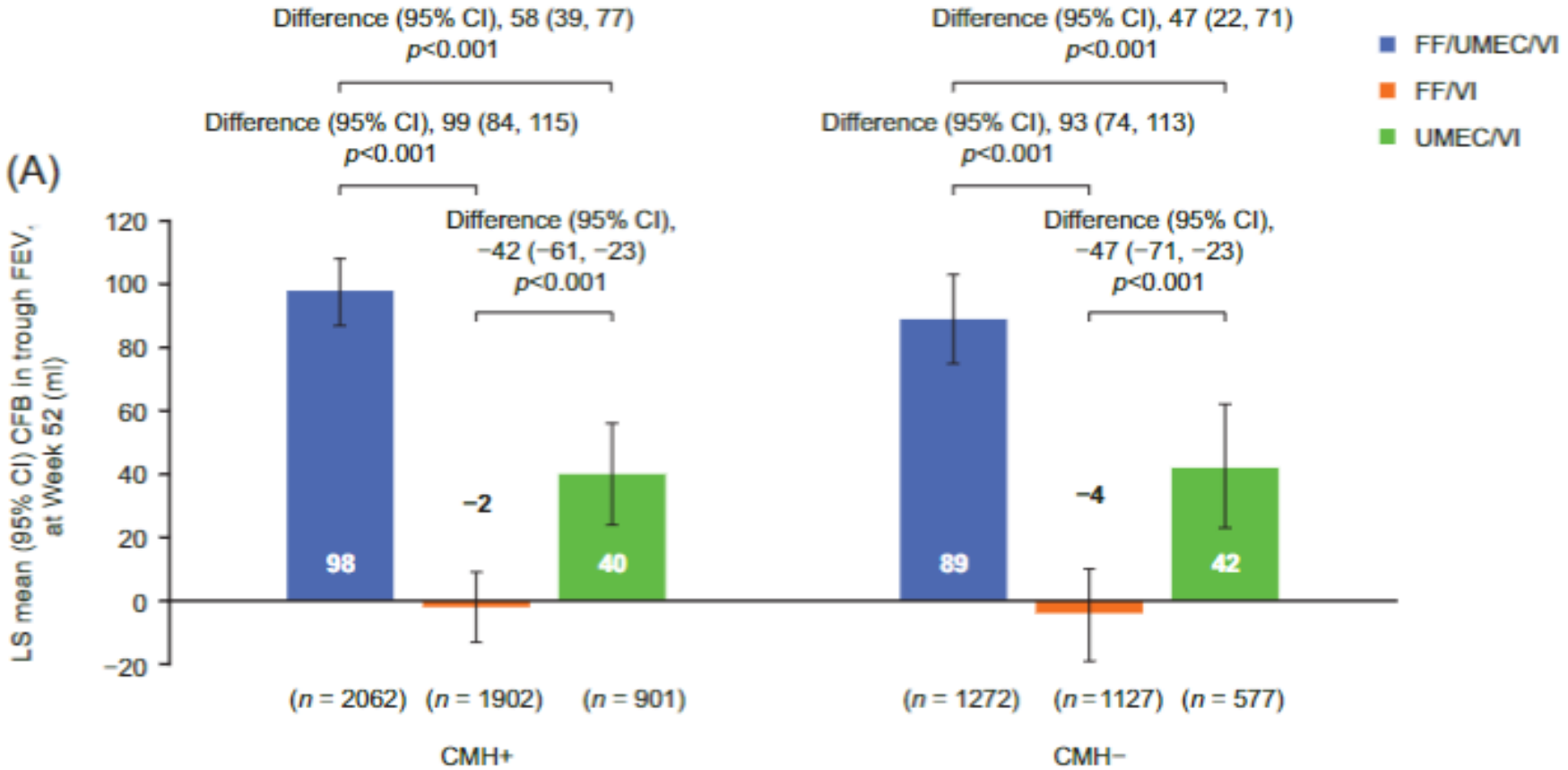
Received: 16 February 2022 | Accepted: 18 July 2022
DOI: 10.1111/resp.14339

ORIGINAL ARTICLE

Respirology WILEY

Effect of chronic mucus hypersecretion on treatment responses to inhaled therapies in patients with chronic obstructive pulmonary disease: Post hoc analysis of the IMPACT trial





Thompson et al. Respirology 2022

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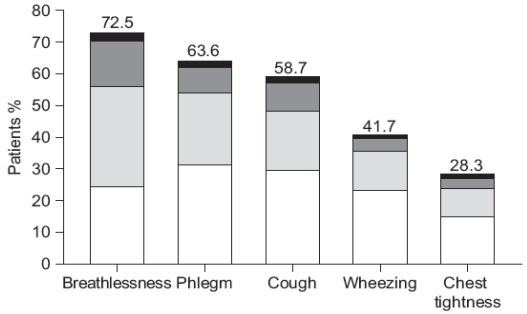
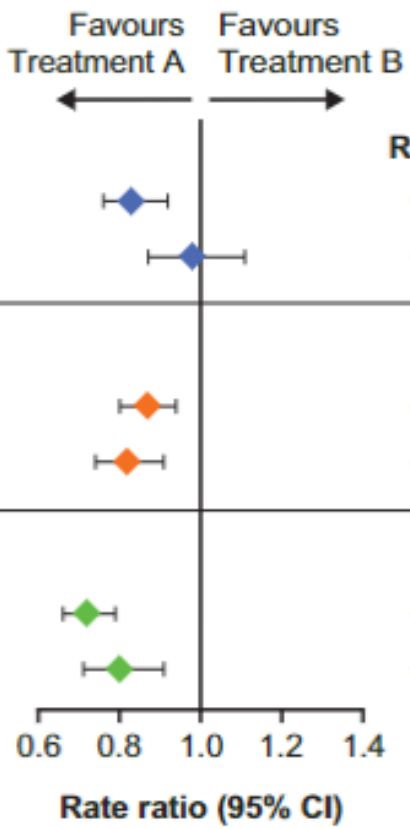


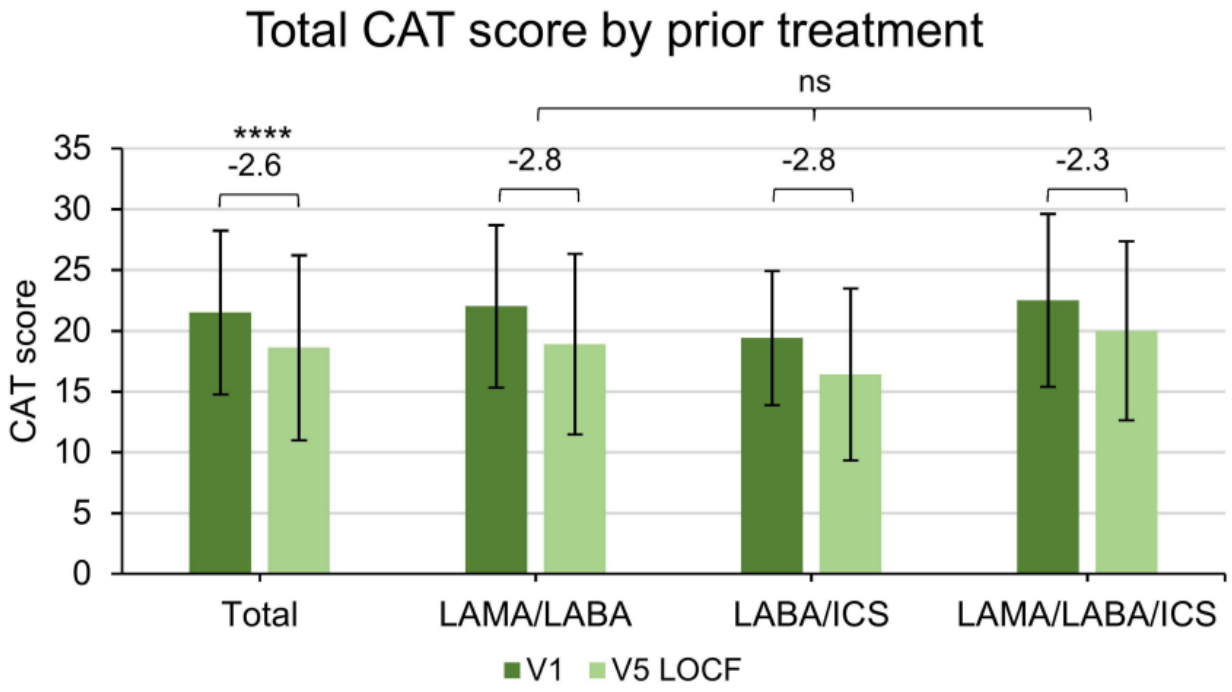
FF/UMEC/VI versus FF/VI ◆ FF/UMEC/VI versus UMEC/VI ◆ FF/VI versus UMEC/VI

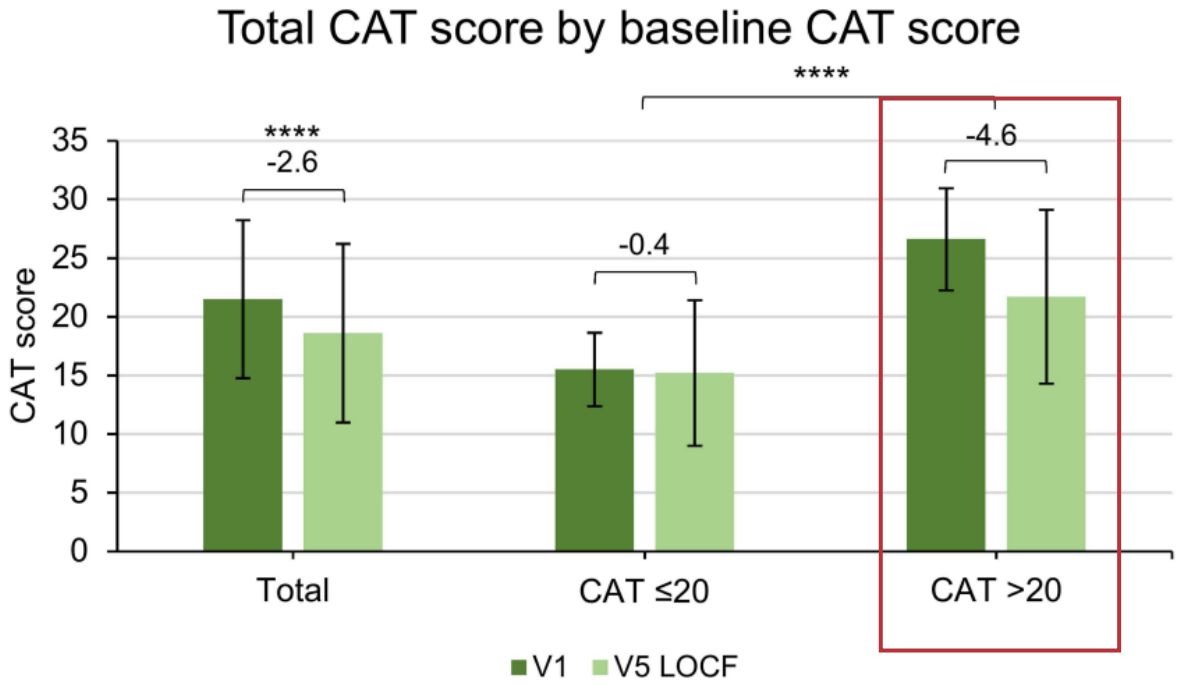
	Modelled annual exacerbation rate (95% CI)		
	Treatment A	Treatment B	
FF/VI versus UMEC/VI	**FF/VI**	**UMEC/VI**	**Rate ratio (95% CI)** **p-value**
CMH+ (FF/VI n = 2579; UMEC/VI *n* = 1264)	1.08 (1.02, 1.14)	1.30 (1.20, 1.40)	0.83 (0.76, 0.92) <0.001
CMH− (FF/VI n = 1512; UMEC/VI *n* = 785)	1.05 (0.97, 1.13)	1.07 (0.96, 1.18)	0.98 (0.87, 1.11) 0.810
FF/UMEC/VI versus FF/VI	**FF/UMEC/VI**	**FF/VI**	
CMH+ (FF/UMEC/VI n = 2537; FF/VI *n* = 2579)	0.94 (0.89, 0.99)	1.08 (1.02, 1.14)	0.87 (0.80, 0.94) <0.001
CMH− (FF/UMEC/VI n = 1566; FF/VI *n* = 1512)	0.86 (0.80, 0.92)	1.05 (0.97, 1.13)	0.82 (0.74, 0.91) <0.001
FF/UMEC/VI versus UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**	
CMH+ (FF/UMEC/VI n = 2537; UMEC/VI *n* = 1264)	0.94 (0.89, 0.99)	1.30 (1.20, 1.40)	0.72 (0.66, 0.79) <0.001
CMH− (FF/UMEC/VI n = 1566; UMEC/VI *n* = 785)	0.86 (0.80, 0.92)	1.07 (0.96, 1.18)	0.80 (0.71, 0.91) <0.001



Thompson et al. Respirology 2022

Real world effectiveness of FF/UMEC/VI in symptomatic COPD: ELLITHE non-interventional trial



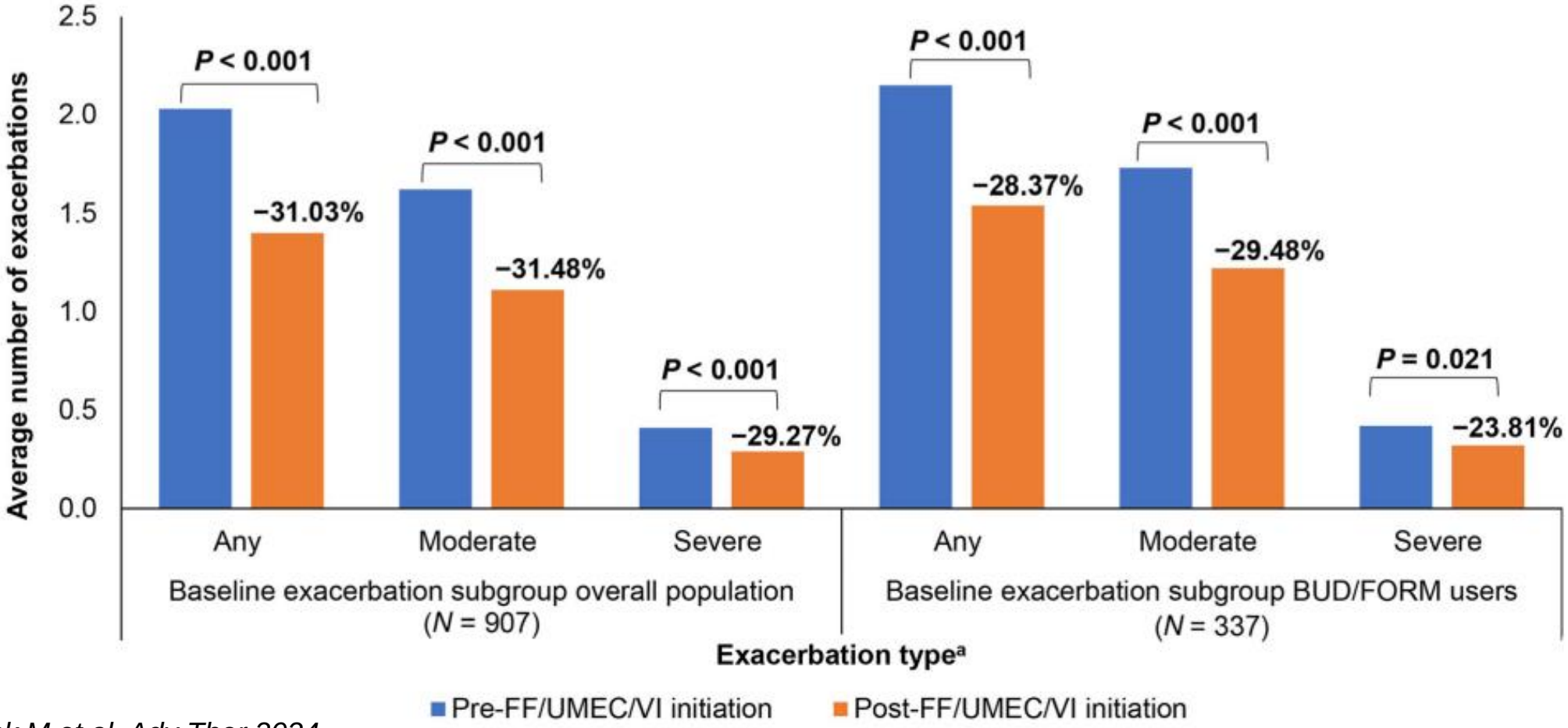


68.6% GOLD B
31.4% GOLD D

64% escalated from dual therapies
18% switched from multiple inhaler thrapies

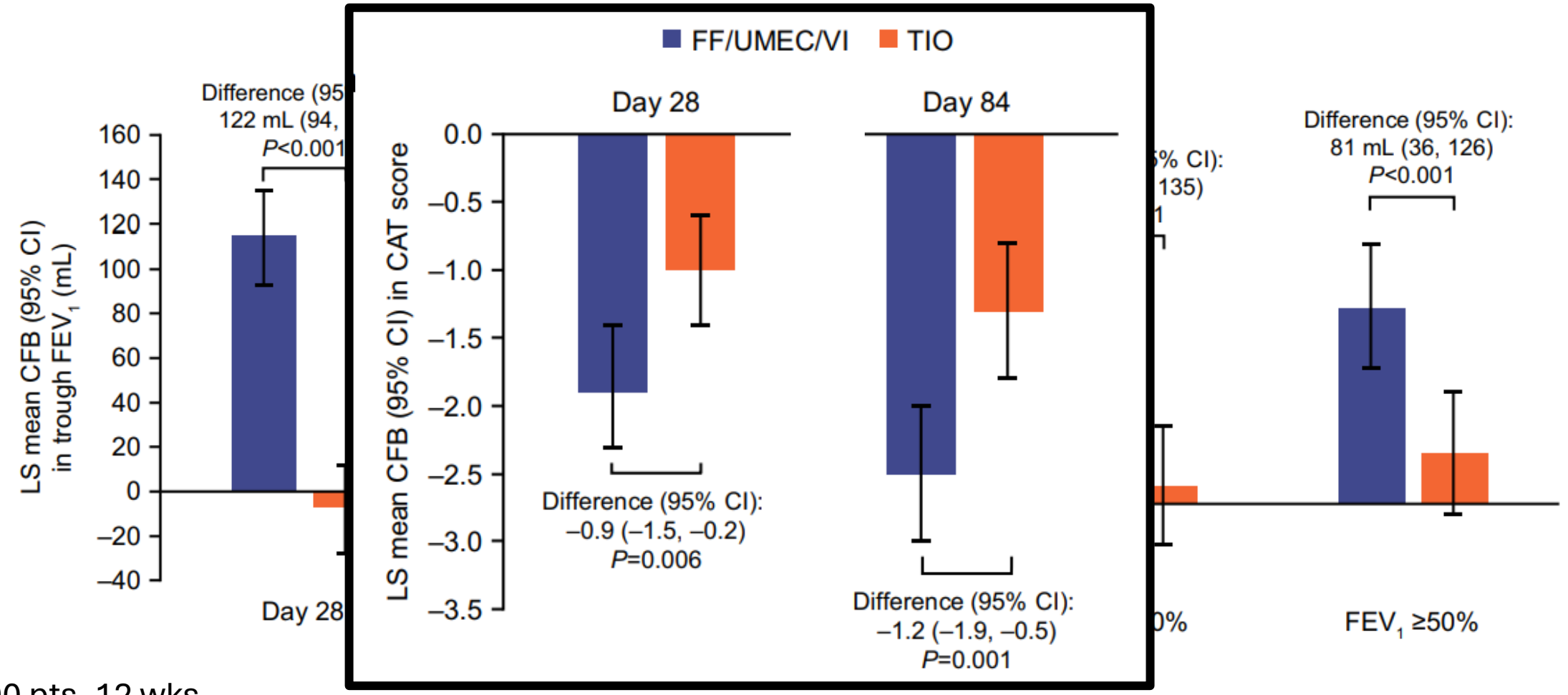
Beeh K-M et al. Int J COPD 2024

Exacerbations in patients switching to FF/UMEC/VI from ICS/LABA: real world data



McCormack M et al. Adv Ther 2024

Optimizing therapy with FF/UMEC/VI vs TIO

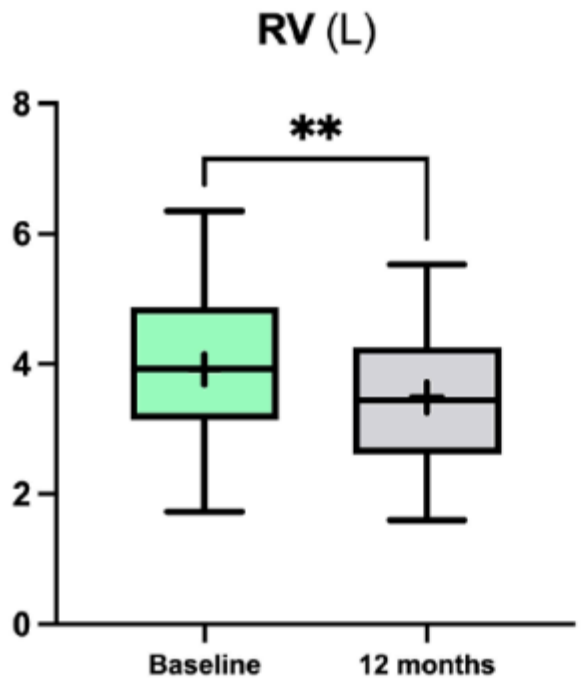


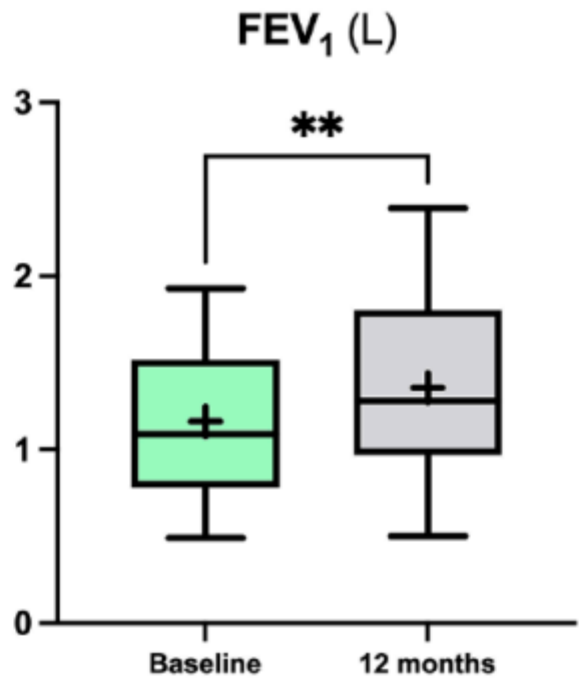
800 pts, 12 wks

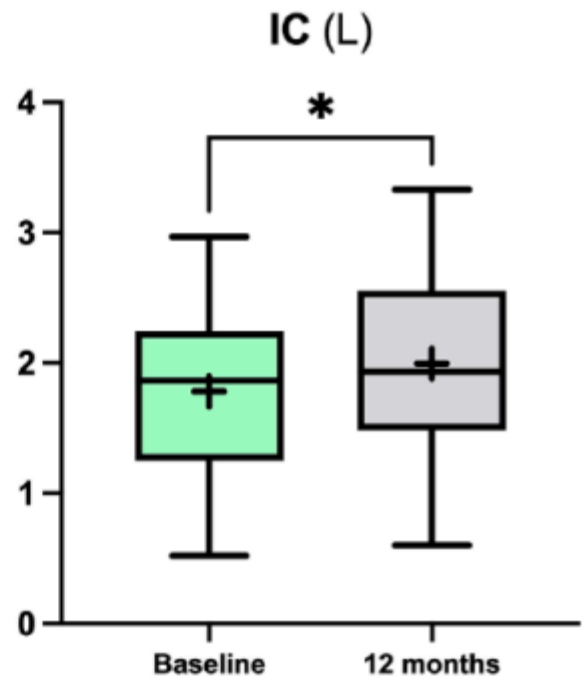
53% ≥ 2 mod AECOPD; 11% severe AECOPD

Bansal S et al. Primary Care Respiratory Medicine 2021

Effect of bechlometasone/glycopyrronium/formoterol extrafine real life data

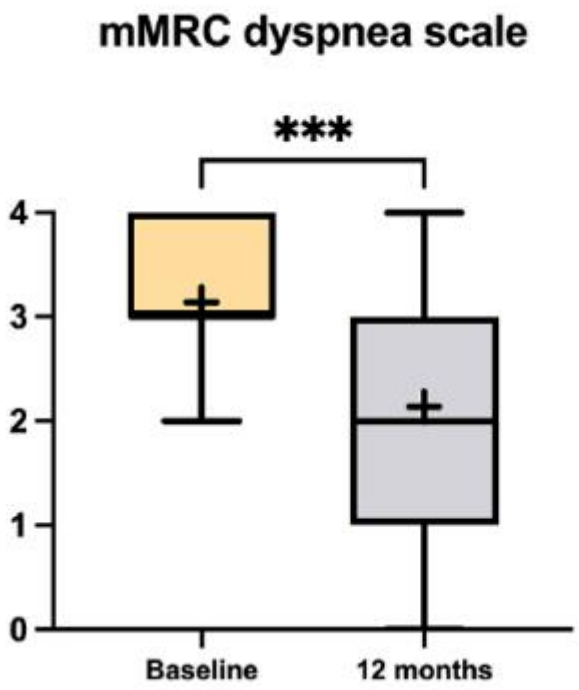


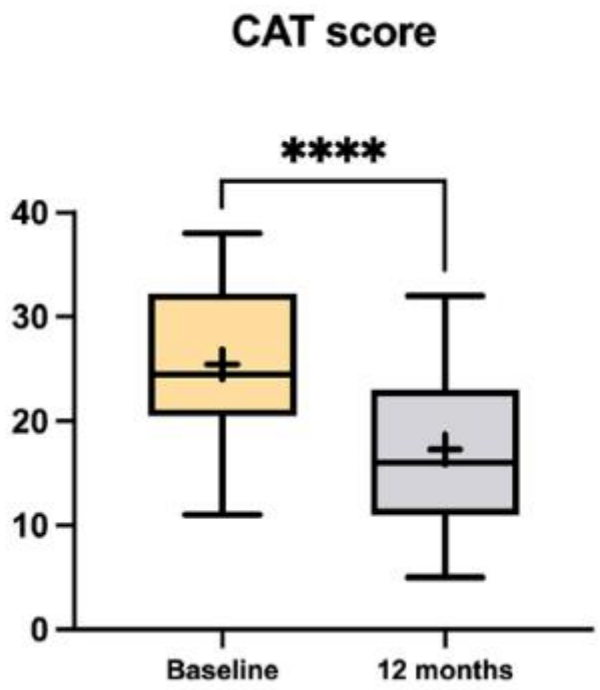


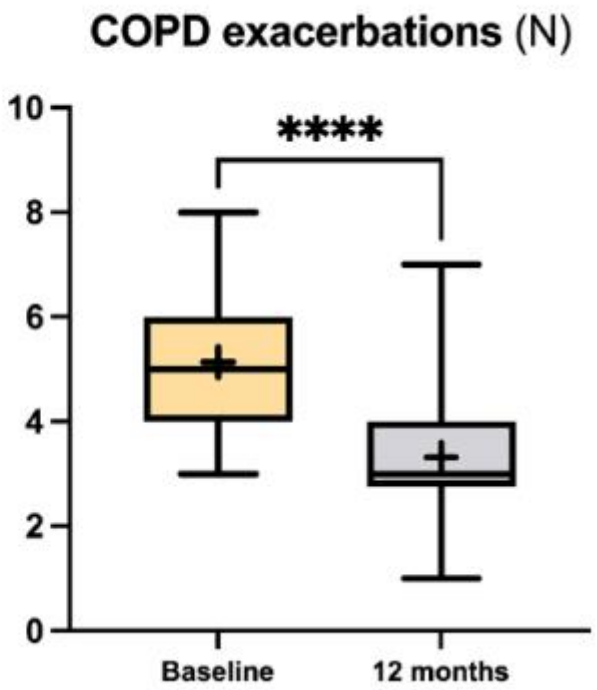


Pelaia C et al. Ther Adv Respir Dis 2023

Effect of bechlometasone/glycopyrronium/formoterol extrafine real life data







Pelaia C et al. Ther Adv Respir Dis 2023

TRITRIAL study: Digital approach and Patient-centric nature

The study plan included a **brief retrospective phase** to allow data collection from the time of the switch from previous therapy to BDP/FF/G to the patient's enrolment. After an initial visit (baseline, Visit 1), patients were **followed for up to 12 months** and performed follow-up visits after 6±1 months (Visit 2) and 12±1 months (Visit 3).

The **primary endpoint** is the change of CAT score at 12 months versus baseline.

Secondary endpoints are adherence, health-related quality of life, sleep quality, disease-related outcomes (lung function and COPD exacerbations), device usability, economic resources consumption, and safety

- ❑ Specific focus on capturing patients' perceptions and points of view
- ❑ **Digital approach in collecting data, fundamental to facing the challenges** caused in 2020 by the SARS-CoV-2 pandemic

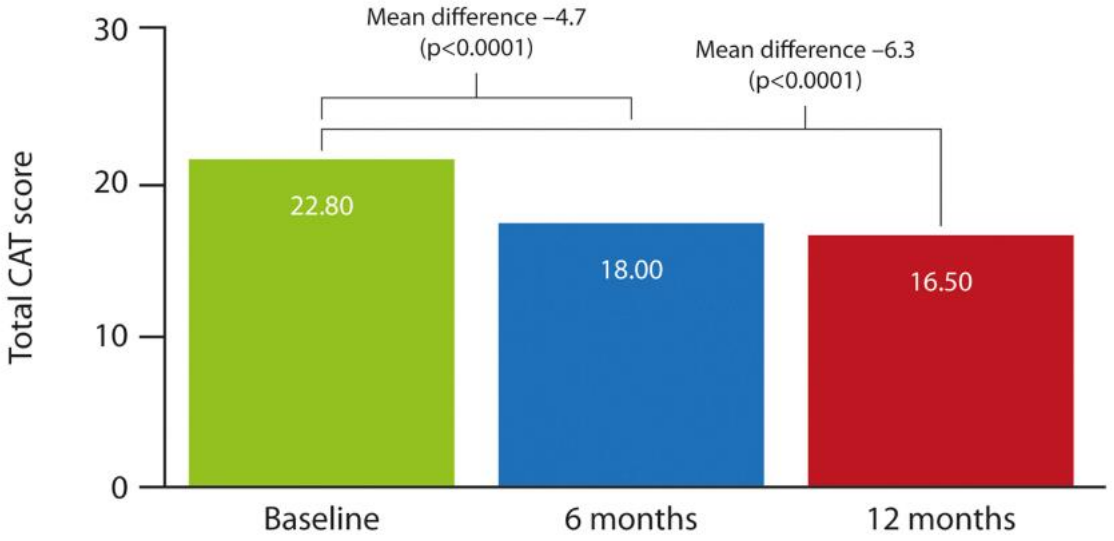
Richeldi et al. Int J Chron Obstruct Pulmon Dis 2024:19 475–487

	Patients (n=655)
Demographics	
Sex, n (%)	
Male	447 (68.2%)
Female	208 (31.8%)
Age (years), mean (SD)	71.2 (9.0)
Body mass index (kg/m^2), mean (SD)	26.9 (5.4)
Smoking habit, n (%)	
Non-smoker	76 (11.6%)
Ex-smoker	411 (62.7%)
Current smoker	168 (25.6%)

	Patients (n=655)
Concomitant diseases	
At least one concomitant disease	506 (77.3%)
Most frequent concomitant diseases (>10%):	
Vascular disorders	279 (42.6%)
Cardiac disorders	166 (25.3%)
Metabolism and Nutrition disorders	149 (22.7%)
Respiratory, Thoracic and mediastinal disorders	146 (22.3%)
Gastrointestinal disorders	77 (11.8%)

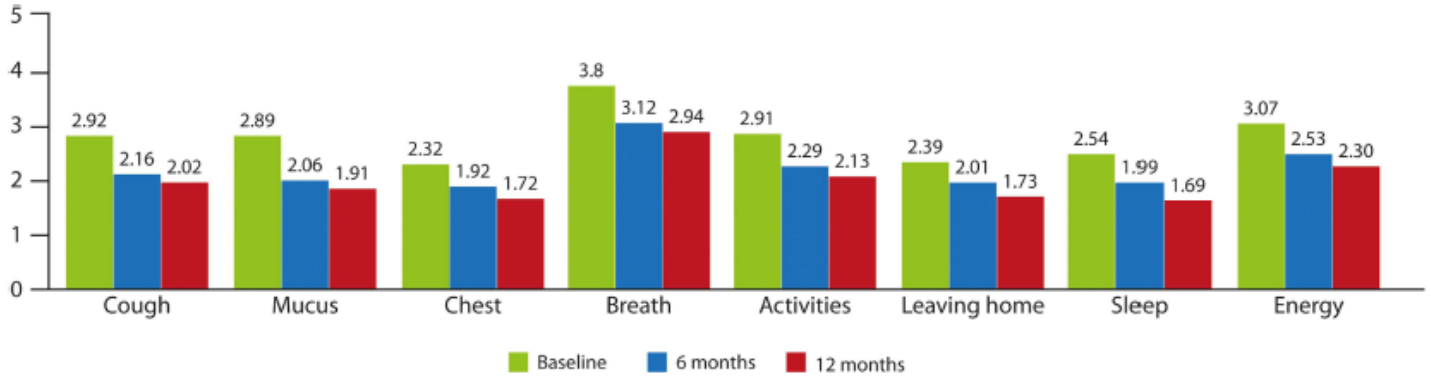
Medical history	
Time (years) since first COPD diagnosis, mean (SD)	9.8 (8.0)
CAT score at baseline, mean (SD)	22.5 (7.5)
Severity of last exacerbation*, n (%)	
Moderate	583 (89.0%)
Severe	177 (27.0%)
Number of prior exacerbations per patients*, mean (SD)	
Moderate	1.8 (0.8)
Severe	1.1 (0.4)
All	1.9 (0.9)
Patients with at least one prior exacerbation*, n (%)	652 (99.5%)
Previous therapies	
SITT	62 (9.5%)
MITT	162 (24.7%)
LABA+LAMA	47 (7.20%)
LABA/LAMA	140 (21.40%)
ICS+LABA	27 (4.10%)
ICS/LABA	168 (25.60%)
Others	49 (7.50%)

Primary Endpoint: CAT score



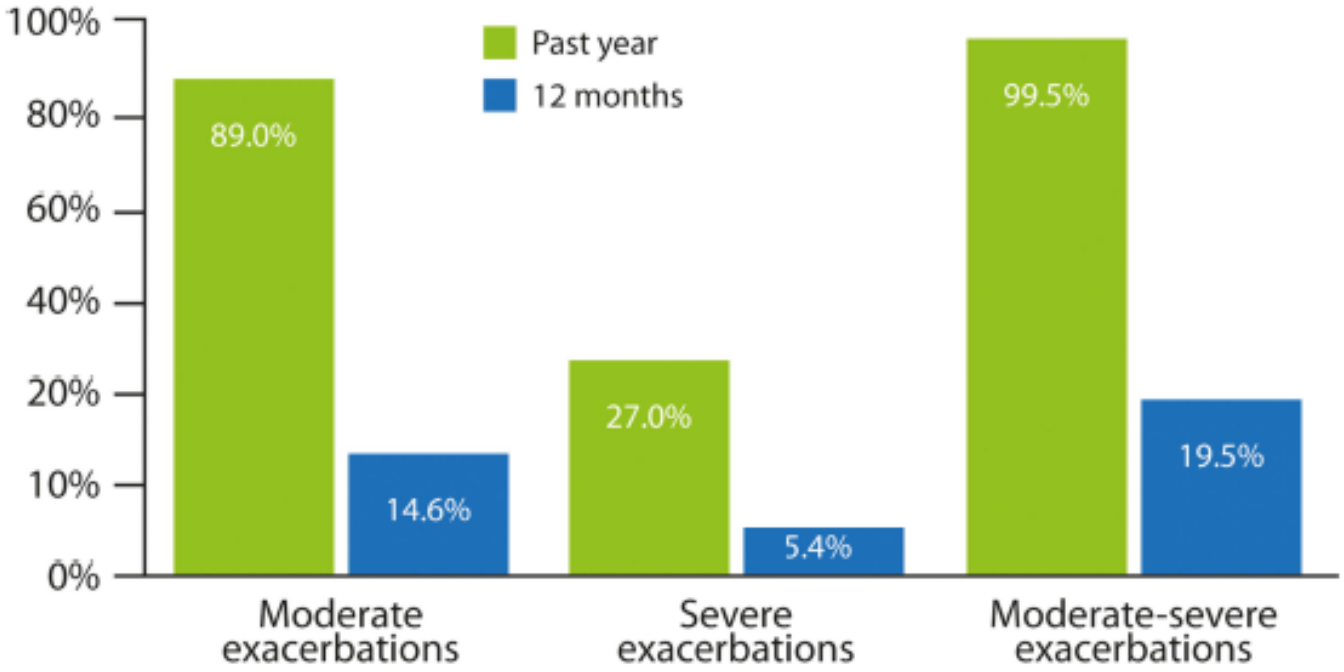
- CAT score significantly decreased, both at 6- and 12-months visits
- Approximately 75.4% of the patients benefited from an improvement of at least 2 points in the mean total CAT score starting from 6 months after treatment; the improvement was also maintained after 12 months

- statistically significant decrease for all the 8 CAT su-items both at 6 and 12 months compared with baseline



Richeldi et al. Int J Chron Obstruct Pulmon Dis 2024:19 475–487

Secondary endpoint: Exacerbations



Exacerbations of COPD represent the main cause of disease progression and health resources consumption.

- Exacerbations prevalence was **99.5% in the previous year and decreased to 19.5% during the trial** (p<0,001)

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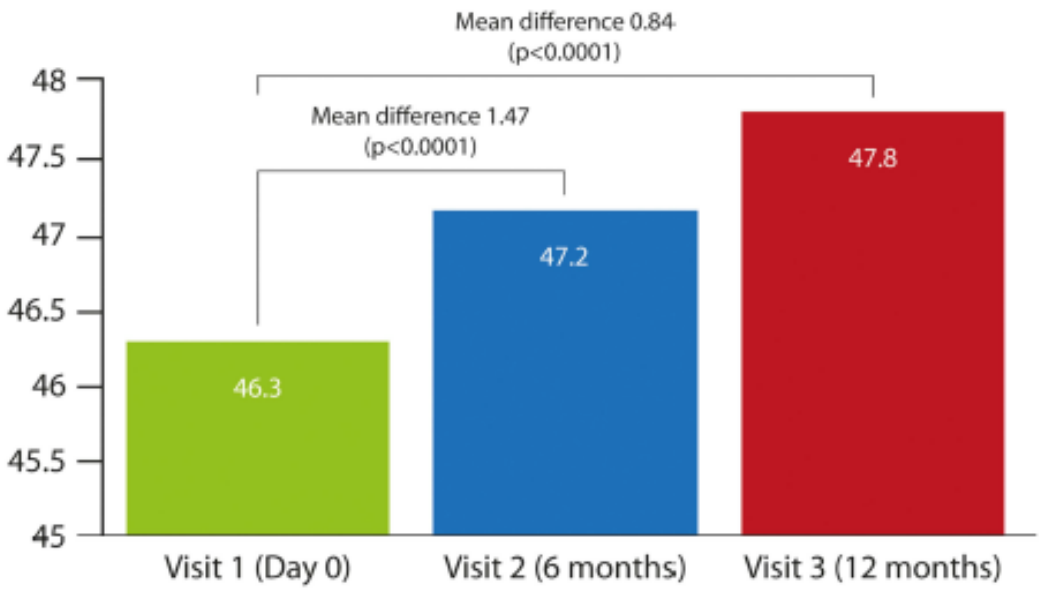
Secondary endpoint: Adherence



	Baseline	6 months	12 months
Poor (TAI ≤45)	30.1%	23.0%	18.3%
Moderate (TAI 46–96)	18.0%	26.5%	23.4%
Good (TAI = 50)	51.8%	50.5%	58.3%

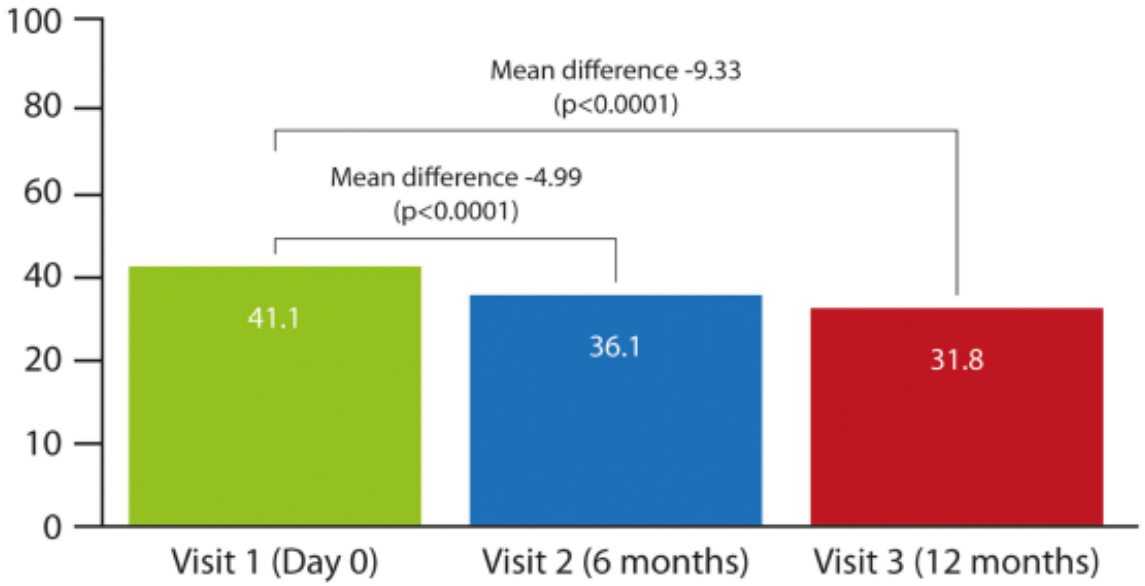
According to TAI-10:

- the **percentage of patients with poor adherence decreased from 30.1% to 18.3% over 12 months**;
- good adherence was well maintained and even slightly increased during the study (from 50% to 58%)

Patient satisfaction and usability of the inhaler improved during the study; the percentage of **patients fully satisfied** increased from 34.8% at baseline to 46.6% after 12 months ($p < 0.001$)

Richeldi et al. Int J Chron Obstruct Pulmon Dis 2024:19 475–487

Secondary endpoint: Sleep impairment



The COPD and Asthma Sleep Impact Scale (CASIS) is a validated questionnaire which evaluates sleep impairment associated with obstructive pulmonary diseases.

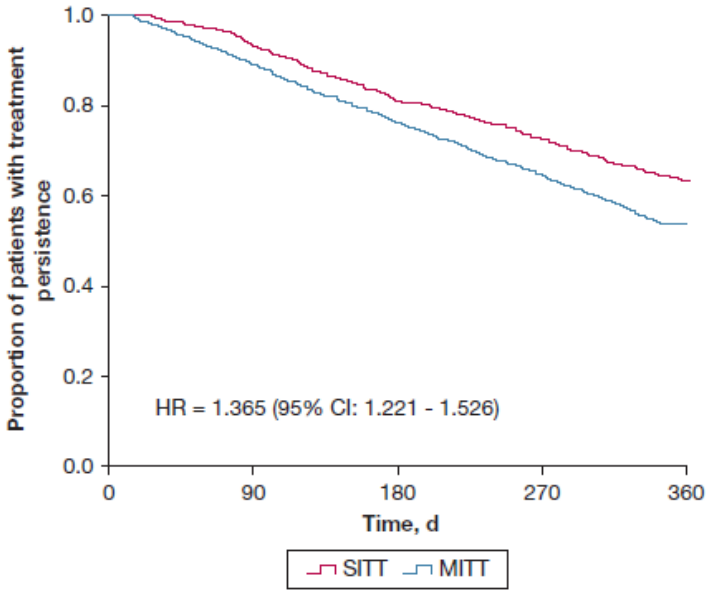
- It comprises 5 items and 2 items specifically investigate **sleep quality**

CASIS total score at the baseline was 41.1 vs 36.1 at 6-month follow up (p<0.0001)] and 31.8 (p<0.0001) at 12-month follow-up

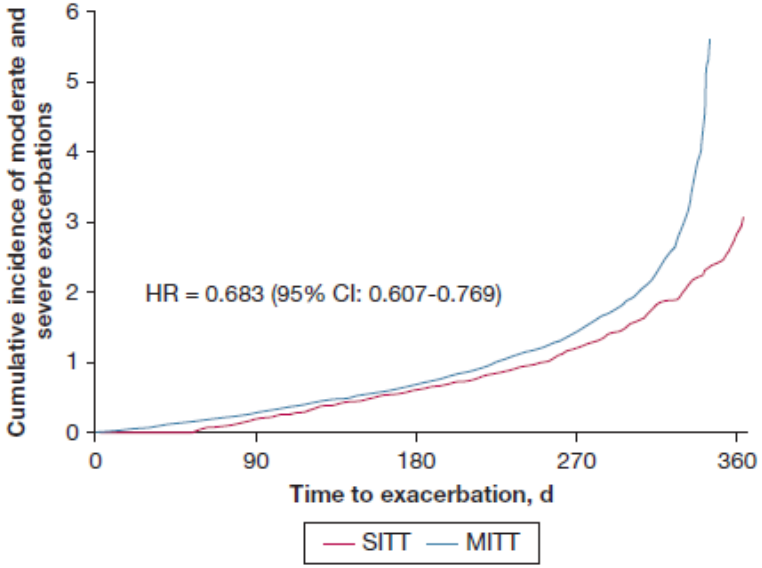
- The **quality of sleep became better** from baseline to follow-up visits.

Richeldi et al. Int J Chron Obstruct Pulmon Dis 2024:19 475–487

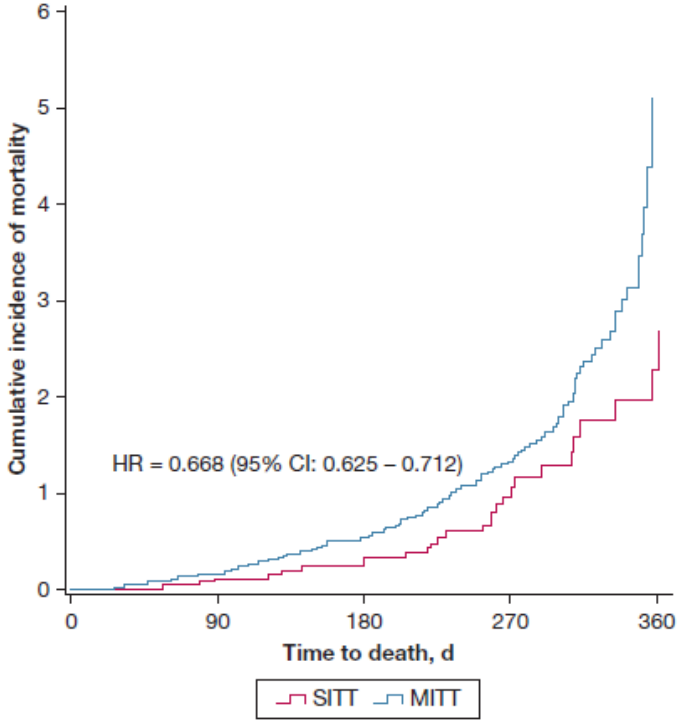
Single vs Multiple Inhaler Triple Therapy in COPD: real life



Treatment persistence



Moderate and severe exacerbations



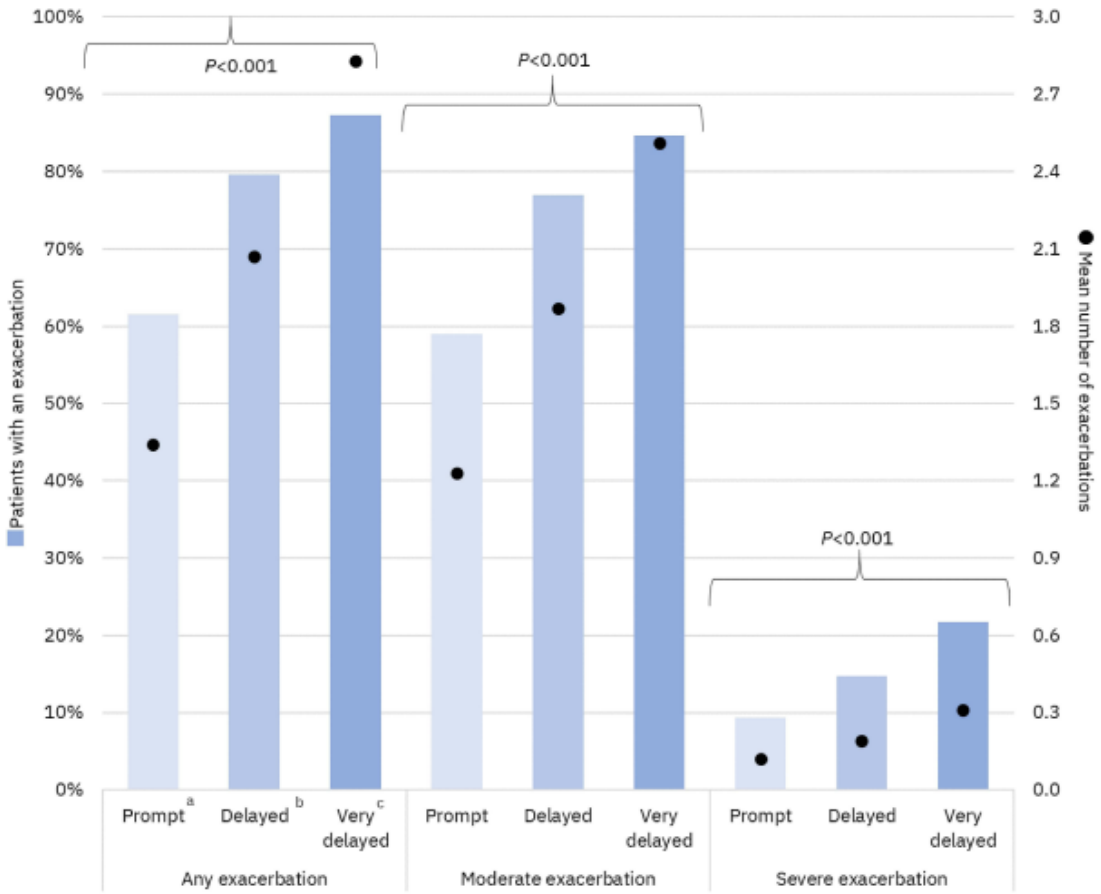
Mortality

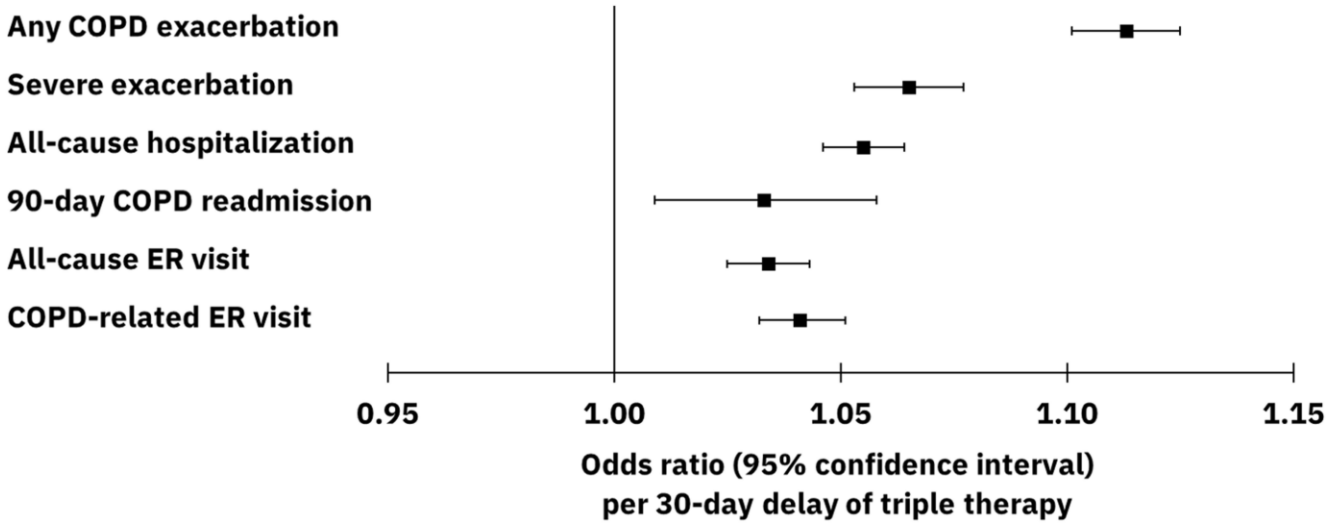
At 12-month follow-up, SITT (Single Inhaler Triple Therapy) patients had a **37% improvement in persistence compared with MITT** (Multiple Inhaler Triple Therapy) patients, leading to

- 33% risk reduction in **all-cause mortality**
- 32% risk reduction in the **incidence of exacerbations**

Alcázar-Navarrete B, et al. Chest. 2022. PMID: 35787391

Promptly Initiating Triple Therapy Is Associated with Decreased Morbidity and Economic Burden in COPd

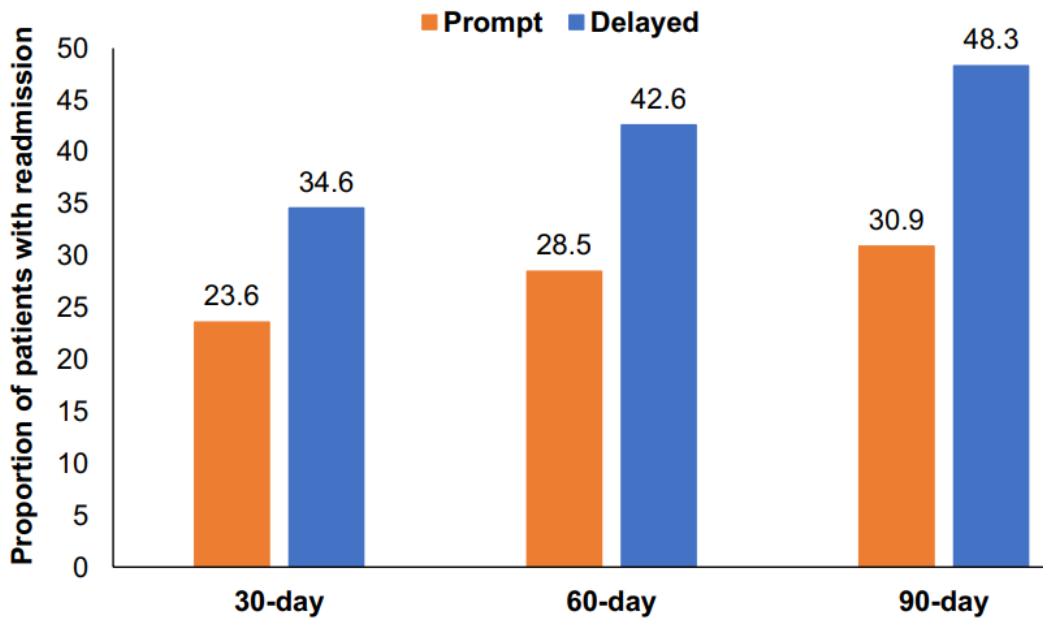




Tkacz J et al. Int J Chron Obstruct Pulmon Dis. 2022

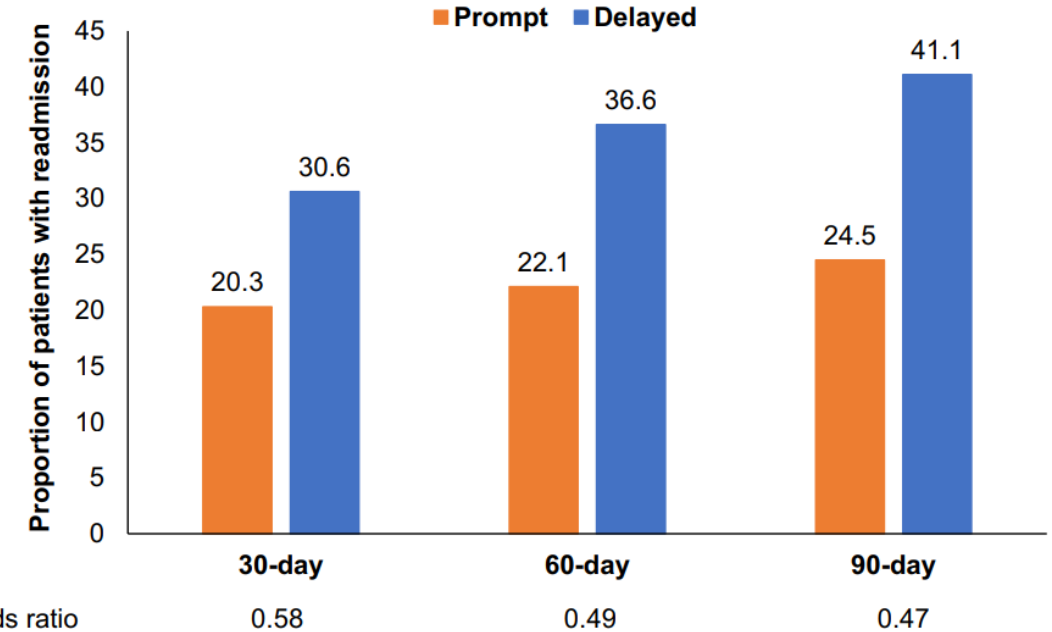
Detrimental effect of late initiation of triple therapy: the value of prompt intervention with FF/UMEC/VIL post-exacerbation

a) All-cause



	30-day	60-day	90-day
Odds ratio (95% CI)	0.58 (0.36–0.94)	0.54 (0.34–0.85)	0.48 (0.31–0.75)
p-value	**0.0293**	**0.008**	**0.0013**

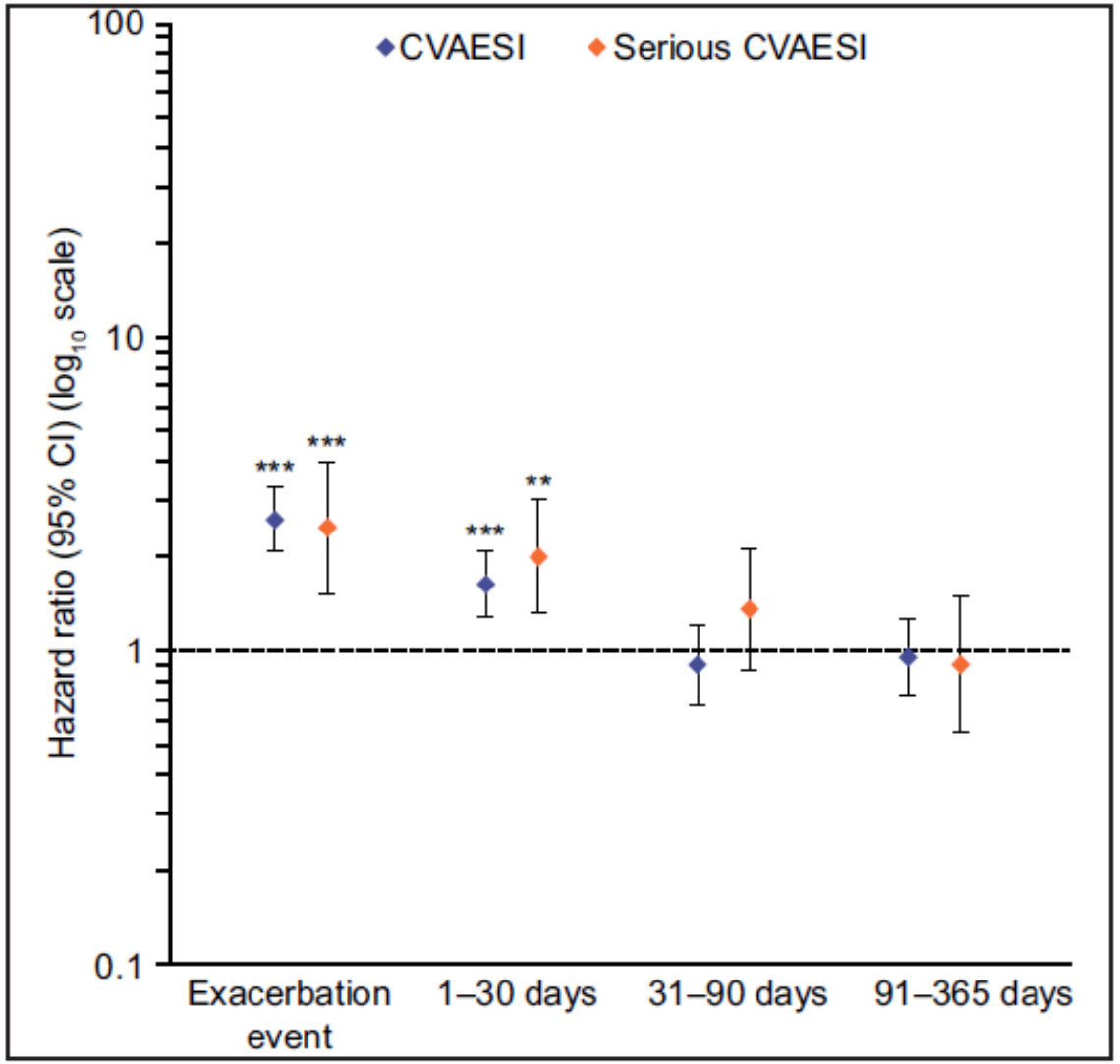
b) COPD-related



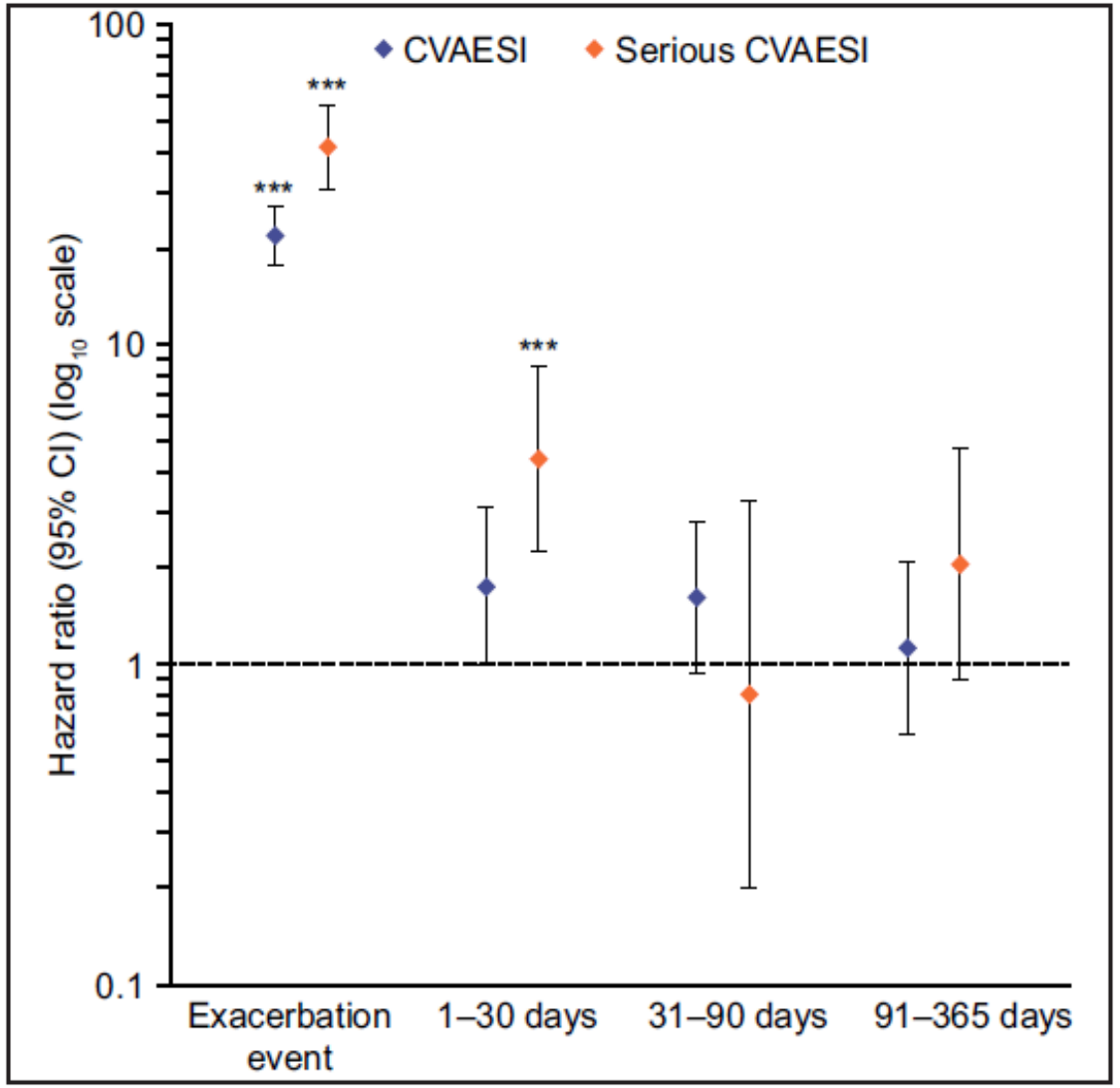
	30-day	60-day	90-day
Odds ratio (95% CI)	0.58 (0.35–0.96)	0.49 (0.30–0.81)	0.47 (0.29–0.75)
p-value	**0.0347**	**0.0047**	**0.0016**

Ismaila et al. Respir Res 2023

Following a moderate AECOPD



Following a severe AECOPD



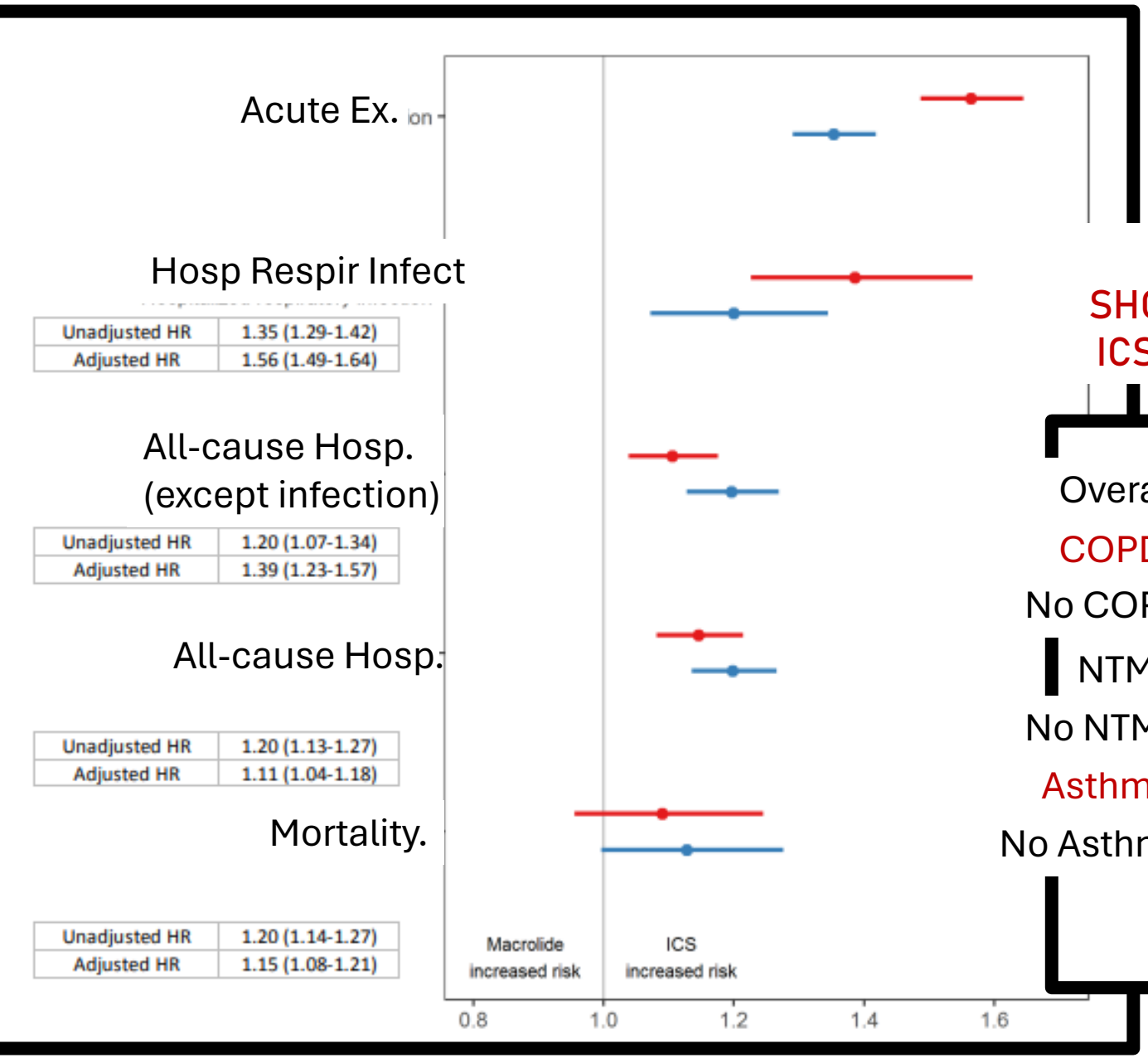
Data from IMPACT trial

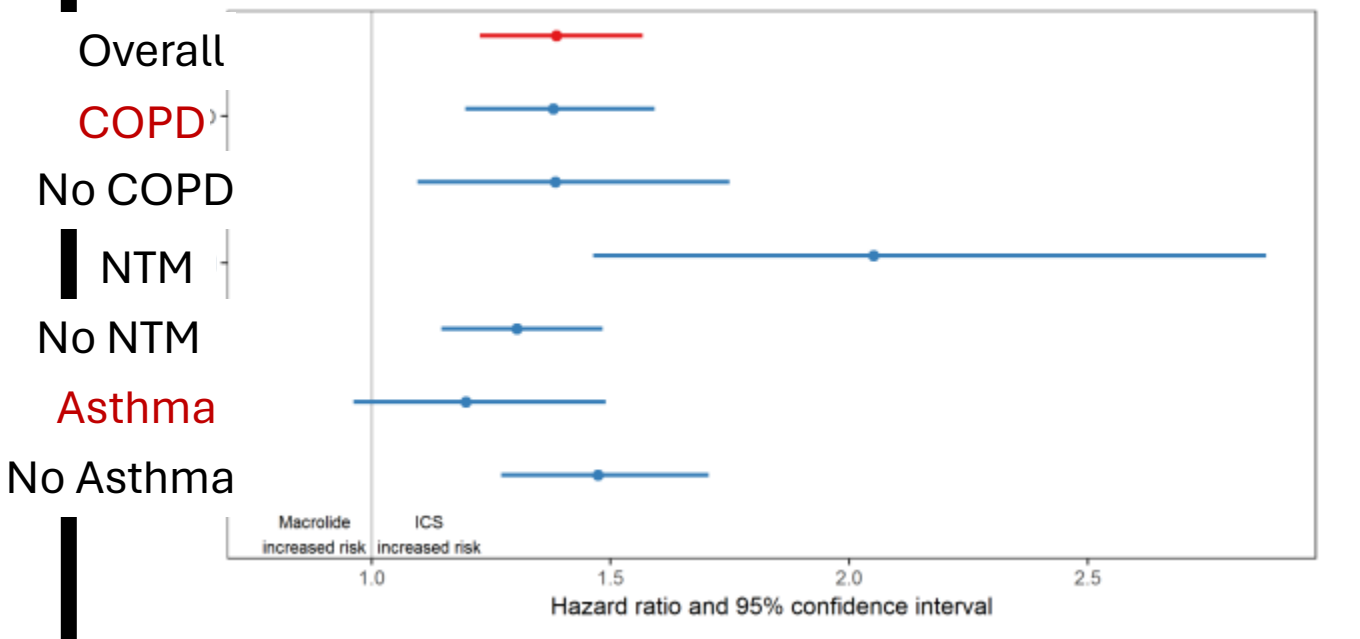
Dransfield et al. J Am Heart Assoc 2022

Who should not receive triple (or ICS containing) therapy

Patients with Bx
83,589 new users of ICS
6,500 of macrolides

PATIENTS WITH CLINICALLY SIGNIFICANT BX SHOULD NOT RECEIVE ICS-CONTAINING TPY UNLESS ICS IS NEEDED TO TREAT AN UNDERLINING DISEASE





Henkle E et al. Eur Respir J 2019

Association between Inhaled Corticosteroid Use and Pulmonary Nontuberculous Mycobacterial Infection

Vincent X. Liu[1,2], Kevin L. Winthrop[3], Yun Lu[1], Husham Sharifi[4], Hekmat U. Nasiri[2], and Stephen J. Ruoss[4]

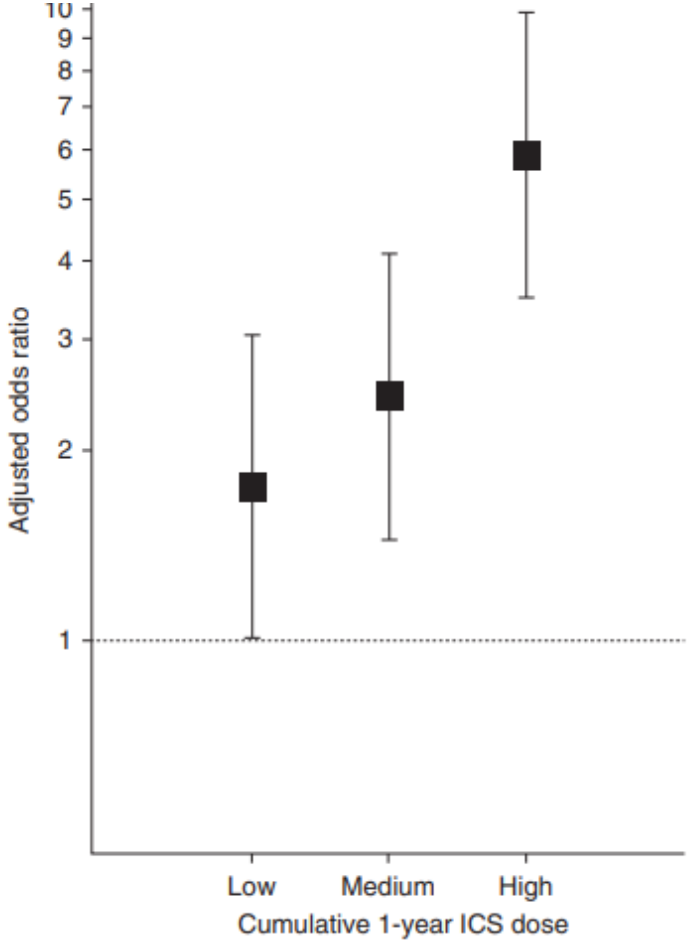


Table 3. Association of inhaled corticosteroid use with risk of nontuberculous mycobacterial pulmonary infection, stratified by period of inhaled corticosteroid use before cohort entry and diagnosis at cohort entry

Any ICS use	*n*	Odds Ratios (95% Confidence Interval) for NTM Infection with ICS Use		
		Unadjusted OR	Medication-adjusted OR*	Fully Adjusted OR†
Within prior 120 d	2,728	3.88 (2.87–5.26)	2.86 (2.02–4.05)	2.74 (1.83–4.09)
Within past 1 yr	2,321	4.14 (2.80–6.13)	3.04 (1.97–4.68)	2.80 (1.79–4.37)
Within past 2 yr	1,829	4.49 (2.62–7.70)	2.82 (1.59–5.00)	2.51 (1.40–4.49)

Association between cumulative ICS therapy and risk of NTM infection

Vincent XL et al. Ann Am Thorac Soc 2018