COPD

Updated Treatment Guidelines

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Global Initiative for Chronic Obstructive Lung Disease

2024 REPORT

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

Definition

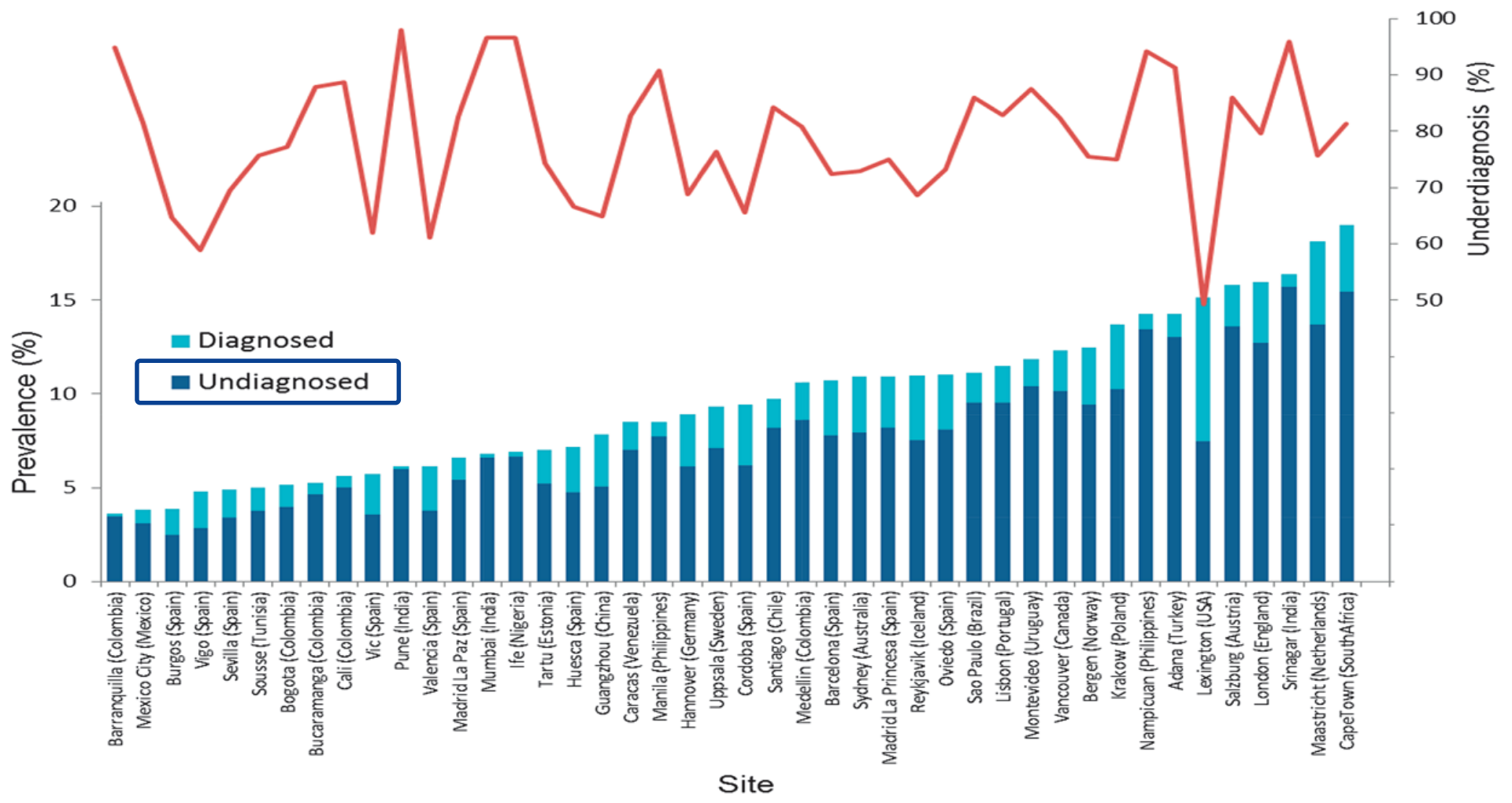
GOLD 2022

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.

GOLD 2024

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

Extensive under-diagnosis



Lamprecht B et al. CHEST 2015; 148: 971 - 85

History of COPD classification by GOLD

2001: Classification

Stage
0: At risk
I: Mild COPD
II: Moderate COPD
III: Severe COPD

Respiratory failu
P_{aCO_2} >6.7 kPa (50 r

2006: Spirometric clas
disease severity based

Stage I: Mild

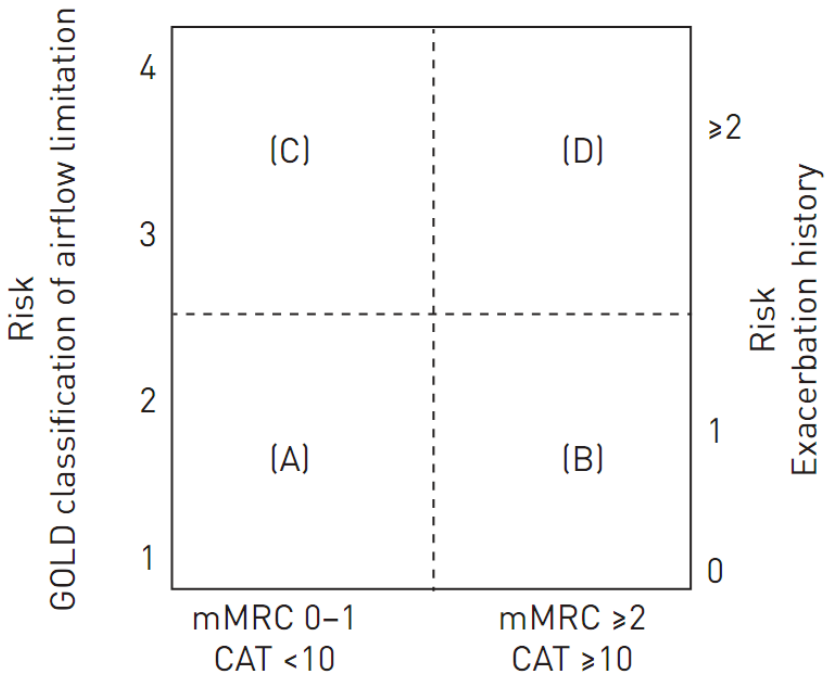
Stage II: Moderate

Stage III: Severe

Stage IV: Very severe

¶ Respiratory failure:
<8.0 kPa (60 mmHg) wi
(P_{aCO_2}) >6.7 kPa (50 mr

2011: Combined COPD assessment. When assessing risk, choose the highest risk according to GOLD spirometric grade or exacerbation history.



Eur Respir J 2017; 50: 1700671

Can GOLD Stage 0 Provide Information of Prognostic Value in Chronic Obstructive Pulmonary Disease?

Jørgen Vestbo and Peter Lange

Department of Respiratory Medicine, Hvidovre University Hospital, Hvidovre, Denmark

TABLE 2. PREVALENCE OF DIFFERENT STAGES OF COPD AFTER 5 AND 15 YEARS IN SUBJECTS WITHOUT COPD AND WITH COPD STAGE 0 AT BASELINE

	No COPD at Baseline	COPD Stage 0 at Baseline
5-yr follow-up		
COPD Stage 1	364 (4.3%)/239 (4.9%)	33 (5.7%)/26 (5.8%)
COPD Stage 2	443 (5.3%)/332 (6.7%)	39 (6.7%)/33 (7.4%)
COPD Stage 3	5 (0.1%)/4 (0.1%)	—/—
15-yr follow-up		
COPD Stage 1	393 (7.2%)/304 (9.9%)	51 (13.5%)/44 (14.8%)
COPD Stage 2	317 (5.8%)/260 (8.4%)	19 (5.0%)/17 (5.7%)
COPD Stage 3	10 (0.2%)/7 (0.2%)	—/—

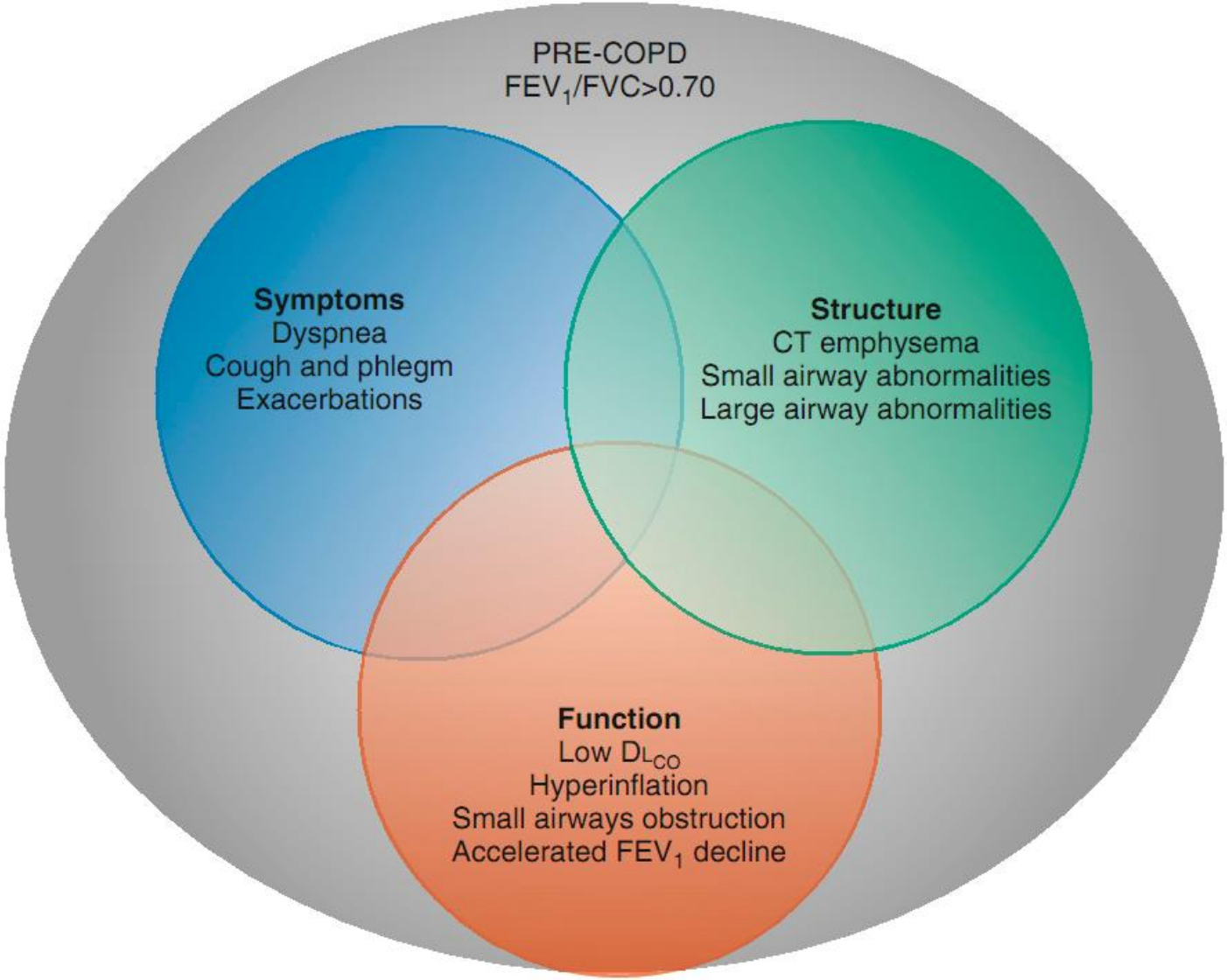
Numbers and percentages are given for all subjects/all subjects smoking at baseline.

Am J Respir Crit Care Med. 2002;166(3):329-32

Precursor Conditions

Pre-COPD

Pre-COPD



Han MK, et al. Am J Respir Crit Care Med. 2021 ;203(4):414-423

Precursor Conditions

PRISm

(Preserved Ratio Impaired Spirometry)

PRISm

- **PRISm** (Preserved Ratio Impaired Spirometry)

  preserved ratio (**FEV1/FVC ≥ 0.7** after bronchodilation)

  but impaired spirometry

  (**FEV1 < 80%** of reference, after bronchodilation)
- Prevalence : 7.1% ~ 11%
- Transition to obstructed spirometry : 20 ~ 30%
- Associated with increased risk of
  - cardiopulmonary disease
  - all-cause & cardiovascular mortality
  - hospitalization
  - developing airways obstruction

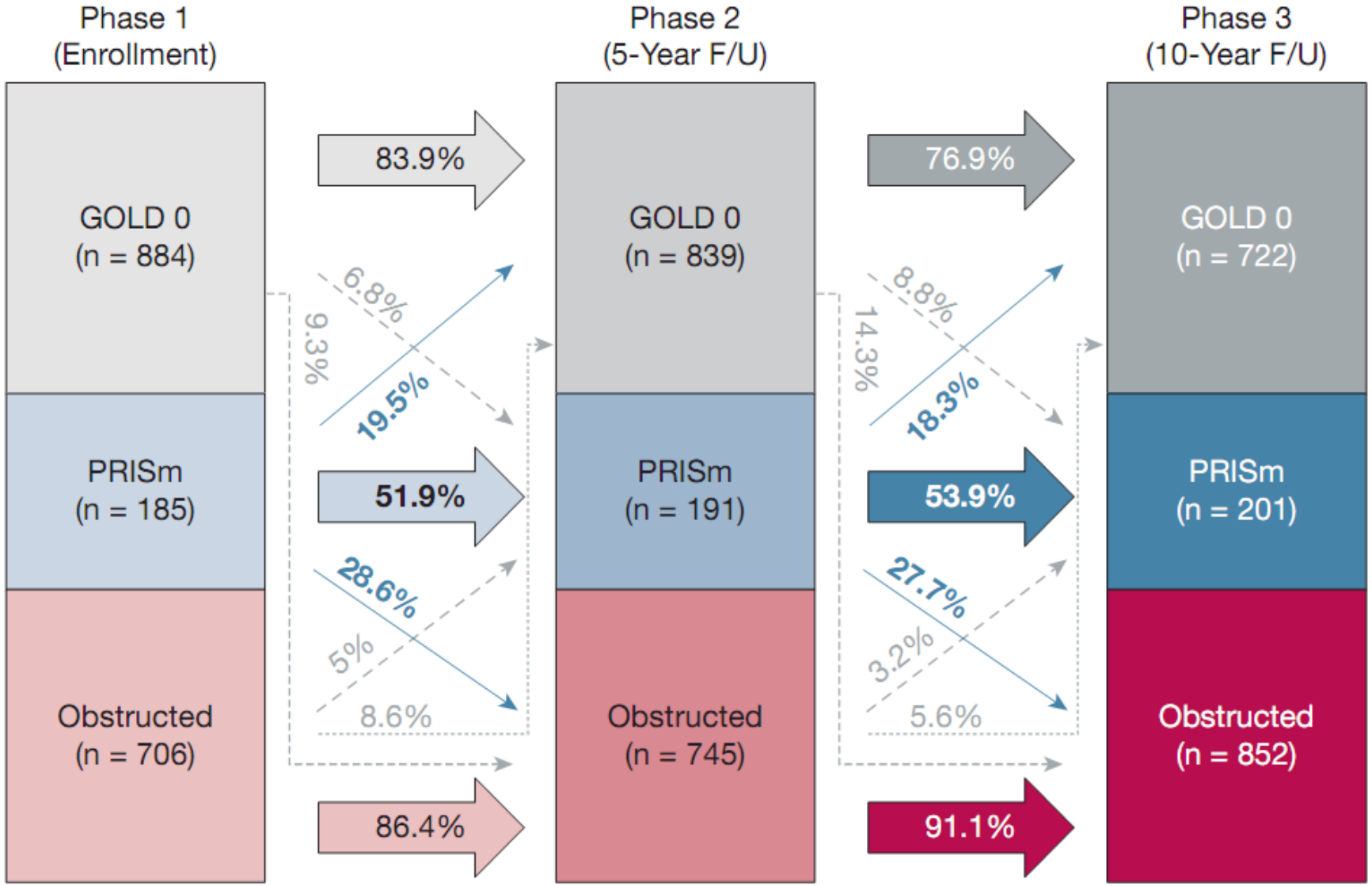
CHEST

Significant Spirometric Transitions and Preserved Ratio Impaired Spirometry Among Ever Smokers

Emily S. Wan, MD, MPH; John E. Hokanson, PhD; Elizabeth A. Regan, MD, PhD; Kendra A. Young, PhD; Barry J. Make, MD; Dawn L. DeMeo, MD, MPH; Stefanie E. Mason, MD, MPH; Raul San Jose Estepar, PhD; James D. Crapo, MD; and Edwin K. Silverman, MD, PhD

- COPDGene study (1,775 ever smokers)
- longitudinal data over 10.1 follow-up

CHEST 2022; 161:651-661



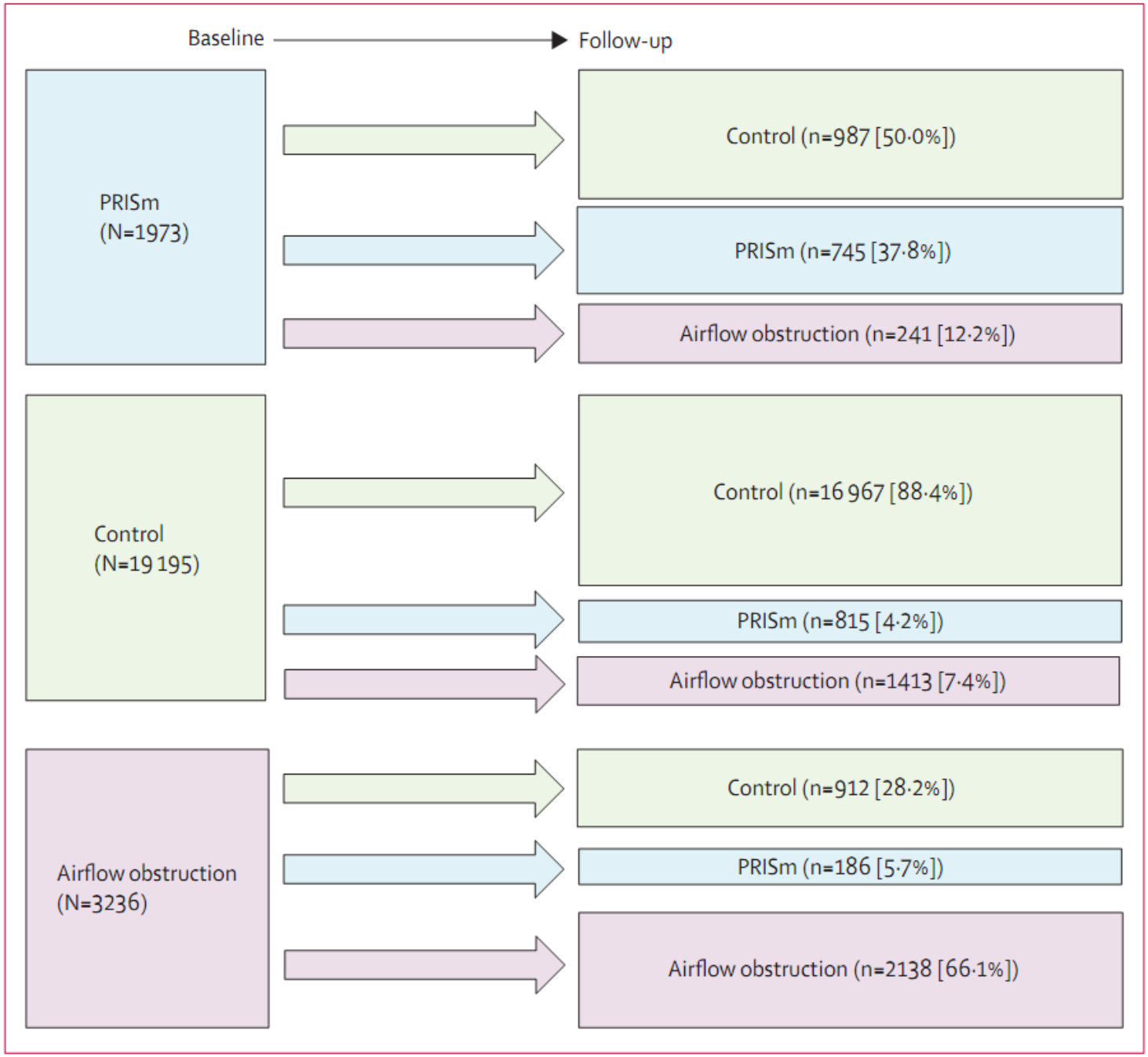
CHEST 2022; 161:651-661

Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis

Daniel H Higbee, Raquel Granell, George Davey Smith, James W Dodd

- 351,874 UK Biobank participants
- a median follow-up of 9·0 years
- PRISm at baseline : 38,639 (11·0%) of 351,874

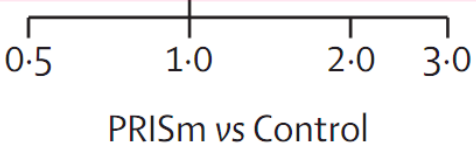
Lancet Respir Med 2022;10:149–57



Lancet Respir Med 2022;10:149–57

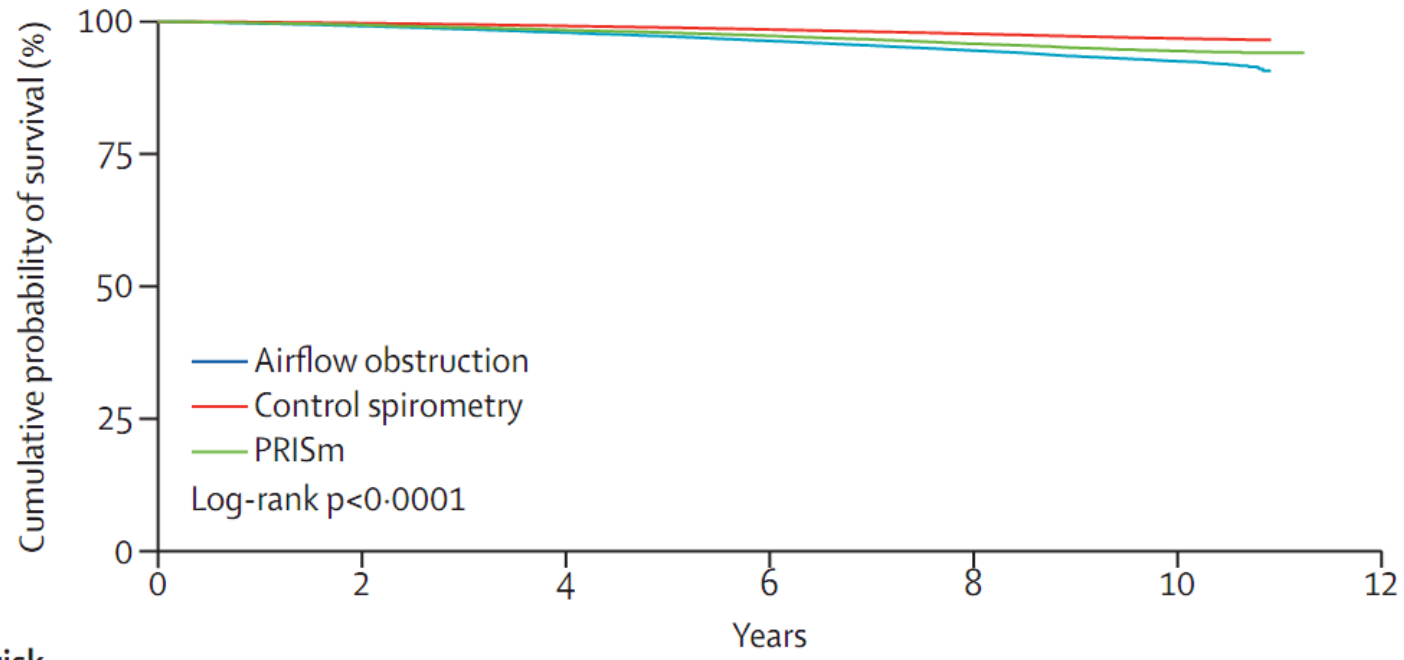
Risk factors associated with PRISm

	PRISm (n=8472)	Control (n=71281)	OR (95% CI)	p value
Age	8472	71281	1·00 (0·99–1·01)	0·17
Sex (female)	4878	40412	1·08 (1·03–1·13)	0·0010
Ex-smoker	2967	24826	1·00 (0·95–1·05)	0·95
Current smoker	681	4044	1·48 (1·36–1·62)	<0·0001
Overweight (BMI ≥25 to <30 kg/m^2)	3332	30328	1·30 (1·23–1·37)	<0·0001
Obesity (BMI ≥30 kg/m^2)	2785	13353	2·40 (2·26–2·55)	<0·0001
Asthma	1436	7078	1·76 (1·66–1·88)	<0·0001



Lancet Respir Med 2022;10:149–57

Kaplan-Meier survival



Number at risk (number censored)							
Airflow obstruction	55 592 (0)	55 123 (0)	54 443 (0)	53 573 (0)	46 783 (5850)	8418 (43 515)	0 (51 895)
Control spirometry	257 643 (0)	256 920 (0)	255 575 (0)	253 798 (0)	222 245 (29 754)	40 928 (209 559)	0 (250 441)
PRISm	38 639 (0)	38 407 (0)	38 013 (0)	37 606 (0)	32 763 (4310)	6146 (30 590)	0 (36 728)

Lancet Respir Med 2022;10:149–57

JAMA | Original Investigation

Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults

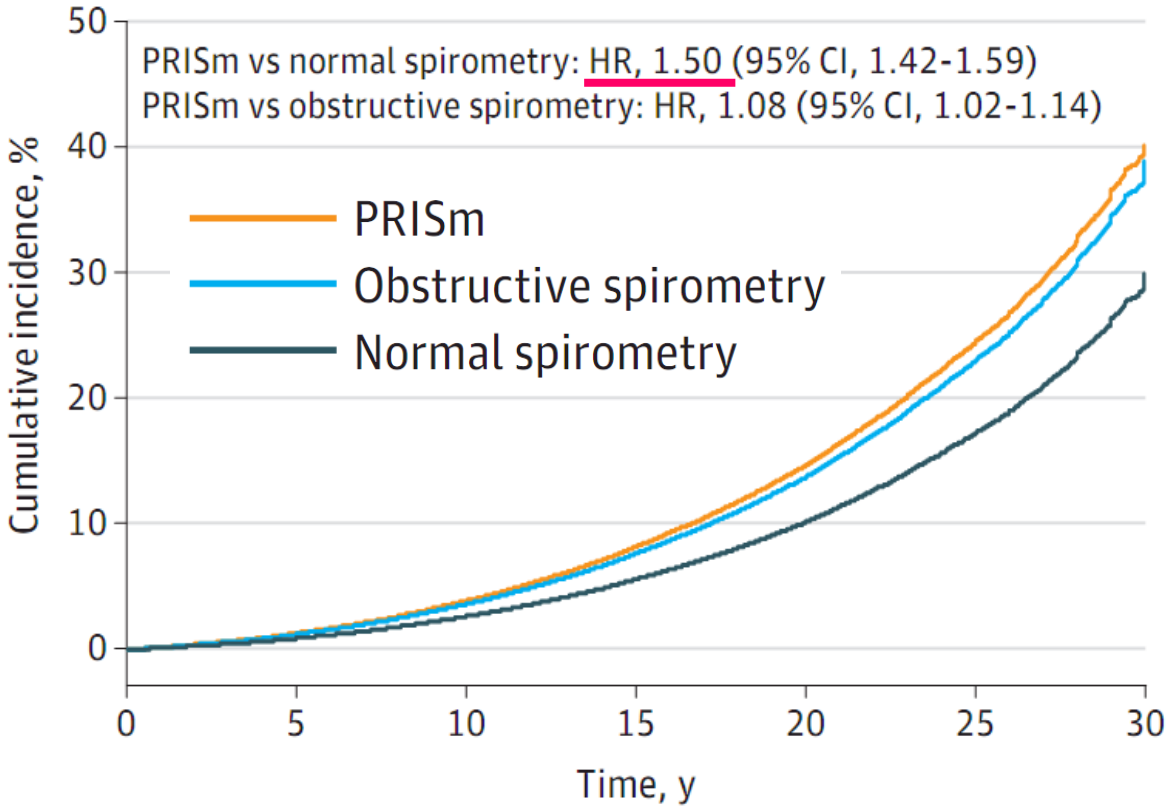
Emily S. Wan, MD, MPH; Pallavi Balte, MBBS, PhD; Joseph E. Schwartz, PhD; Surya P. Bhatt, MD; Patricia A. Cassano, PhD, MPH; David Couper, PhD; Martha L. Daviglus, MD, PhD; Mark T. Dransfield, MD; Sina A. Gharib, MD; David R. Jacobs Jr, PhD; Ravi Kalhan, MD, MS; Stephanie J. London, MD, DrPH; Ana Navas-Acien, MD, PhD; George T. O'Connor, MD, MS; Jason L. Sanders, MD, PhD; Benjamin M. Smith, MD, MSc; Wendy White, PhD, MPH; Sachin Yende, MD, MS; Elizabeth C. Oelsner, MD, MPH

- The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study
- retrospective cohort study (n=53,701)

JAMA 2021;326:2287-2298

All-cause mortality

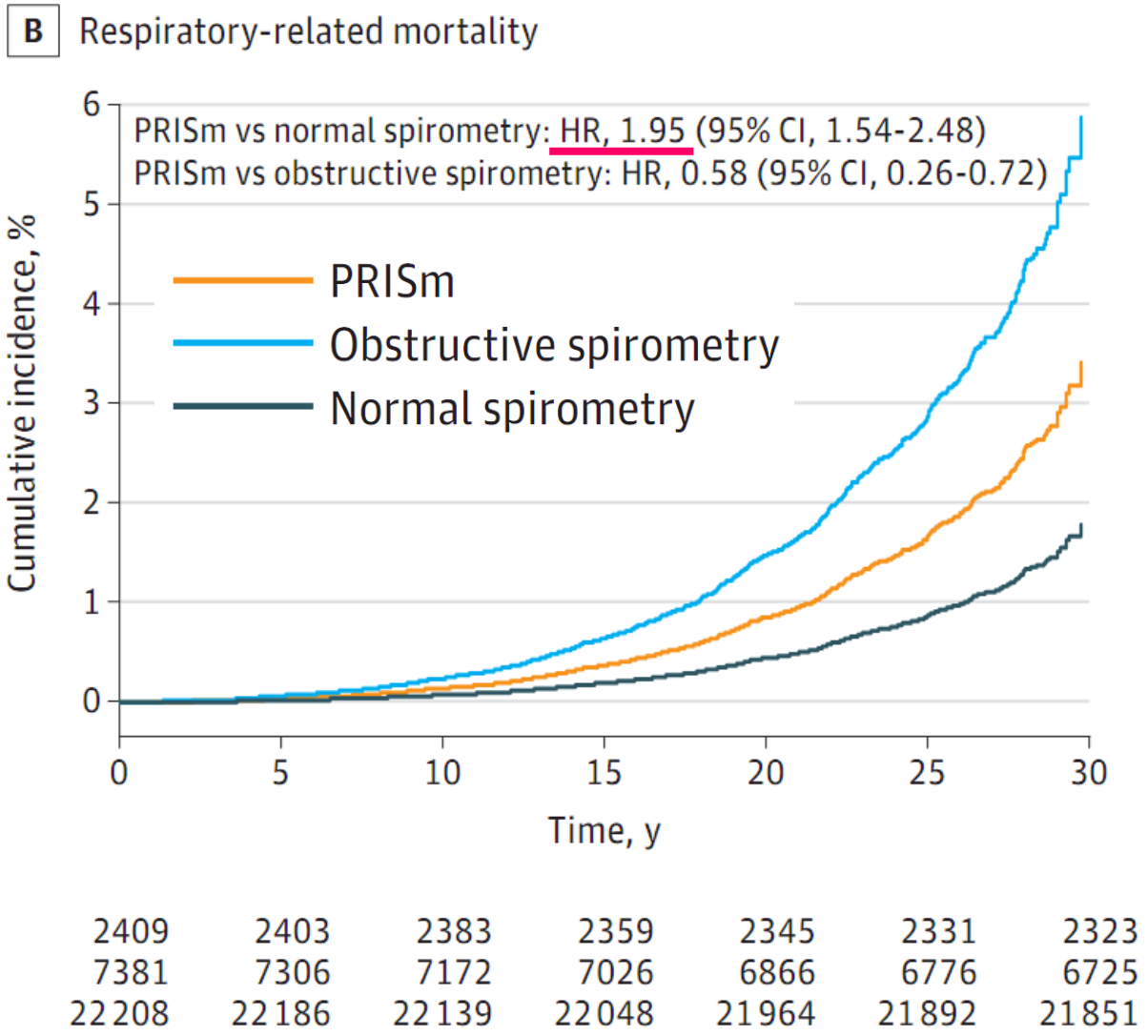
A All-cause mortality



No. at risk							
PRISm	3147	2877	2529	2158	1917	1709	1611
Obstructive spirometry	8518	7675	6455	5262	4282	3630	3279
Normal spirometry	28 170	27 221	25 611	23 685	21 978	20 382	19 304

JAMA 2021;326:2287-2298

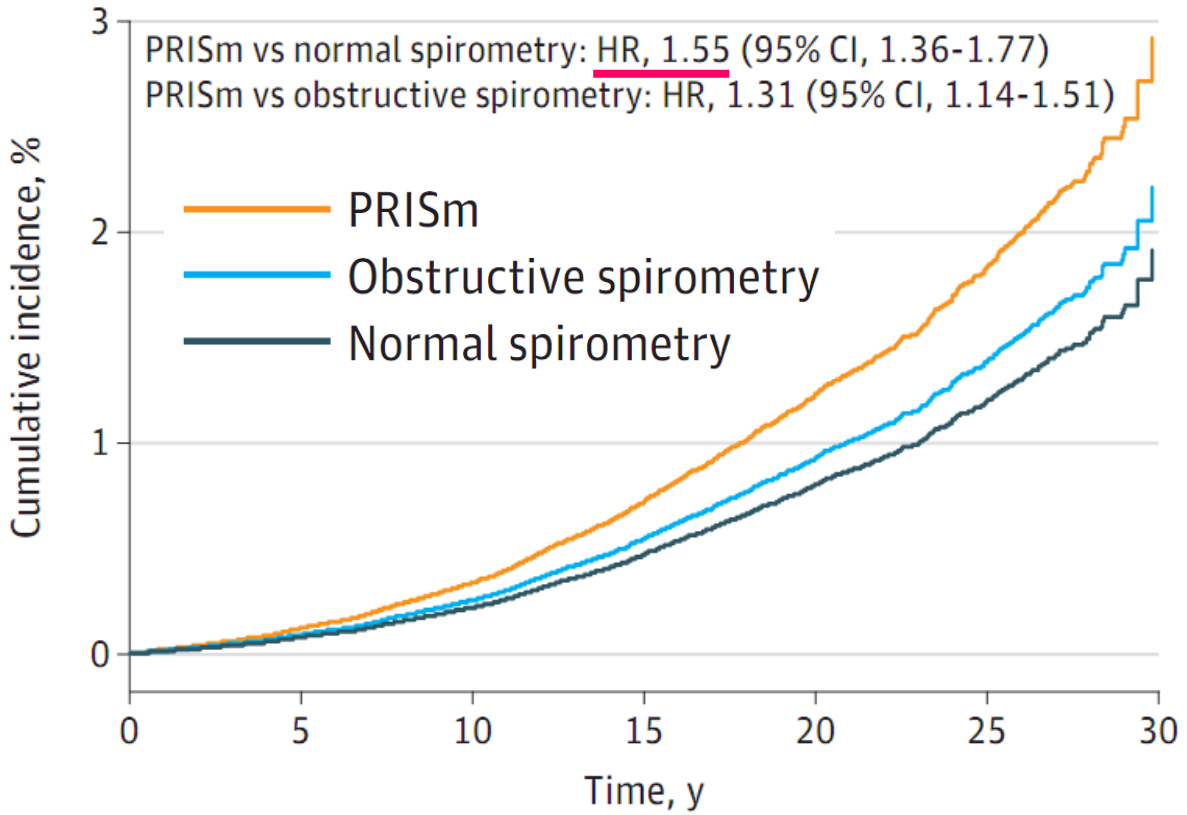
Respiratory-related mortality



JAMA 2021;326:2287-2298

CHD-related mortality

C CHD-related mortality

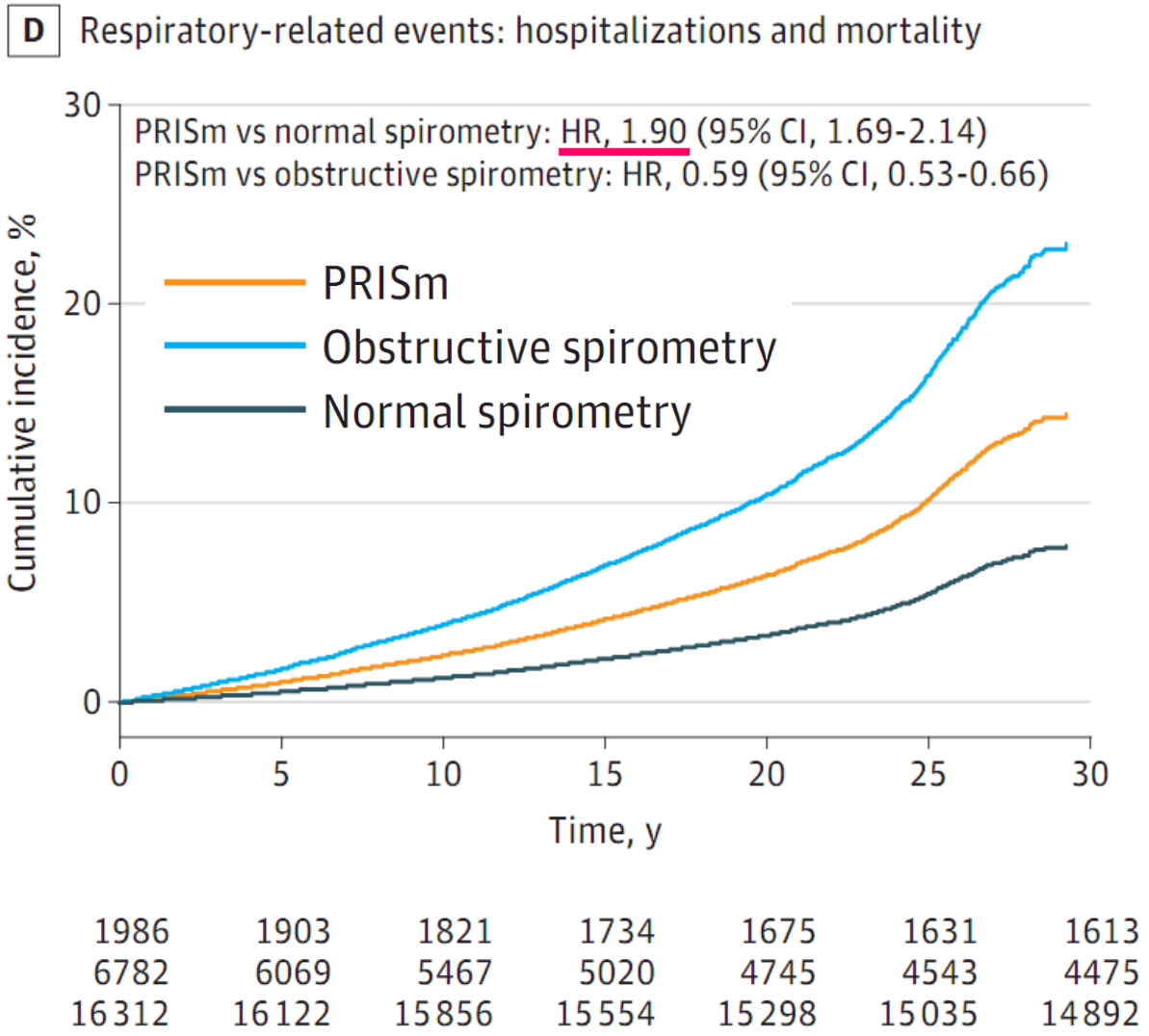


No. at risk

PRISm	3104	3039	2974	2892	2854	2837	2829
Obstructive spirometry	8508	8317	8096	7909	7795	7743	7723
Normal spirometry	28016	27816	27514	27152	26899	26781	26724

JAMA 2021;326:2287-2298

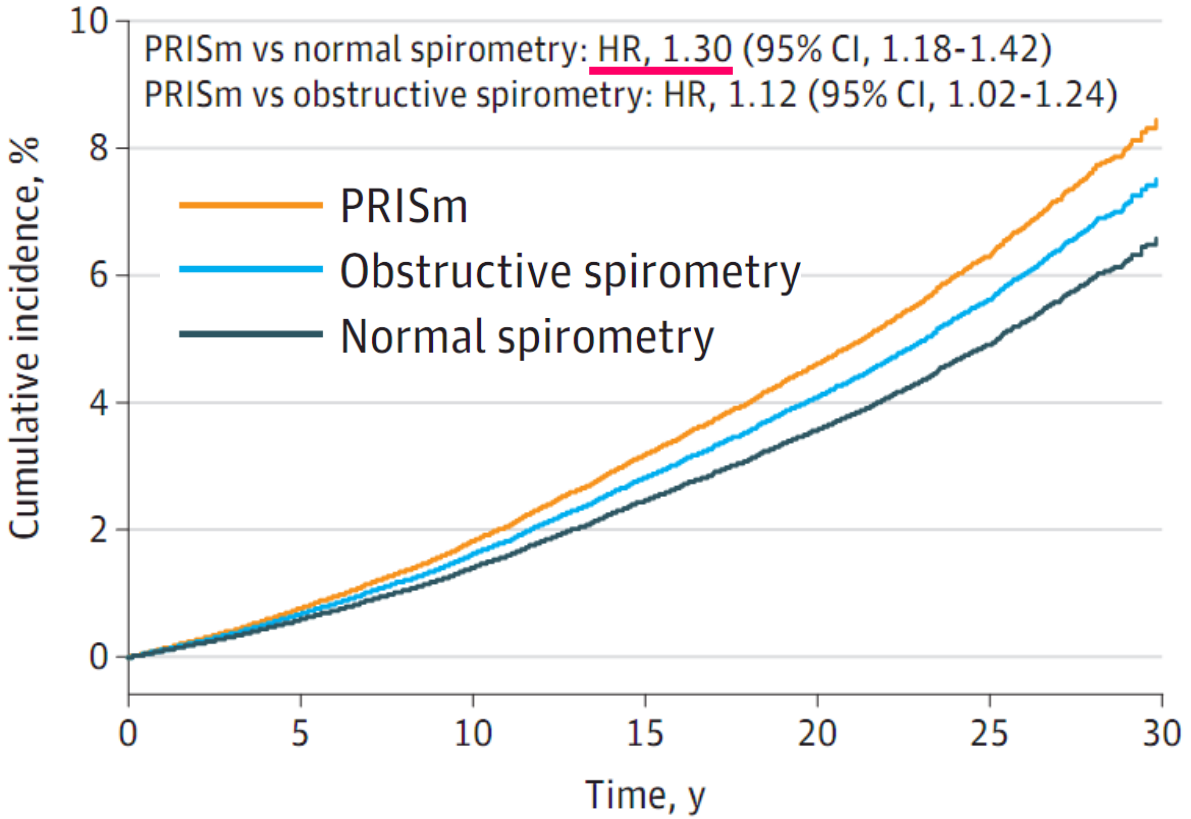
Respiratory-related events: hospitalizations and mortality



JAMA 2021;326:2287-2298

CHD-related events: hospitalizations and mortality

E CHD-related events: hospitalizations and mortality



No. at risk							
PRISm	2920	2777	2638	2513	2435	2380	2362
Obstructive spirometry	7891	7411	6952	6633	6439	6311	6259
Normal spirometry	27 257	26 586	25 820	25 045	24 499	24 107	23 895

JAMA 2021;326:2287-2298

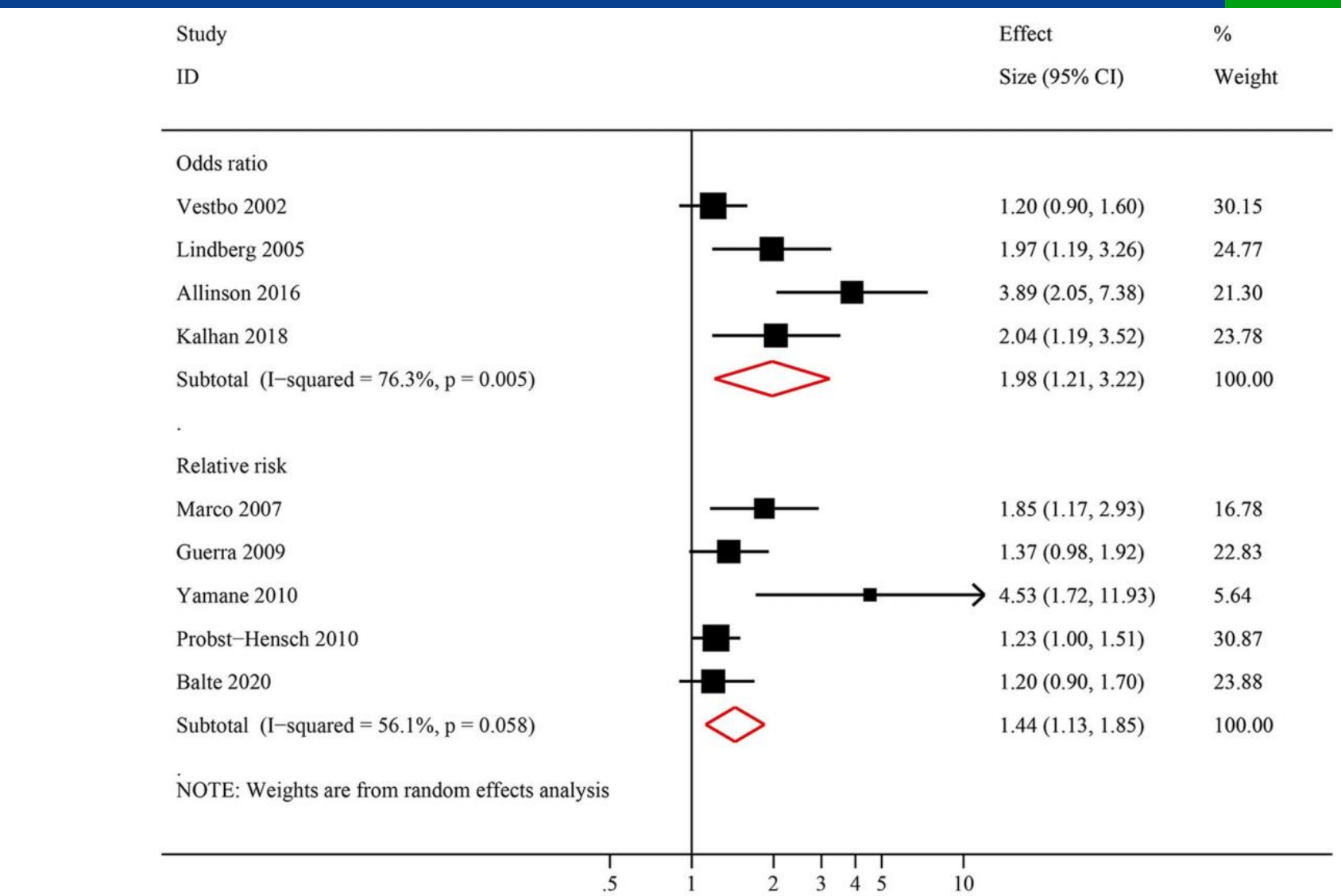
NOCB (Non-obstructive Chronic Bronchitis)

Association Between Non-obstructive Chronic Bronchitis and Incident Chronic Obstructive Pulmonary Disease and All-Cause Mortality: A Systematic Review and Meta-Analysis

Fan Wu[1†], Huanhuan Fan[2†], Jing Liu[1], Haiqing Li[1], Weifeng Zeng[3], Silan Zheng[1], Heshen Tian[1], Zhishan Deng[1], Youlan Zheng[1], Ningning Zhao[1], Guoping Hu[2], Yumin Zhou[1] and Pixin Ran[1*]*

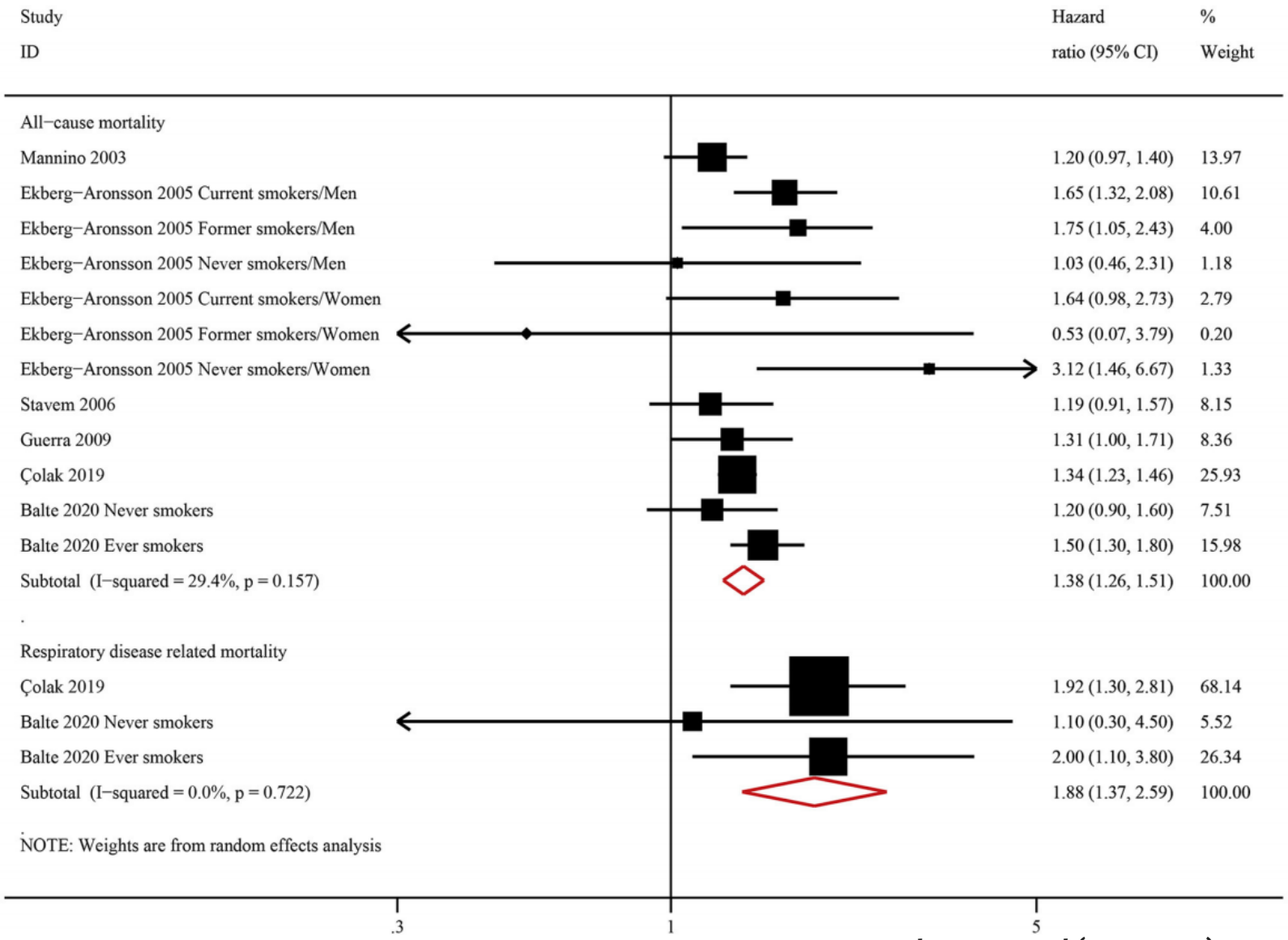
Front Med (Lausanne). 2022;8:805192

Risk of incident COPD



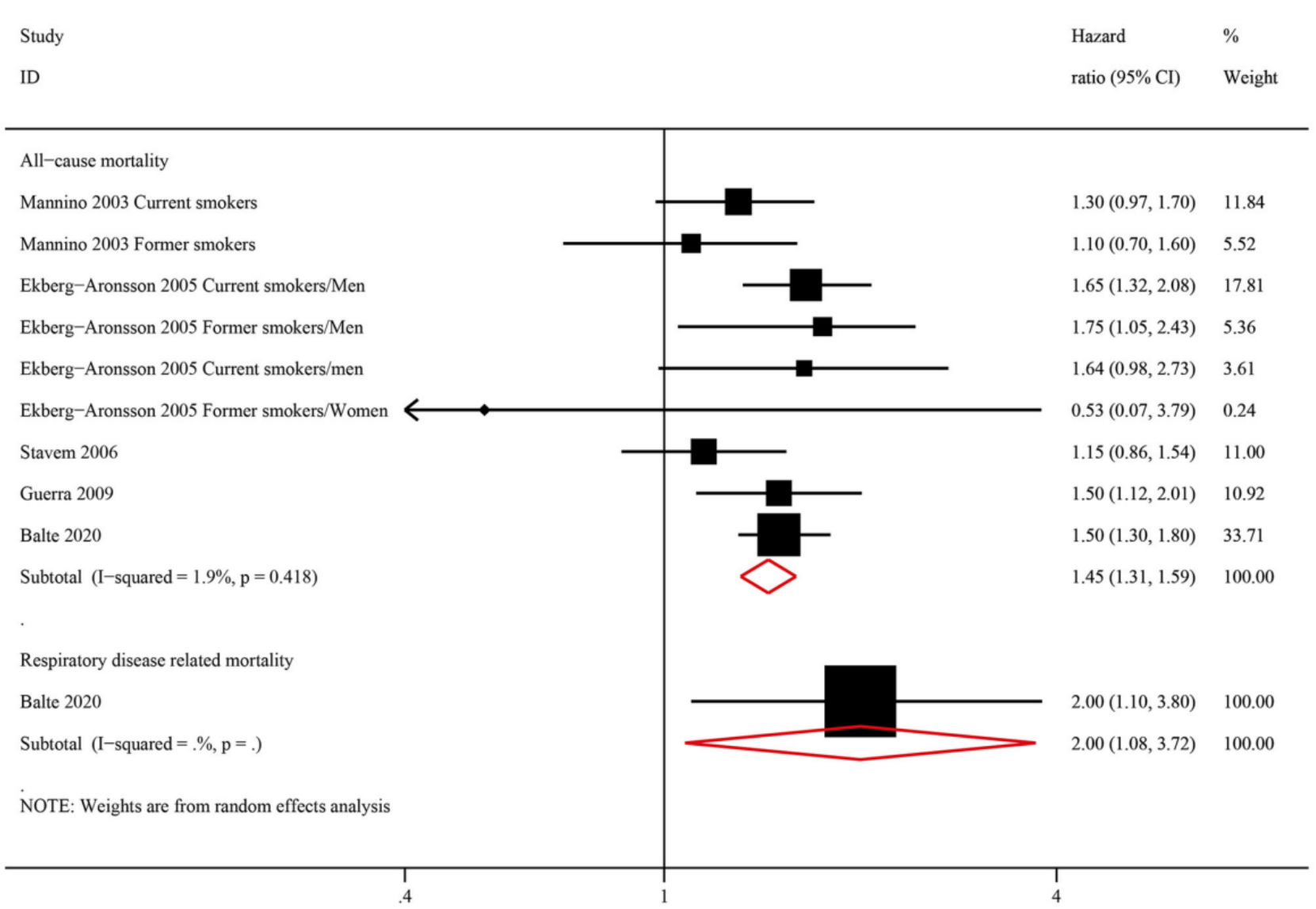
Wu F, et al. Front Med (Lausanne). 2022;8:805192

All-cause mortality & respiratory-related mortality



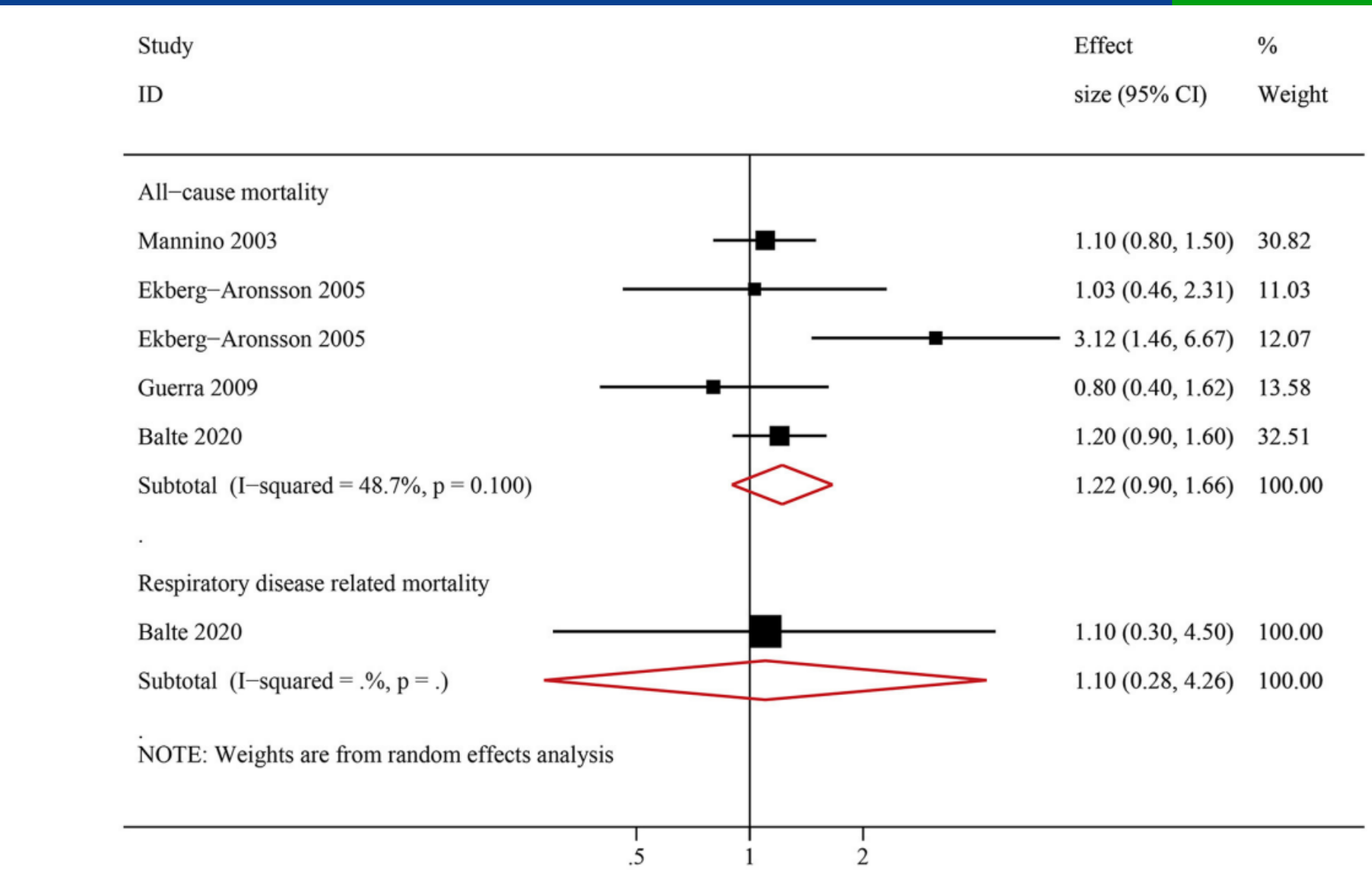
Wu F, et al. Front Med (Lausanne). 2022;8:805192

Mortality in ever smokers



Wu F, et al. Front Med (Lausanne). 2022;8:805192

Mortality in never smokers



Wu F, et al. Front Med (Lausanne). 2022;8:805192

Etiotypes

2024 REPORT

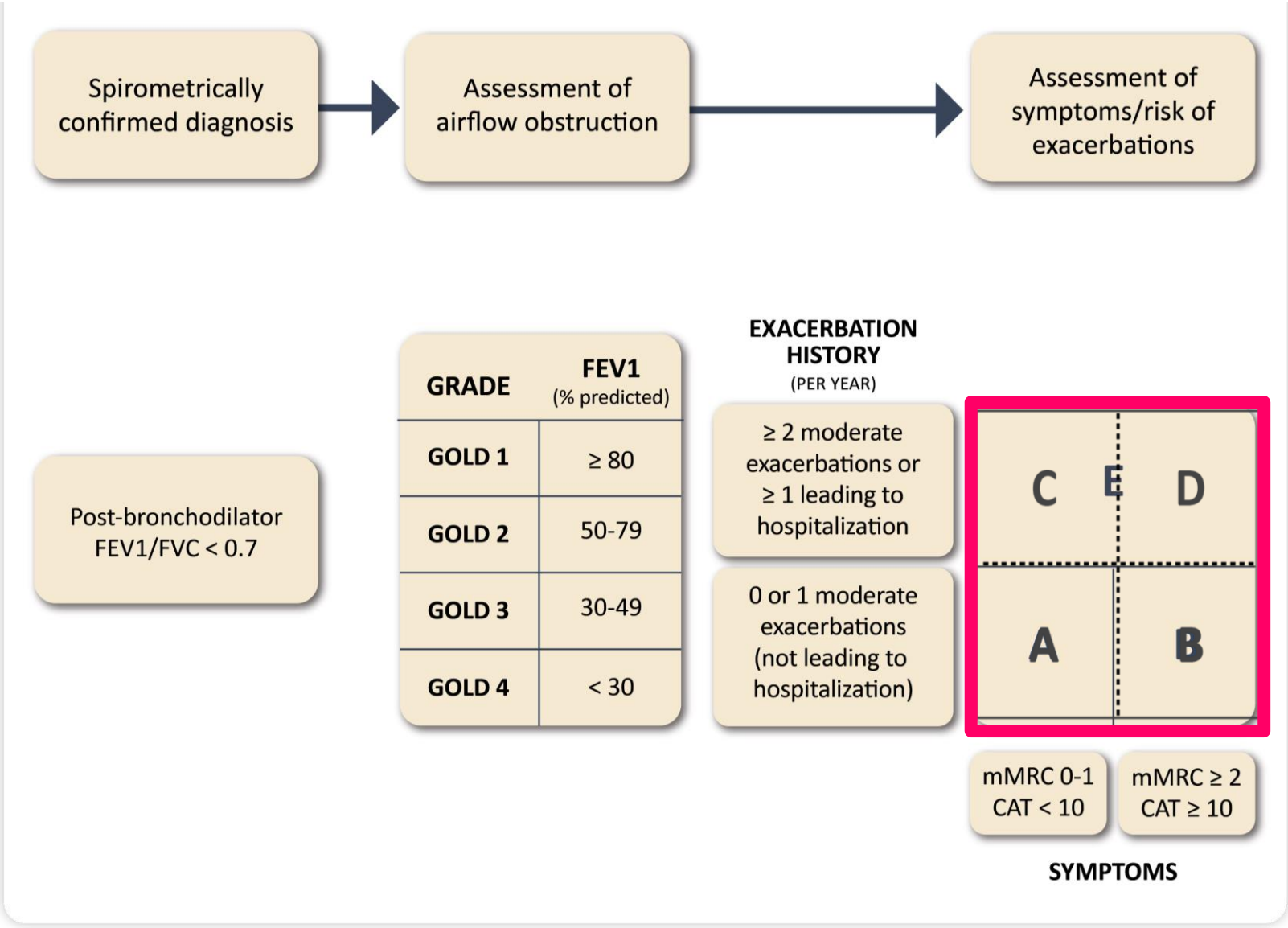
Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

COPD Assessment

ABCD -> ABE

GOLD ABE Assessment Tool

2024 REPORT

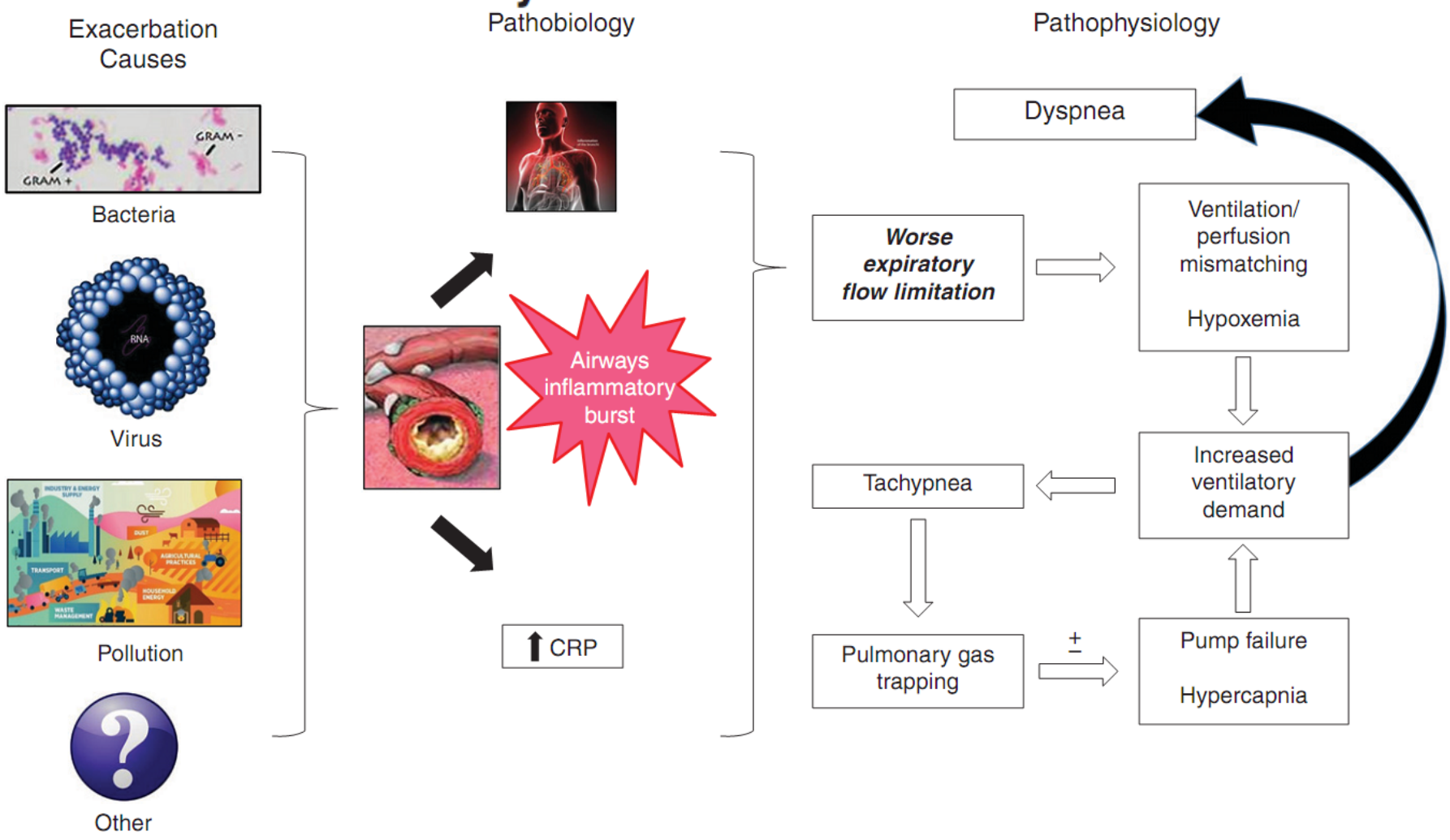


Diagnosis & Assessment

Exacerbation

PULMONARY PERSPECTIVE

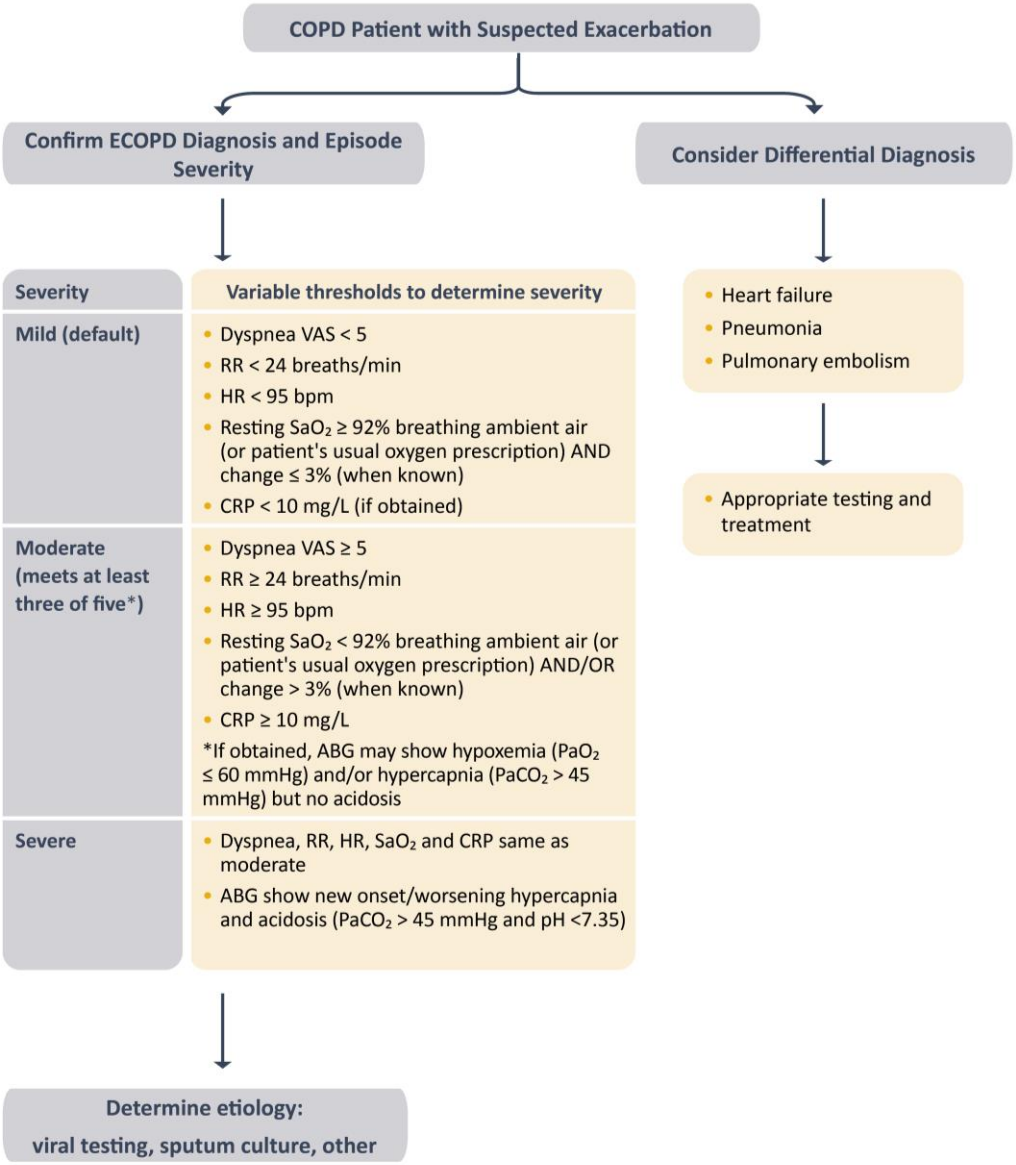
An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations



Am J Respir Crit Care Med. 2021;204(11):1251-1258

Classification of the Severity of COPD Exacerbations

Figure 5.1

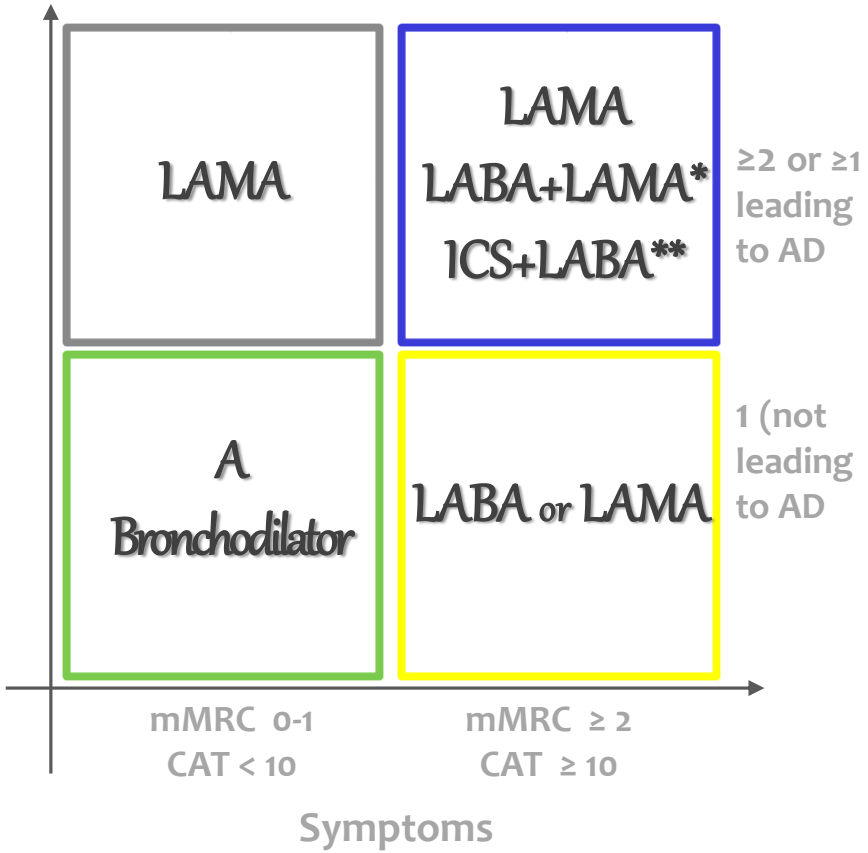


Adapted from: The ROME Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8. Abbreviations: VAS visual analog dyspnea scale; RR respiratory rate; HR heart rate; SaO_2 oxygen saturation; CRP C-reactive protein; ABG arterial blood gases; PaO_2 Arterial pressure of oxygen.

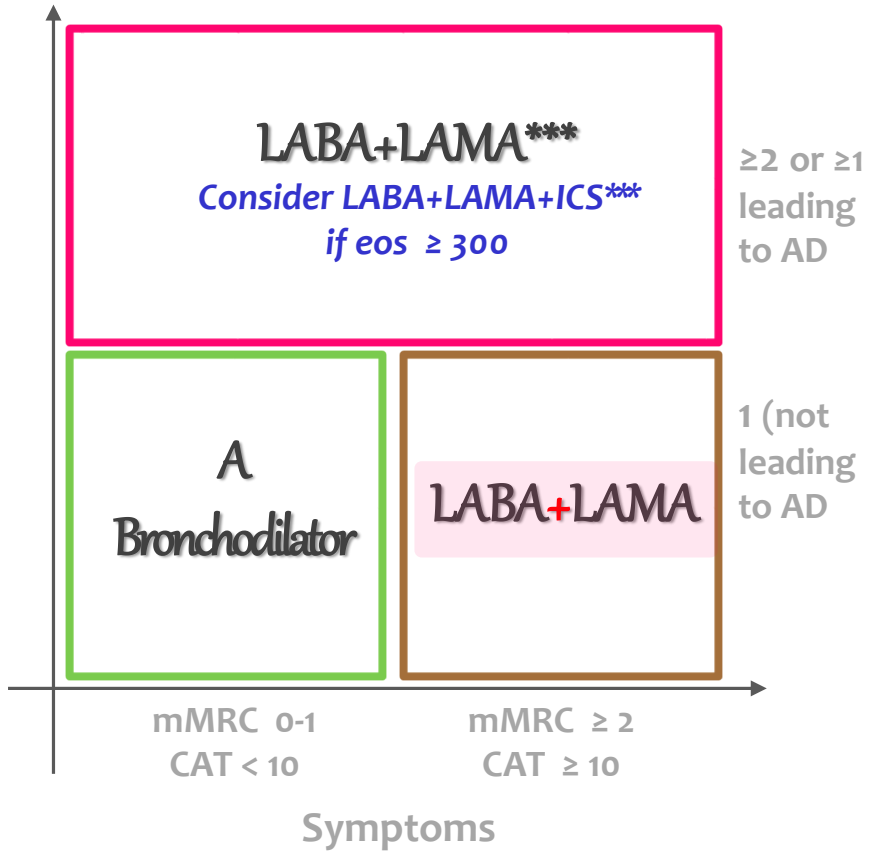
CONTENTS

Initial pharmacological treatment

GOLD 2022



GOLD 2023



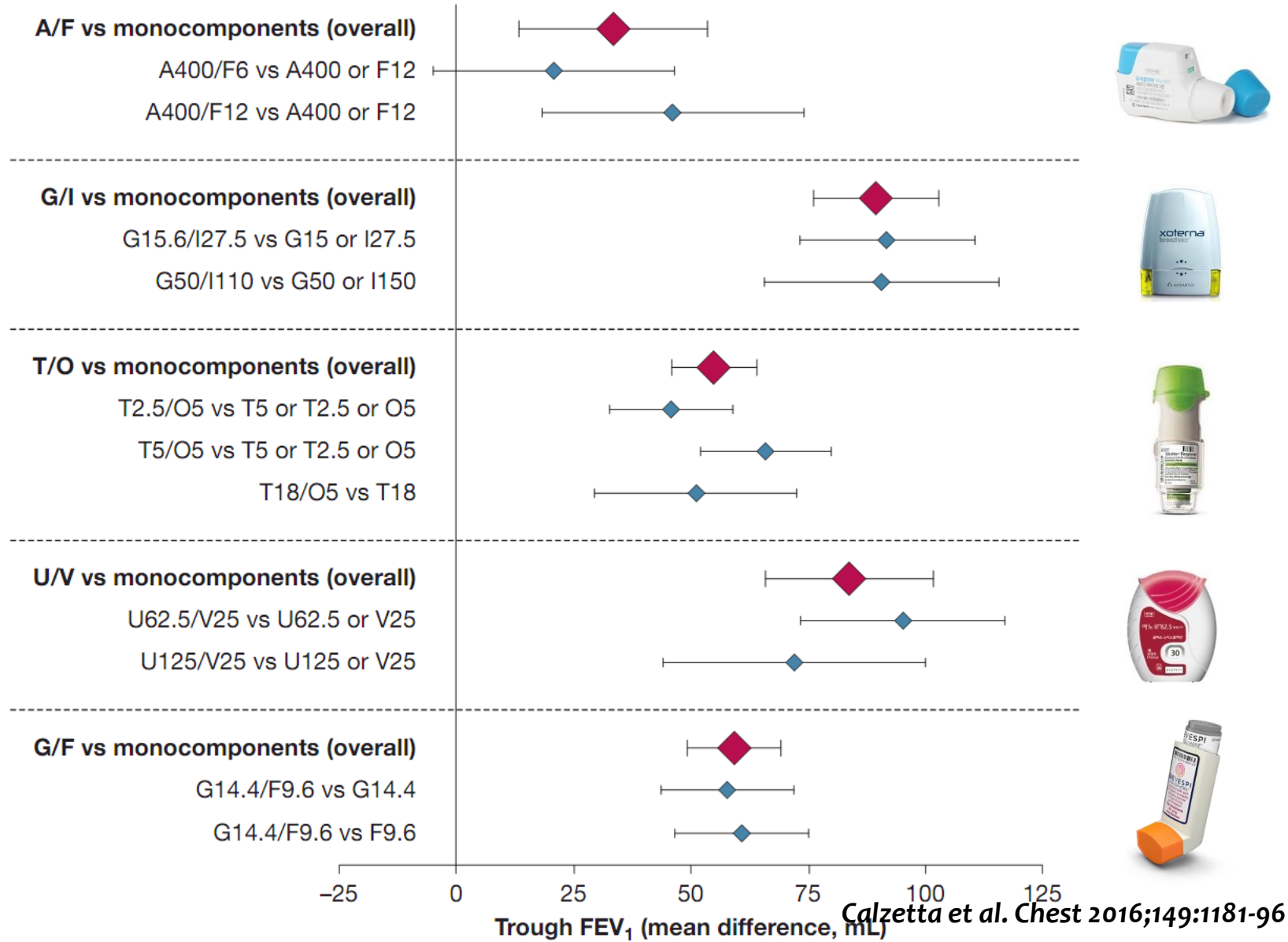
*Consider if highly symptomatic (e.g. CAT > 20)

**Consider if eos ≥ 300

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

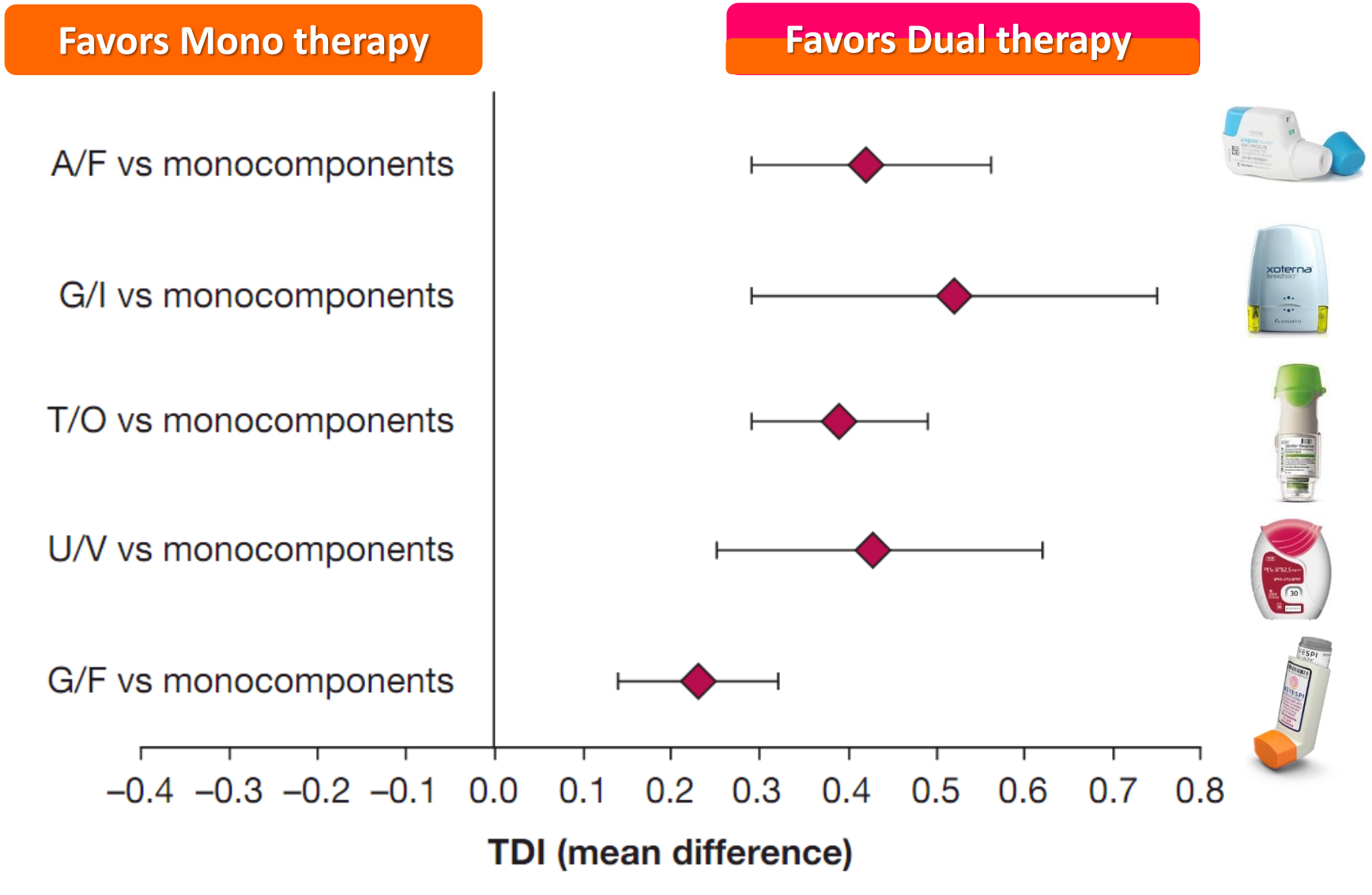
Trough FEV1

Favors Monotherapy | **Favors Dual therapy**



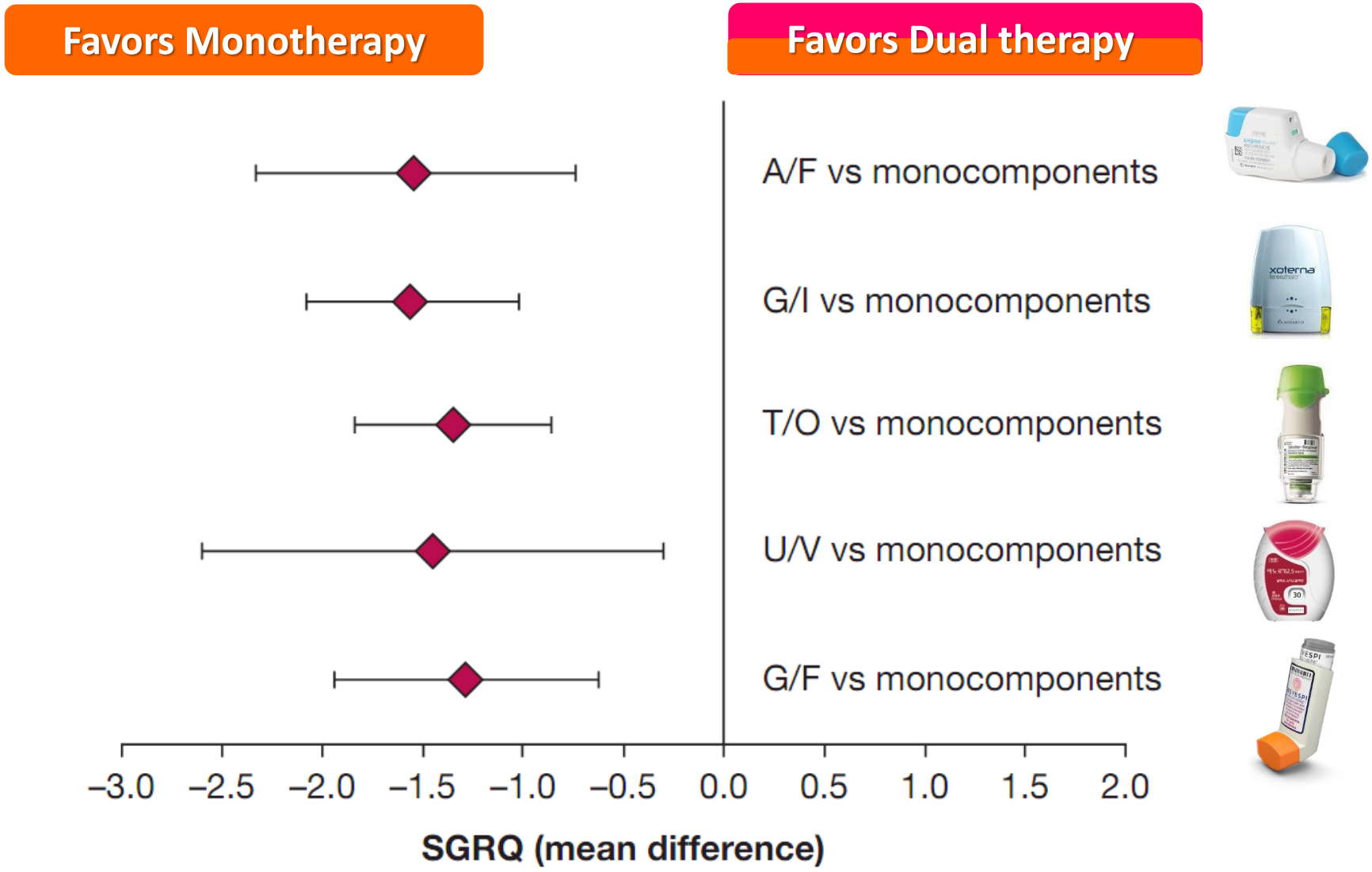
Calzetta et al. Chest 2016;149:1181-96

TDI



Calzetta et al. Chest 2016;149:1181-96

SGRQ



Calzetta et al. Chest 2016;149:1181-96

RESEARCH Open Access

Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial

François Maltais[1*], Leif Bjermer[2], Edward M. Kerwin[3], Paul W. Jones[4], Michael L. Watkins[5], Lee Tombs[6], Ian P. Naya[4], Isabelle H. Boucot[4], David A. Lipson[7,8], Chris Compton[4], Mitra Vahdati-Bolouri[9] and Claus F. Vogelmeier[10]

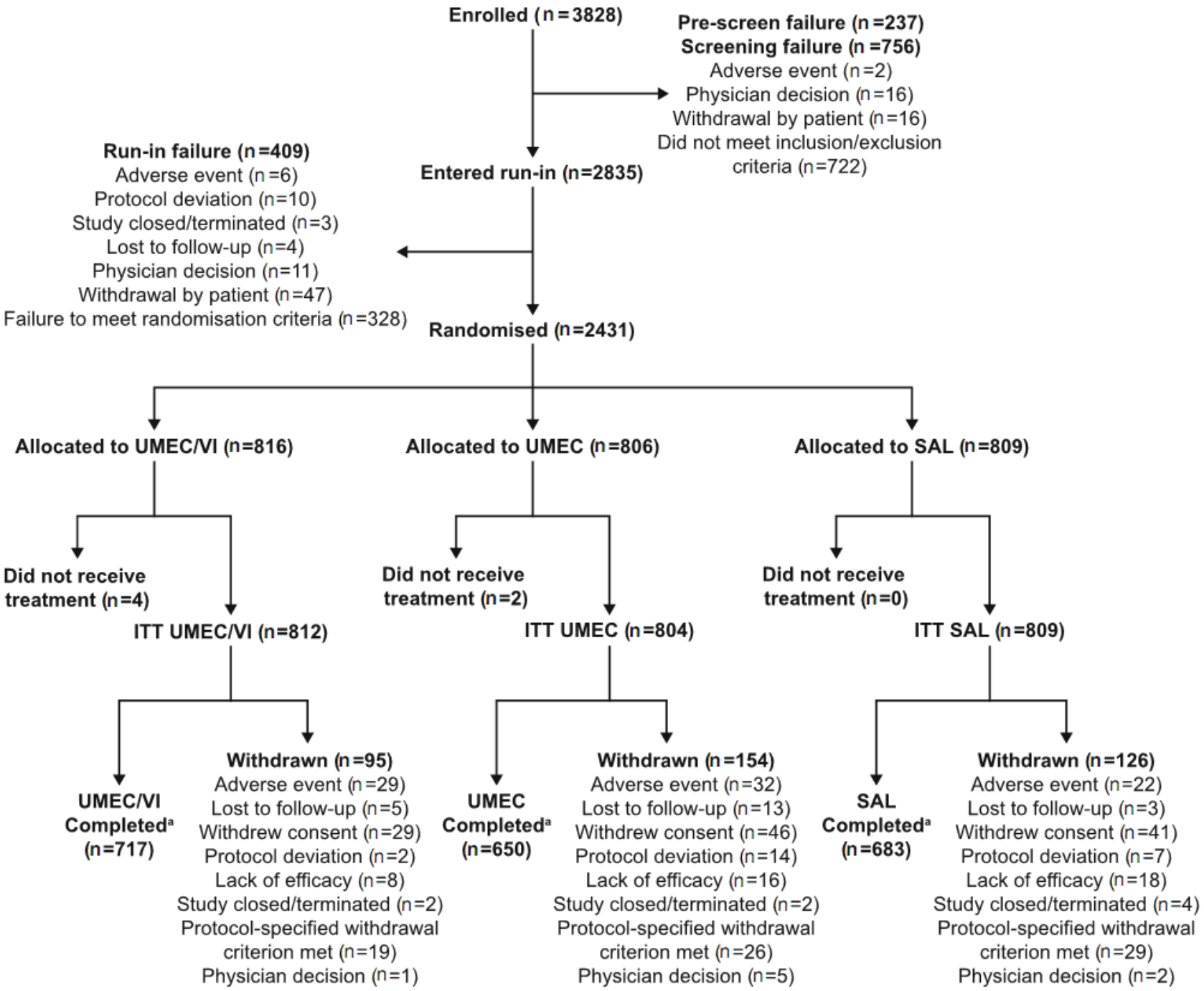
- 24-week, double-blind, double-dummy, parallel study
- Early MAXimisation of bronchodilation for improving COPD stability (EMAX) trial
- patients at low exacerbation risk not receiving ICS
- primary endpoint : trough FEV1 at Week 24

Respir Res 2019;20(1):238

Table 1 Patient demographics and baseline characteristics

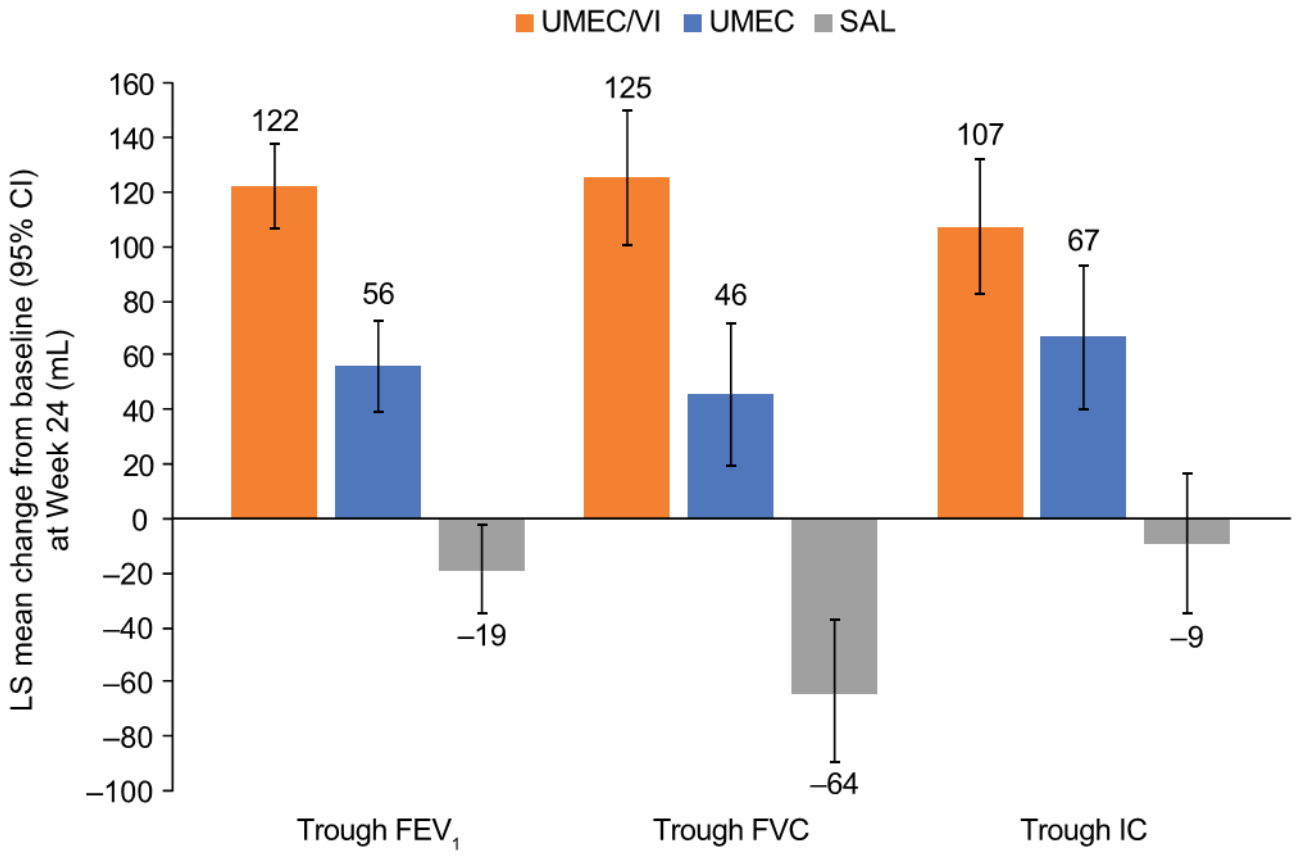
Characteristic	UMEC/VI (*N* = 812)	UMEC (*N* = 804)	SAL (*N* = 809)	Total (*N* = 2425)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)	988 (41)
Race, n (%)				
White	767 (94)	764 (95)	766 (95)	2297 (95)
Black/African American	24 (3)	23 (3)	25 (3)	72 (3)
American Indian/Alaska Native	13 (2)	12 (1)	12 (1)	37 (2)
Asian	5 (< 1)	1 (< 1)	1 (< 1)	7 (< 1)
Multiple[a]	3 (1)	4 (< 1)	5 (< 1)	12 (< 1)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)	1203 (50)
Smoking pack-years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
Use of LABD during run-in, n (%)[b]	531 (65)	521 (65)	524 (65)	1576 (65)
LAMA	399 (49)	392 (49)	403 (50)	1194 (49)
LABA	130 (16)	142 (18)	132 (16)	404 (17)
No maintenance medication during run-in, n (%)	250 (31)	250 (31)	249 (31)	749 (31)
Moderate COPD exacerbation history in prior year[c], n (%)	123 (15)	124 (15)	146 (18)	393 (16)
Duration of COPD, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Post-salbutamol FEV_1, mL, mean (SD)	1577 (506)	1609 (503)	1600 (523)	1595 (511)
Post-salbutamol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
Post-salbutamol FEV_1/FVC, mean (SD)	0.51 (0.10)	0.52 (0.10)	0.52 (0.10)	0.52 (0.10)
% reversibility to salbutamol, mean (SD)	10.4 (12.8)	10.2 (13.3)	10.7 (13.3)	10.5 (13.1)
GOLD spirometric grade[d], n (%)				
2	518 (64)	529 (66)	522 (65)	1569 (65)
3	294 (36)	271 (34)	286 (35)	851 (35)
Baseline FEV_1, mL, mean (SD)	1474 (513)	1503 (505)	1495 (533)	1491 (517)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)	7.01 (1.9)
Baseline E-RS total score	10.7 (5.6)	10.7 (5.8)	10.4 (5.7)	10.6 (5.7)
Baseline SGRQ score, mean (SD)	44.5 (16.1)	45.0 (16.1)	44.6 (16.3)	44.7 (16.2)
Baseline CAT score, mean (SD)	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)	19.2 (6.1)
Baseline rescue salbutamol, puffs/day, mean (SD)	2.2 (2.6)	2.1 (2.3)	2.2 (2.5)	2.2 (2.5)
Any cardiac comorbidities[e], n (%)	111 (14)	136 (17)	117 (14)	364 (15)
Any vascular comorbidities[f], n (%)	444 (55)	434 (54)	448 (55)	1326 (55)

Maltais F et al. Respir Res 2019;20:238



Maltais el al. Respir Res 2019;20(1):238

Lung function outcomes

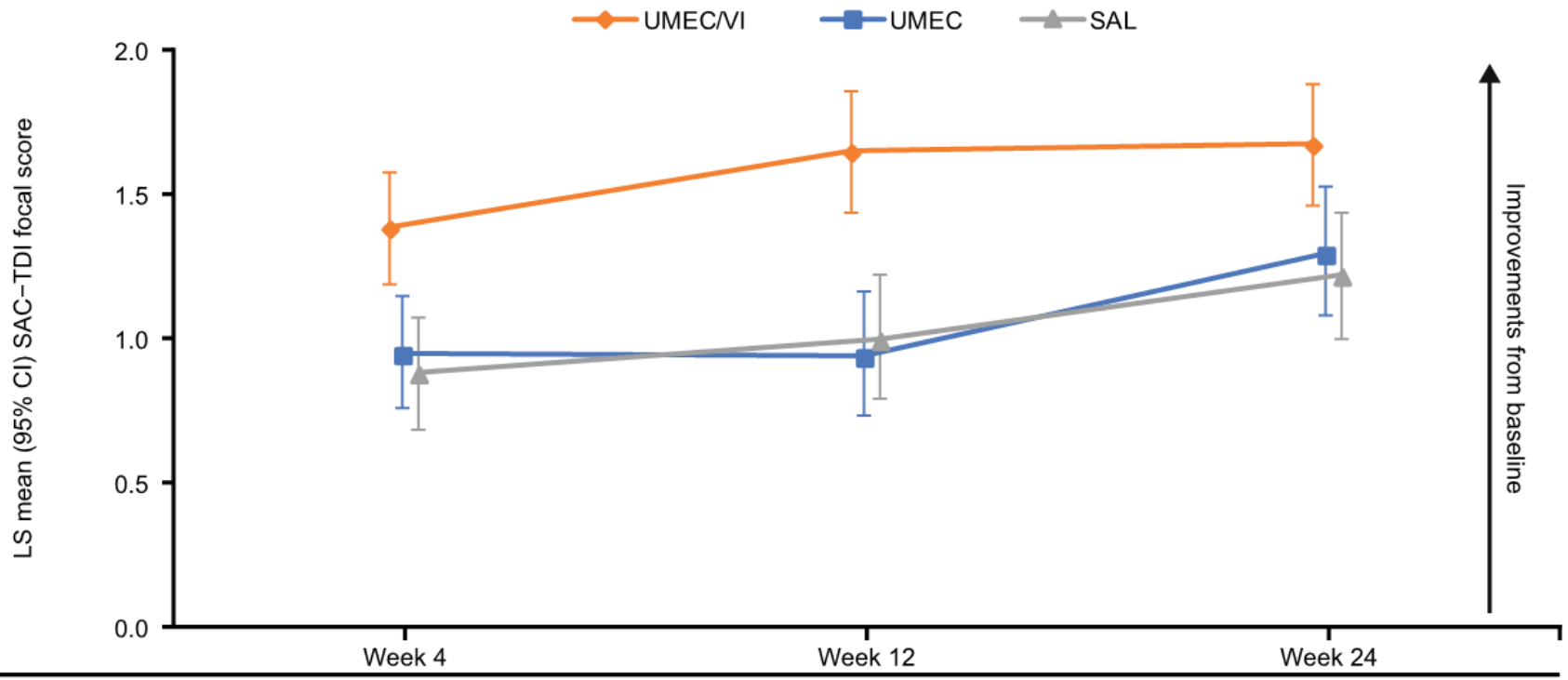


	Difference (95% CI)		
UMEC/VI vs UMEC	66 mL (43, 89), $p < 0.001$	79 mL (42, 116), $p < 0.001$	41 mL (4, 77), $p = 0.028$
UMEC/VI vs SAL	141 mL (118, 164), $p < 0.001$	189 mL (152, 225), $p < 0.001$	116 mL (80, 152), $p < 0.001$

Maltais el al. Respir Res 2019;20(1):238

Symptom - TDI

a

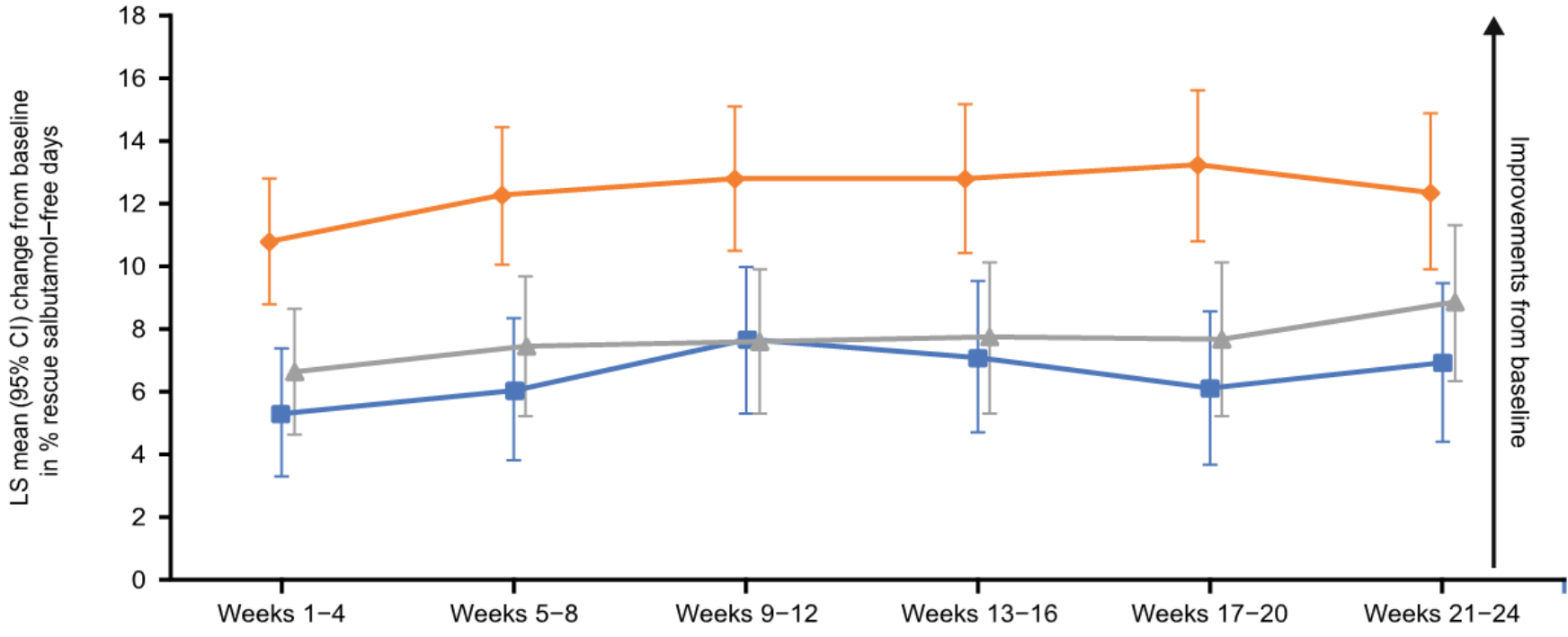


	Difference (95% CI)		
UMEC/VI vs UMEC	0.44 (0.16, 0.71), $p = 0.002$	0.70 (0.40, 1.00), $p < 0.001$	0.37 (0.06, 0.68), $p = 0.018$
UMEC/VI vs SAL	0.51 (0.24, 0.78), $p < 0.001$	0.64 (0.34, 0.94), $p < 0.001$	0.45 (0.15, 0.76), $p = 0.004$

Maltais el al. Respir Res 2019;20(1):238

Rescue free days

C

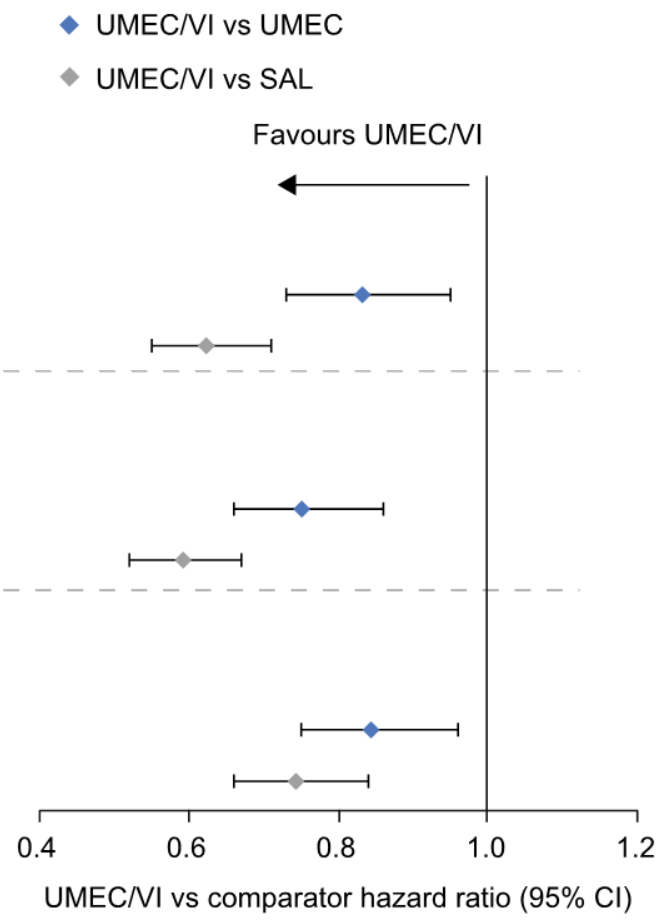


	Difference (95% CI)					
UMEC/VI vs UMEC	5.48 (2.62, 8.33), $p < 0.001$	6.18 (3.03, 9.33), $p < 0.001$	5.16 (1.88, 8.44), $p = 0.002$	5.67 (2.28, 9.06), $p = 0.001$	7.11 (3.68, 10.55), $p < 0.001$	5.44 (1.91, 8.97), $p = 0.003$
UMEC/VI vs SAL	4.17 (1.32, 7.02), $p = 0.004$	4.80 (1.66, 7.94), $p = 0.003$	5.20 (1.93, 8.47), $p = 0.002$	5.05 (1.66, 8.43), $p = 0.003$	5.53 (2.11, 8.95), $p = 0.002$	3.53 (0.01, 7.04), $p = 0.049$

Maltais F et al. Respir Res 2019;20:238

Risk of a first CID up to Day 168

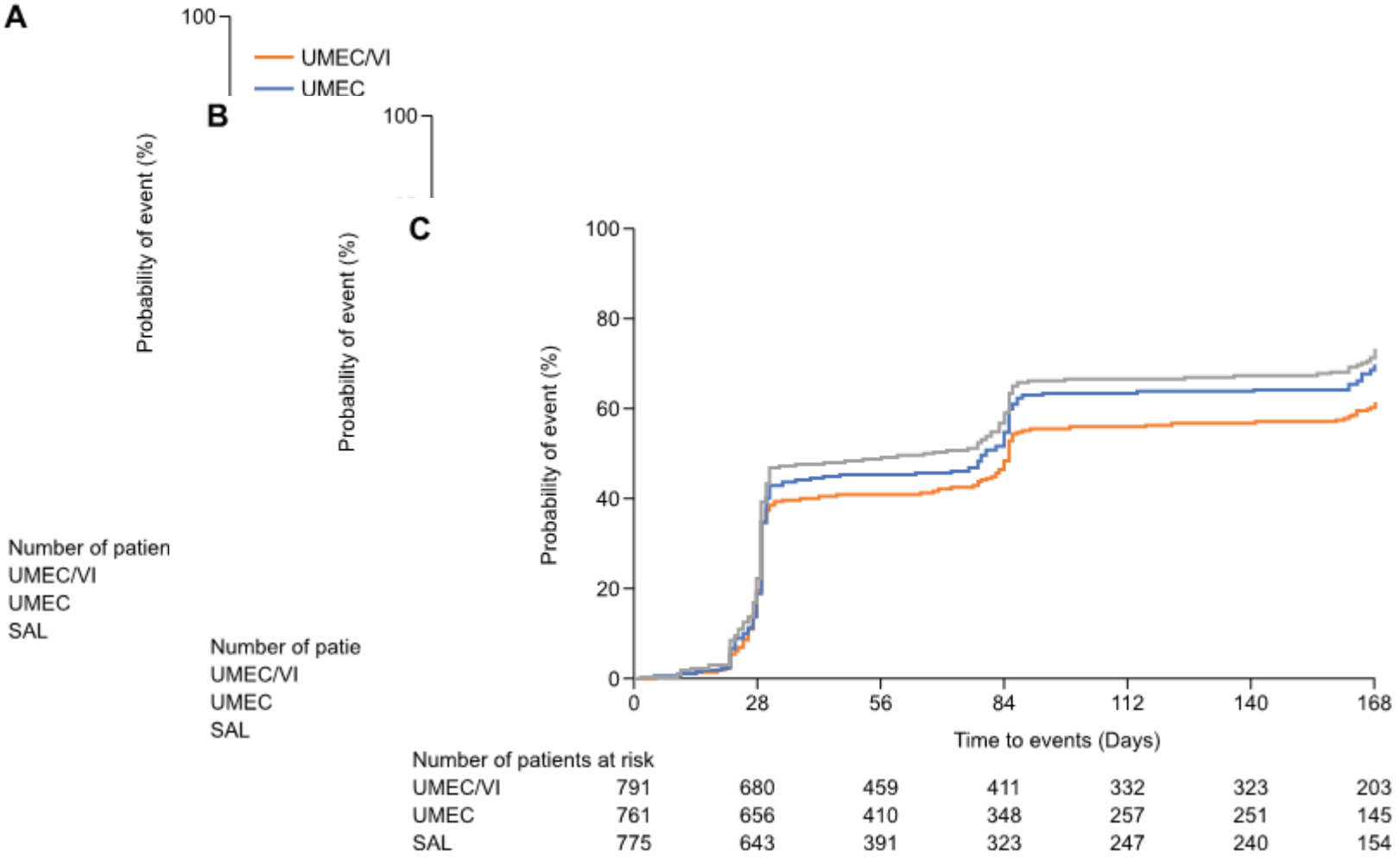
Treatment	Incidence of CID n/N[a] (%)	% Probability of event (95% CI)	UMEC/VI vs comparator HR (95% CI)	P-value
Composite CID definitions				
A) Exacerbation[b], FEV_1, SGRQ				
UMEC/VI	430/780 (55)	52.8 (49.3, 56.5)	–	–
UMEC	439/741 (59)	60.2 (56.5, 63.9)	0.83 (0.73, 0.95)	0.006
SAL	545/758 (72)	69.5 (66.1, 72.8)	0.62 (0.55, 0.71)	< 0.001
B) Exacerbation[b], FEV_1, CAT				
UMEC/VI	402/781 (51)	49.3 (45.8, 53.0)	–	–
UMEC	449/743 (60)	60.4 (56.7, 64.1)	0.75 (0.66, 0.86)	< 0.001
SAL	530/758 (70)	67.1 (63.7, 70.5)	0.59 (0.52, 0.67)	< 0.001
C) Exacerbation[b], CAT, SGRQ, TDI[c]				
UMEC/VI	500/791 (63)	61.3 (57.8, 64.8)	–	–
UMEC	524/761 (69)	69.8 (66.3, 73.2)	0.84 (0.75, 0.96)	0.007
SAL	578/775 (75)	73.4 (70.1, 76.5)	0.74 (0.66, 0.84)	< 0.001



* CID = Clinically Important Deterioration

Maltais el al. Respir Res 2019;20(1):238

Kaplan–Meier plots of Time to first CID for three definitions



Maltais F et al. Respir Res 2019;20:238

Adverse events

Table 3 Adverse events

	UMEC/VI (*N* = 812)	UMEC (*N* = 804)	SAL (*N* = 809)
AE, n (%)			
AE	315 (39)	316 (39)	314 (39)
Drug-related AE	29 (4)	37 (5)	27 (3)
AE leading to study withdrawal	32 (4)	36 (4)	26 (3)
SAE, n (%)			
Non-fatal SAE	46 (6)	31 (4)	38 (5)
Drug-related non-fatal SAE	0	0	0
Fatal SAE[a]	4 (< 1)	4 (< 1)	0
Drug-related fatal SAE	0	0	0
Most frequent AEs[a], n (%)			
Nasopharyngitis	68 (8)	87 (11)	84 (10)
Upper respiratory tract infection	19 (2)	12 (1)	20 (2)
Influenza	20 (2)	9 (1)	18 (2)
Back pain	10 (1)	13 (2)	15 (2)
Cough	14 (2)	11 (1)	10 (1)
Headache	10 (1)	17 (2)	6 (< 1)

Maltais F et al. Respir Res 2019;20:238

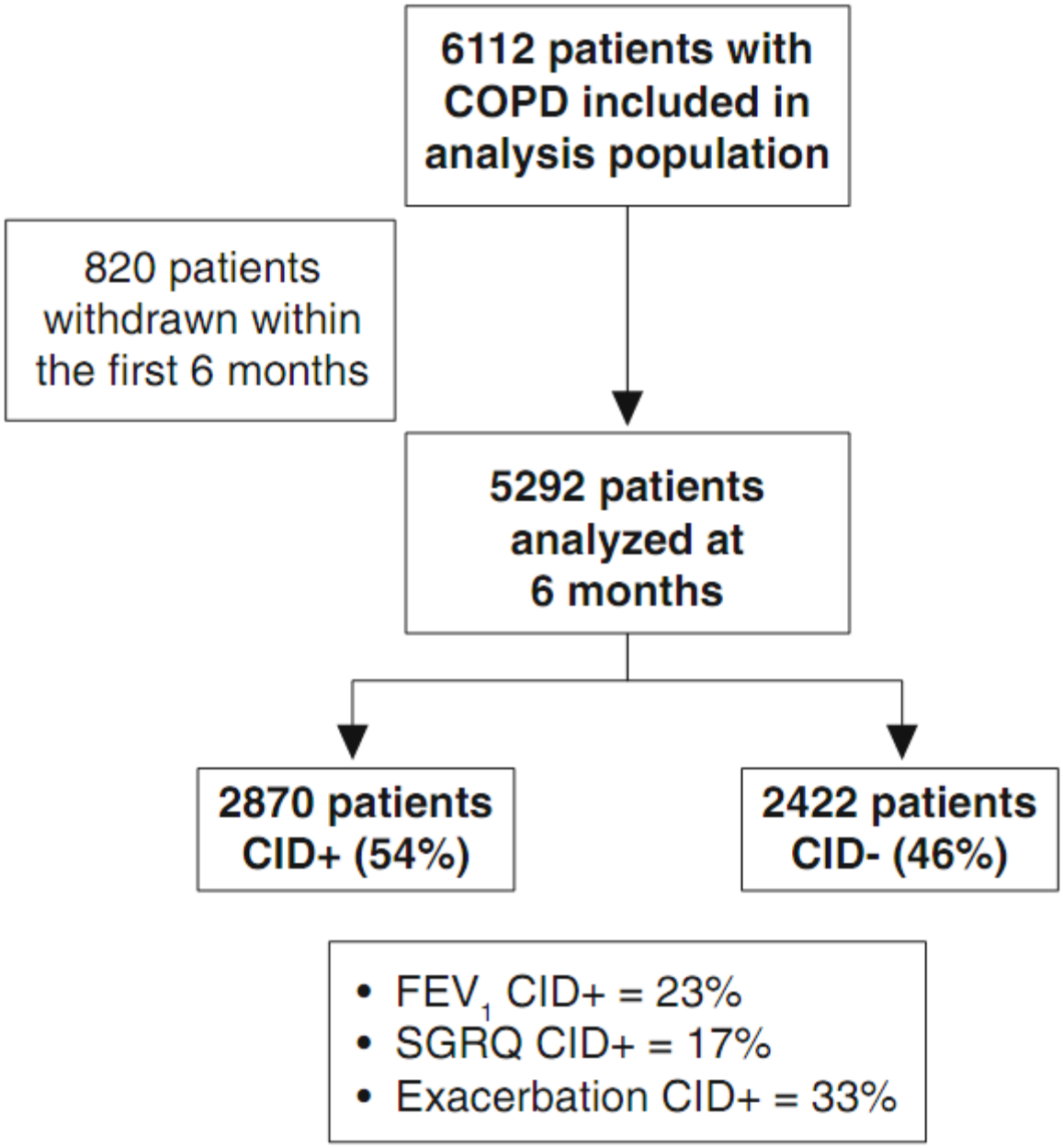
RESEARCH Open Access

Long-term outcomes following first short-term clinically important deterioration in COPD

Ian P. Naya[1*], Lee Tombs[2], Hana Muellerova[1], Christopher Compton[1] and Paul W. Jones[1]

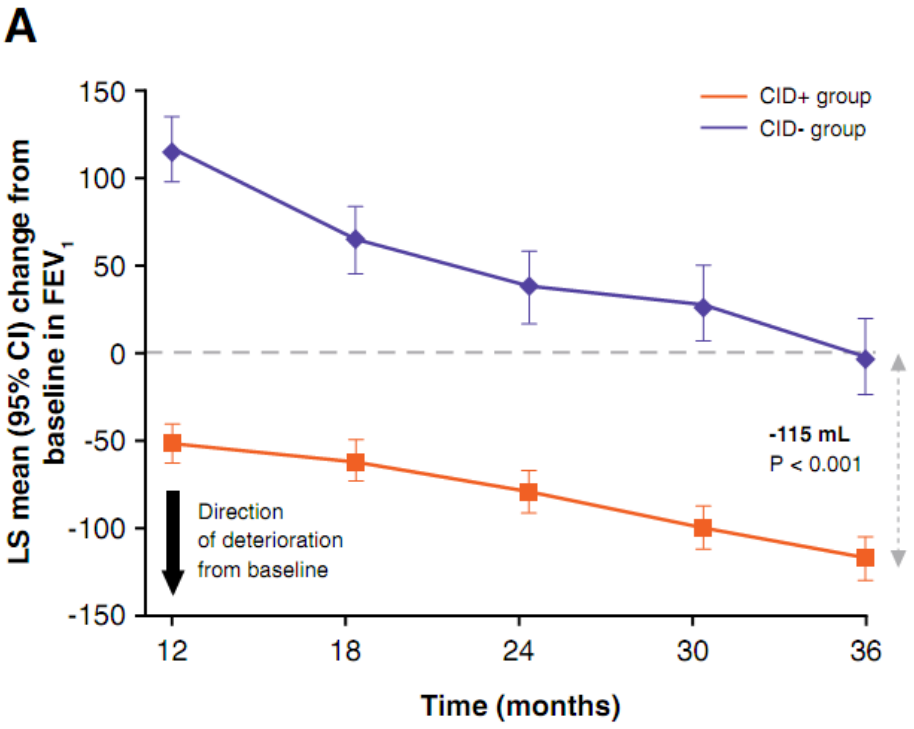
- two 3-year studies
- Presence of CID was assessed
  - at 6 months for the principal analysis (TORCH)
  - at 12 months for the confirmatory analysis (ECLIPSE)

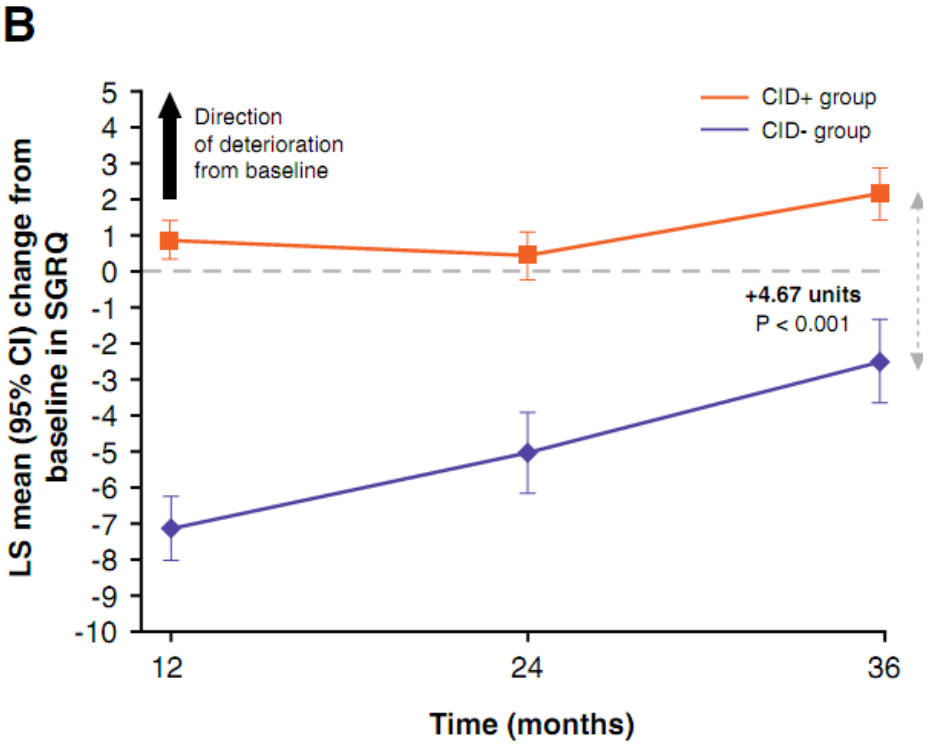
Respir Res 2018;19:222



Naya IP et al. Respir Res 2018;19:222

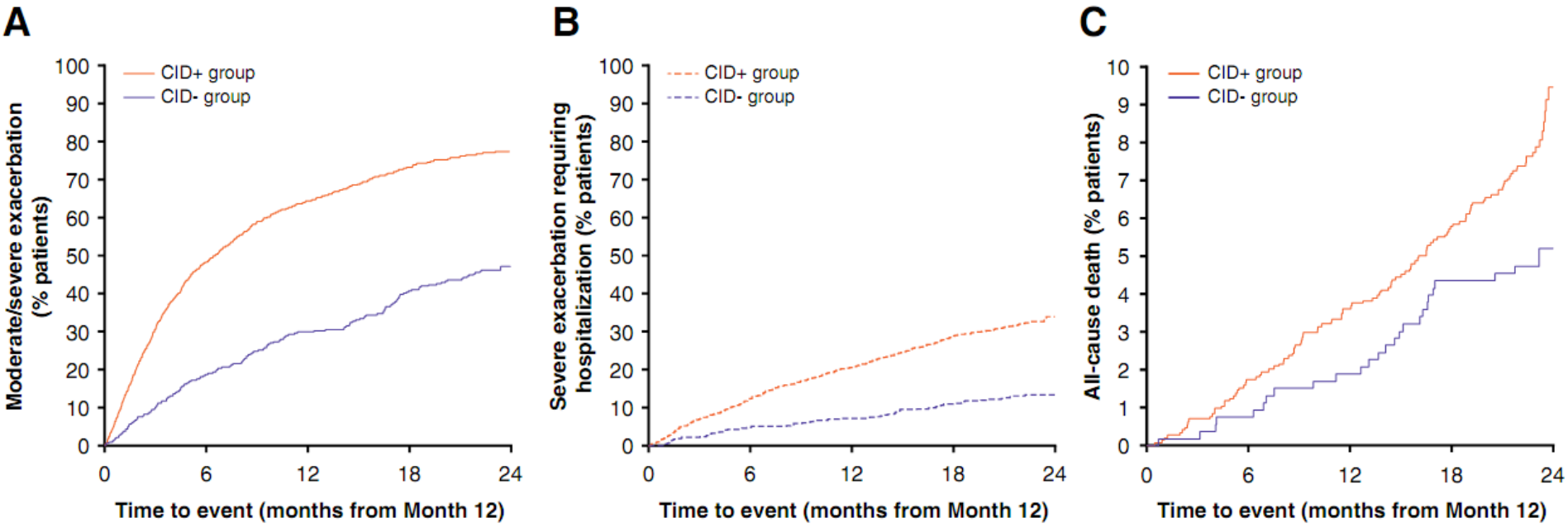
Δ FEV1 & SGRQ over time based on CID status





Naya IP et al. Respir Res 2018;19:222

Exacerbation & Mortality based on CID status



Naya IP et al. Respir Res 2018;19:222

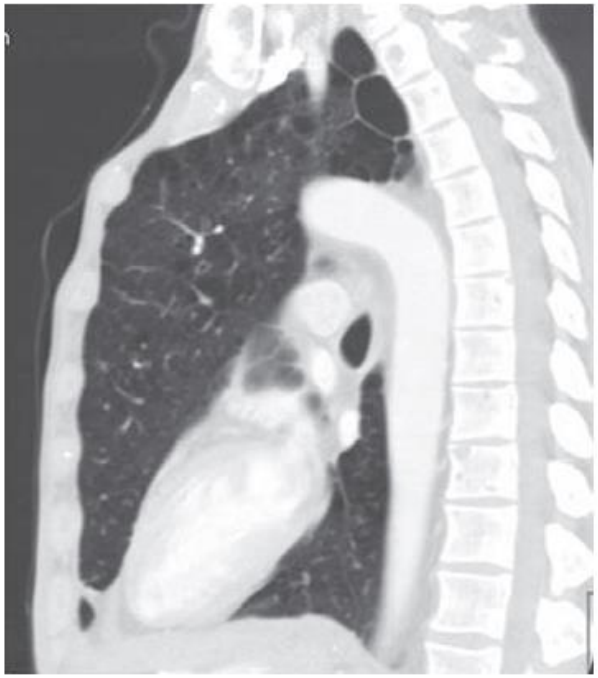
Effects of emphysema on the left ventricle

Physiological stress
hypoxia
increase in CF
neurohumoral activation

Coronary artery disease
smoking
reduced FEV_1
endothelial dysfunction
inflammation/oxidative stress
alteration in hemostasis
aging
sedentary lifestyle

Ventricular interdependence
RV overload
PH

Hyperinflation/emphysema
pulmonary vascular remodeling
↓ dimension pulmonary veins
↓ IC/TLC
increase RVol



Effects on the left ventricle:

- Ventricular hypertrophy
- Diastolic dysfunction
- Systolic dysfunction
- Heart failure

Portillo et al. Arch Bronconeumol 2015; 51: 227-34

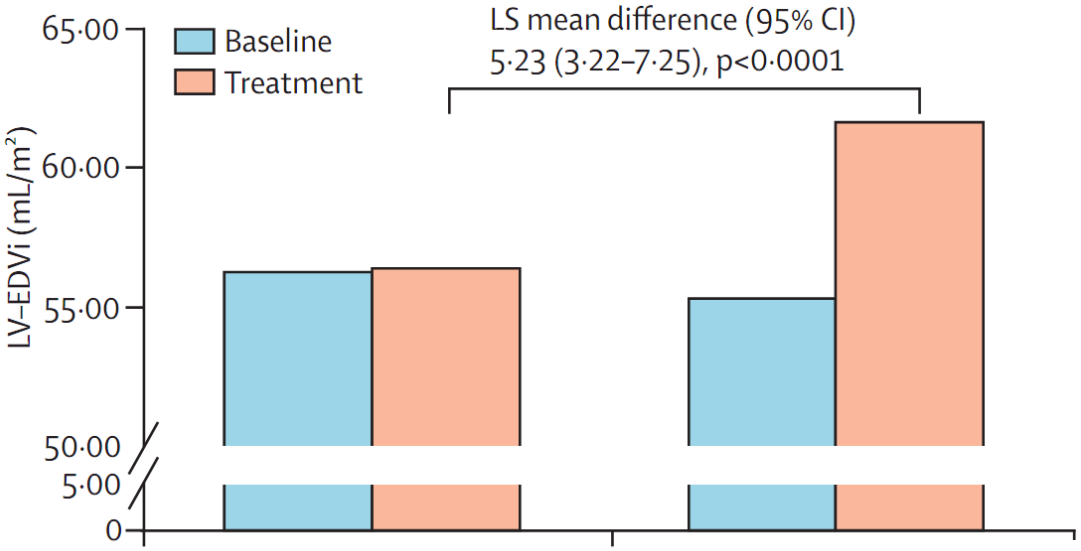
Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial

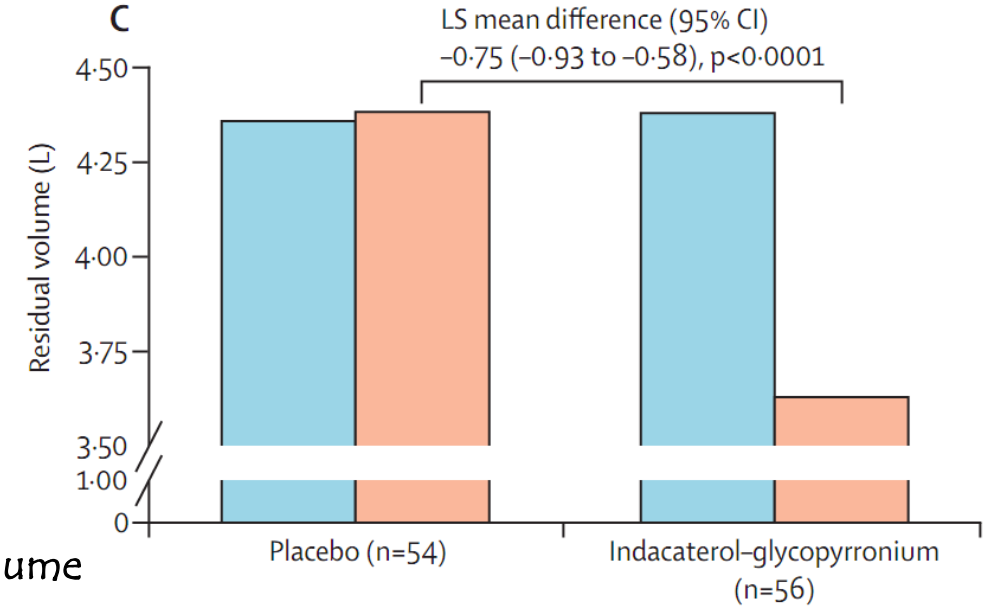
Jens M Hohlfeld, Jens Vogel-Claussen*, Heike Biller, Dominik Berliner, Korbinian Berschneider, Hanns-Christian Tillmann, Simone Hiltl, Johann Bauersachs, Tobias Welte*

- 60 COPD patients
  - Pulmonary hyperinflation (Residual volume > 135% of pred)
  - FEV1 < 80% pred, postBD FEV1/FVC <0.7
- Exclusion
  - arrhythmias, heart failure, unstable IHD, or uncontrolled hypertension
- Primary endpoint : left-ventricular end-diastolic volume (LV-EDV)

Lancet Respir Med 2018; 6: 368-78

LV-EDV & Residual volume





* LV-EDV = left ventricular end-diastolic volume

Hohlfeld et al. Lancet Respir Med 2018; 6: 368-78

CHEST

Original Research

COPD

Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD

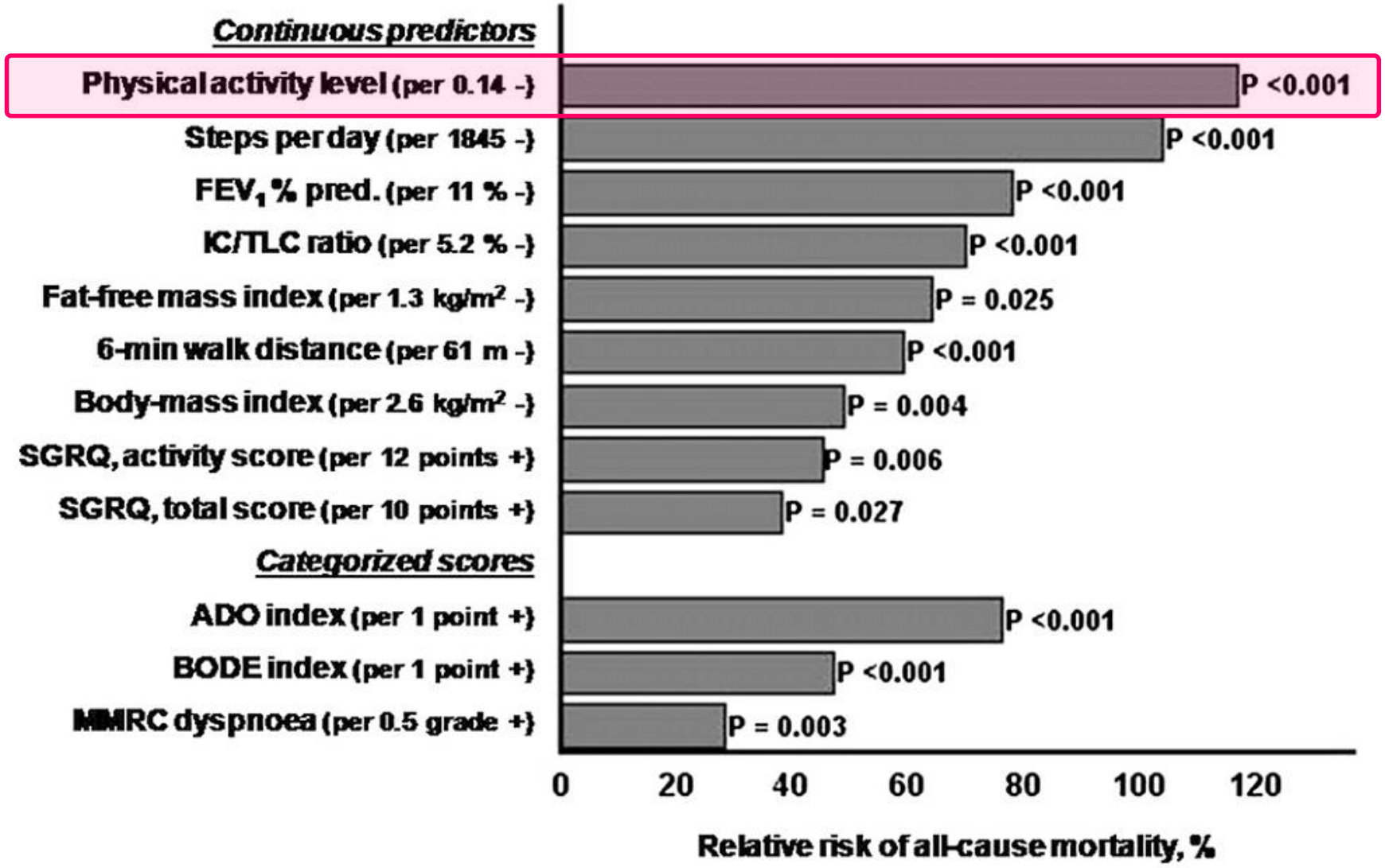
A Prospective Cohort Study

Benjamin Waschki, MD; Anne Kirsten, MD; Olaf Holz, PhD; Kai-Christian Müller, PhD; Thorsten Meyer, PhD; Henrik Watz, MD; and Helgo Magnussen, MD

- prospective cohort study
- stable COPD (n=170)
- multisensory armband
- median follow-up : 48 months

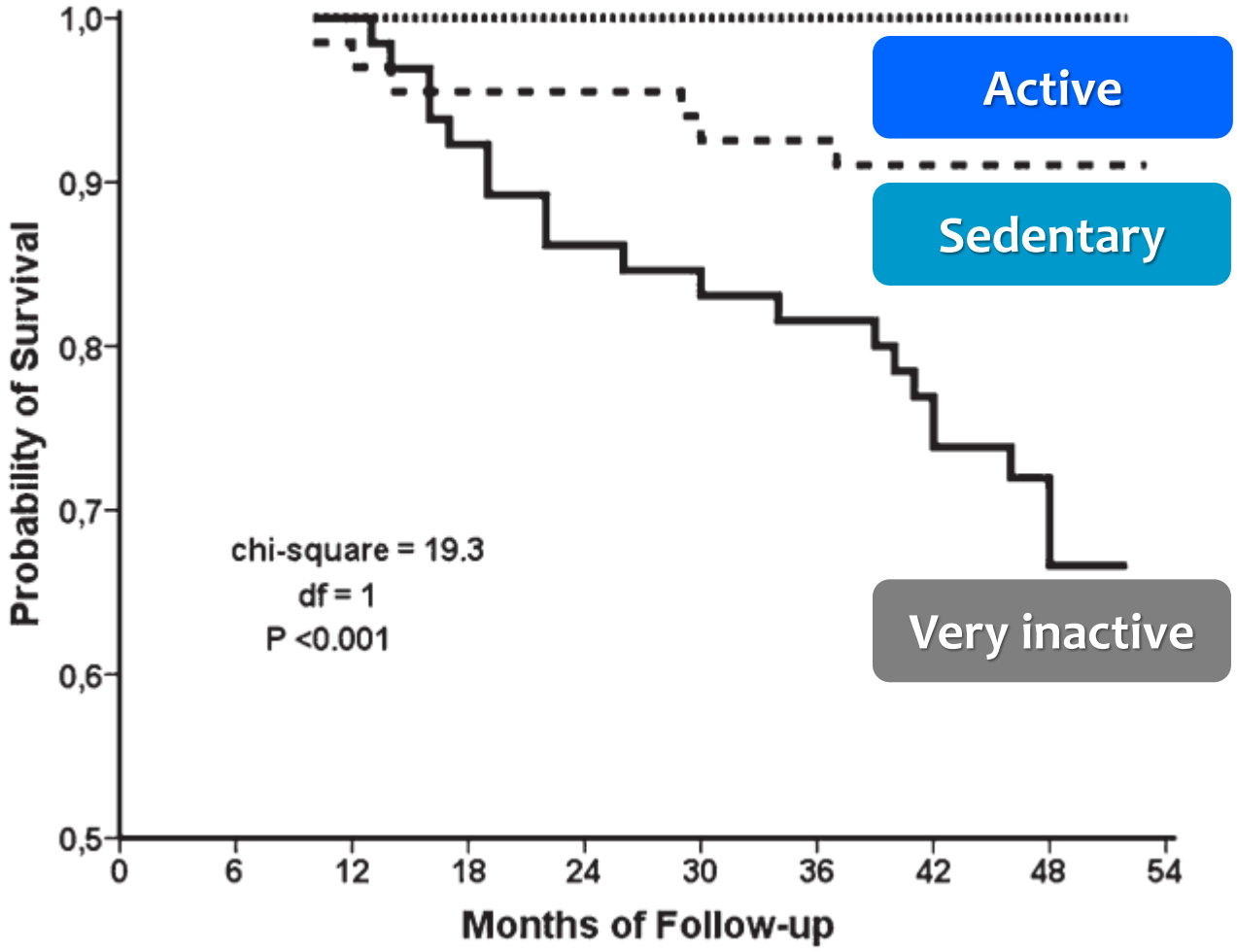
Chest 2011; 140: 331-42

Relative risk of death



Waschki B et al. Chest 2011; 140: 331-42

Survival & PA



Waschki B et al. Chest 2011; 140: 331-42

Exercise capacity and physical activity in COPD patients treated with a LAMA/LABA combination: a systematic review and meta-analysis

Marc Miravitlles[1*], Juan Luís García-Rivero[2], Xavier Ribera[3], Jordi Galera[4], Alejandra García[5], Rosa Palomino[5] and Xavier Pomares[6]

- 17 articles with 4041 patients with COPD

Respir Res 2022;23:347

Table 2 Summary of meta-analysis comparisons and main results in weighted mean differences (WMD) and standardised mean differences (SMD)

	LAMA/LABA comparator	Characteristics		Weighted results		Standardized results	
		Number of CT	N	MD	95% CI	MD	95% CI
ESWT	Placebo*	4	1730	31.75 s	16.03 s to 47.47 s	0.21	0.12 to 0.31
	Monotherapy	1	689	11.36%	− 0.03% to 22.74%	0.16	− 0.00 to 0.33
CWRCE	Placebo*	3	2466	72.45 s	46.77 s to 98.13 s	0.22	0.14 to 0.30
	Monotherapy	2	3398	24.23 s	− 0.86 s to 49.32 s	0.06	− 0.00 to 0.13
T_{lim} CWRT	Monotherapy*	1	38	43.80%	38.77% to 48.83%	5.42	3.99 to 6.86
6MWT	Placebo	1	125	11.87 m	− 9.32 m to 33.06 m	0.20	− 0.16 to 0.55
	Monotherapy*	4	634	9.77 m	1.22 m to 18.31 m	0.17	0.02 to 0.33
Steps/day	Placebo*	3	710	471.89 steps/day	206.08 steps/day to 737.71 steps/day	0.26	0.11 to 0.41
	Monotherapy**	3	521	398.48 steps/day	− 264.40 steps/day to 1061.36 steps/day	0.18	0.01 to 0.36
≥ 1.0–1.5 METs	Monotherapy*	2	315	− 9.93 min	− 17.91 min to − 1.95 min	− 0.30	− 0.53 to − 0.08
≥ 2.0 METs	Monotherapy*	3	645	5.59 min	2.13 min to 9.05 min	0.24	0.08 to 0.39
≥ 3.0 METs	Placebo***	2	612	7.73 min	3.07 min to 12.39 min	0.24	− 0.05 to 0.53
	Monotherapy*	2	315	2.60 min	0.74 min to 4.46 min	0.29	0.07 to 0.51
Energy expenditure	Placebo*	2	612	39.33 kcal/day	17.95 kcal/day to 60.71 kcal/day	0.28	0.12 to 0.44

* Statistically significant differences, both in WMD and SMD. **Statistically significant differences in SMD. ***Statistically significant differences in WMD

CI confidence interval, *CT* clinical trial, *CWRCE* constant work rate cycle ergometry, *ESWT* endurance shuttle walk test, *kcal* kilocalories, *LABA* long-acting beta-2 agonists, *LAMA* long-acting muscarinic antagonists, *m* meters, *MD* mean difference, *MET* metabolic equivalent of task, *min* minutes, *N* number of patients, *s* seconds, *SMD* standardized mean difference, T_{lim} *CWRT* tolerance limit in constant work rate test, *WMD* weighted mean difference, *6MWT* 6-min walking test

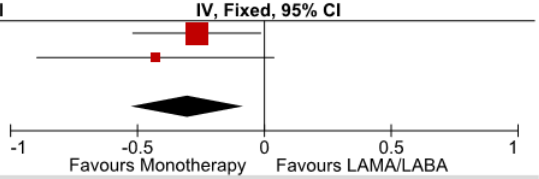
Daily duration of activity

b) Daily duration of activity (≥1.0-1.5, ≥2.0 and ≥3.0 METs), minutes: mean change from baseline

≥1.0- 1.5 METs

Treatments	Study or Subgroup	Std. Mean Difference	SE	LAMA/LABA Total	Monotherapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Tio 5µg/Olo 5µg vs Tio 5µg	Minakata Y et al., 2019	-0.2666	0.1289	121	122	77.4%	-0.27 [-0.52, -0.01]
Tio 5µg/Olo 5µg vs Tio 5µg	Takahashi K et al., 2020	-0.4293	0.2386	36	36	22.6%	-0.43 [-0.90, 0.04]
	Total (95% CI)			**157**	**158**	**100.0%**	**-0.30 [-0.53, -0.08]**

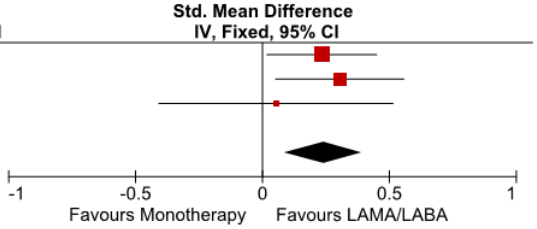
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.67 (P = 0.007)



≥2.0 METs

Treatments	Study or Subgroup	Std. Mean Difference	SE	LAMA/LABA Total	Monotherapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Tio 5µg/Olo 5µg vs Tio 5µg	Ichinose M et al., 2018	0.2335	0.1105	163	167	51.2%	0.23 [0.02, 0.45]
Tio 5µg/Olo 5µg vs Tio 5µg	Minakata Y et al., 2019	0.3047	0.1291	121	122	37.5%	0.30 [0.05, 0.56]
Tio 5µg/Olo 5µg vs Tio 5µg	Takahashi K et al., 2020	0.0531	0.2357	36	36	11.3%	0.05 [-0.41, 0.52]
	Total (95% CI)			**320**	**325**	**100.0%**	**0.24 [0.08, 0.39]**

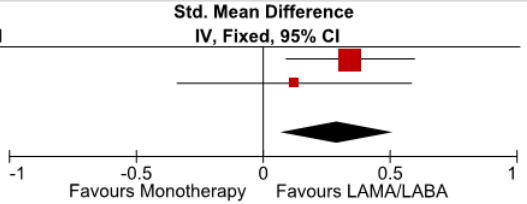
Heterogeneity: Chi² = 0.88, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)



≥3.0 METs

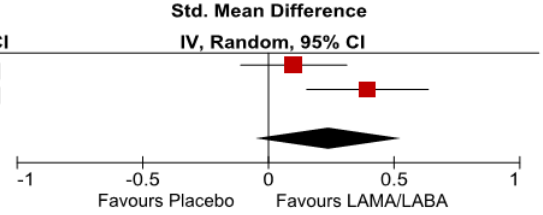
Treatments	Study or Subgroup	Std. Mean Difference	SE	LAMA/LABA Total	Monotherapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Tio 5µg/Olo 5µg vs Tio 5µg	Minakata Y et al., 2019	0.3430	0.1293	121	122	76.9%	0.34 [0.09, 0.60]
Tio 5µg/Olo 5µg vs Tio 5µg	Takahashi K et al., 2020	0.1222	0.2359	36	36	23.1%	0.12 [-0.34, 0.58]
	Total (95% CI)			**157**	**158**	**100.0%**	**0.29 [0.07, 0.51]**

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.01)



Treatments	Study or Subgroup	Std. Mean Difference	SE	LAMA/LABA Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Inda 110µg/Glicopi 50µg vs Plcb	Watz H et al., 2016	0.1007	0.1078	175	170	52.1%	0.10 [-0.11, 0.31]
Aclid 800µg/Formo 24µg vs Plcb	Watz H et al., 2017	0.3943	0.1236	134	133	47.9%	0.39 [0.15, 0.64]
	Total (95% CI)			**309**	**303**	**100.0%**	**0.24 [-0.05, 0.53]**

Heterogeneity: Tau² = 0.03; Chi² = 3.20, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 1.65 (P = 0.10)

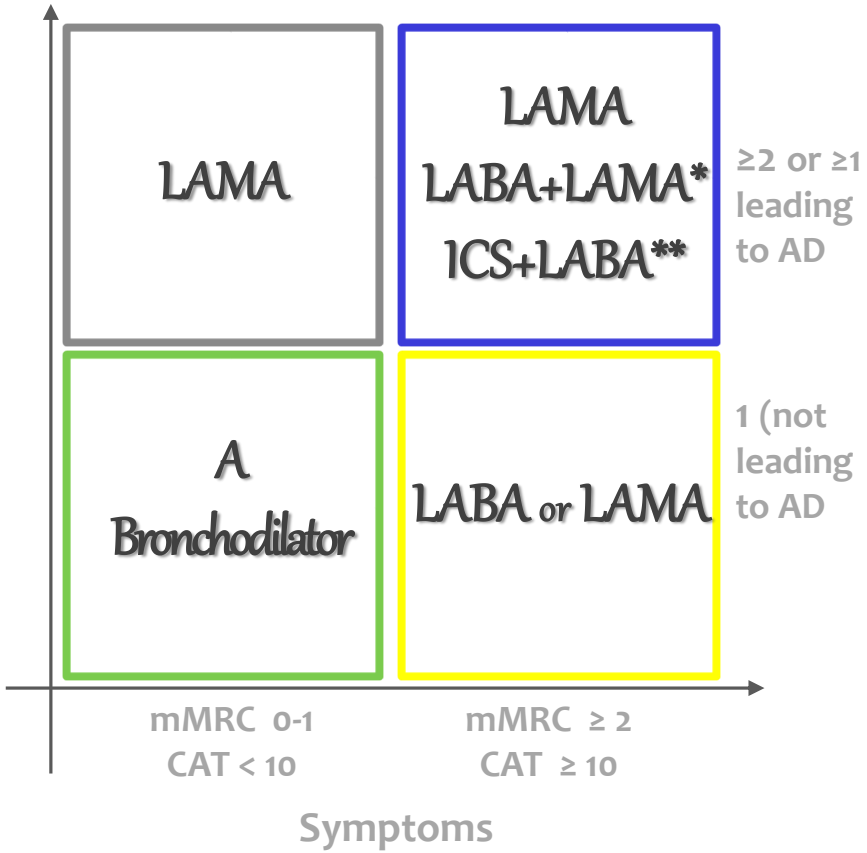


Miravitlles M, et al. Respir Res 2022;23:347

CONTENTS

Initial pharmacological treatment

GOLD 2022



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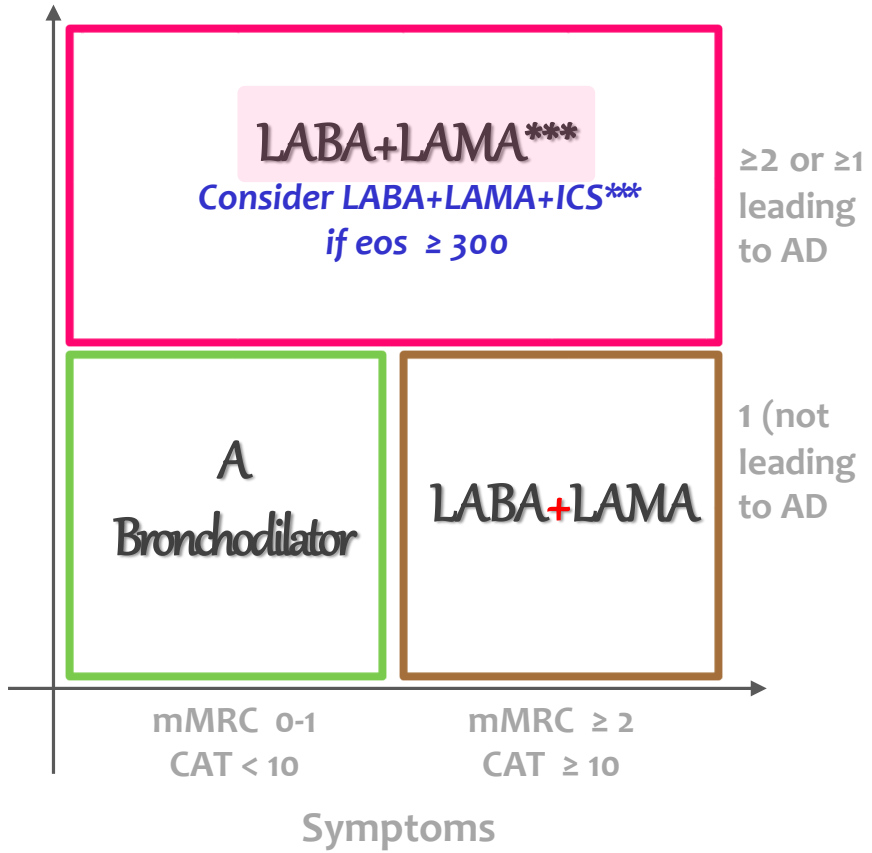


*Consider if highly symptomatic (e.g. CAT > 20)

**Consider if eos ≥ 300

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

Cochrane Library

Cochrane Database of Systematic Reviews

Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis (Review)

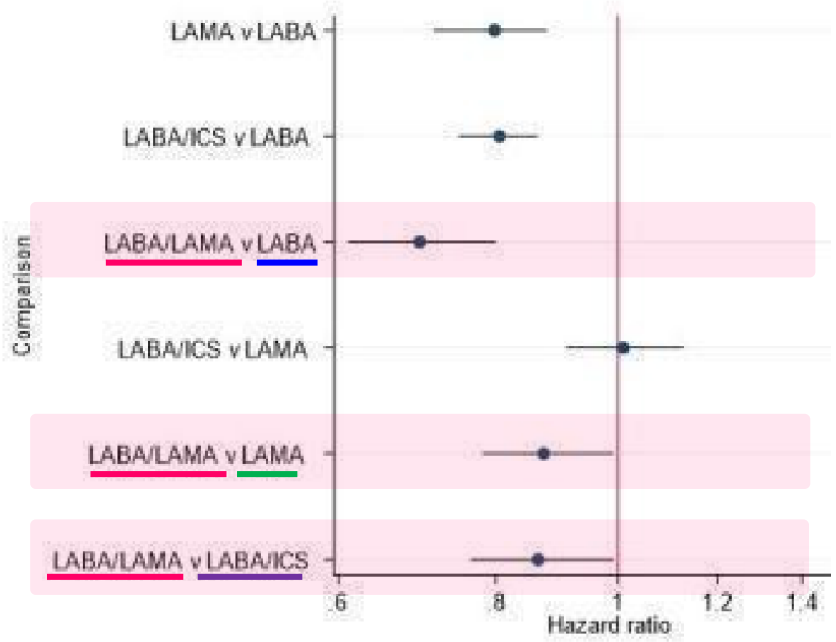
Oba Y, Keeney E, Ghatehorde N, Dias S

- 99 studies
- 101,311 participants

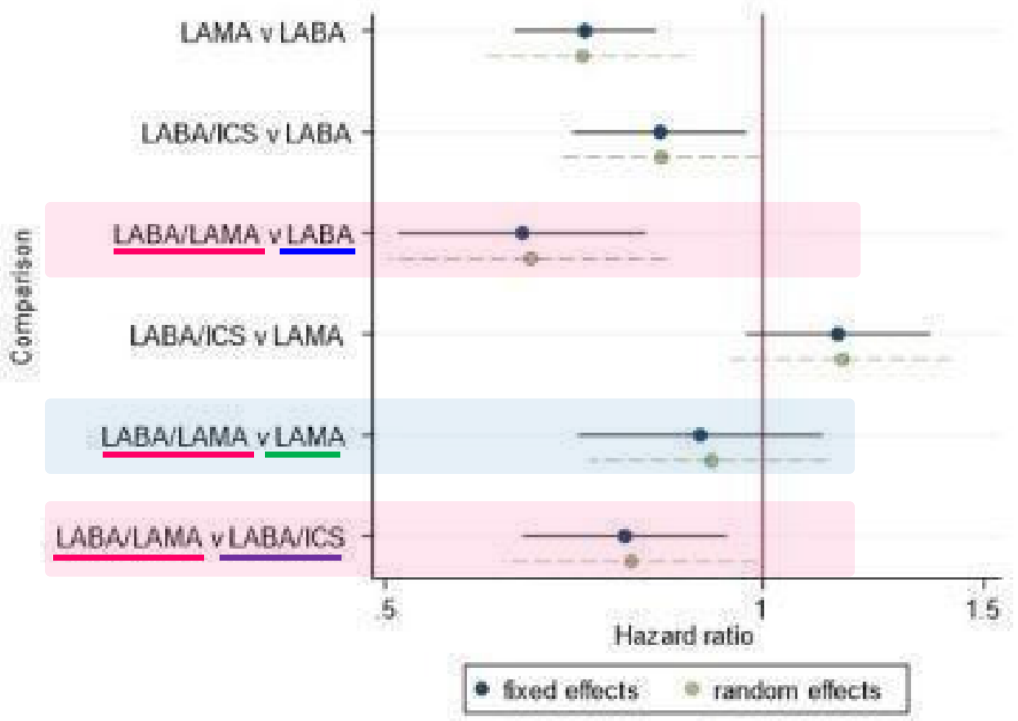
Cochrane Database Syst Rev 2018; 12: CD012620

Exacerbation in the high-risk population

Moderate/Severe

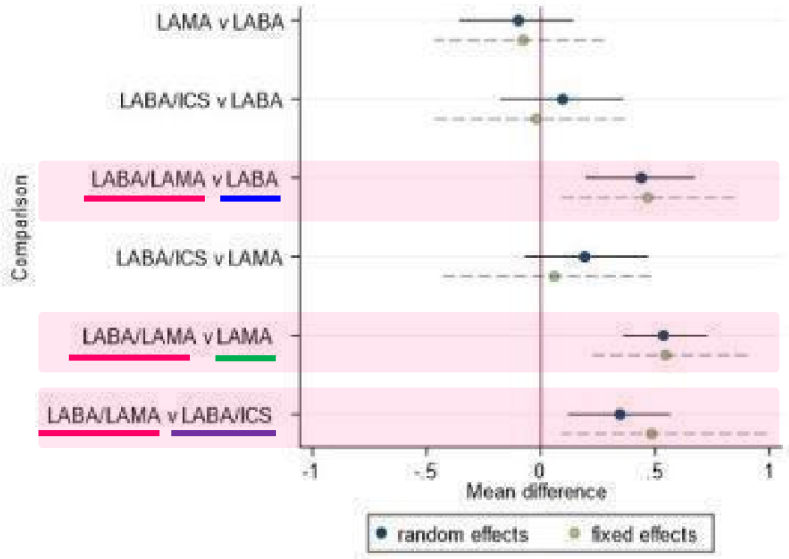


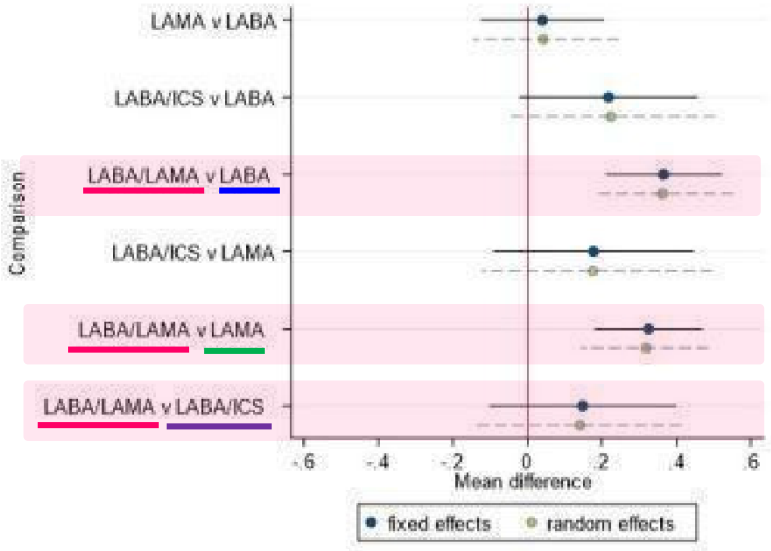
Severe

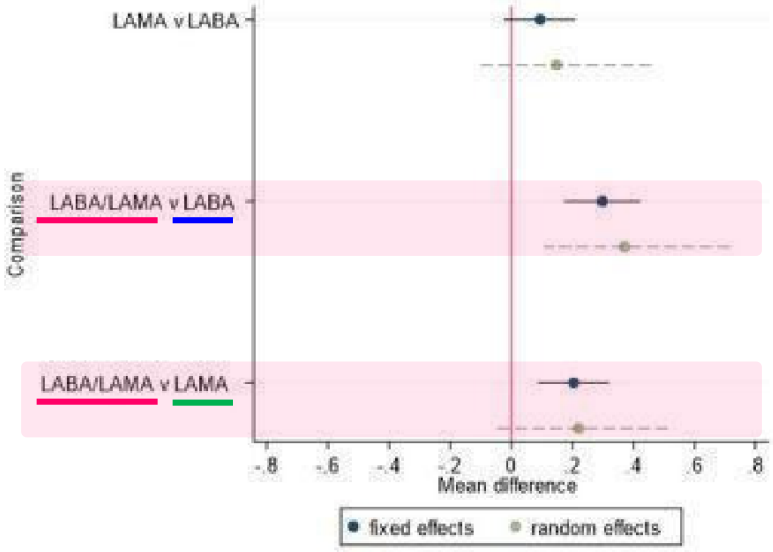


Cochrane Database Syst Rev 2018; 12: CD012620

TDI (Transition Dyspnea Index) at 3 mo, 6 mo, 12 mo







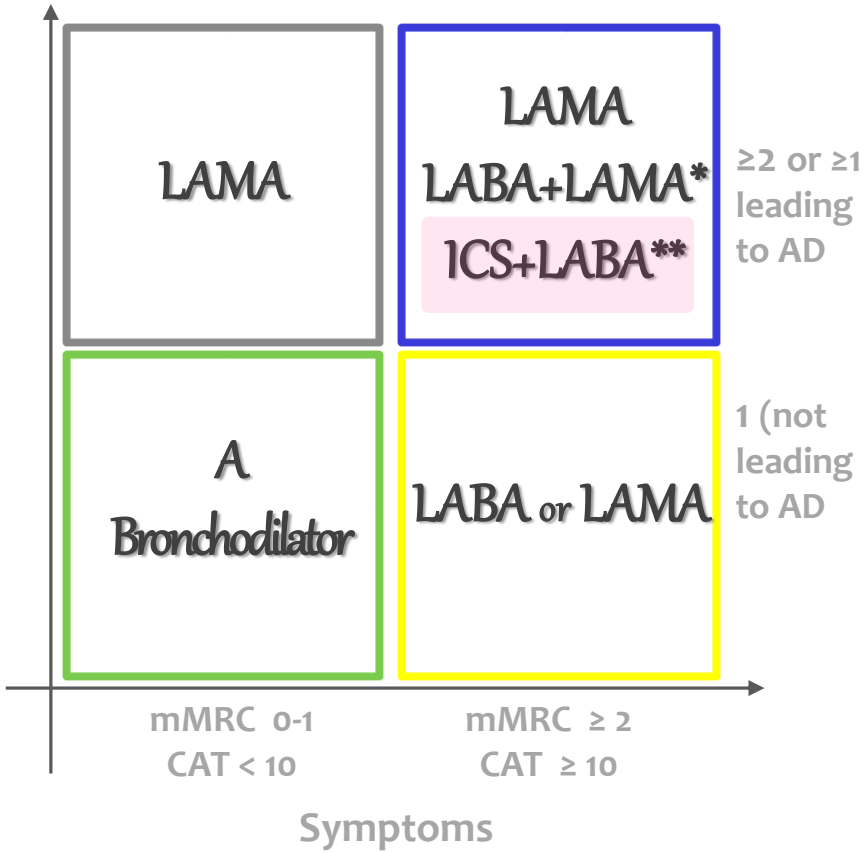
Cochrane Database Syst Rev 2018; 12: CD012620

Management of COPD

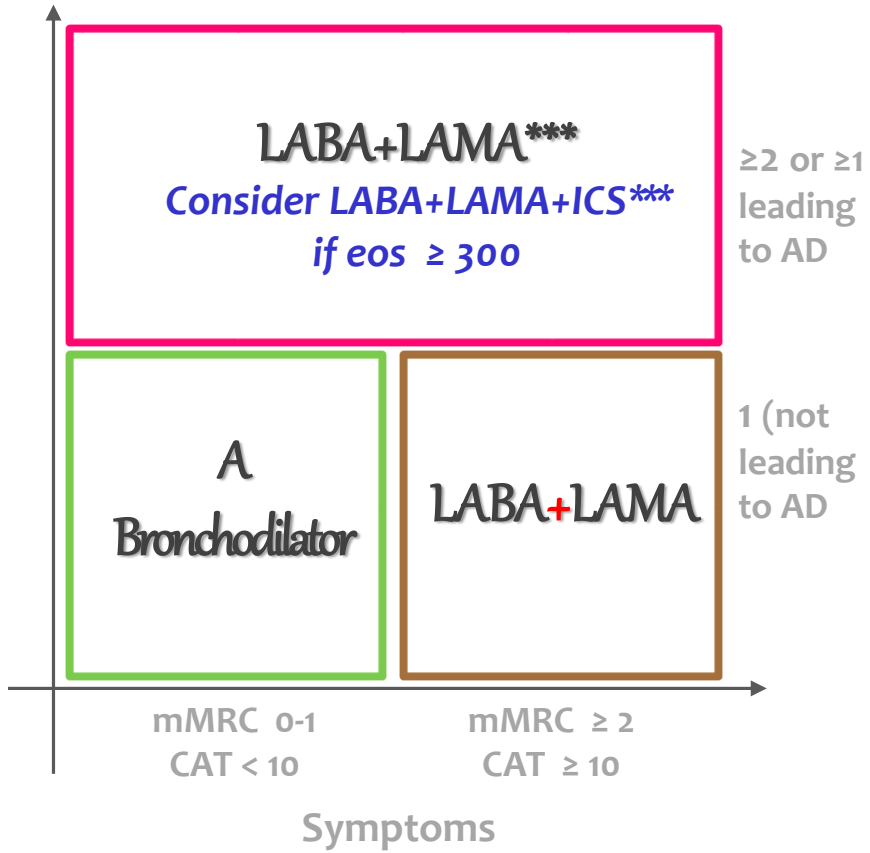
ICS + LABA

Initial pharmacological treatment

GOLD 2022



GOLD 2023



Consider if highly symptomatic (e.g. CAT > 20)

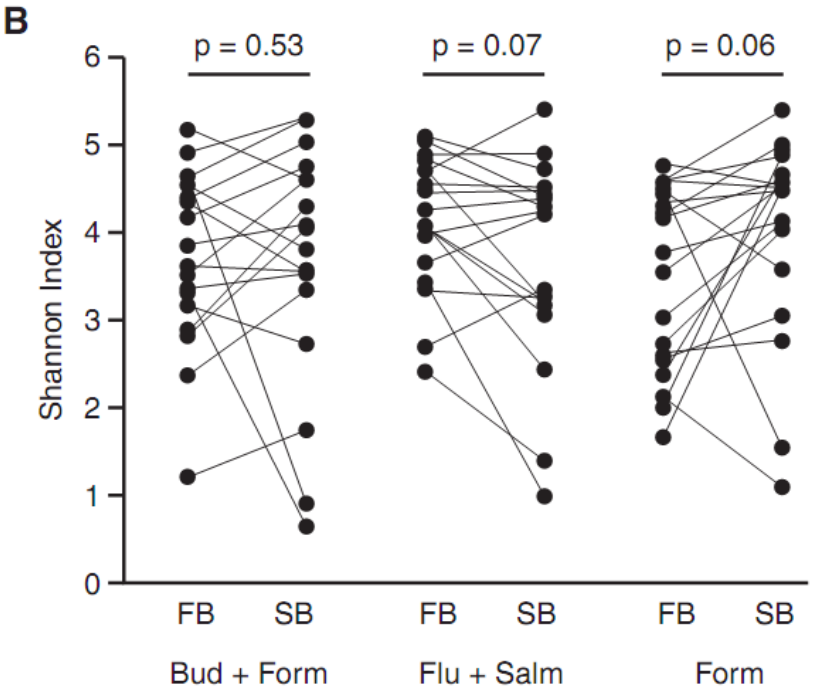
**Consider if eos ≥ 300*

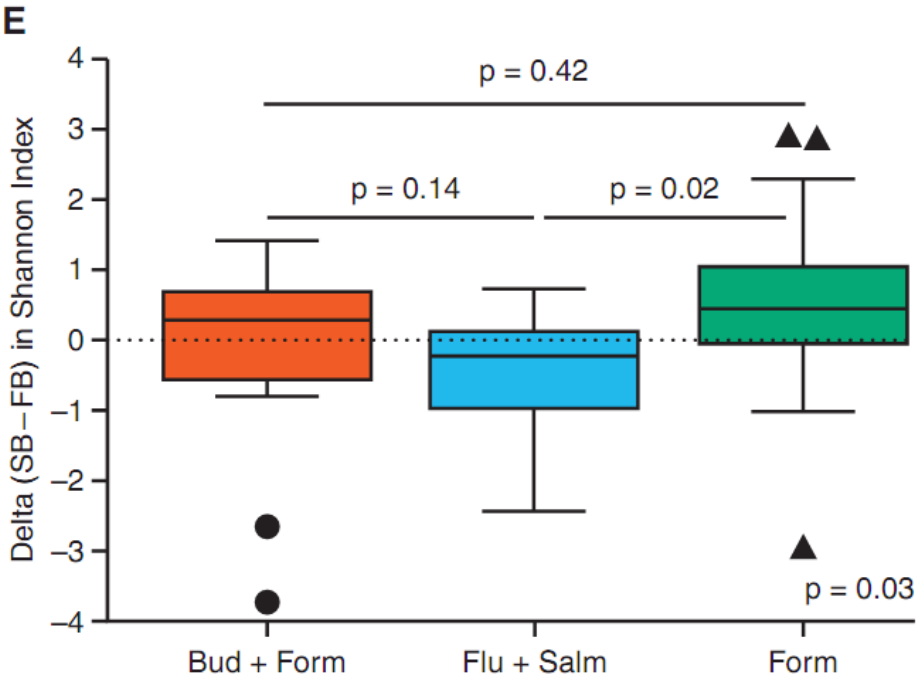
***Single inhaler therapy may be more convenient and effective than multiple inhalers*

Effects of Inhaled Corticosteroid/Long-Acting β_2-Agonist Combination on the Airway Microbiome of Patients with Chronic Obstructive Pulmonary Disease

A Randomized Controlled Clinical Trial (DISARM)

Fernando Sergio Leitao Filho[1,2], Hiroto Takiguchi[1,2,3], Kentaro Akata[1,2,4], Seung Won Ra[1,2,5], Ji-Yong Moon[1,2,6], Hyun Kuk Kim[1,2,7], Yuji Cho[1,2,8], Kei Yamasaki[1,2,9], Stephen Milne[1,2,10], Julia Yang[1,2], Cheng Wei Tony Yang[1,2], Xuan Li[1,2], Corey Nislow[11], Stephan F. van Eeden[1,2], Tawimas Shaipanich[1,2], Stephen Lam[1,2,12], Janice M. Leung[1,2], and Don D. Sin[1,2]





Am J Respir Crit Care Med. 2021;204(10):1143-1152

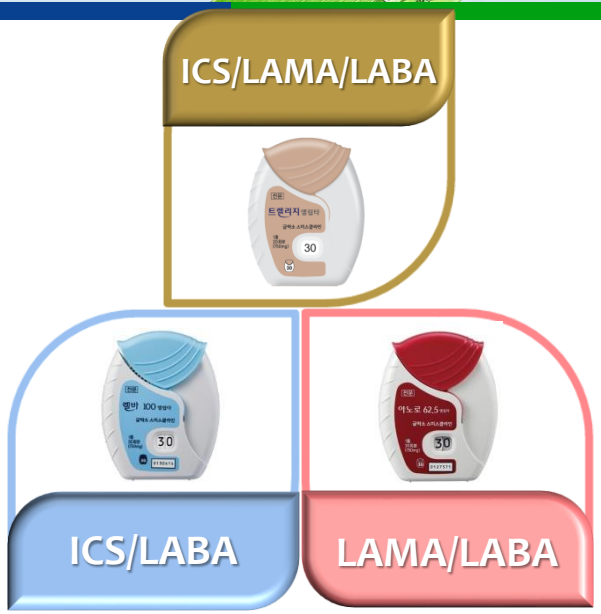
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D., Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S., for the IMPACT Investigators

IMPACT



- a 52-wk, randomized, double-blind, parallel-group, multicenter trial
- 10,355 patients with COPD
  - CAT ≥ 10
  - FEV1 < 50% & ≥ 1 mod/severe exacerbation in the previous year or
  - 50% < FEV1 < 80% & ≥ 2 moderate or 1 severe exacerbation in the previous year
- a once-daily combination of fluticasone furoate/umeclidinium/vilanterol vs fluticasone furoate/vilanterol and umeclidinium/vilanterol
- Primary outcome : the annual rate of moderate or severe exacerbations

N Engl J Med 2018;378:1671-80

IMPACT

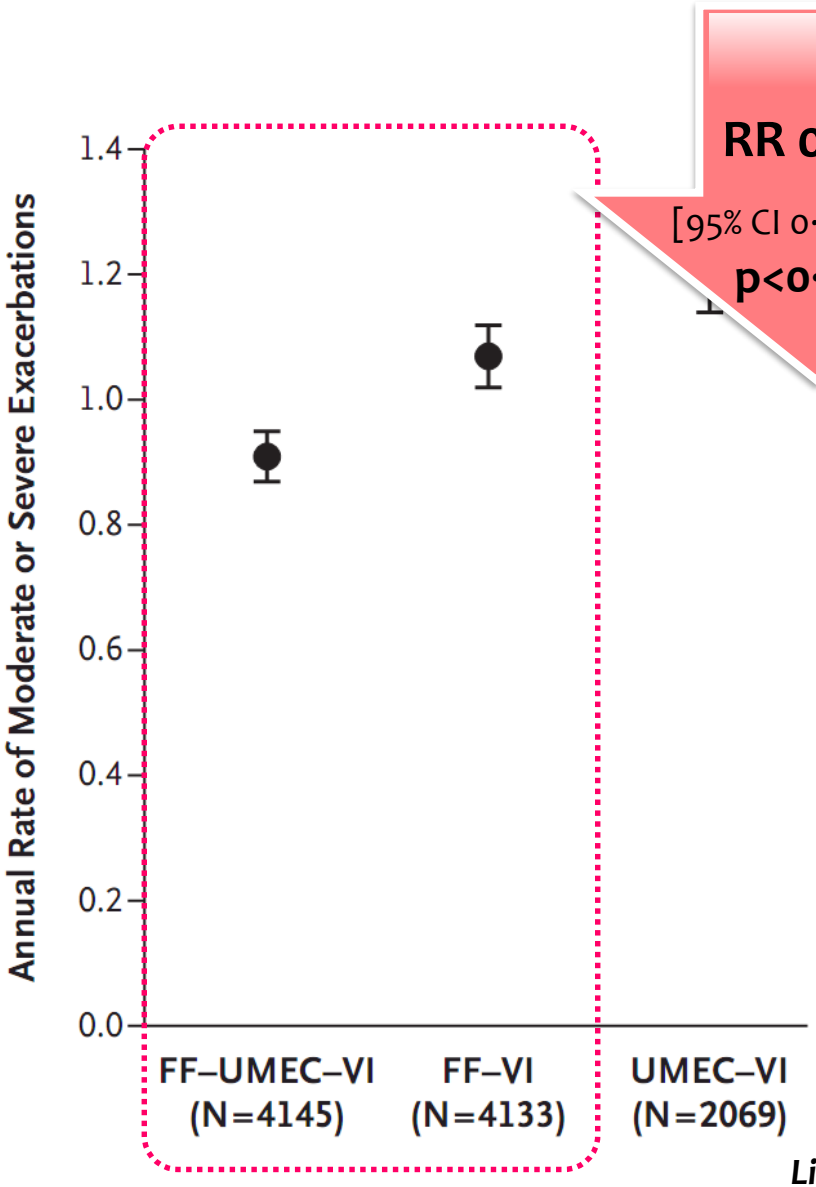
Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Triple Therapy (N=4151)	Fluticasone Furoate–Vilanterol (N=4134)	Umeclidinium–Vilanterol (N=2070)	Total (N=10,355)
Age — yr	65.3±8.2	65.3±8.3	65.2±8.3	65.3±8.3
Female sex — no. (%)	1385 (33)	1386 (34)	714 (34)	3485 (34)
Body-mass index†	26.6	26.7	26.6	26.6
Former smokers — no. (%)‡	2715 (65)	2711 (66)	1342 (65)	6768 (65)
Moderate or severe COPD exacerbations in the previous yr — no. (%)				
0	2 (<1)	5 (<1)	2 (<1)	9 (<1)
1	1853 (45)	1907 (46)	931 (45)	4691 (45)
2	1829 (44)	1768 (43)	890 (43)	4487 (43)
≥3	467 (11)	454 (11)	247 (12)	1168 (11)
≥2 Moderate COPD exacerbations in the previous yr — no. (%)	1967 (47)	1921 (46)	989 (48)	4877 (47)
≥1 Severe COPD exacerbation in the previous yr — no. (%)	1087 (26)	1069 (26)	515 (25)	2671 (26)
≥2 Severe COPD exacerbations in the previous yr — no. (%)	147 (4)	148 (4)	76 (4)	371 (4)
Postbronchodilator FEV_1 — % of predicted normal value	45.7±15.0	45.5±14.8	45.4±14.7	45.5±14.8
Mean score on the COPD Assessment Test at screening§	20.1±6.1	20.1±6.1	20.2±6.2	20.1±6.1

Lipson et al. N Engl J Med 2018;378:1671-80

Moderate or severe exacerbation rate

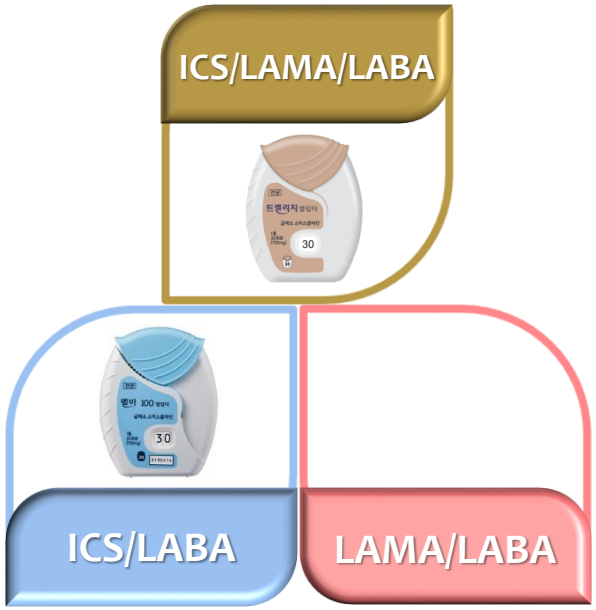
IMPACT



RR 0·85

[95% CI 0·80-0·90]

p<0·001



Lipson et al. N Engl J Med 2018;378:1671-80

[Original Research COPD]

CHEST

Adding a LAMA to ICS/LABA Therapy

A Meta-analysis of Triple Combination Therapy in COPD

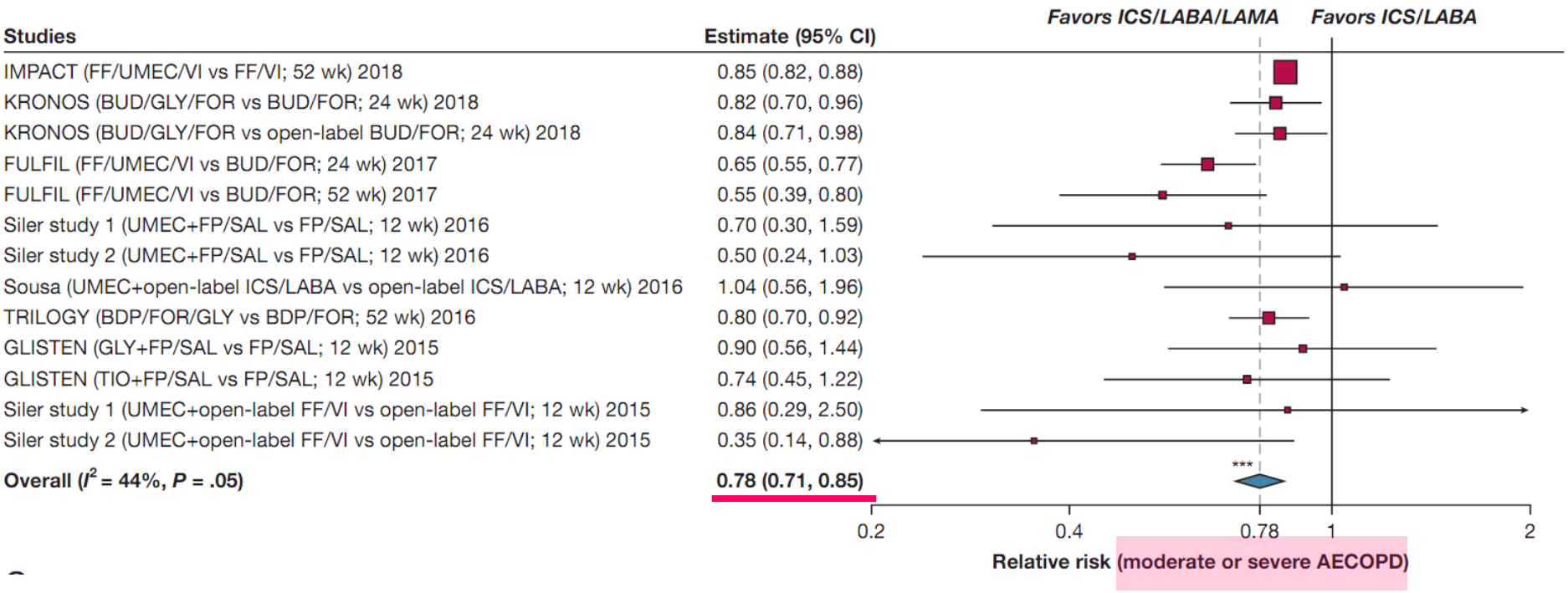
Luigino Calzetta, DVM, PGDip, Mphil, PhD; Mario Cazzola, MD; Maria Gabriella Matera, MD, PhD; and Paola Rogliani, MD

- 13 RCTs (n=15,519)
- Primary endpoints
  - Trough FEV1
  - Risk of acute exacerbation (AE)
  - Risk of cardiovascular serious adverse events (SAEs)

CHEST 2019; 155: 758-70

Risk of moderate/severe exacerbation

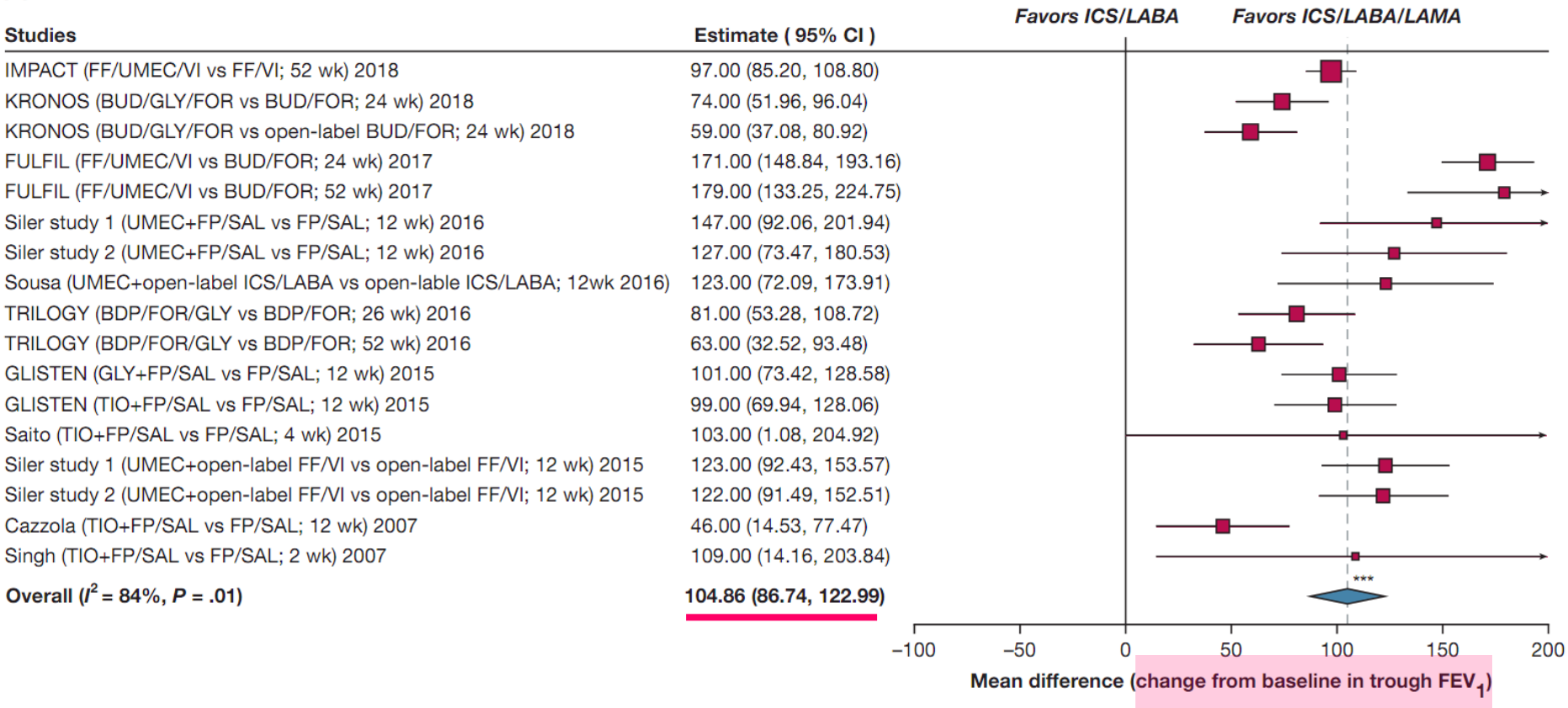
B



Calzetta L et al. CHEST 2019; 155: 758-70

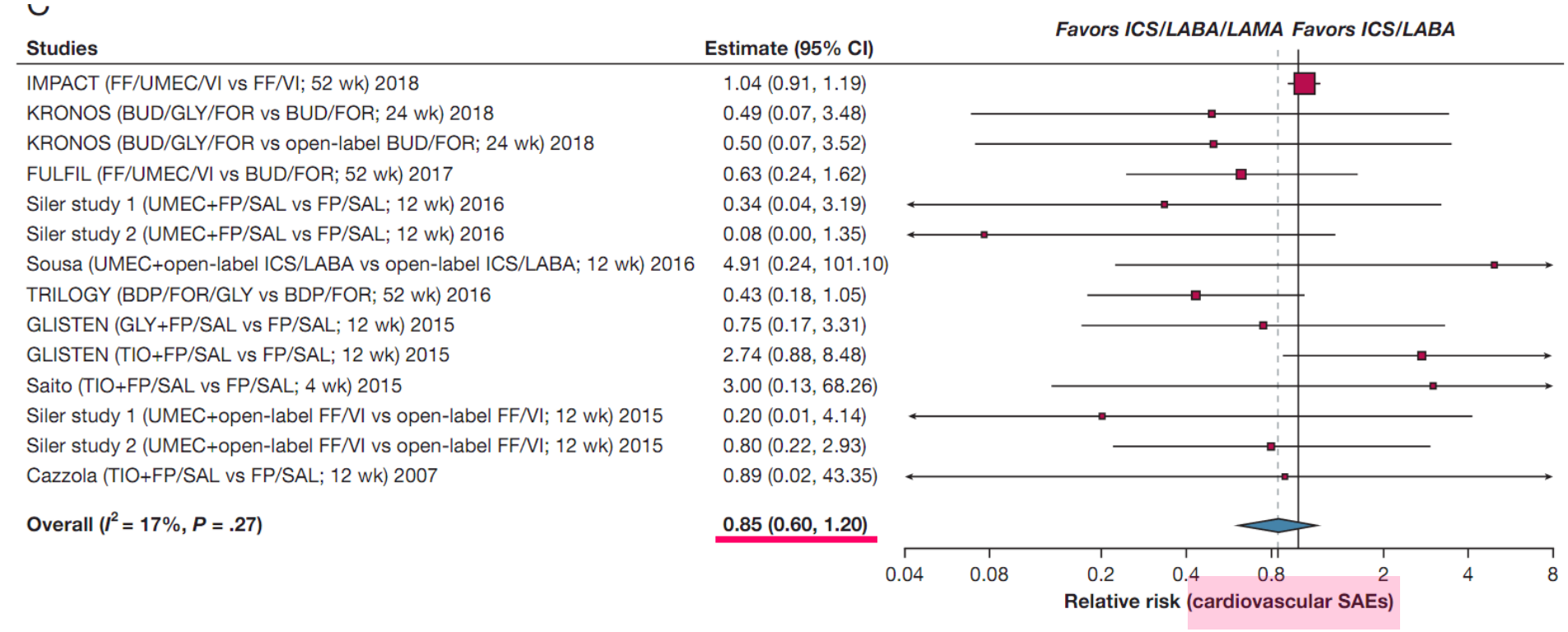
Trough FEV1

A



Calzetta L et al. CHEST 2019; 155: 758-70

Risk of cardiovascular SAEs



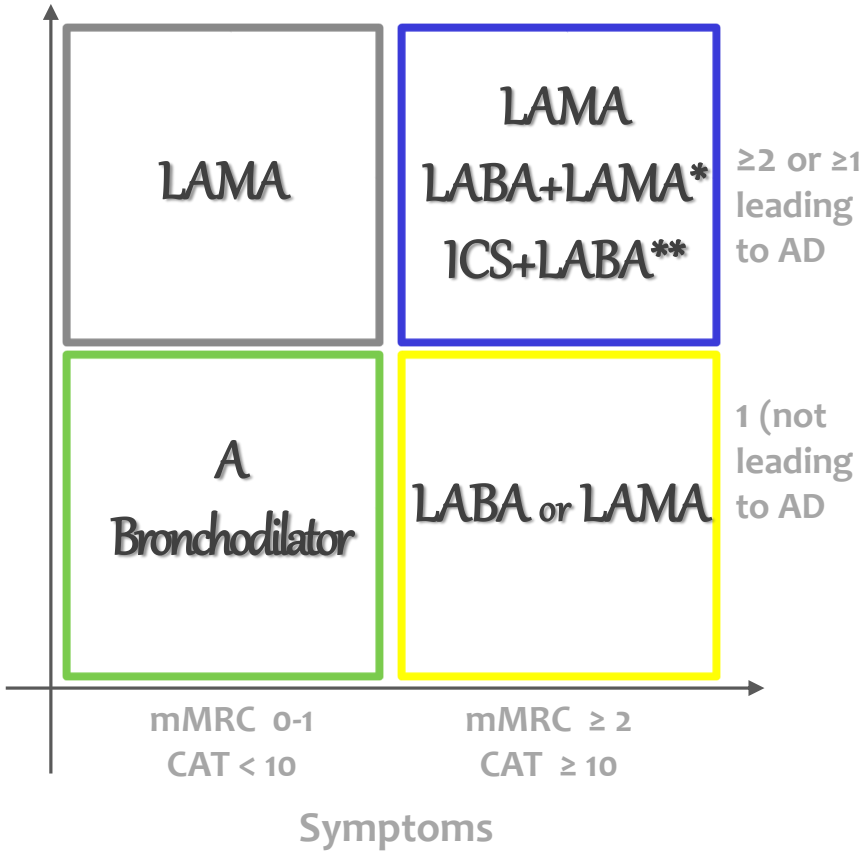
Calzetta L et al. CHEST 2019; 155: 758-70

Management of COPD

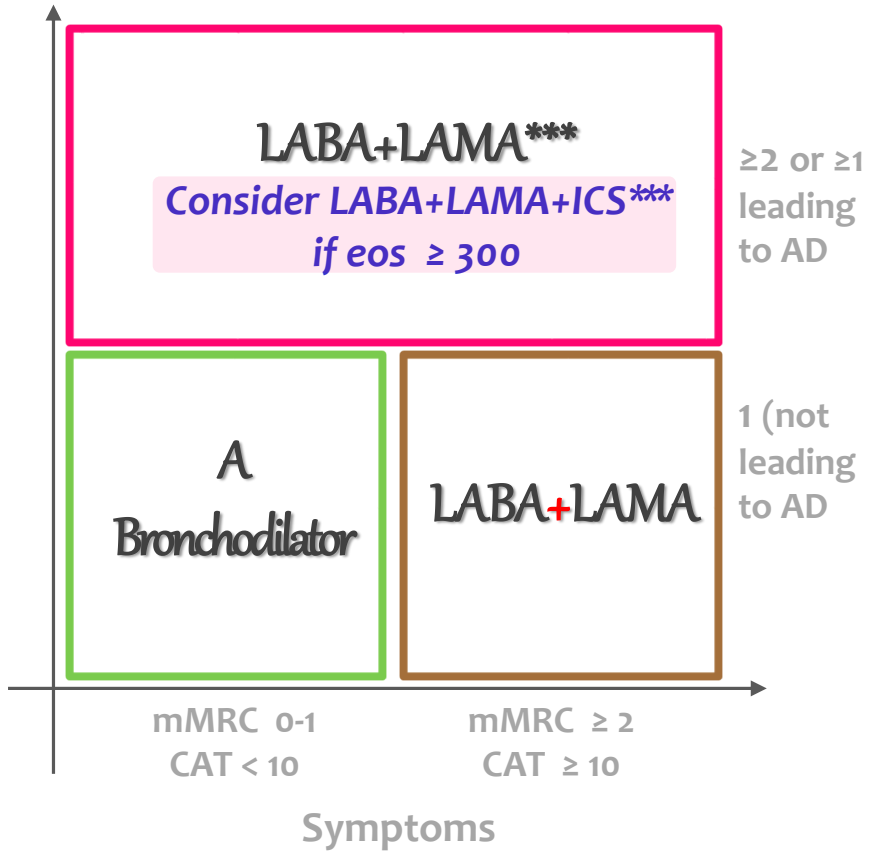
Single Inhaler Triple Therapy (SITT)

Initial pharmacological treatment

GOLD 2022



GOLD 2023



*Consider if highly symptomatic (e.g. CAT > 20)

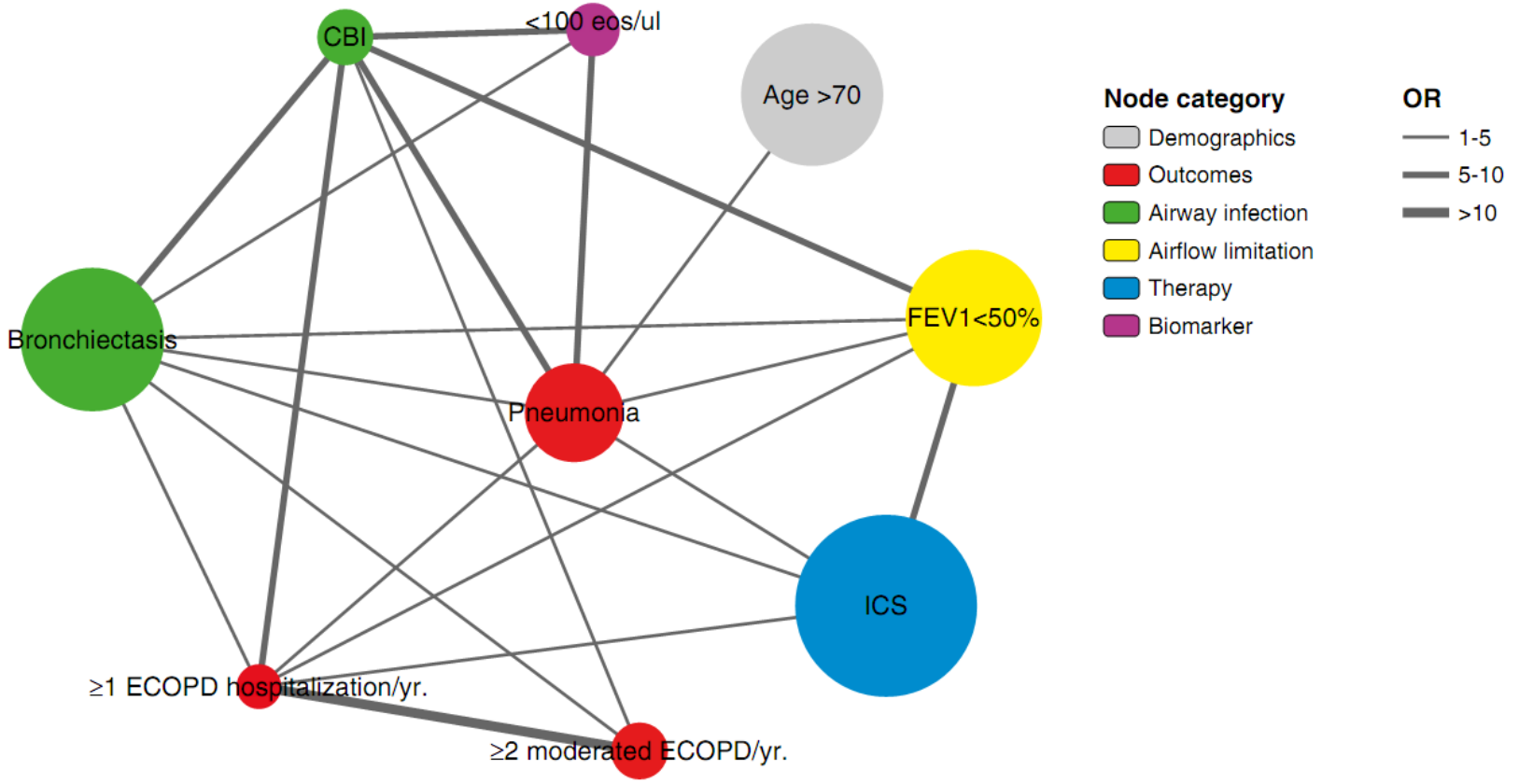
**Consider if eos ≥ 300

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

Inhaled Steroids, Circulating Eosinophils, Chronic Airway Infection, and Pneumonia Risk in Chronic Obstructive Pulmonary Disease

A Network Analysis

Miguel Angel Martinez-Garcia[1], Rosa Faner[2,3], Grace Oscullo[1], David de la Rosa[4*], Juan-Jose Soler-Cataluña[5], Marta Ballester[6], and Alvar Agusti[2,3,7]



Martinez-Garcia MA, et al. Am J Respir Crit Care Med. 2020;201(9):1078-1085

Benefits of Triple Therapy in COPD

↓ *Exacerbation*

ORIGINAL ARTICLE

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D., Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S., for the IMPACT Investigators

- a 52-wk, randomized, double-blind, parallel-group, multicenter trial
- 10,355 patients with COPD
  - CAT ≥ 10
  - FEV1 < 50% & ≥ 1 mod/sev exacerbation in the previous year or
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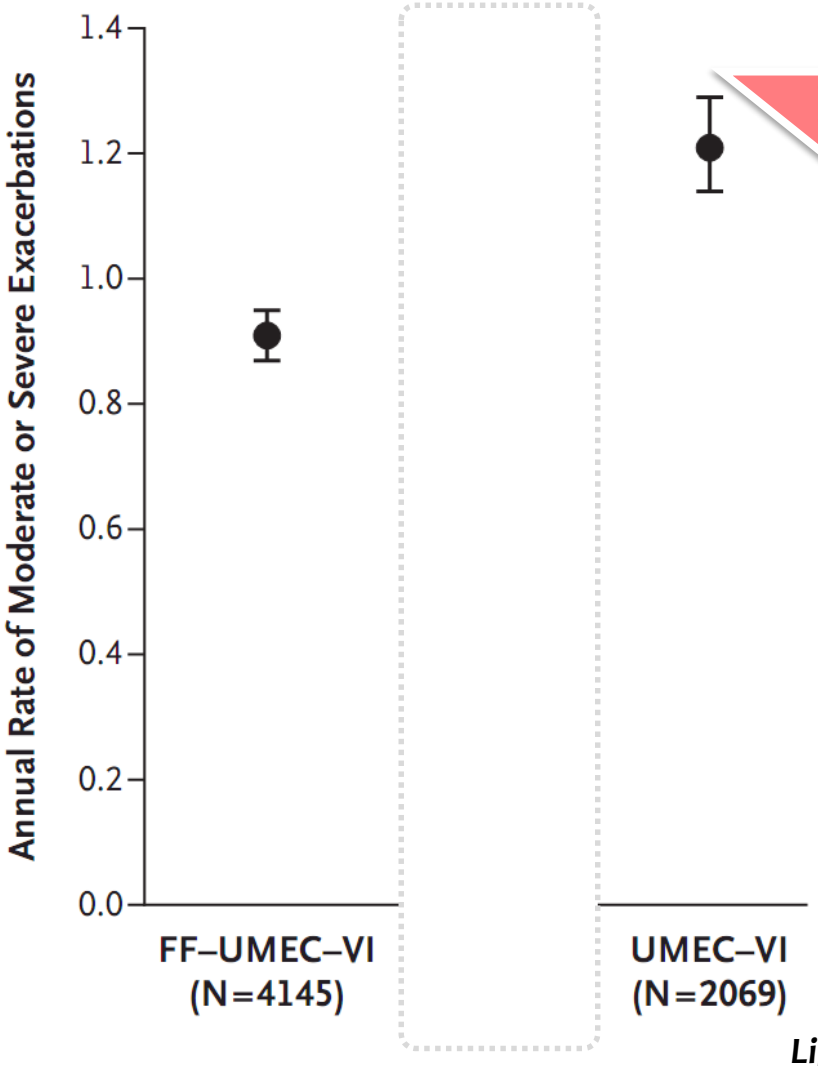
- a once-daily combination of fluticasone furoate/umeclidinium/vilanterol vs fluticasone furoate/vilanterol and umeclidinium/vilanterol
- Primary outcome : the annual rate of moderate or severe exacerbations

N Engl J Med 2018;378:1671-80

Moderate or severe exacerbation rate



RR 0·75

[95% CI 0·70-0·81]

p<0·001

Lipson et al. N Engl J Med 2018;378:1671-80

ORIGINAL ARTICLE

Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

Klaus F. Rabe, M.D., Ph.D., Fernando J. Martinez, M.D., Gary T. Ferguson, M.D., Chen Wang, M.D., Ph.D., Dave Singh, M.D., Jadwiga A. Wedzicha, M.D., Roopa Trivedi, M.S., Earl St. Rose, M.S., Shaila Ballal, M.S., Julie McLaren, M.D., Patrick Darken, Ph.D., Magnus Aurivillius, M.D., Ph.D., Colin Reisner, M.D., and Paul Dorinsky, M.D., for the ETHOS Investigators*

- 52-week, phase 3, randomized trial
- 8509 COPD patients
  - CAT ≥ 10 despite treatment with ≥ 2 inhaled maintenance therapies
  - FEV1 25~ 65%
  - ≥ 1 mod or severe exacerbations in the previous year if FEV1 <50%
  - ≥ 2 mod or ≥ 1 severe exacerbations in the previous year if FEV1 ≥ 50%
  - 320 μg-budesonide or 160 μg-budesonide/glycopyrrolate/formoterol
- Primary endpoint : rate of moderate or severe exacerbations

N Engl J Med 2020;383:35-48

Moderate or severe exacerbation rate

ETHOS

End Point	320-μg–Budesonide Triple Therapy (N=2137)	160-μg–Budesonide Triple Therapy (N=2121)	Glycopyrrolate–Formoterol (N=2120)	Budesonide–Formoterol (N=2131)
Primary end point				
Primary analysis: model-estimated annual rate of moderate or severe COPD exacerbations		1.07	1.42	1.24
320-μg–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)		1.00 (0.91–1.10)	0.76 (0.69–0.83)	0.87 (0.79–0.95)
P value†			<0.001	0.003
160-μg–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)	—		0.75 (0.69–0.83)	0.86 (0.79–0.95)
P value			<0.001	0.002

RR 0·76
[95% CI 0·69-0·83]
p<0·001

RR 0·75
[95% CI 0·69-0·83]
p<0·001

Rabe et al. N Engl J Med 2020;383:35-48

REVIEW

Evaluating triple ICS/LABA/LAMA therapies for COPD patients: a network meta-analysis of ETHOS, KRONOS, IMPACT, and TRILOGY studies

Luigino Calzetta [a], Beatrice Ludovica Ritondo[b], Patrizia de Marco[b], Mario Cazzola [b] and Paola Rogliani [b]

- network meta-analysis
- RCTs that directly compared triple ICS/LABA/LAMA vs. either dual LABA/LAMA or ICS/LABA therapies administered at FDC via the same inhaler device
- Data from ETHOS, KRONOS, IMPACT, and TRILOGY studies
- 21, 909 patients with COPD

Expert Rev Respir Med 2021 ;15:143-152

Rank probability of best therapy and SUCRA values

Rank probability of best therapy	Moderate to severe AECOPD		
	Overall	Low eosinophil count	High eosinophil count
1	ICS/LABA/ LAMA (0.99)	ICS/LABA/ LAMA (0.99)	ICS/LABA/LAMA (0.99)
2	ICS/LABA (0.51)	LABA/LAMA (0.43)	ICS/LABA (0.52)
3	LABA/LAMA (0.01)	ICS/LABA (0.09)	LABA/LAMA (0.00)

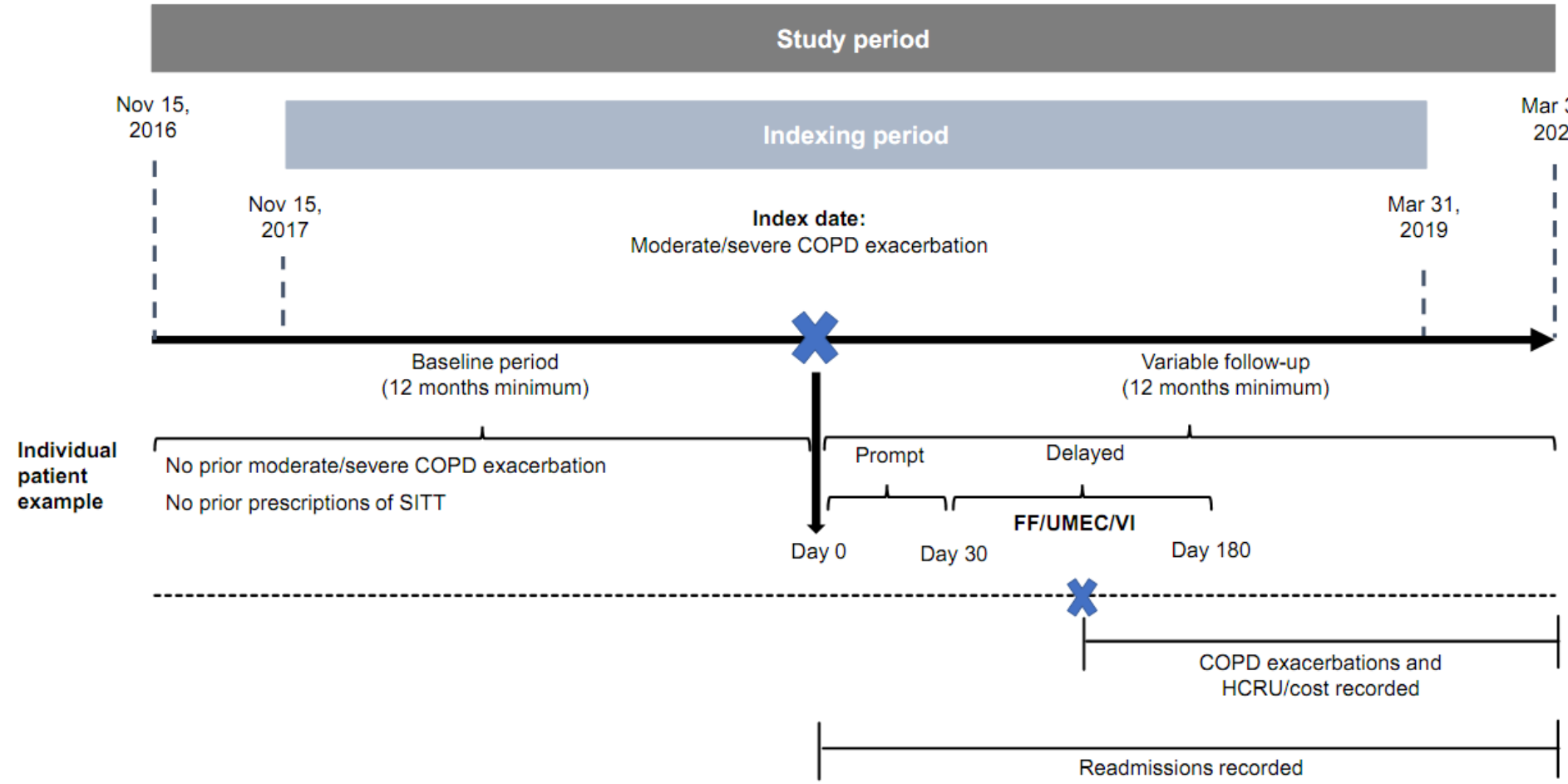
Calzetta L et al. Expert Rev Respir Med 2021 ;15:143-152

Benefit of prompt initiation of single-inhaler fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) in patients with COPD in England following an exacerbation: a retrospective cohort study

Afisi S. Ismaila[1,2*], Kieran J. Rothnie[3], Robert P. Wood[4], Victoria L. Banks[4,5†], Lucinda J. Camidge[4], Alexandrosz Czira[3], Chris Compton[6], Raj Sharma[6], Shannon N. Millard[4,7†], Olivia Massey[4] and David M. G. Halpin[8]

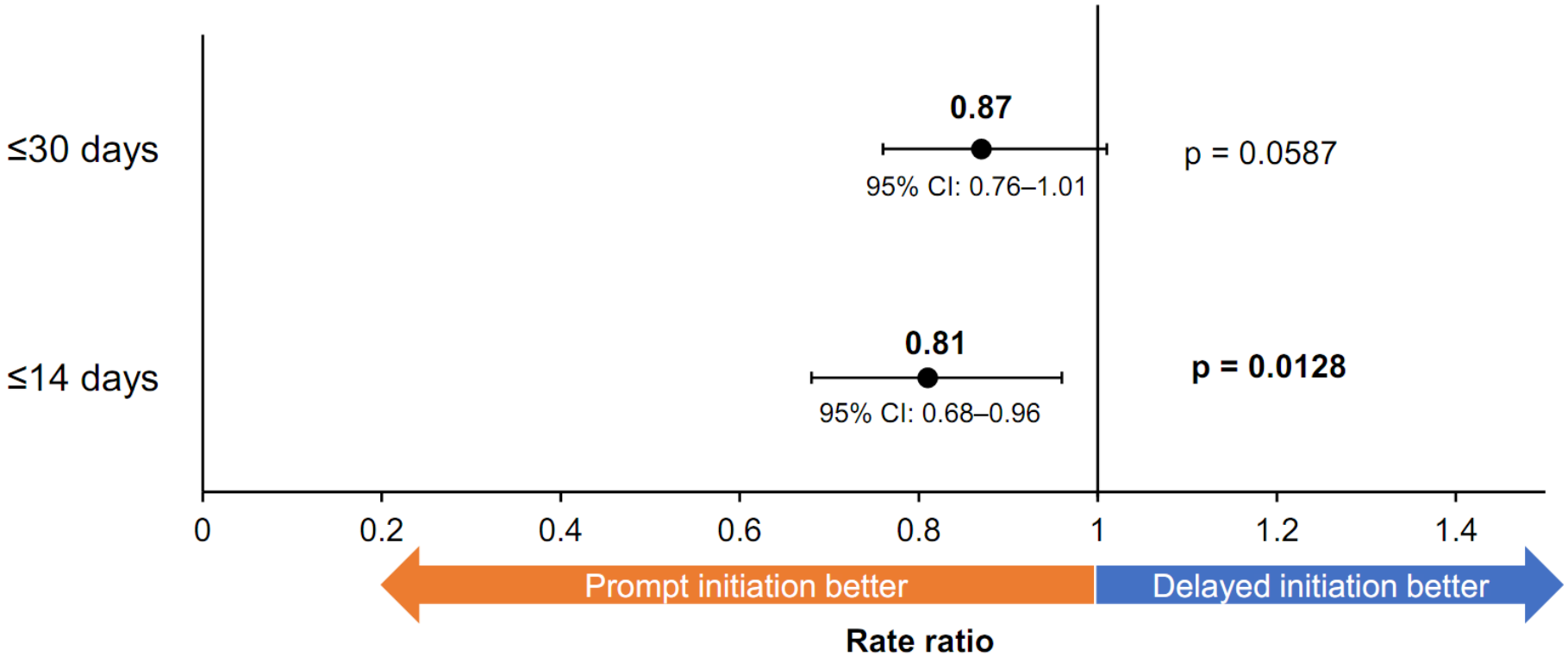
- a retrospective cohort study of linked English primary (Clinical Practice Research Datalink) & secondary (Hospital Episode Statistics) care data
- optimal timing of triple therapy following an exacerbation
- 1599 patients
- prompt (≤ 30 d) n=393 vs delayed (31~180 d) n= 1206

Ismaila AS et al, Respir Res 2023;24:229



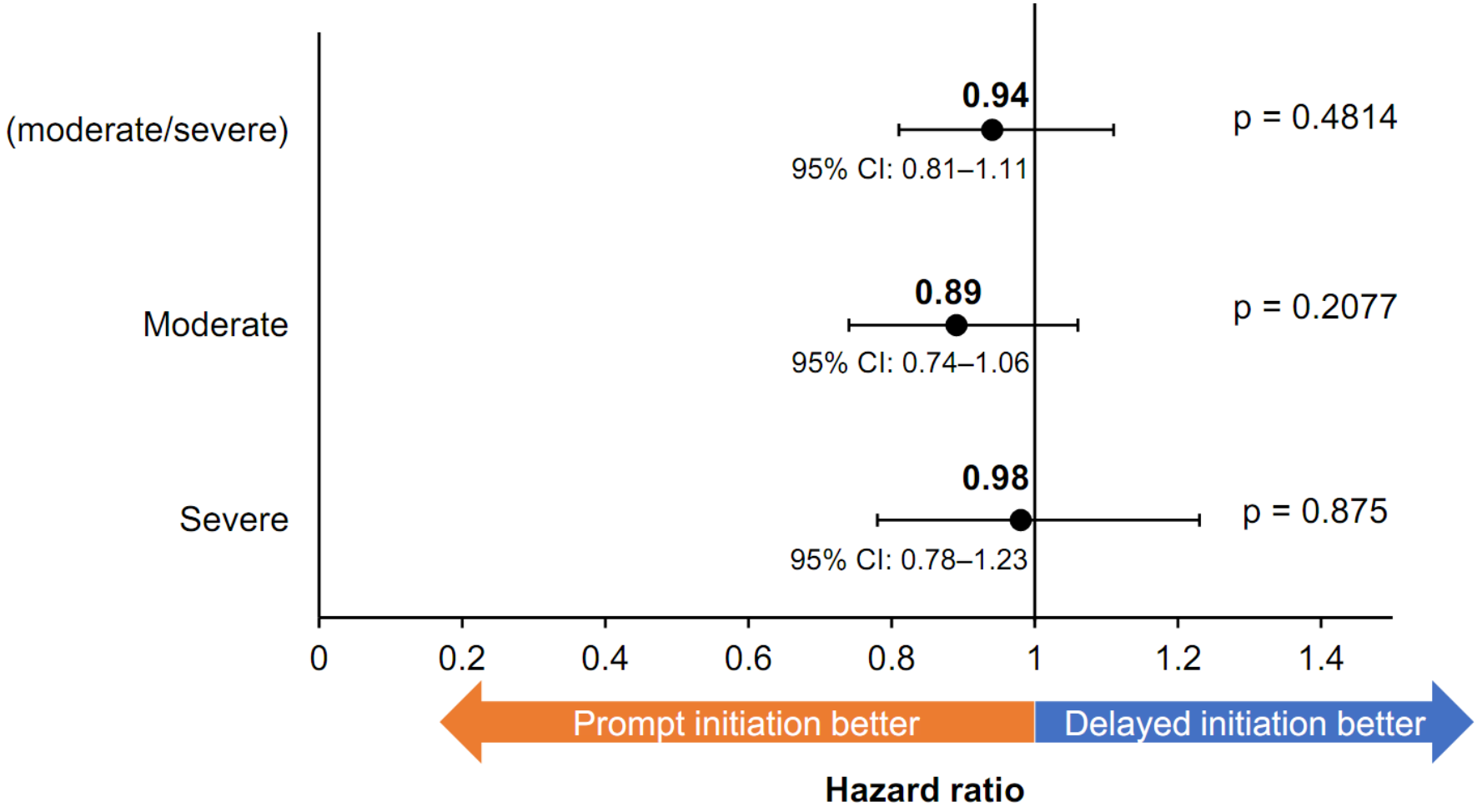
Ismaila AS et al, Respir Res 2023;24:229

Rate of subsequent exacerbations following FF/UMEC/VI initiation



Ismaila AS et al, Respir Res 2023;24:229

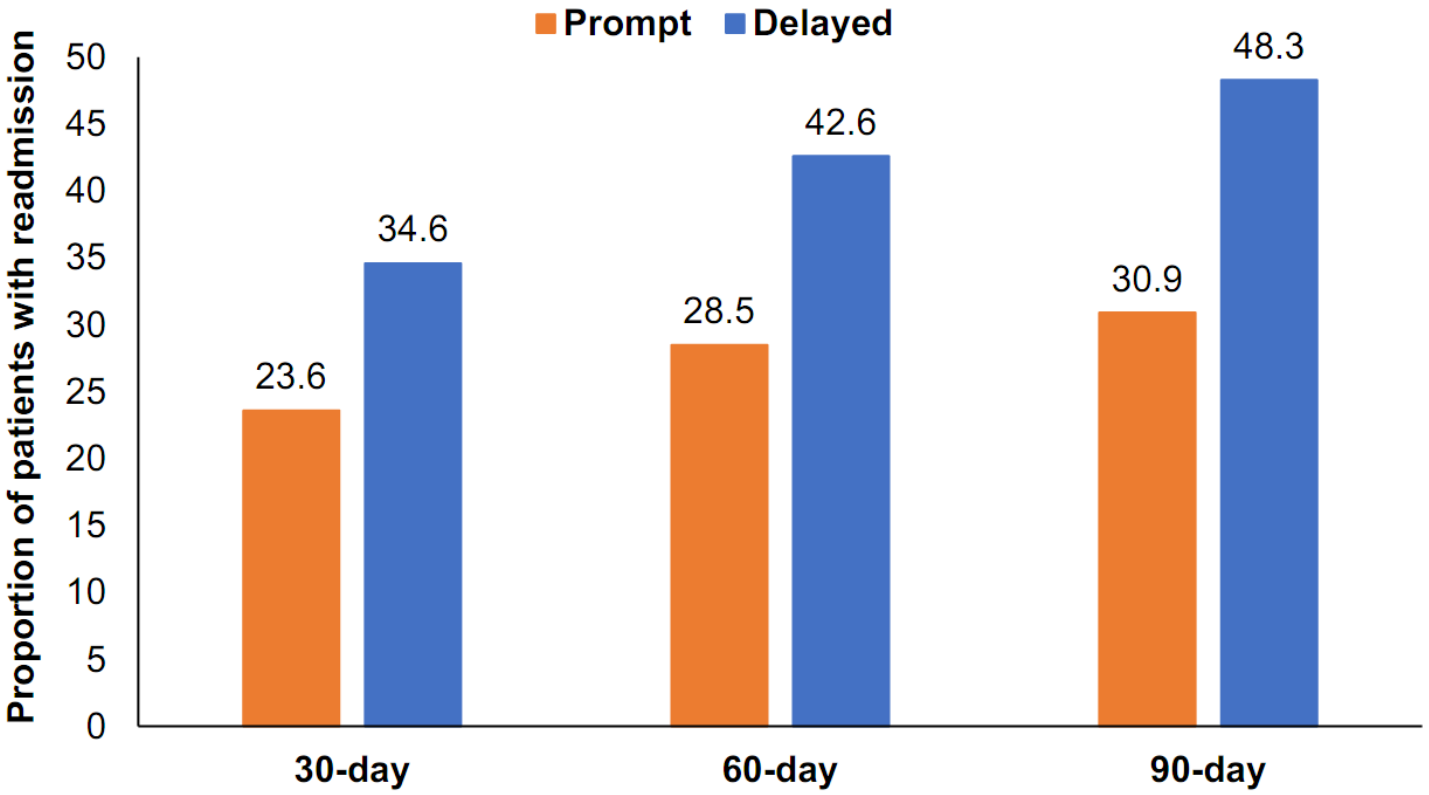
Time-to-first exacerbation following FF/UMEC/VI initiation



Ismaila AS et al, Respir Res 2023;24:229

Readmission following FF/UMEC/VI initiation

a) All-cause

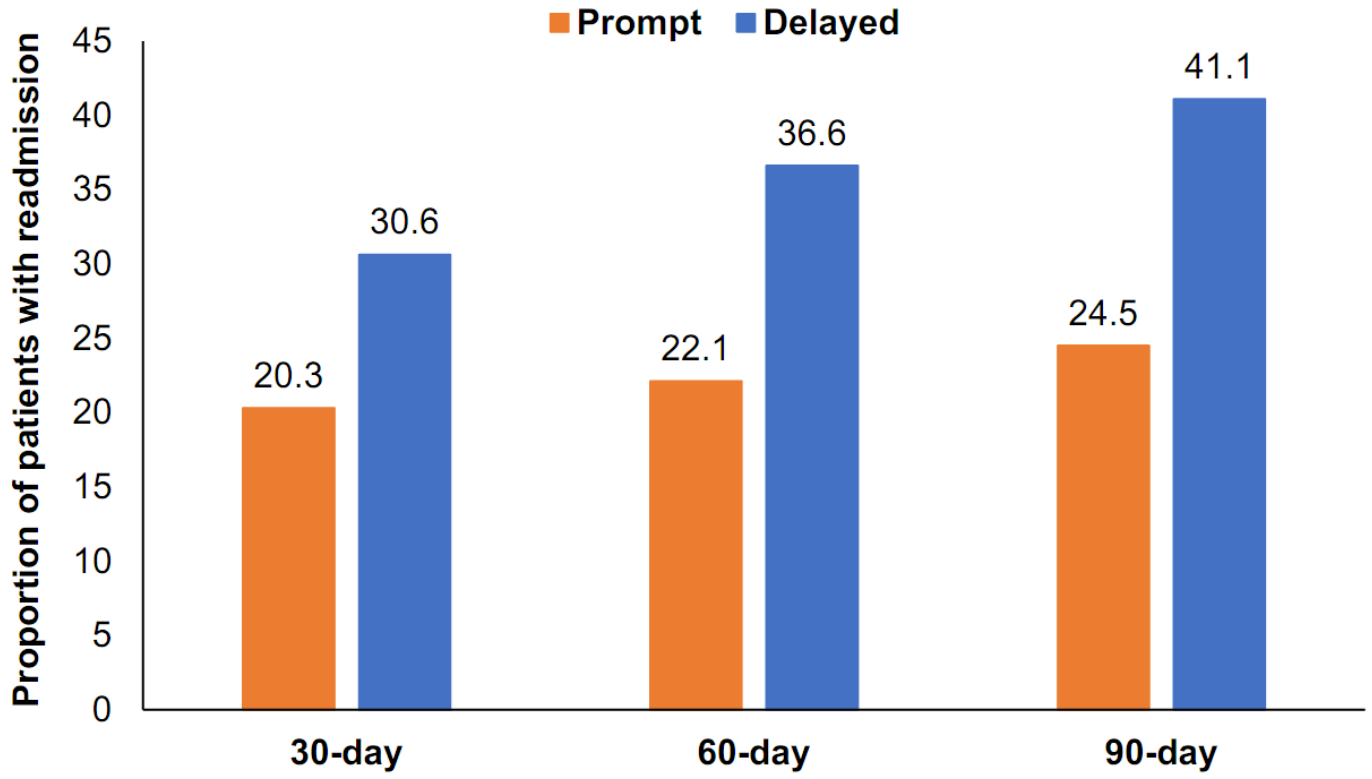


	30-day	60-day	90-day
Odds ratio (95% CI)	0.58 (0.36–0.94)	0.54 (0.34–0.85)	0.48 (0.31–0.75)
p-value	**0.0293**	**0.008**	**0.0013**

Ismaila AS et al, Respir Res 2023;24:229

Readmission following FF/UMEC/VI initiation

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**

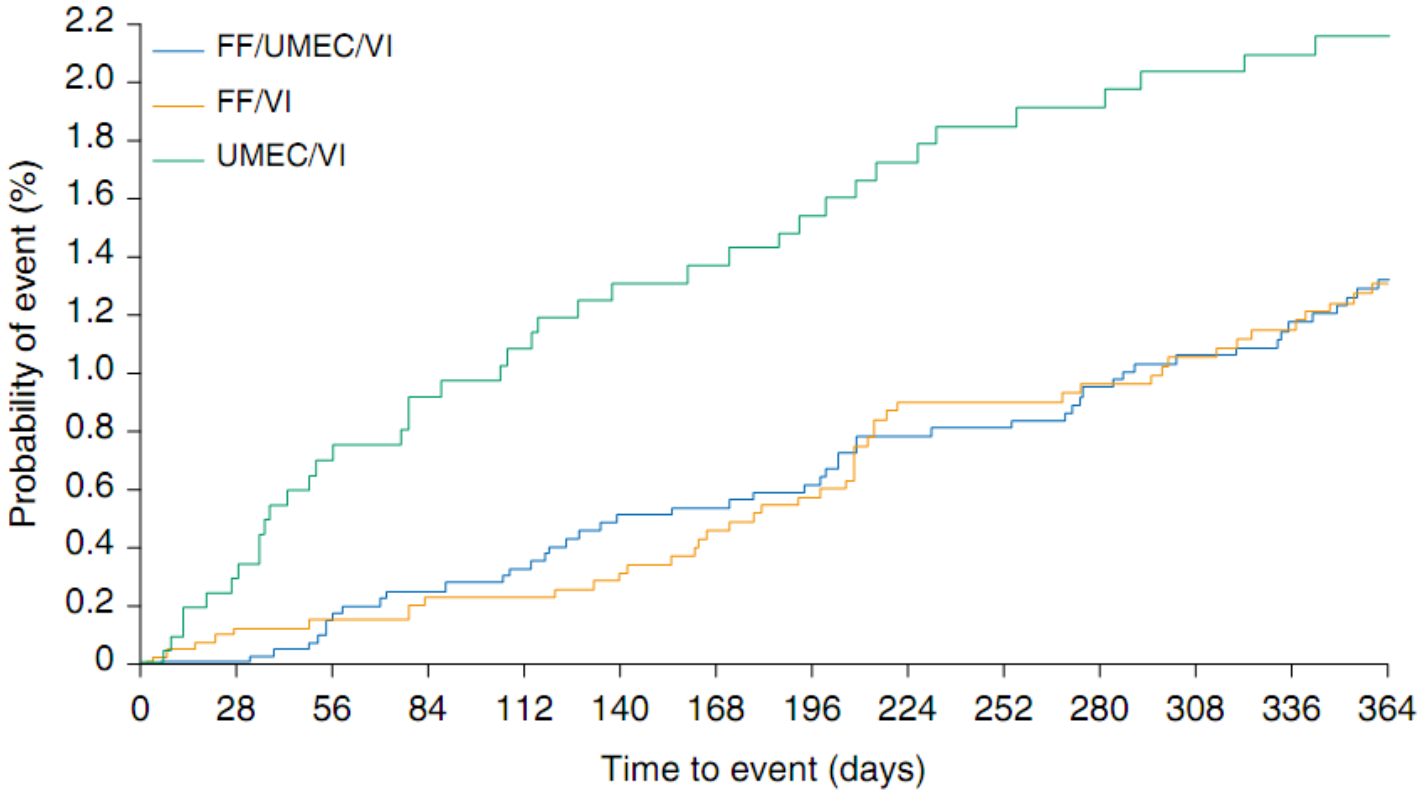
Ismaila AS et al, Respir Res 2023;24:229

Benefits of Triple Therapy in COPD

↓ *Mortality*

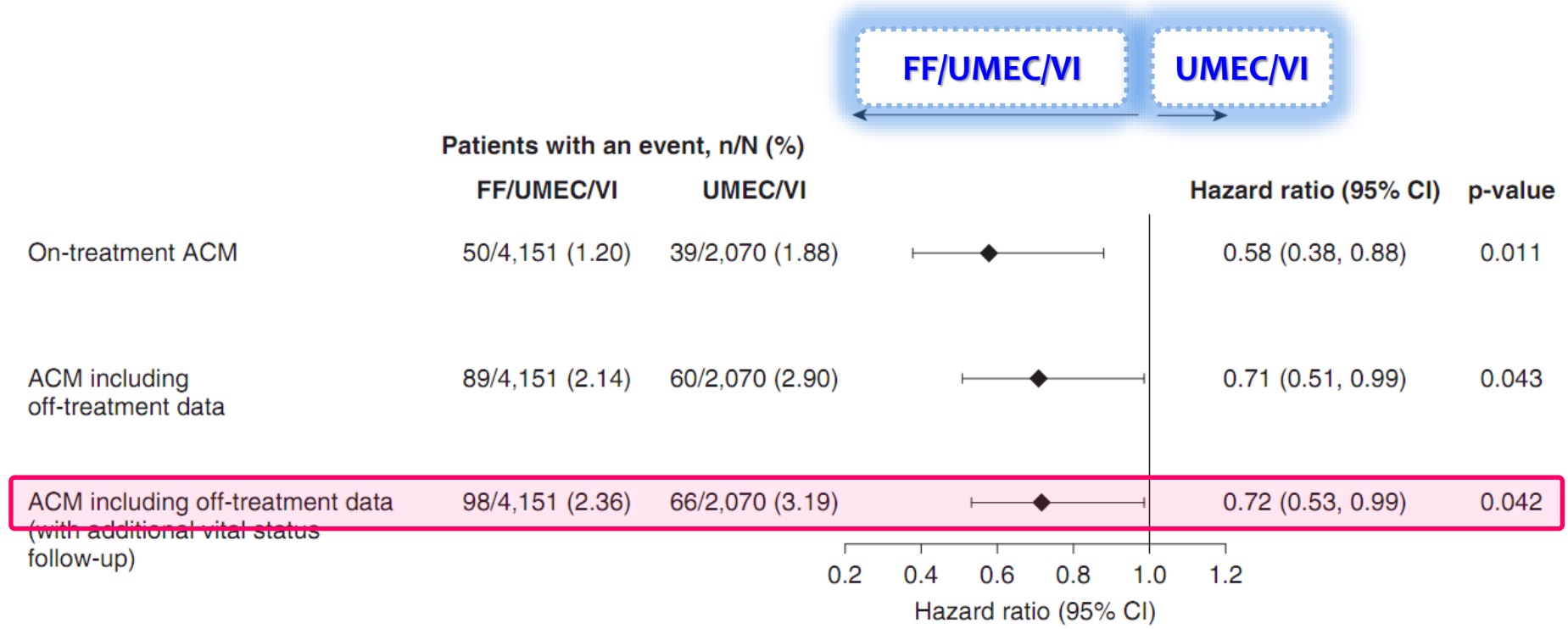
Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease

David A. Lipson[1,2], Courtney Crim[3], Gerard J. Criner[4*], Nicola C. Day[5], Mark T. Dransfield[6], David M. G. Halpin[7], MeiLan K. Han[8*], C. Elaine Jones[9], Sally Kilbride[10], Peter Lange[11,12], David A. Lomas[13], Sally Lettis[10], Pamela Manchester[14], Neil Martin[15,16], Dawn Midwinter[10], Andrea Morris[3], Steven J. Pascoe[1], Dave Singh[17], Robert A. Wise[18], and Fernando J. Martinez[19*]; on behalf of the IMPACT Investigators



Am J Respir Crit Care Med 2020;201:1508-1516

All-cause mortality



ACM= All-cause Mortality

Lipson DA et al. Am J Respir Crit Care Med 2020;201:1508-1516

Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for Chronic Obstructive Pulmonary Disease

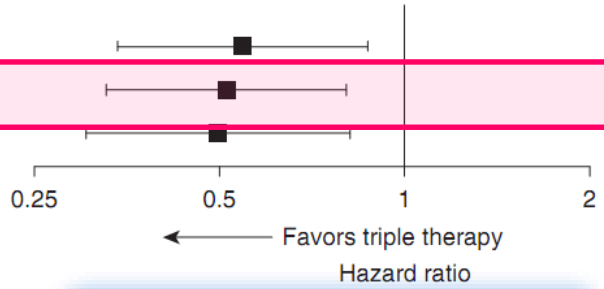
A Randomized, Double-Blind, Multicenter, Parallel-Group Study

Fernando J. Martinez[1*], Klaus F. Rabe[2*], Gary T. Ferguson[3], Jadwiga A. Wedzicha[4*], Dave Singh[5], Chen Wang[6], Kimberly Rossman[7], Earl St. Rose[7], Roopa Trivedi[8], Shaila Ballal[7], Patrick Darken[9], Magnus Aurivillius[10], Colin Reisner[7], and Paul Dorinsky[8]; on behalf of the ETHOS Investigators

A

BGF 320/18/9.6 µg vs GFF

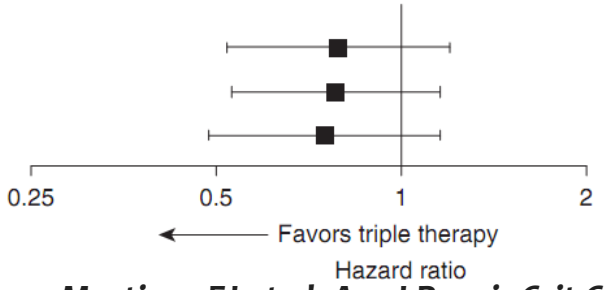
	Patients with an event, n (%) BGF 320/18/9.6 µg (N=2,137)	GFF 18/9.6 µg (N=2,120)	HR (95% CI)	P-value
On- and off-treatment (original dataset)	28 (1.3)	49 (2.3)	0.54 (0.34, 0.87)	0.0111
On- and off-treatment (final retrieved dataset)	30 (1.4)	56 (2.6)	0.51 (0.33, 0.80)	0.0035
On-treatment (final retrieved dataset)	25 (1.2)	45 (2.1)	0.50 (0.30, 0.81)	0.0056



B

BGF 160/18/9.6 µg vs GFF

	Patients with an event, n (%) BGF 160/18/9.6 µg (N=2,121)	GFF 18/9.6 µg (N=2,120)	HR (95% CI)	P-value
On- and off-treatment (original dataset)	39 (1.8)	49 (2.3)	0.79 (0.52, 1.20)	0.2690
On- and off-treatment (final retrieved dataset)	44 (2.1)	56 (2.6)	0.78 (0.53, 1.16)	0.2244
On-treatment (final retrieved dataset)	36 (1.7)	45 (2.1)	0.75 (0.48, 1.16)	0.1981



Martinez FJ et al. Am J Respir Crit Care Med 2021;203:553-564

Triple therapy (LABA+LAMA+ICS)

The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches[851] and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.[445,447,448,852-859] A *post-hoc* analysis of one of the RCTs that evaluated the effects of LABA+LAMA+ICS showed that triple therapy improved clinical outcomes versus dual therapy regardless of smoking status.[860]

A *post-hoc* pooled analysis of three triple therapy clinical trials in COPD patients with severe airflow obstruction and a history of exacerbations showed a non-significant trend for lower mortality (assessed as a safety outcome) with triple inhaled therapy compared to non-ICS based treatments.[861] Two large one-year randomized controlled trials (named IMPACT and ETHOS) were reviewed earlier in Chapter 3 (see 'Therapeutic interventions that reduce COPD mortality') and provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.[566,862]

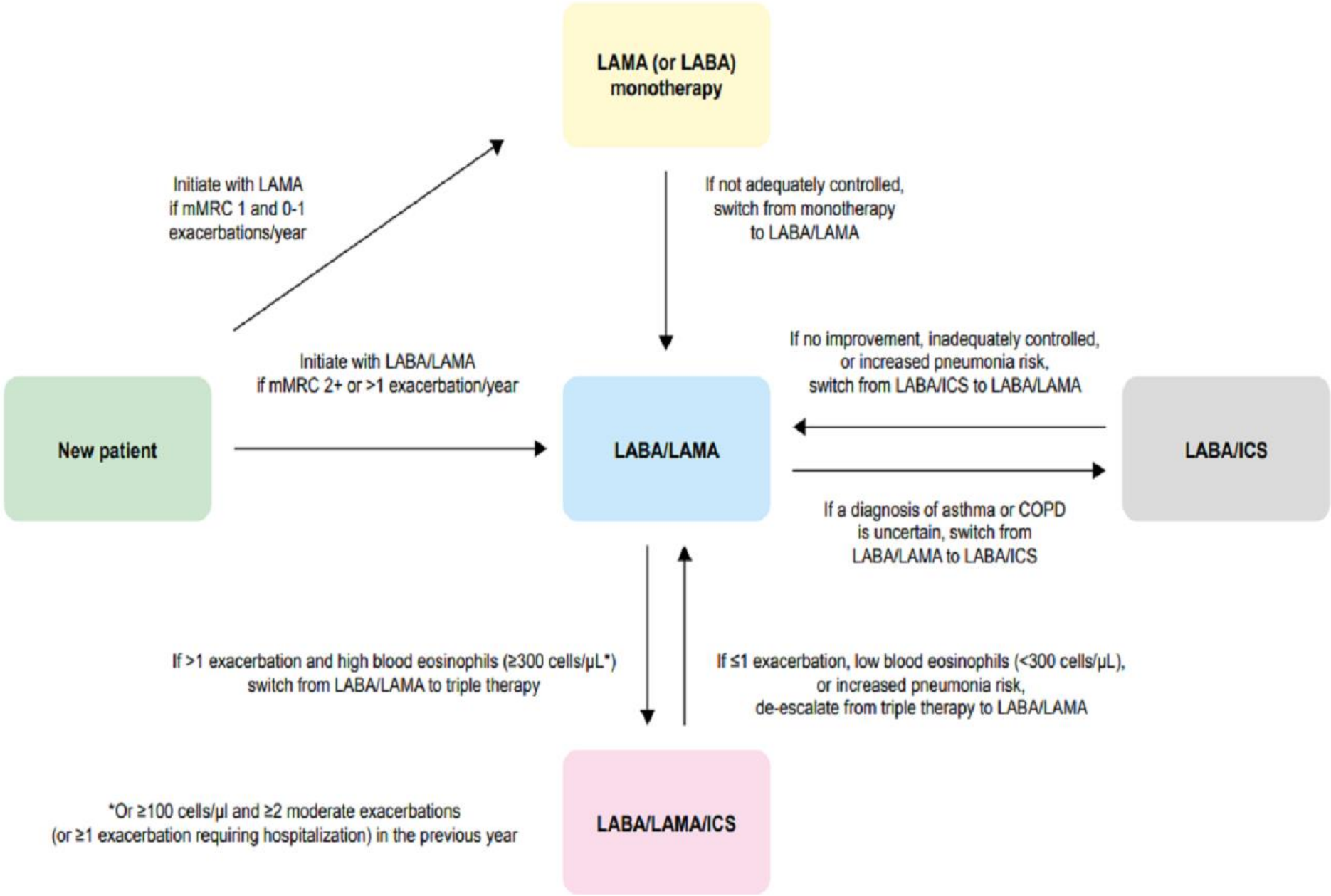
Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Figure 3.17

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations

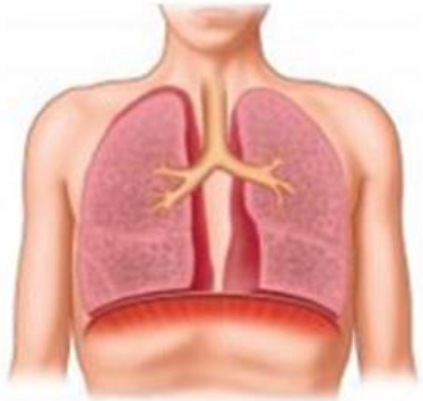
[GOLD 2024]

CONTENTS



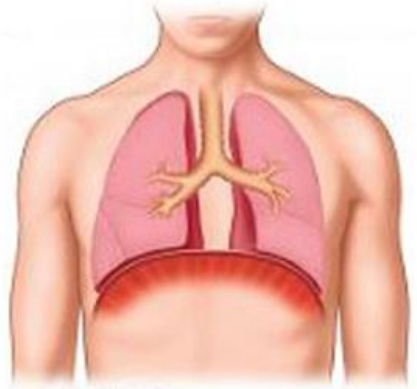
Miravitlles M, et al. J Clin Med. 2022;11:6623

LAMA/LABA

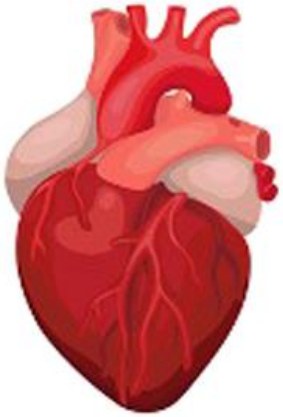


Hyperinflated lung

Air trapping ↓
Compression of pulmonary vasculature ↓
Pulmonary perfusion ↑
Compression of pulmonary veins ↓
Regional ventilation ↑
Ventilation-perfusion mismatch ↓



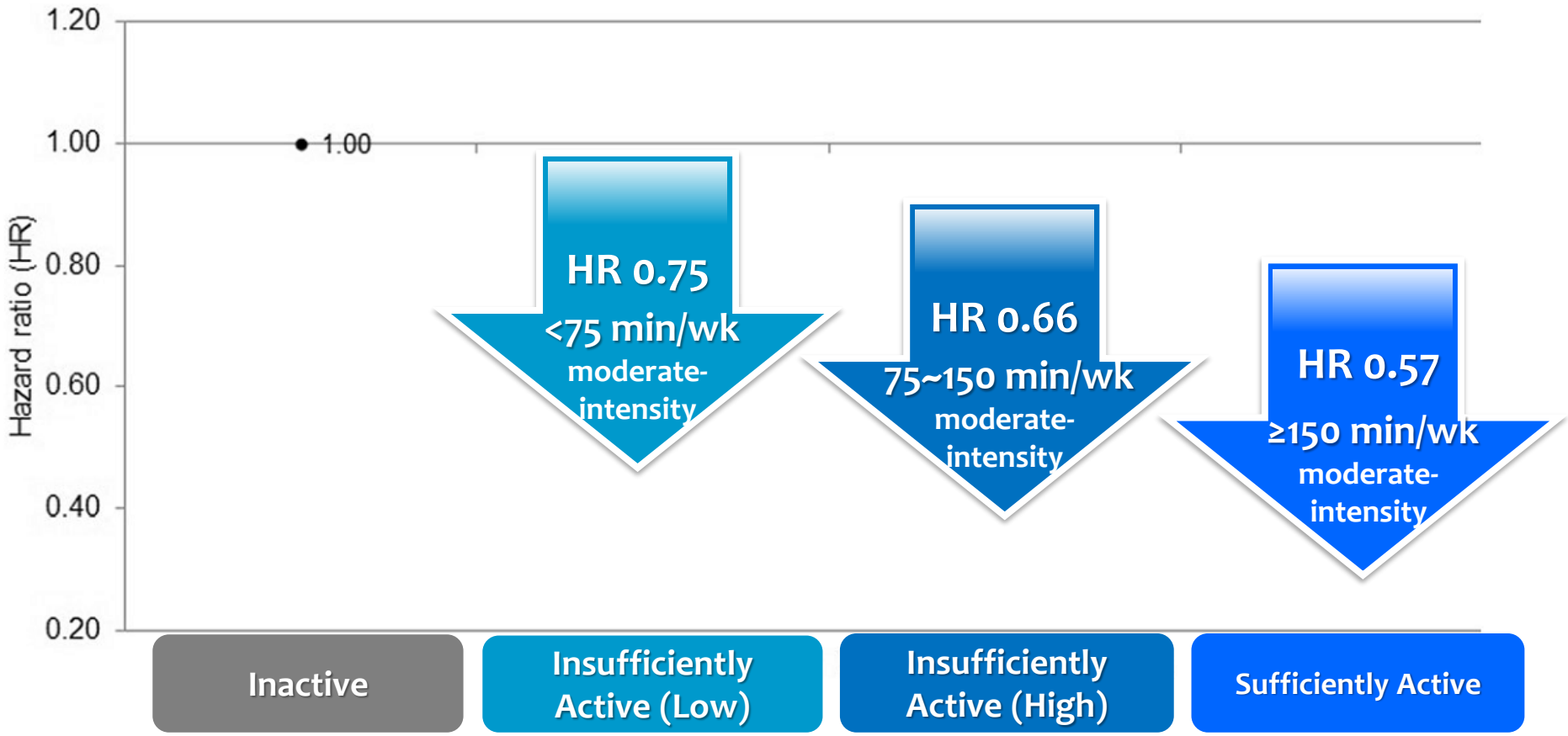
Deflated lung



Pulmonary venous blood flow to left heart ↑
Left ventricular filling ↑
Stroke volume ↑
Cardiac output ↑

Cazzola M, et al. Br J Clin Pharmacol 2022;88:3657-3673

PA & All-cause mortality



Cheng et al. BMC Public Health 2018; 18: 268

Factors to Consider when Initiating ICS Treatment

Figure 3.21

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

#despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.7 & 3.18 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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2024 Teaching Slide Set

THANK YOU