Pharmacological Treatment of COPD

2023. 12. 9.

동탄성심병원 김나영

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- Anti inflammatory agents in COPD
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  - Nebulized PDE3/4 inhibitor
- CFTR potentiator, in COPD
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- ICS and mortality in meta-analysis
- MART in COPD
- MDI technical error

Pharmacologic options in COPD

Bronchodilators

- Beta2-agonists
- Anti-muscarinic
- Methylxanthines (Theophylline)

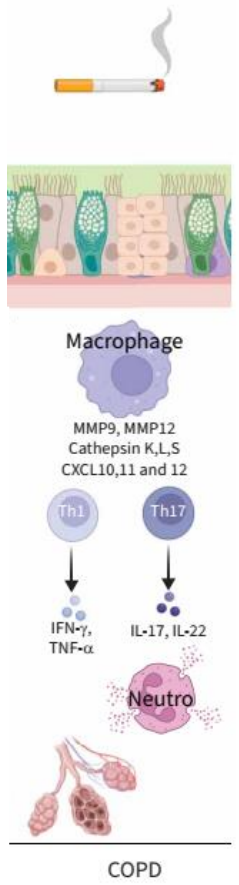
Anti-inflammatory agents

- Inhaled corticosteroids
- Oral corticosteroids
- Phosphodiesterase-4 inhibitors
- Antibiotics
- Mucoregulators and antioxidants

Cytokine targeted therapies

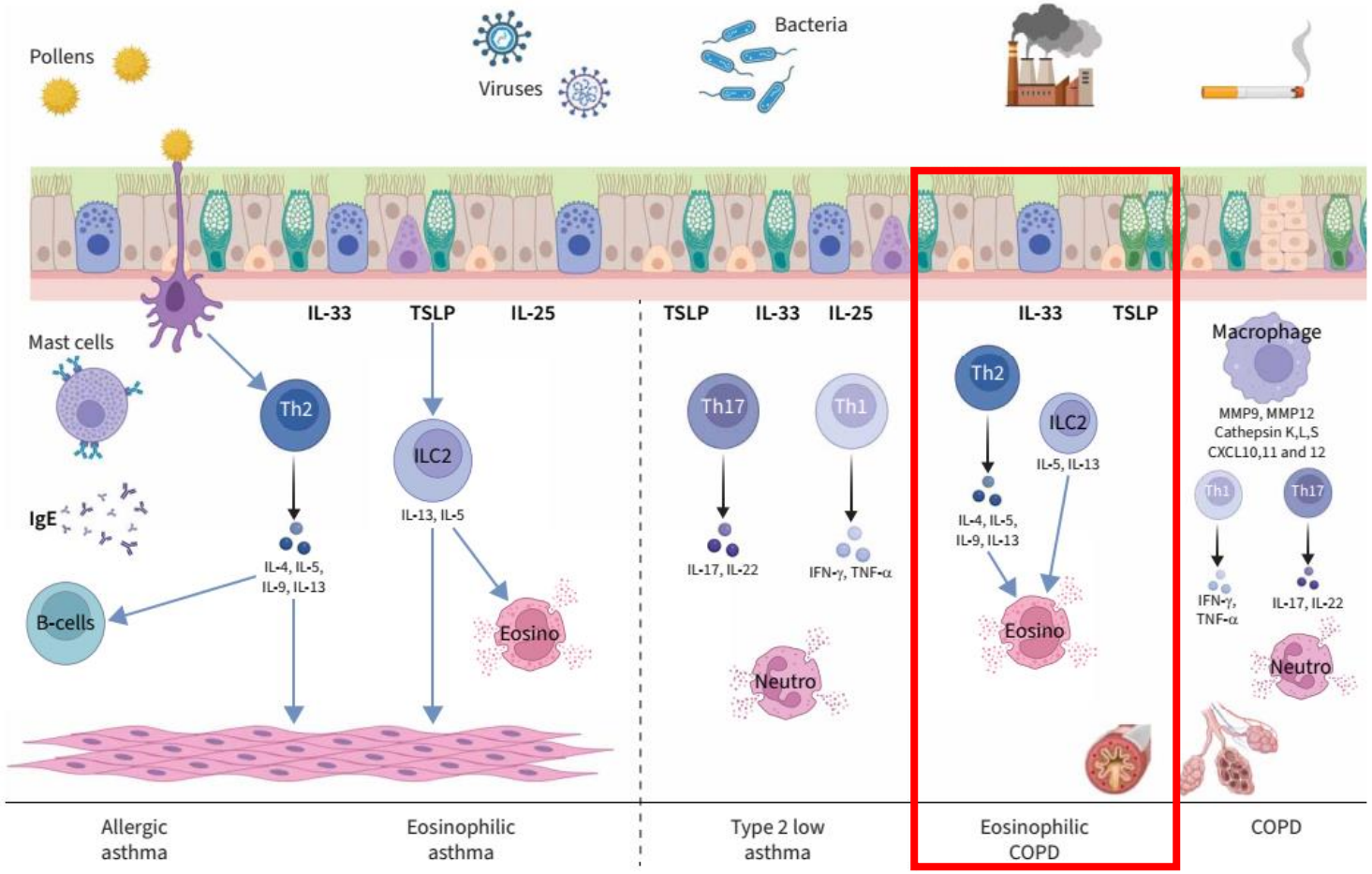
TABLE 2 Randomised placebo-controlled trials of anti-neutrophil, tumour necrosis factor (TNF)- and inflammasome-targeted therapies in chronic obstructive pulmonary disease (COPD)

Drug/target (study) [reference]	Subjects n	Dosage, duration	Primary outcome	Secondary outcome
Anti-IL-8; IL-8 (NCT00035828) [62]	109	800 mg loading dose, 400 mg per month for 3 months, 5-month follow-up	↓ Severity of dyspnoea as measured by TDI	↔ Health status, lung function, 6MWT, rescue use of albuterol
Anti-CXCR2 [63]		50 mg twice daily or 80 mg twice daily, 4 weeks	Safety and tolerability	↓ Blood neutrophil counts
Anti-CXCR2 [64]		10 mg, 30 mg or 50 mg, 6 months	↑ FEV_1 at 6 months	↔ Time to first exacerbation ↓ Absolute and percentage sputum neutrophil counts ↔ SGRQ score ↑ Rate of respiratory infection
Infliximab; anti-TNF (NCT00244192) [65]	22	5 $mg \cdot kg^{-1}$, 8 weeks	↔ Sputum inflammatory cells	↔ FEV_1, SGRQ
Etanercept; anti-TNF (NCT 00789997) [66]	81	50 mg, 90 days	↔ FEV_1 over 14 days from exacerbation onset	↔ 90-day treatment failure, dyspnoea, health status
Infliximab; TNF (NCT00056264) [67]	157	3 $mg \cdot kg^{-1}$ or 5 $mg \cdot kg^{-1}$, 44 weeks	↔ CRQ	↔ FEV_1, 6MWT, TDI ↑ Malignancy, pneumonia
CNTO 6785(61); anti-IL-17 (NCT01966549) [68]	186	6 $mg \cdot kg^{-1}$ every 2 weeks for 4 weeks, then every 4 weeks for remaining 8 weeks	↔ Pre-bronchodilator FEV_1 % predicted	↔ Post-bronchodilator FEV_1 % predicted ↔ SGRQ-C ↔ Frequency of AECOPD ↔ Weekly usage of rescue medication
MEDI 8968; anti-IL-1 (NCT01448850) [69]	160	300 mg every 4 weeks, 52 weeks	↔ Moderate-to-severe exacerbations	↔ SGRQ-C
Canakinumab/IL-1 (NCT00581945) [70]		1×1 $mg \cdot kg^{-1}$, 2×3 $mg \cdot kg^{-1}$, 42×6 $mg \cdot kg^{-1}$, 45 weeks	Changes from baseline in FEV_1, FVC No statistical analysis provided for changes in FEV_1, FVC from baseline	Serious adverse events No statistical analysis provided



Brightling, Christopher; Greening, Neil. ERJ, 2019, 54.2.
Schleich, Florence, et al. ERR, 2023, 32.168.

Cytokine targeted therapies



Schleich, Florence, et al. ERR, 2023, 32.168.

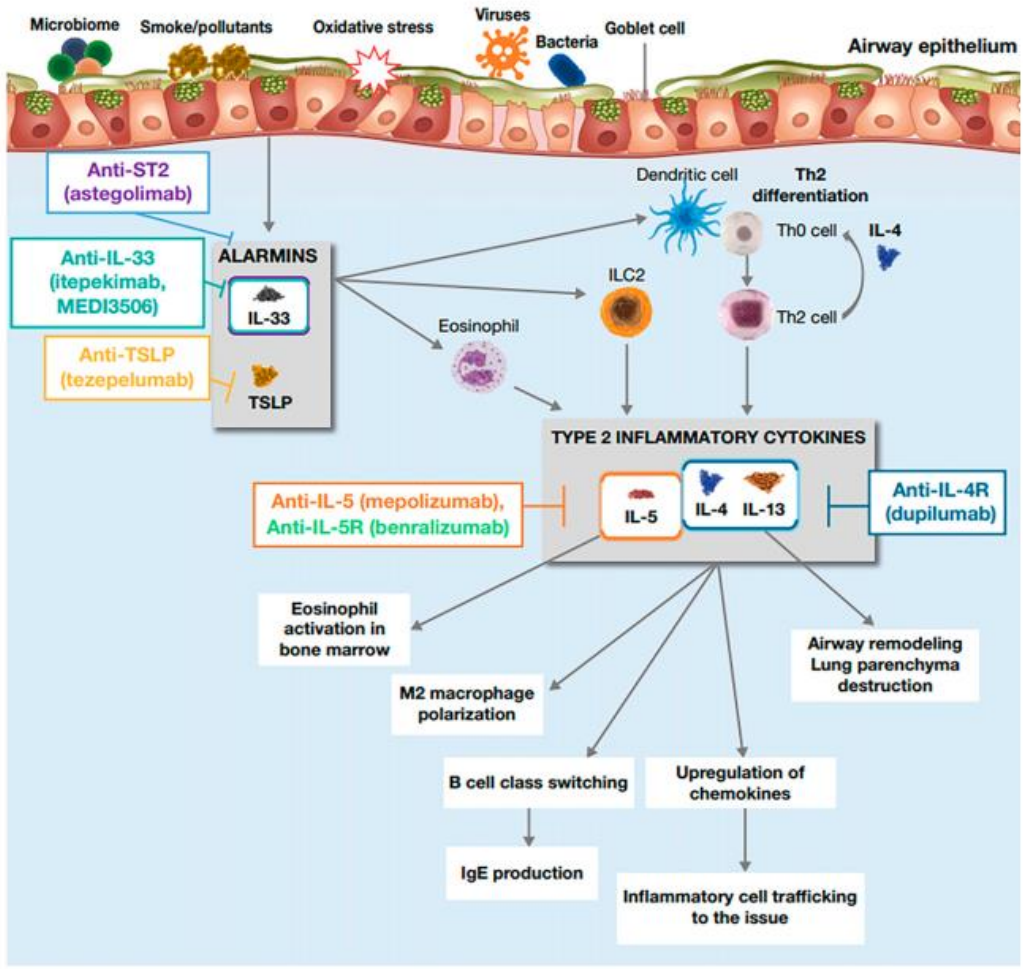
Type 2 inflammation and Epithelial alarmins

CONCISE CLINICAL REVIEW

Targeting Type 2 Inflammation and Epithelial Alarmins in Chronic Obstructive Pulmonary Disease

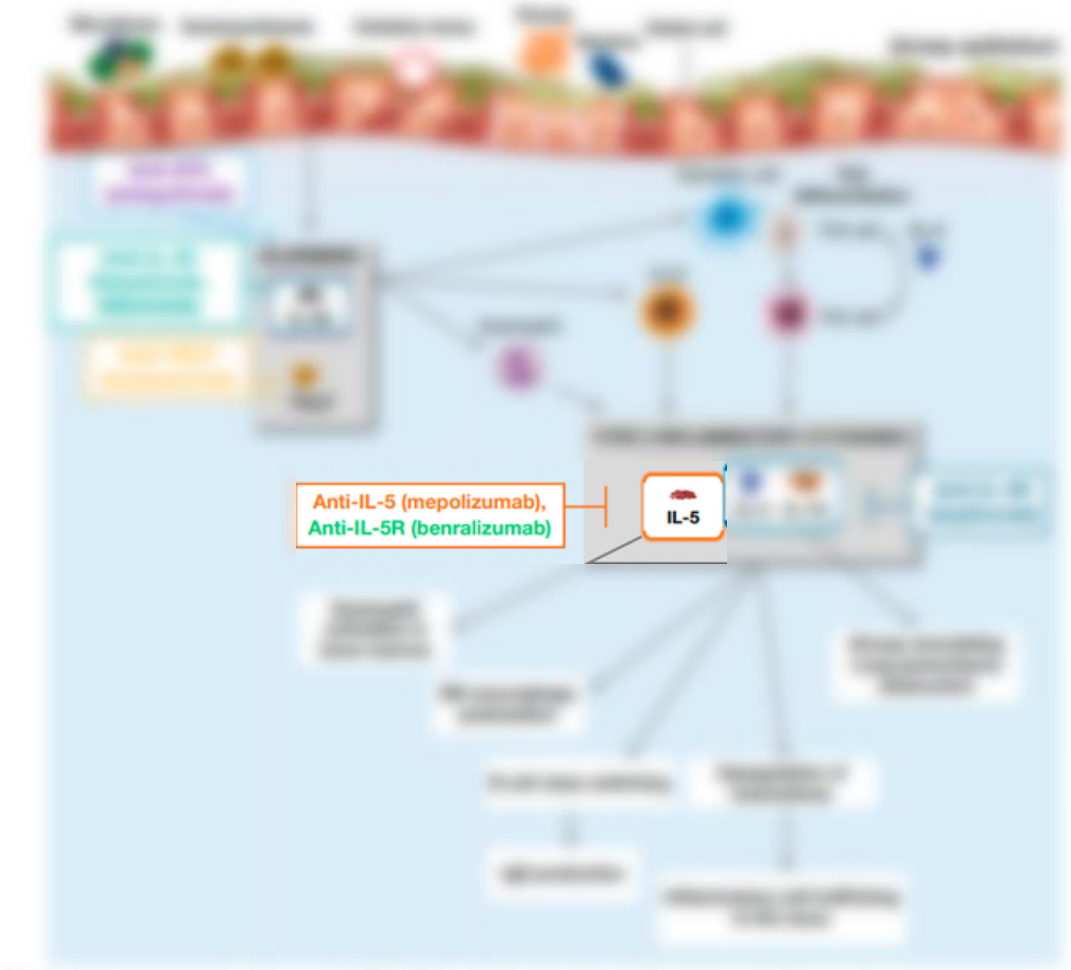
A Biologics Outlook

Klaus F. Rabe[1,2,3], Stephen Rennard[4], Fernando J. Martinez[5], Bartolome R. Celli[6,7], Dave Singh[8], Alberto Papi[9], Mona Bafadhel[10], Jigna Heble[11], Amr Radwan[12], Xavier Soler[12], Juby A. Jacob Nara[11], Yamo Deniz[12], and Paul J. Rowe[11]



Rabe, Klaus F., et al. AJRCCM, 2023.

Anti-IL-5/5R



Rabe, Klaus F., et al. AJRCCM, 2023.

Mepolizumab for eosinophilic COPD

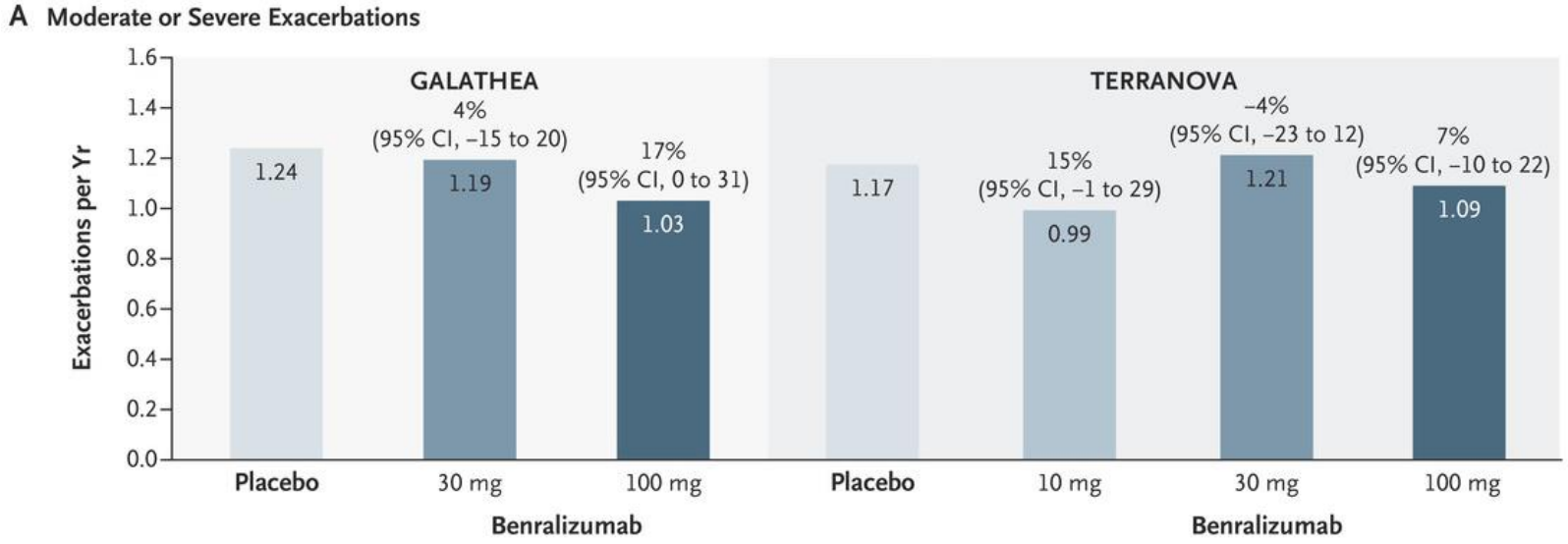
- Two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials
- 100 mg in METREX; 100 or 300 mg in METREO, every 4 weeks for 52 weeks
- Lower annual rate of moderate or severe exacerbations in eosinophilic COPD (BEC ≥ 150 at screening, ≥ 300 in the previous year)

End Point	METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype		METREX Overall Modified Intention-to-Treat Population		METREO Modified Intention-to-Treat Population		
	Mepolizumab, 100 mg (N=233)	Placebo (N=229)	Mepolizumab, 100 mg (N=417)	Placebo (N=419)	Mepolizumab, 100 mg (N=223)	Mepolizumab, 300 mg (N=225)	Placebo (N=226)
Primary end point: moderate or severe exacerbations							
Mean annual rate — events/yr†	1.40	1.71	1.49	1.52	1.19	1.27	1.49
Rate ratio vs. placebo (95% CI)	0.82 (0.68 to 0.98)	—	0.98 (0.85 to 1.12)	—	0.80 (0.65 to 0.98)	0.86 (0.70 to 1.05)	—
Adjusted P value	0.04	—	>0.99	—	0.07	0.14	—

Pavord ID, et al. NEJM, 2017; 377: 1613–1629.

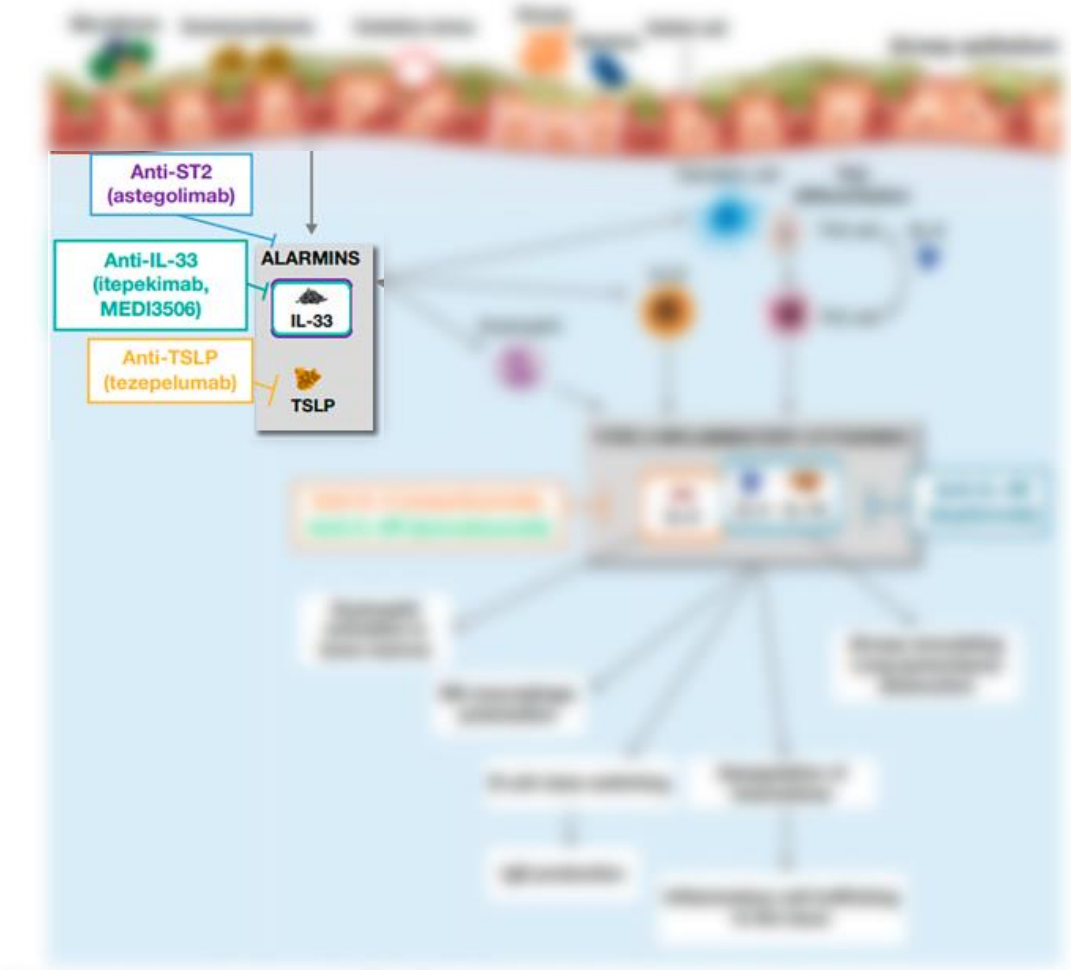
Benralizumab in eosinophilic COPD

- Two phase 3, parallel-group, randomized clinical trials
- 30, 100 mg in GALATHEA; 10, 30, 100 mg in TERRANOVA, every 8 weeks for 56 weeks
- No significant reduction in exacerbations in hyper-eosinophilic COPD (BEC ≥ 220)[1]
- *Post hoc*: triple therapy + BEC ≥ 220 + ≥ 3 exacerbations (ERR = 30%)[2]



1 Criner GJ, et al. NEJM, 2019; 381: 1023–1034
2 Criner, GJ., et Lancet Respir Med, 2020, 8.2: 158-170.

Epithelium-derived alarmins



Rabe, Klaus F., et al. AJRCCM, 2023.

Itepekimab in former smoked COPD

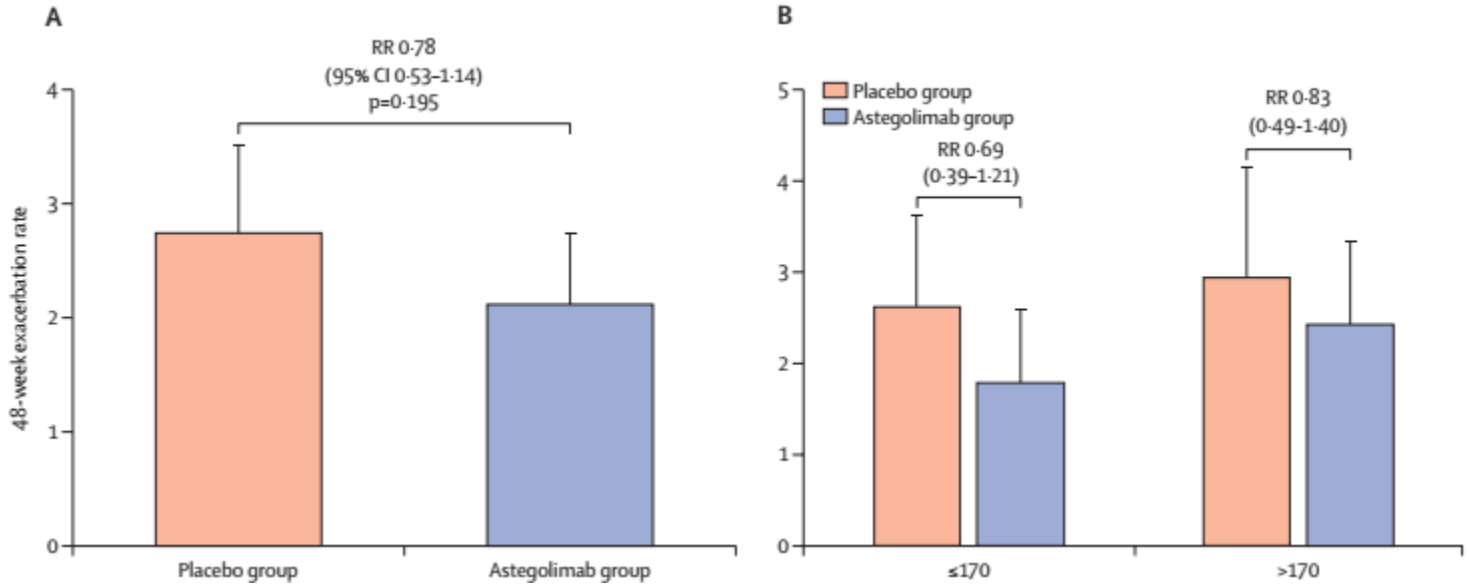
- Phase 2a, randomized, double-blind, placebo-controlled, parallel-group trials
- 300mg every 2 weeks for 24-52 weeks
- No reduction in annualized rate of moderate-to-severe exacerbation
- Former smokers: 42% exacerbation reduction, FEV1 90mL improvement

	mITT population		Baseline blood eosinophils ≥250 per mm³		Baseline blood eosinophils <250 per mm³		Former smokers		Current smokers	
	Placebo group (n=171)	Itepekimab group (n=172)	Placebo group (n=66)	Itepekimab group (n=68)	Placebo group (n=105)	Itepekimab group (n=104)	Placebo group (n=89)	Itepekimab group (n=98)	Placebo group (n=82)	Itepekimab group (n=74)
Moderate-to-severe acute exacerbations of COPD										
Adjusted annualised rate to week 52 (95% CI)	1·61 (1·32 to 1·97)	1·30 (1·05 to 1·61)	1·71 (1·24 to 2·35)	1·34 (0·95 to 1·89)	1·51 (1·17 to 1·94)	1·26 (0·96 to 1·64)	1·55 (1·17 to 2·05)	0·89 (0·66 to 1·21)	1·70 (1·28 to 2·26)	1·86 (1·37 to 2·52)
RR *vs* placebo (95% CI), p value	..	0·81 (0·61 to 1·07), 0·13	..	0·78 (0·50 to 1·22), 0·28	..	0·84 (0·59 to 1·19), 0·32	..	0·58 (0·39 to 0·85), 0·0061	..	1·09 (0·74 to 1·61), 0·65
HR for time to first event *vs* placebo (95% CI), p value	..	0·83 (0·61 to 1·12), 0·22	..	0·88 (0·54 to 1·45), 0·62	..	0·76 (0·52 to 1·12), 0·16	..	0·57 (0·37 to 0·88), 0·011	..	1·15 (0·75 to 1·77), 0·51

Rabe KF, et al. Lancet Respir Med 2021; 9: 1288–1298.

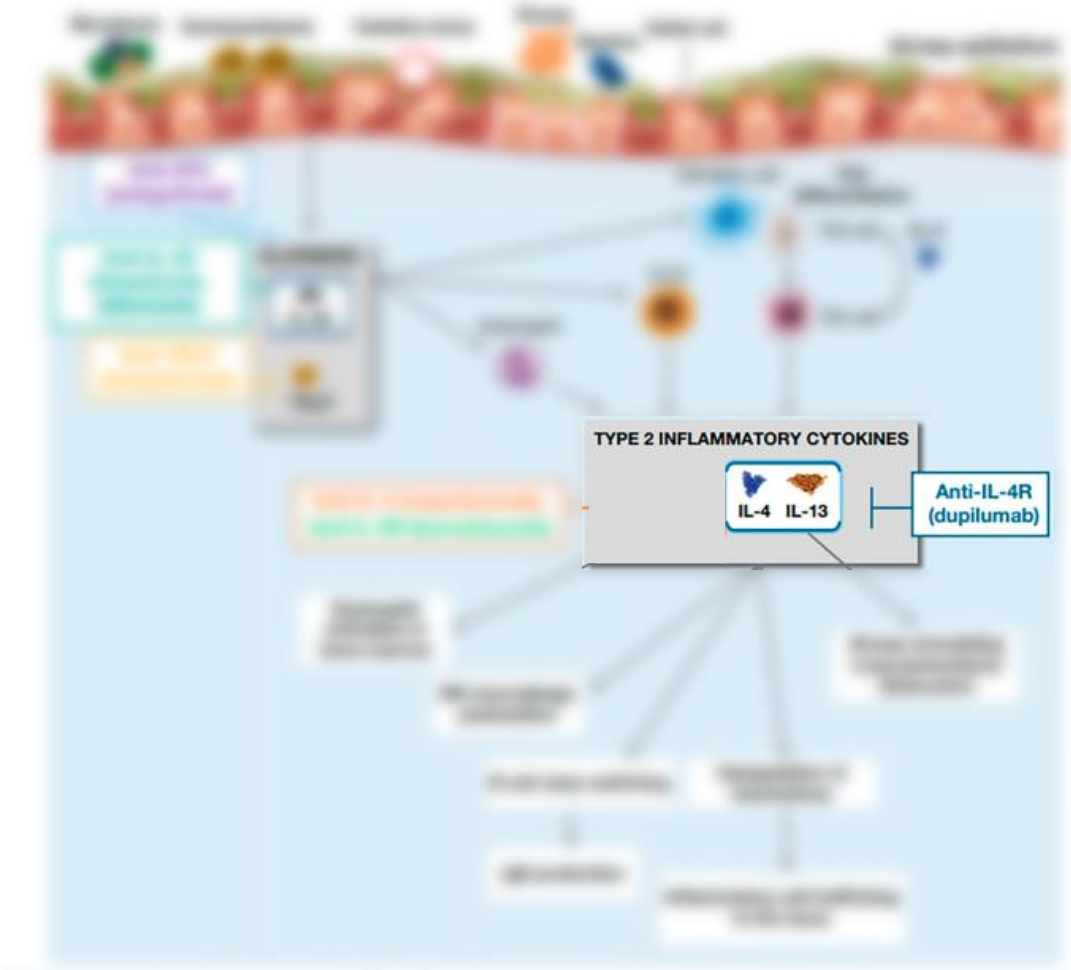
Astegolimab for IL33/ST2 axis

- Phase 2a, single-centre, randomised, double-blinded, placebo-controlled trial
- 490 mg, every 4 weeks for 44 weeks
- No reduction exacerbation rate, but improve health status compared with placebo



Yousuf, Ahmed J., et al. Lancet Respir Med, 2022, 10.5: 469-477.

Anti-IL-4/13



Rabe, Klaus F., et al. AJRCCM, 2023.

The NEW ENGLAND JOURNAL of MEDICINE

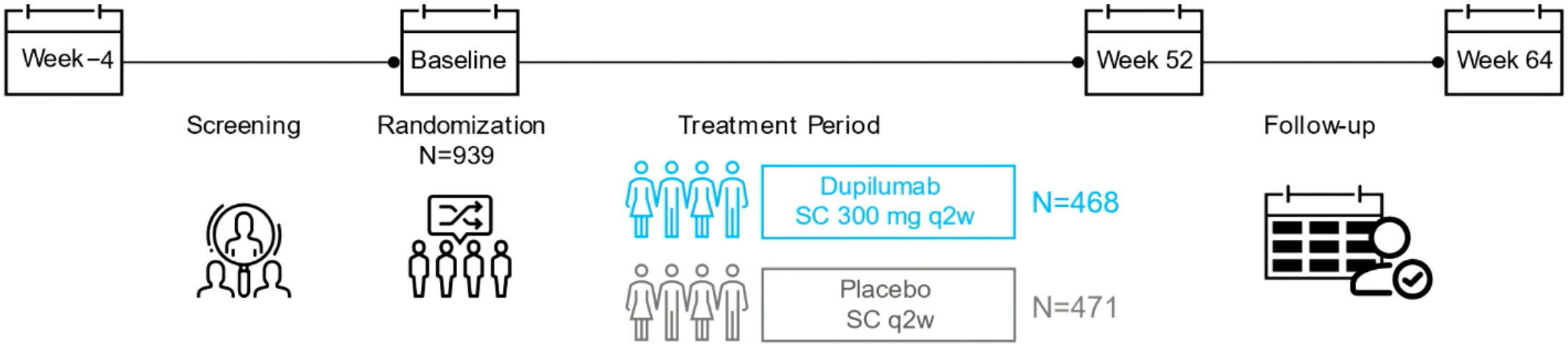
ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

BOREAS Clinical Trial Design

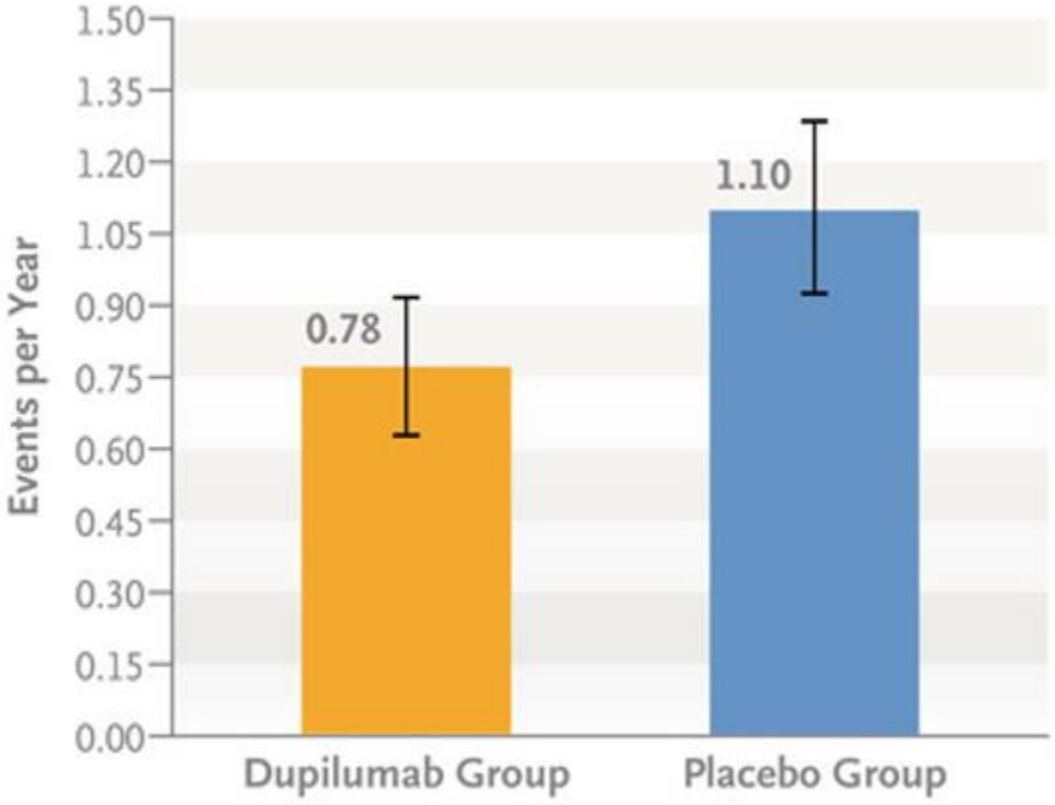
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 study to Evaluate the Efficacy and Safety of Dupilumab Administered Every 2 Weeks in Patients with Moderate or Severe COPD with Type 2 Inflammation

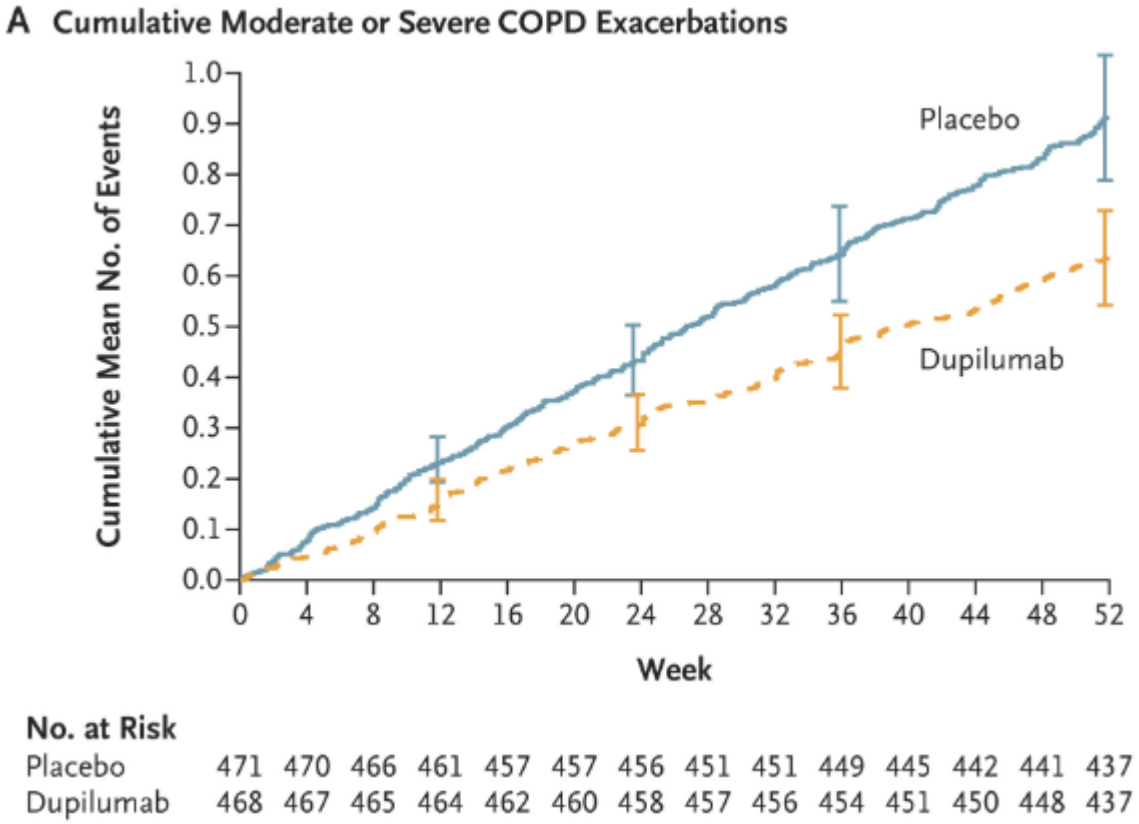


background inhaled triple therapy for ≥3 months
absolute blood eosinophil count of ≥300 cells/mL
chronic bronchitis for ≥3 months

Bhatt, Surya P., et al. NEJM, 2023.

Primary endpoint: exacerbations

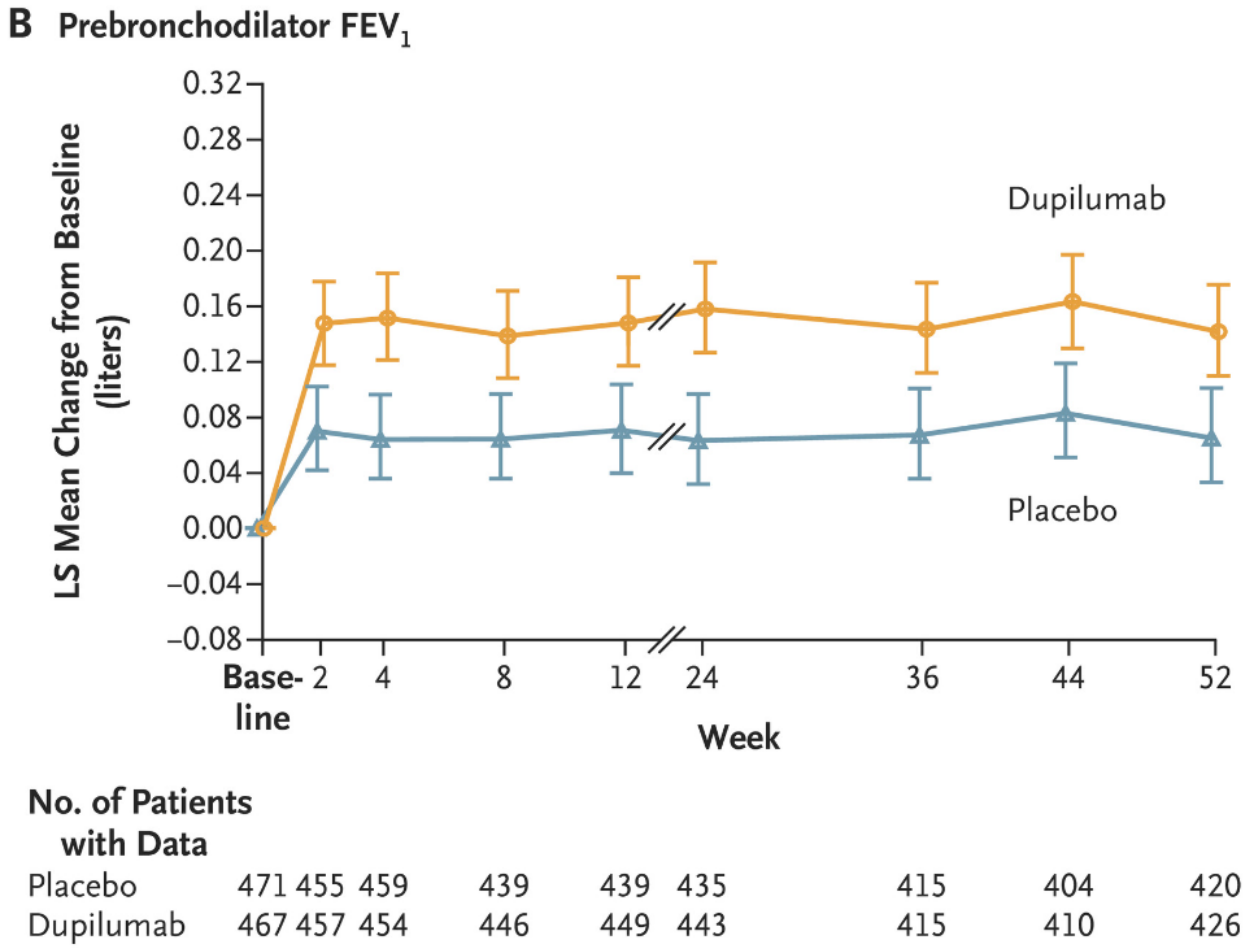




Rate ratio **0.70** (0.58-0.86); p<0.01

Bhatt, Surya P., et al. NEJM, 2023.

Lung function change

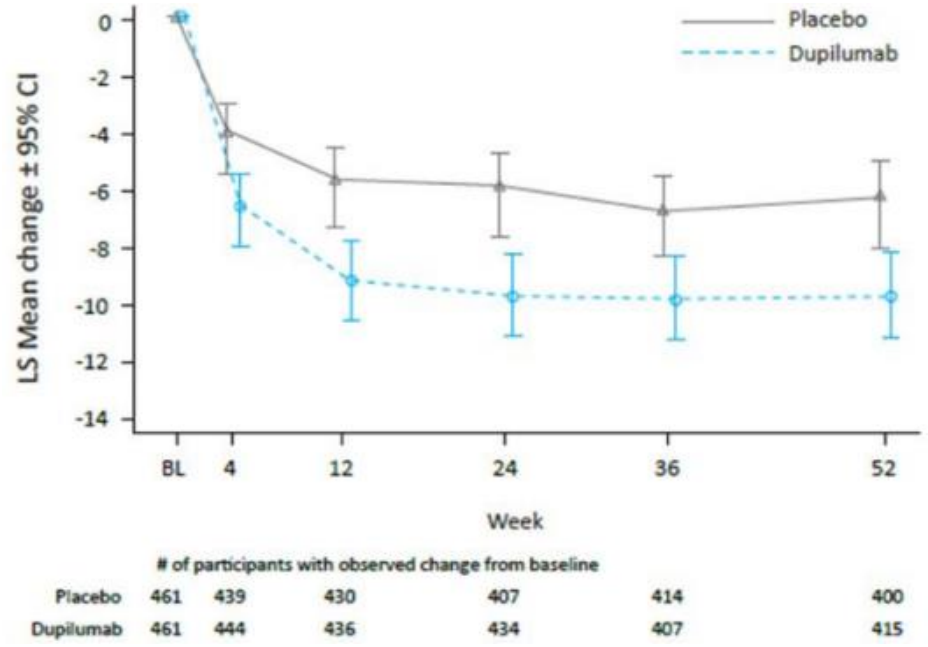


- **LS mean difference (95% CI)**
  - Week 12: **83ml** (42-125); p<0.001
  - Week 52: **83ml** (38-128); p<0.001
- **FeNO ≥ 20 ppb**
  - FEV1 (week 52) 127mL

Bhatt, Surya P., et al. NEJM, 2023.

Health status and symptoms

SGRQ

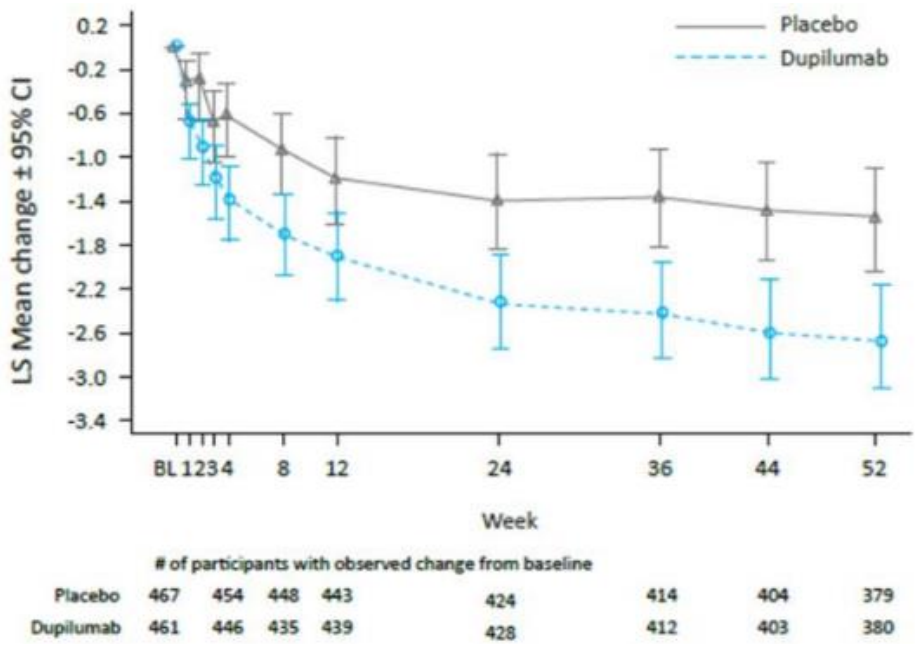


Better QoL

LS mean difference (95% CI)

–3.4 (– 5.5 to –1.3); p=0.002

Symptoms (E-RS)



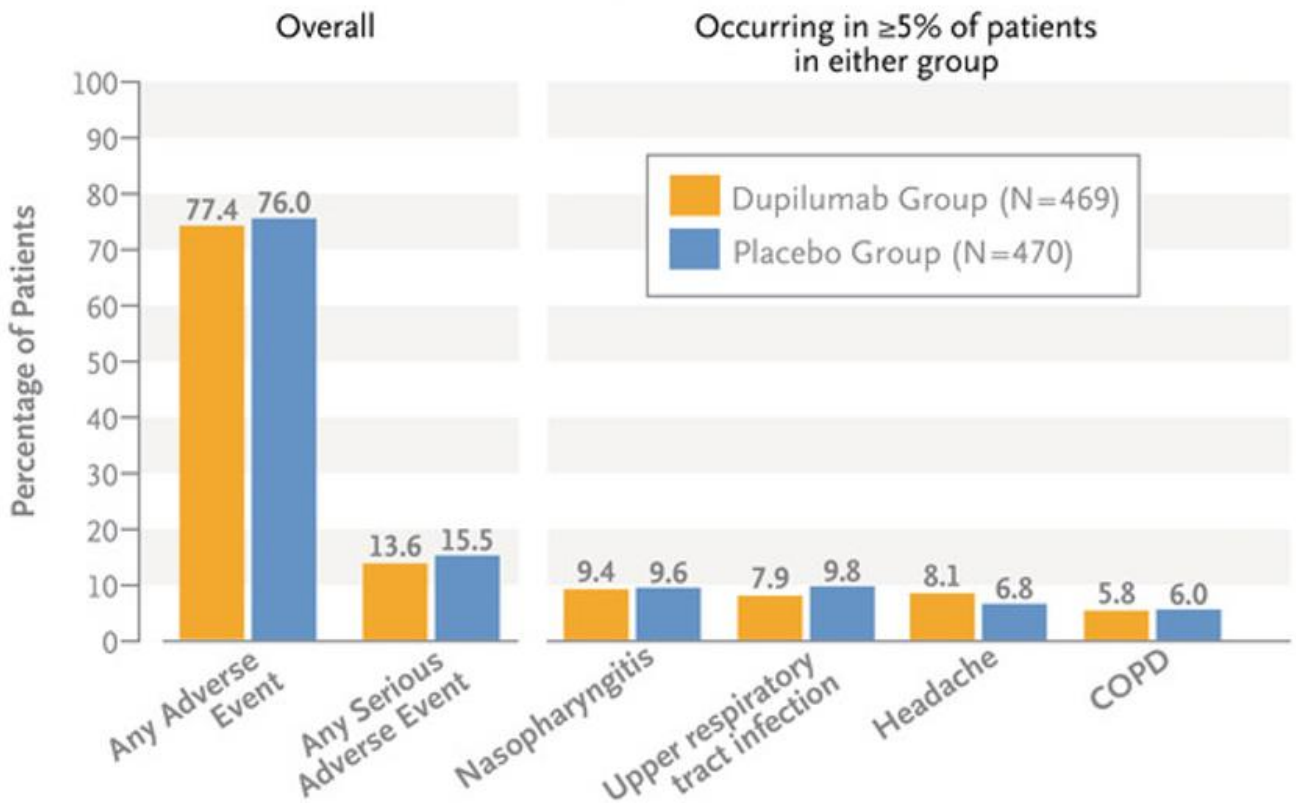
Lesser respiratory symptoms

LS mean difference (95% CI)

–1.1 (–1.8 to –0.4); p=0.001

Bhatt, Surya P., et al. NEJM, 2023.

Adverse events



Bhatt, Surya P., et al. NEJM, 2023.

Study summary

- Patients with COPD and type 2 inflammation despite standard inhaled triple therapy
- Dupilumab in type 2 high COPD as indicated by elevated EOS
  - Reduced moderate or severe exacerbations
  - Better lung function and quality of life
  - Less severe symptoms

Bhatt, Surya P., et al. NEJM, 2023.

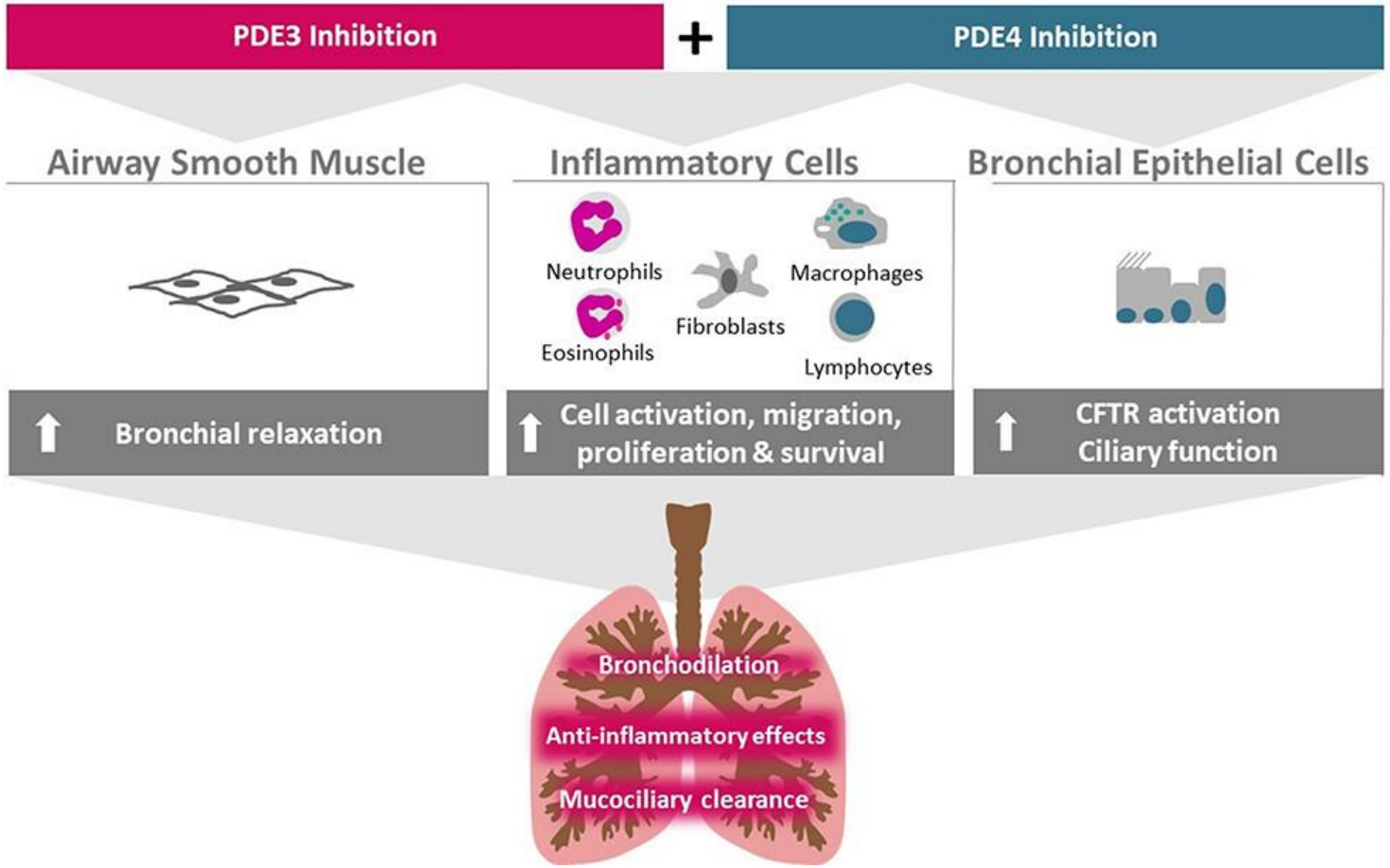
ORIGINAL ARTICLE

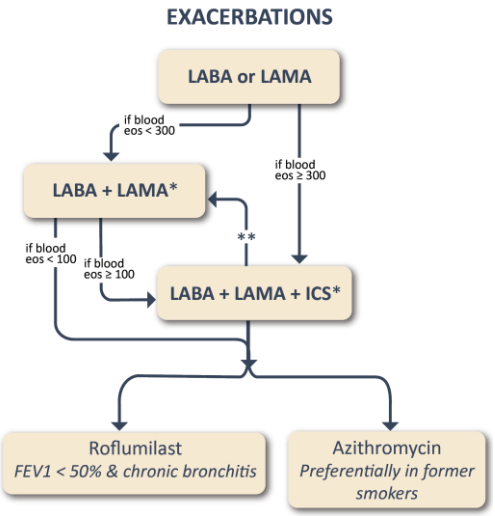
Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease

Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials)

Antonio Anzueto[1,2], Igor Z. Barjaktarevic[3], Thomas M. Siler[4], Tara Rheault[5], Thomas Bengtsson[6], Kathleen Rickard[5], and Frank Sciurba[7]; for the ENHANCE investigators

PDE inhibition in COPD

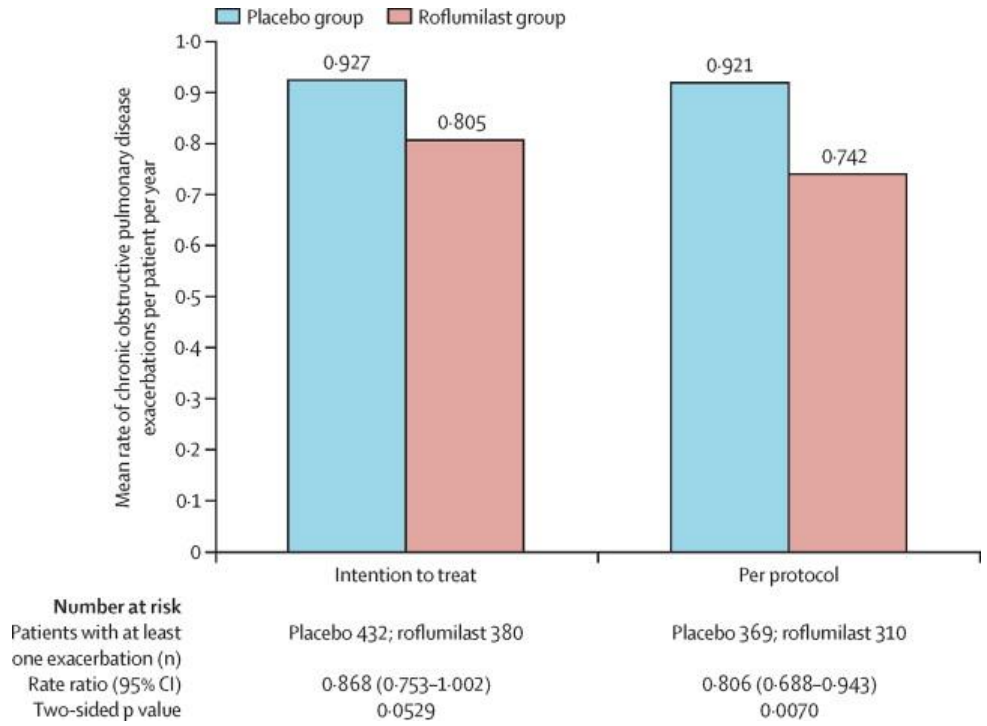




Donohue, James F., et al. IJCOPD, 2023, 1611-1622.

PDE inhibitors

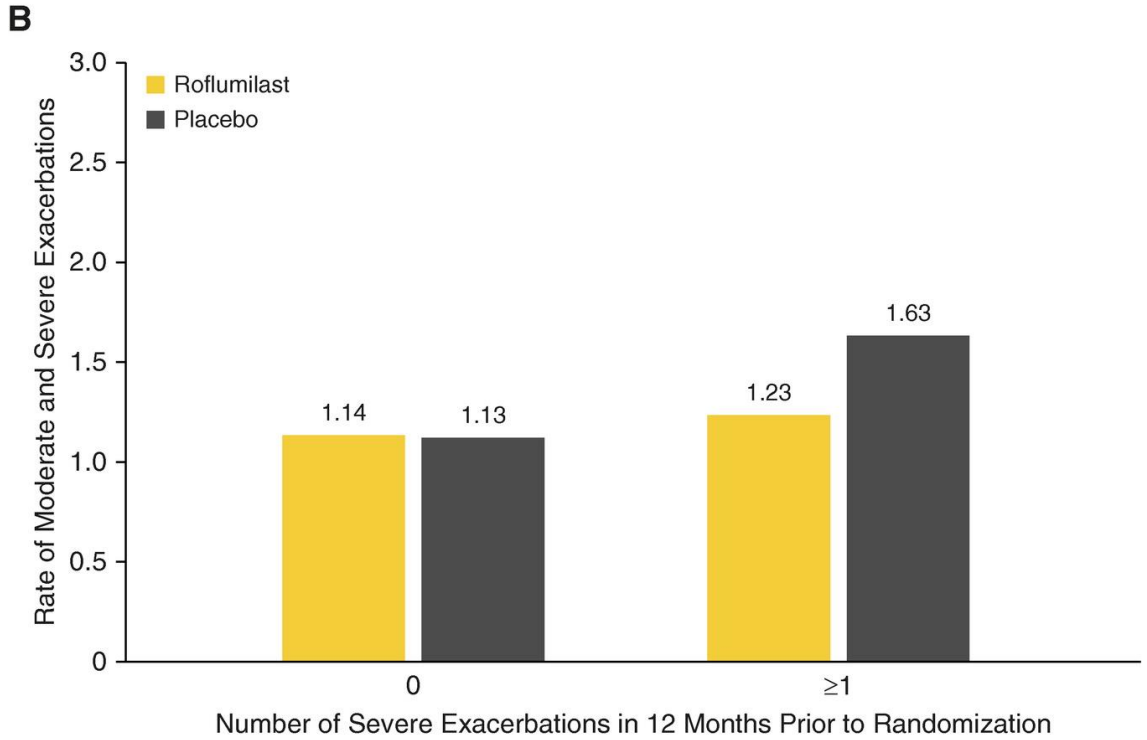
REACT



Roflumilast vs. Placebo + ICS/LABA ± LAMA
Rate ratio **0.858** (0.740-0.995); p=0.0424

Martinez, Fernando J., et al. Lancet, 2015, 385.9971: 857-866.

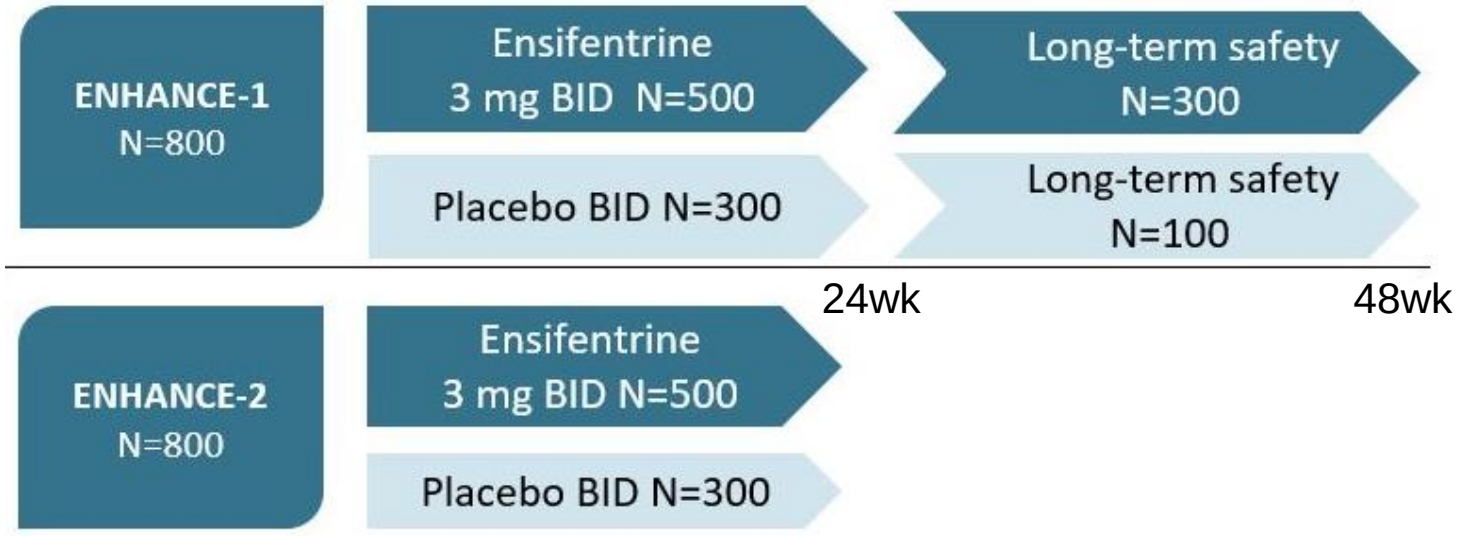
RE²SPOND



Number of Severe Exacerbations in 12 Months Prior to Randomization	Number of Participants at Risk		Rate Ratio (95% CI)	*P*-Value
	Roflumilast (n=1,178)	Placebo (n=1,174)		
0	789	805	1.01 (0.87, 1.18)	0.879
≥1	381	364	0.75 (0.60, 0.93)	0.010

Martinez, Fernando J., et al. AJRCCM. 2016, 194.5: 559-567.

ENHANCE Trial Design



Primary Endpoint

- FEV1 (AUC over 12hours) at week 12

Secondary Endpoints

- Symptoms (E-RS: COPD)
- Quality of Life (SGRQ)
- Other FEV1 (Trough, peak)

Other Endpoints

- Exacerbations in pooled analysis

Patient population:

- LAMA or LABA background allowed
- Symptomatic (mMRC ≥ 2)
- 30-70% predicted FEV1

Additional information:

- Long-term safety established in ENHANCE-1

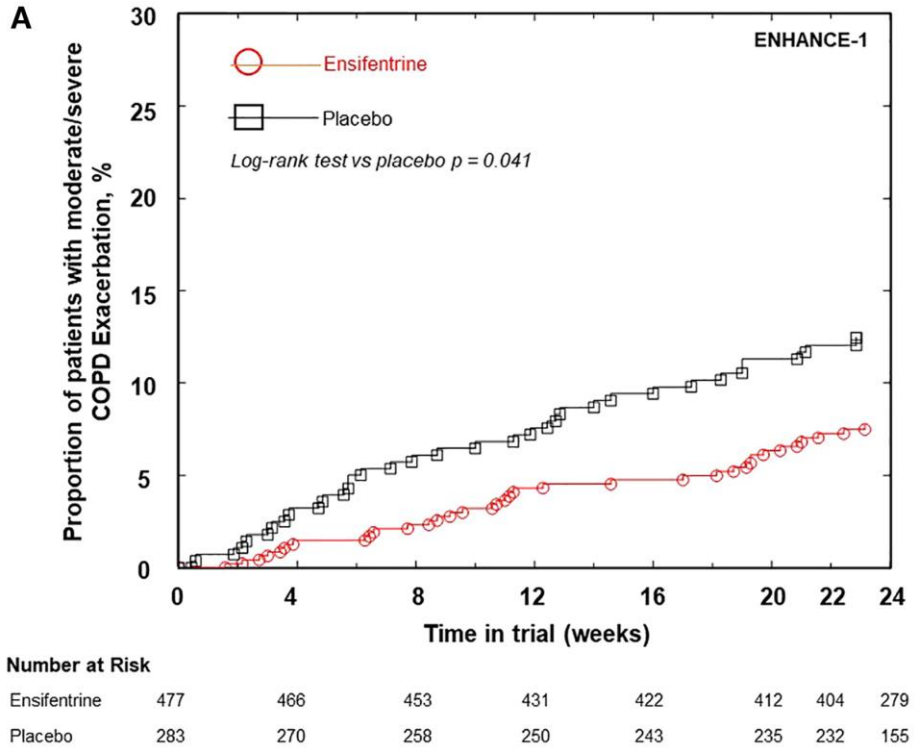
Anzueto, Antonio, et al. AJRCCM, 2023, 208.4: 406.

Efficacy of Ensifentrine

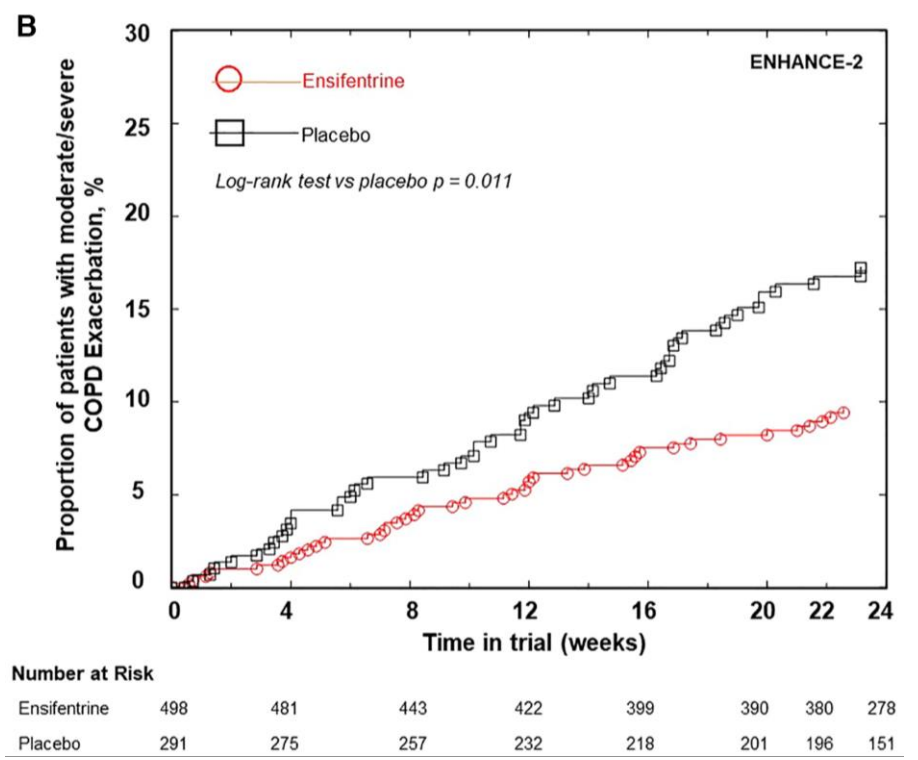
Treatment Group	ENHANCE-1		ENHANCE-2	
	Ensifentrine 3 mg BID ($n = 477$)	Placebo BID ($n = 283$)	Ensifentrine 3 mg BID ($n = 498$)	Placebo BID ($n = 291$)
Primary endpoint				
Mean baseline FEV_1, ml (SD)	1,420 (487)	1,403 (468)	1,285 (451)	1,279 (473)
Week 12 average FEV_1 $AUC_{0-12\,h}$				
LS mean change from baseline, ml (95% CI)	61 (25, 97)	−26 (−64, 13)	48 (30, 66)	−46 (−70, −22)
Ensifentrine vs. placebo, ml (95% CI)	87 (55, 119)	—	94 (65, 124)	—
P value	<0.001	—	<0.001	—
Key secondary endpoints				
Week 12 peak FEV_1				
LS mean change from baseline, ml (95% CI)	204 (165, 244)	57 (15, 100)	195 (175, 214)	48 (22, 75)
Ensifentrine vs. placebo, ml (95% CI)	147 (111, 183)	—	146 (113, 179)	—
P value	<0.001	—	<0.001	—
Week 12 morning trough FEV_1				
LS mean change from baseline, ml (95% CI)	8 (−30, 45)	−27 (−67, 13)	6 (−13, 24)	−44 (−68, −19)
Ensifentrine vs. placebo, ml (95% CI)	35 (1, 68)	—	49 (19, 80)	—
P value	0.041	—	0.002	—
Week 24 E-RS total score				
Mean baseline (SD)	14.1 (6.8)	13.3 (6.1)	13.3 (6.7)	13.3 (6.2)
LS mean change from baseline (95% CI)	−2.2 (−3.1, −1.4)	−1.3 (−2.2, −0.4)	−2.1 (−2.6, −1.6)	−1.5 (−2.2, −0.9)
Ensifentrine vs. placebo (95% CI)	−1.0 (−1.7, −0.2)	—	−0.6 (−1.4, 0.2)	—
P value	0.011	—	0.134	—
Week 24 SGRQ total score				
Mean baseline (SD)	48.1 (18.3)	46.9 (17.1)	50.6 (17.4)	51.2 (16.4)
LS mean change from baseline (95% CI)	−6.2 (−8.4, −3.9)	−3.9 (−6.3, −1.5)	−4.5 (−5.9, −3.2)	−4.1 (−5.8, −2.3)
Ensifentrine vs. placebo (95% CI)	−2.3 (−4.3, −0.3)	—	−0.5 (−2.7, 1.7)	—
P value	0.025	—	0.669	—

Anzueto, Antonio, et al. AJRCCM, 2023, 208.4: 406.

Moderate-to-Severe Exacerbations



Hazard ratio versus placebo (95% CI)
0.62 (0.39, 0.97); p = 0.038



Hazard ratio versus placebo (95% CI)
0.58 (0.38, 0.87); p = 0.009

Anzueto, Antonio, et al. AJRCCM, 2023, 208.4: 406.

Adverse events

	ENHANCE-1		ENHANCE-2	
	Ensifentrine 3 mg BID	Placebo BID	Ensifentrine 3 mg BID	Placebo BID
TEAEs over 24 wk (including follow-up period), no. of patients reported (%)	*n* = 477	*n* = 283	*n* = 498	*n* = 291
Any TEAE	183 (38.4)	103 (36.4)	176 (35.3)	103 (35.4)
Any TEAE (by preferred term) that occurred >1% in ensifentrine group and greater than placebo				
Nasopharyngitis	13 (2.7)	16 (5.7)	9 (1.8)	3 (1.0)
Hypertension	12 (2.5)	4 (1.4)	5 (1.0)	1 (0.3)
Back pain	10 (2.1)	1 (0.4)	8 (1.6)	5 (1.7)
COPD	7 (1.5)	6 (2.1)	11 (2.2)	5 (1.7)
Toothache	6 (1.3)	2 (0.7)	0	1 (0.3)
Pneumonia*	6 (1.3)	2 (0.7)	4 (0.8)	5 (1.7)
Urinary tract infection	5 (1.0)	1 (0.4)	8 (1.6)	5 (1.7)
Diarrhea	2 (0.4)	2 (0.7)	8 (1.6)	2 (0.7)
Sinusitis	1 (0.2)	1 (0.4)	6 (1.2)	0
Any TEAE causally related to treatment	24 (5.0)	11 (3.9)	20 (4.0)	12 (4.1)
Any serious TEAE	32 (6.7)	19 (6.7)	28 (5.6)	17 (5.8)
Any TEAE with an outcome of death	2 (0.4)	4 (1.4)	4 (0.8)	1 (0.3)
Any TEAE leading to discontinuation of treatment	29 (6.1)	18 (6.4)	45 (9.0)	29 (10.0)
Any TEAE leading to withdrawal from trial	19 (4.0)	10 (3.5)	35 (7.0)	20 (6.9)
No. with a diagnosis of COVID-19	8 (1.7)	5 (1.8)	16 (3.2)	10 (3.4)
No. with no diagnosis of COVID-19	11 (2.3)	5 (1.8)	19 (3.8)	10 (3.4)
Any severe TEAE	27 (5.7)	15 (5.3)	22 (4.4)	12 (4.1)

Anzueto, Antonio, et al. AJRCCM, 2023, 208.4: 406.

Study summary

- Ensifentrine
  - Substantial efficacy with reduction in exacerbations
  - Improvement in lung function
  - Not associated gastrointestinal tolerability issues related to oral PDE inhibitor
- Symptomatic patients with moderate to severe COPD in addition to other classes of maintenance therapies.

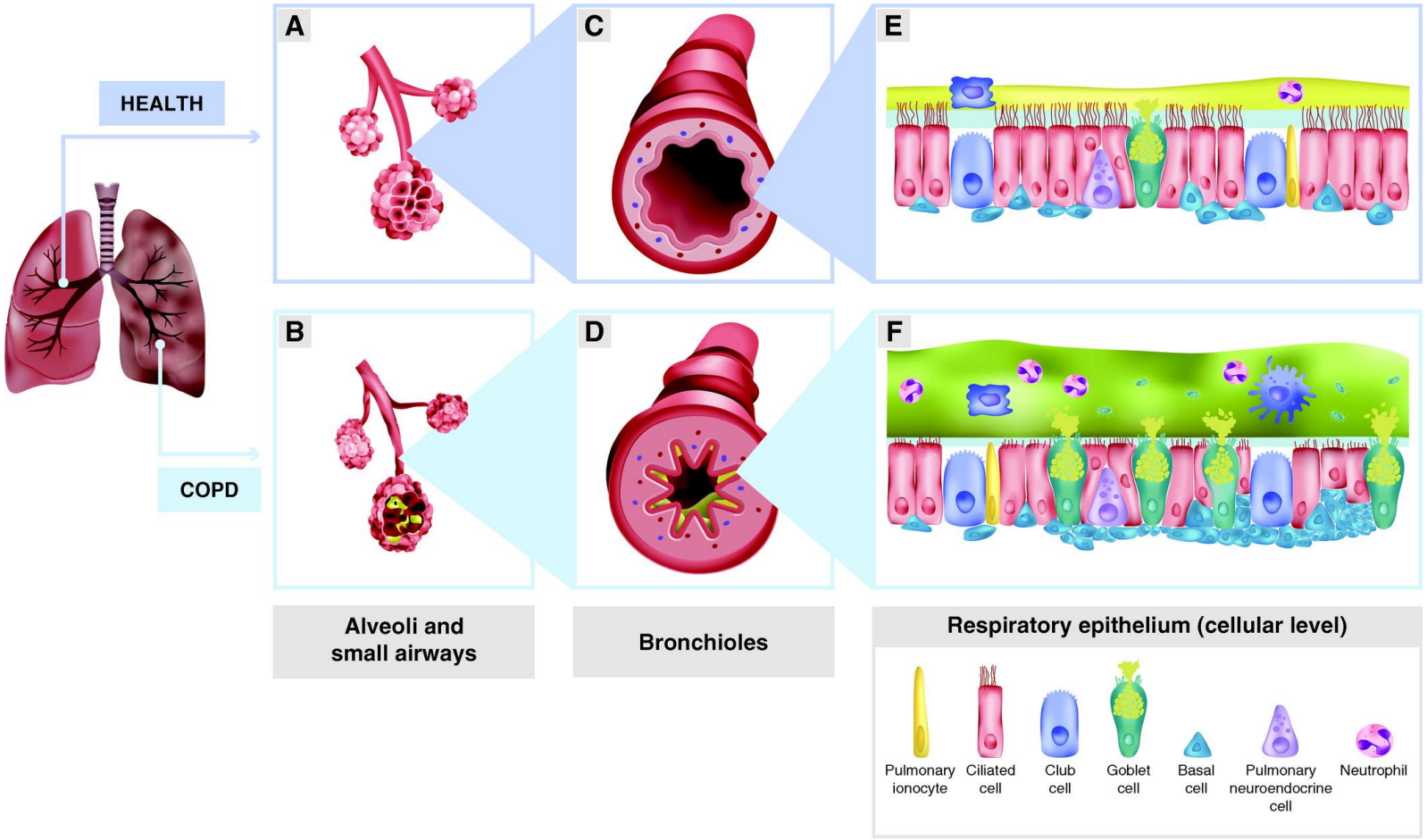
Anzueto, Antonio, et al. AJRCCM, 2023, 208.4: 406.

ORIGINAL ARTICLE

Icenticaftor, a CFTR Potentiator, in COPD: A Multicenter, Parallel-Group, Double-Blind Clinical Trial

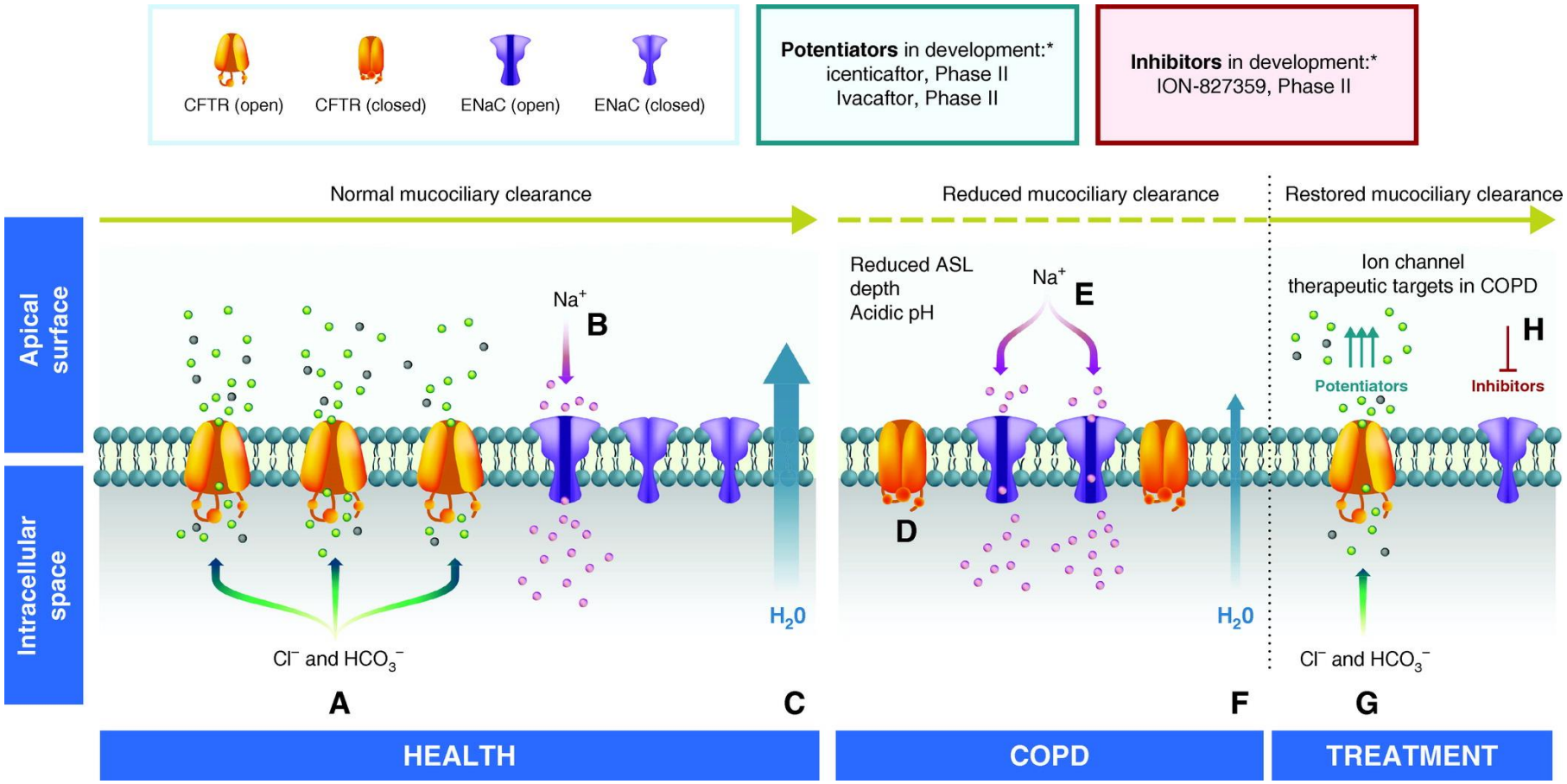
Fernando J. Martinez[1*], Gerard J. Criner[2], Christian Gessner[3], Margret Jandl[4], Fernando Scherbovsky[5], Masaharu Shinkai[6], Thomas M. Siler[7], Claus F. Vogelmeier[8], Robert Voves[9], Jadwiga A. Wedzicha[10], Christian Bartels[11], Ivan Bottoli[11], Stuart Byiers[11], Pamela Cardenas[12], Joerg H. Eckert[11], Florian S. Gutzwiller[11], Barbara Knorr[12], Mahavir Kothari[13], Rutvick Parlikar[13], Ana-Maria Tanase[11], and Frits M.E. Franssen[14*]

Pathological features of COPD



Dransfield, Mark, et al. AJRCCM, 2022, 205.6: 631-640.

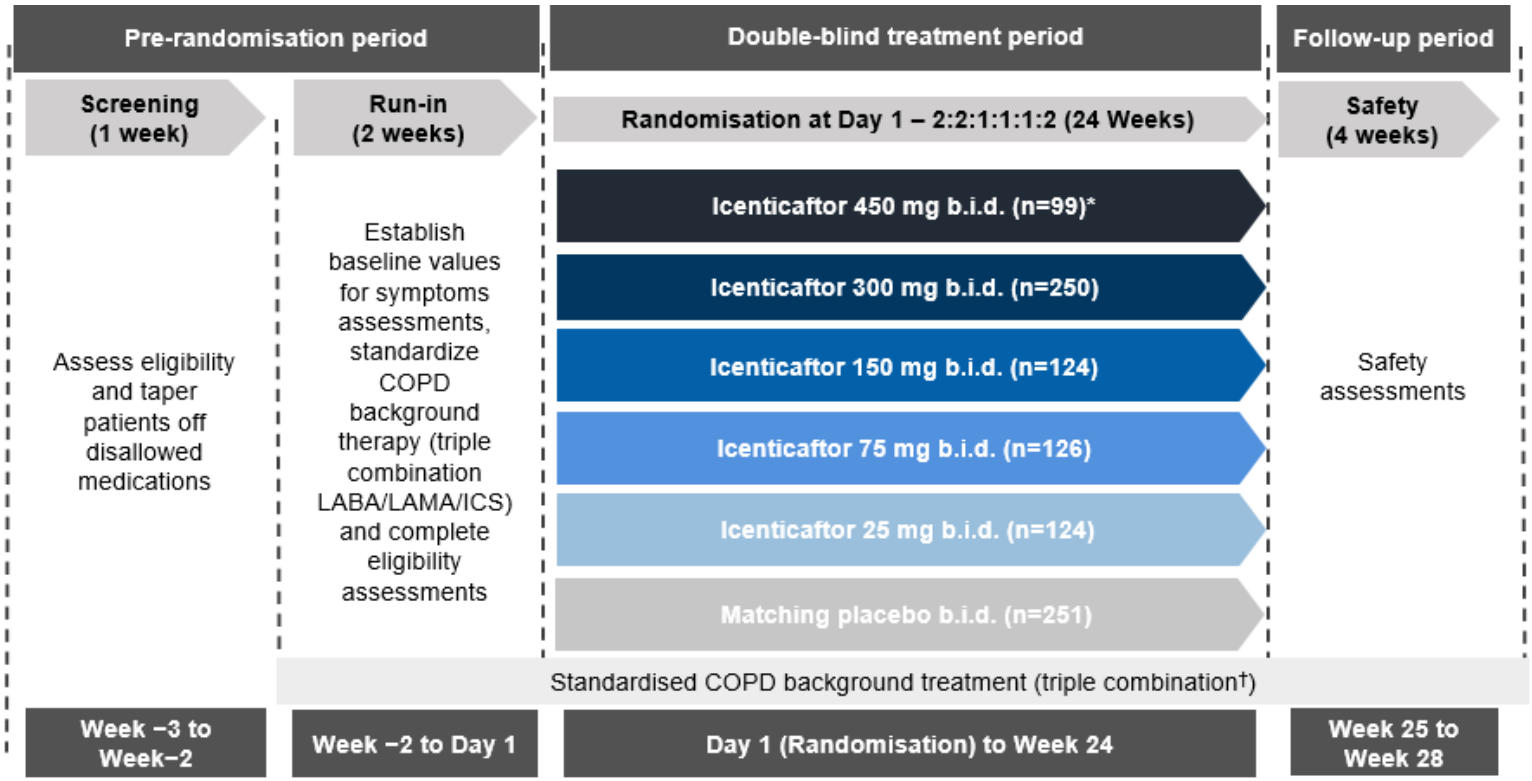
Correction of CFTR dysfunction



Dransfield, Mark, et al. AJRCCM, 2022, 205.6: 631-640.

Study design

- Randomized, multicenter, parallel-group, double-blind, placebo-controlled, 24-week, exploratory, phase II, dose range–finding study
- Symptomatic moderate to severe **COPD** and **CB** with histories of exacerbations despite triple inhaled therapy



Primary Endpoint

- Change of FEV1 at week 12

Secondary Endpoints

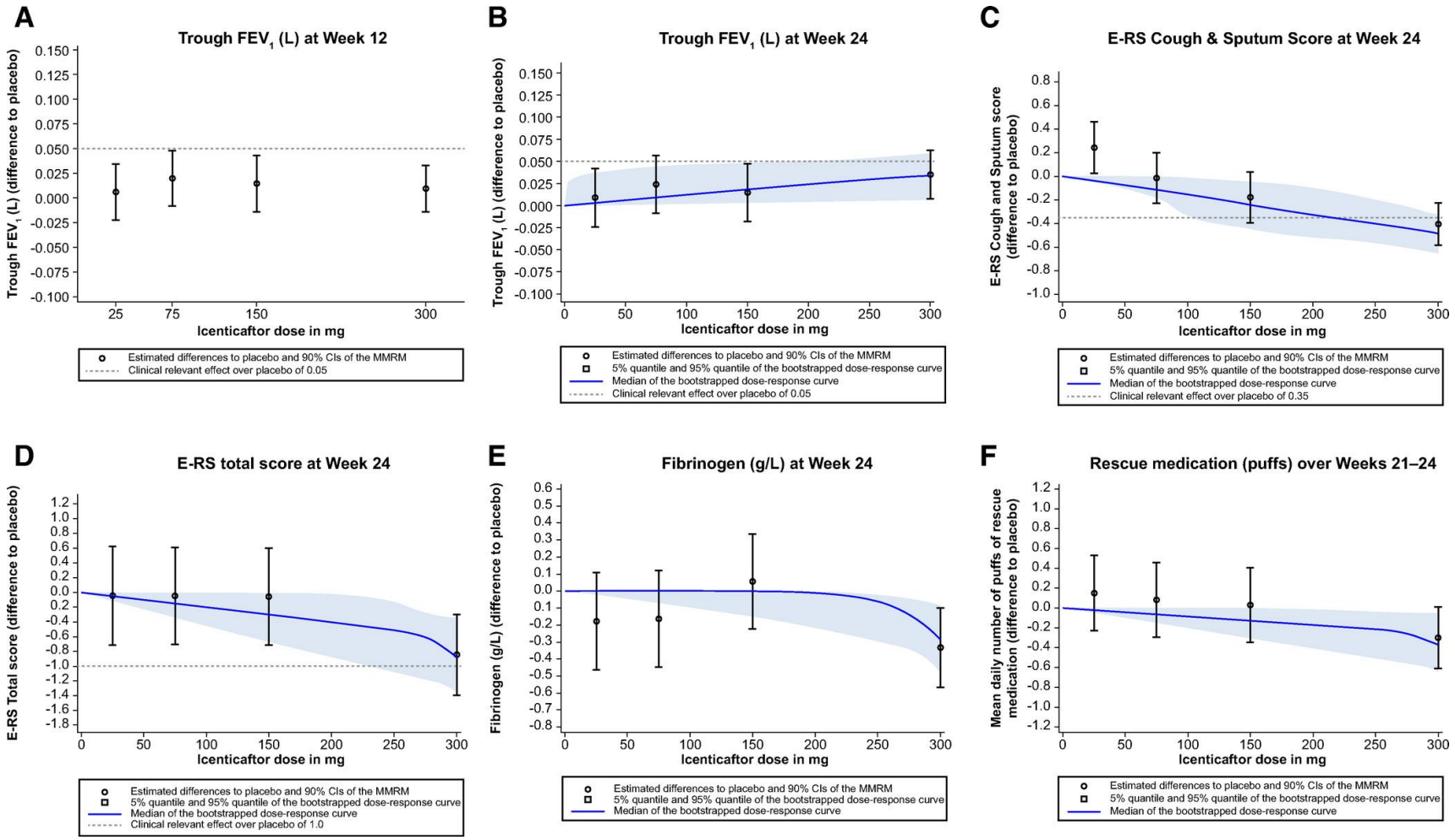
- Symptoms (E-RS: COPD)
- Quality of Life (SGRQ)
- Trough FEV1
- CASA-Q

Post hoc analyses

- Fibrinogen
- CRP

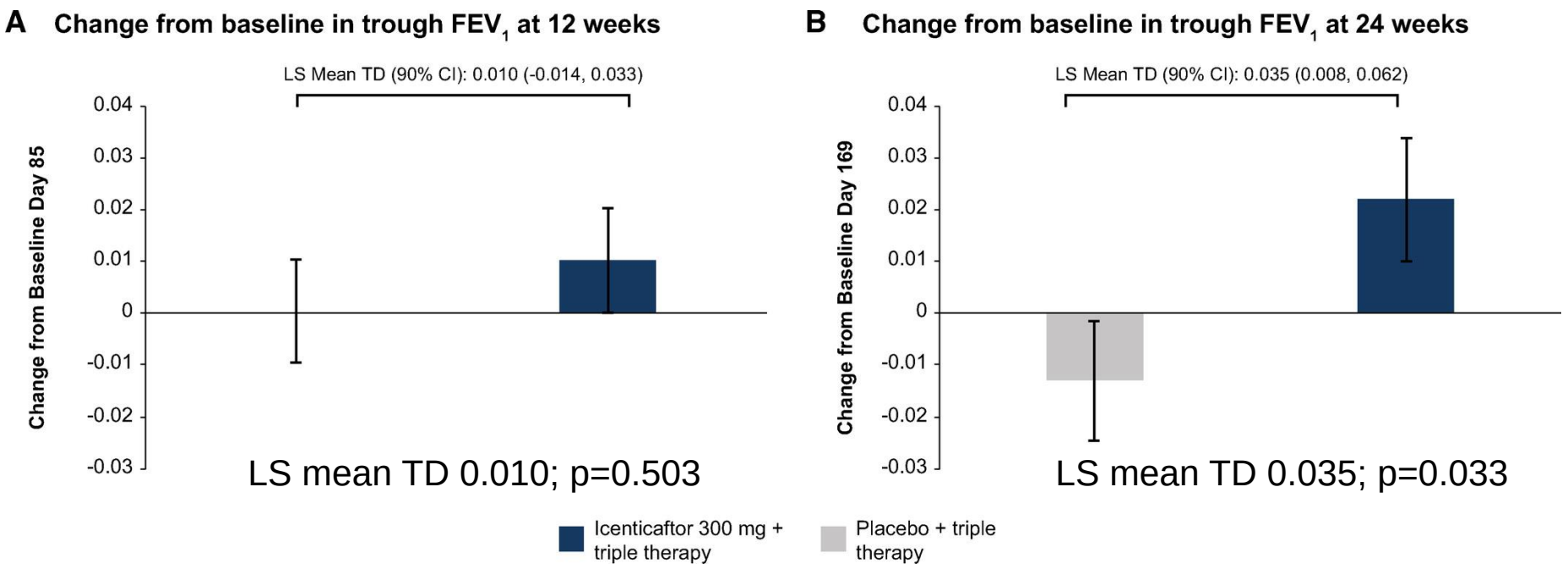
Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Dose-response analysis



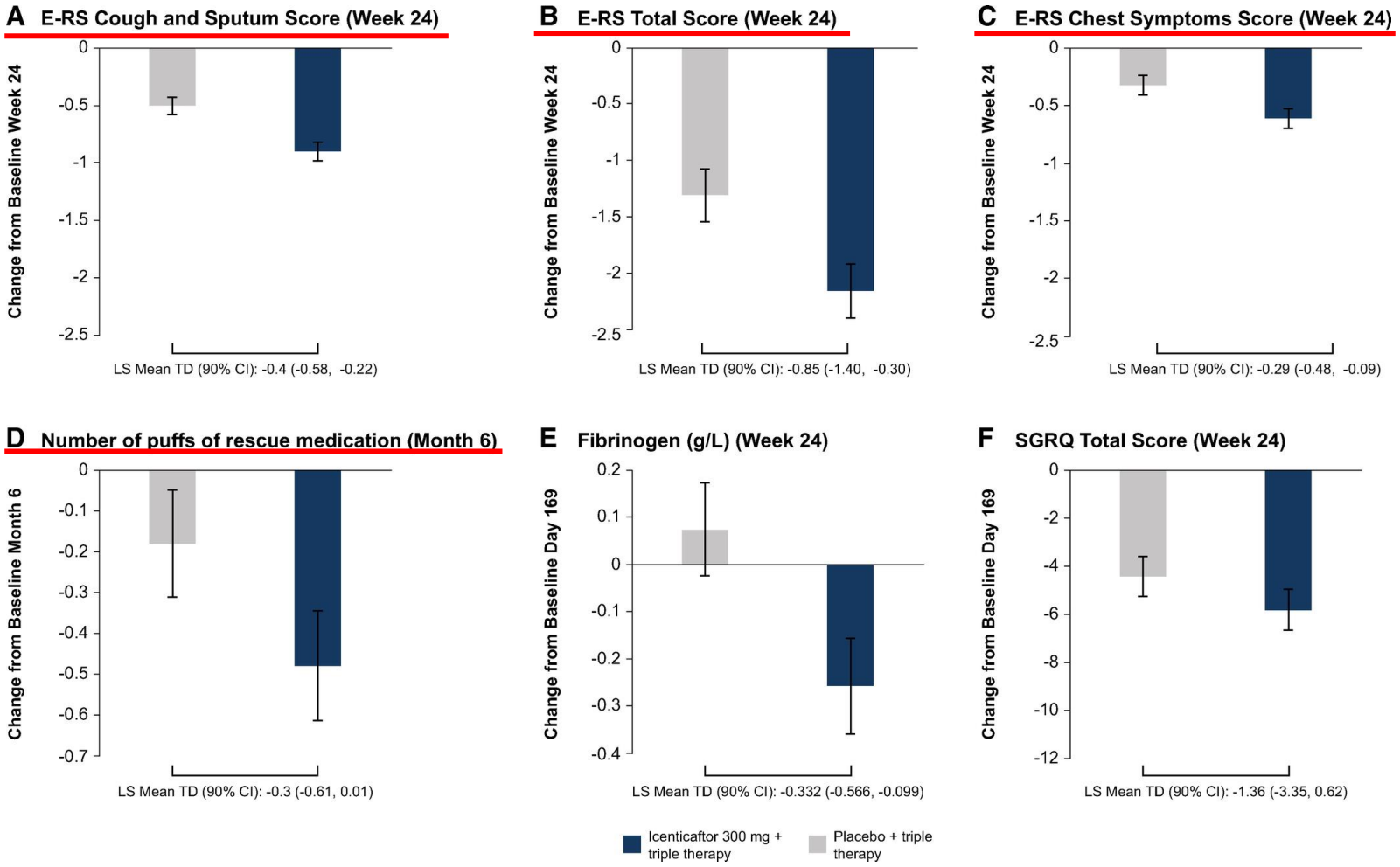
Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

FEV1 changes



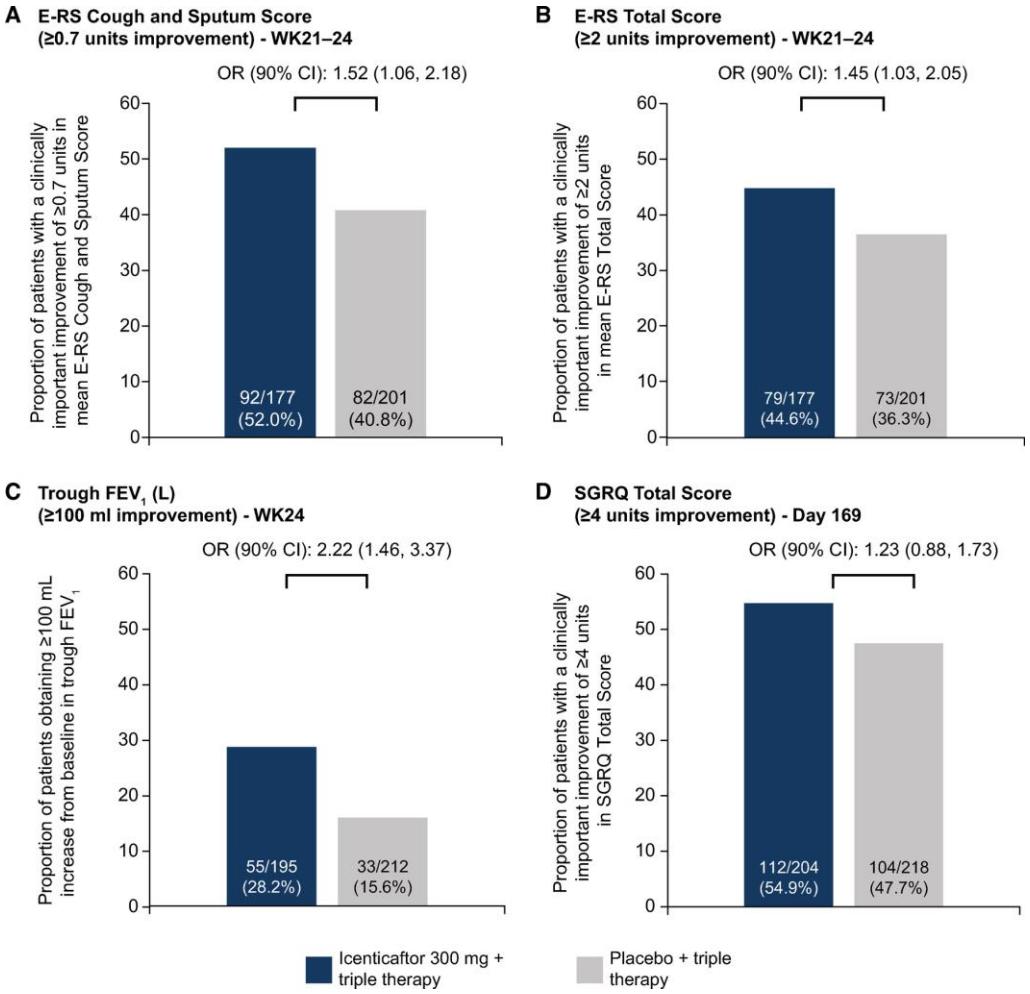
Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Symptom scores



Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Responder analyses



Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Adverse events

Table 2. Adverse Events

	Icenticaftor 450 mg (*N* = 99)* [*n* (%)]	Icenticaftor 300 mg (*n* = 250) [*n* (%)]	Icenticaftor 150 mg (*n* = 124) [*n* (%)]	Icenticaftor 75 mg (*n* = 126) [*n* (%)]	Icenticaftor 25 mg (*n* = 124) [*n* (%)]	Placebo (*n* = 251) [*n* (%)]
Patients with at least one AE	61 (61.6)	166 (66.4)	77 (62.1)	76 (60.3)	81 (65.3)	153 (61.0)
Any serious AEs	10 (10.1)	33 (13.2)	6 (4.8)	14 (11.1)	12 (9.7)	15 (6.0)
Any AE leading to death	0	2 (0.8)	0	2 (1.6)	3 (2.4)	0
Any AEs leading to permanent discontinuation of the intervention	8 (8.1)	20 (8.0)	4 (3.2)	10 (7.9)	8 (6.5)	10 (4.0)
AEs occurring in ⩾5% of patients in any group in the overall population						
COPD	21 (21.2)	56 (22.4)	32 (25.8)	27 (21.4)	36 (29.0)	60 (23.9)
Diarrhea	6 (6.1)	7 (2.8)	1 (0.8)	2 (1.6)	3 (2.4)	6 (2.4)
Nausea	5 (5.1)	4 (1.6)	2 (1.6)	3 (2.4)	1 (0.8)	5 (2.0)
Nasopharyngitis	4 (4.0)	12 (4.8)	5 (4.0)	10 (7.9)	6 (4.8)	10 (4.0)
COVID-19	0	7 (2.8)	1 (0.8)	2 (1.6)	7 (5.6)	5 (2.0)

Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Study summary

- CFTR potentiator: not improved trough FEV1 over 12 weeks
- Clinically relevant benefits
  - Lung function, symptoms, QoL outcomes, and fibrinogen
- 300 mg twice daily: a potential dose for its future development
- Well tolerated across icenticaftor doses

Martinez, Fernando J., et al. AJRCCM, 2023, 208.4: 417-427.

Comparison of Clinical Outcomes Among Different Fixed-Dose Combinations of Long-Acting Muscarinic Antagonists and Long-Acting β_2-Agonists in Patients With COPD

Ching-Fu Weng, MD, PhD; Chien-Chih Wu, MSCP, BCCCP; Mei-Hsuan Wu, MS; and Fang-Ju Lin, MSCP, PhD

RCTs comparing different LAMA/LABA

- Notable paucity of large scale head-to-head comparison studies of the various FDCs
- A network meta-analysis (74 RCTs) [1]
  No significant differences of FEV1 among the different LAMA/LABA combinations
- RCTs directly comparing different LAMA/ LABA FDCs [2,3]
  No significant differences in effect on FEV1

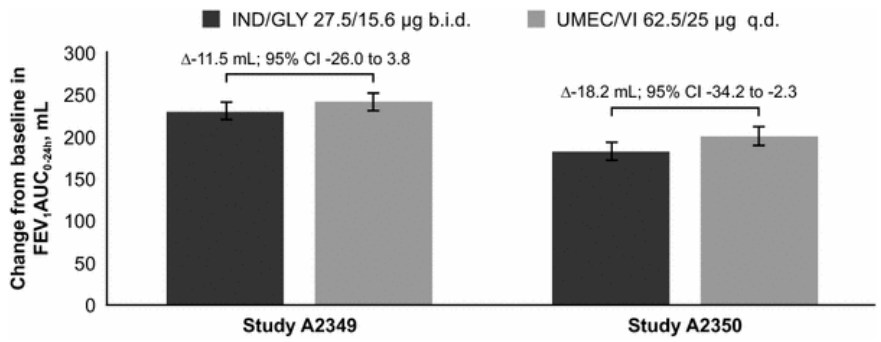
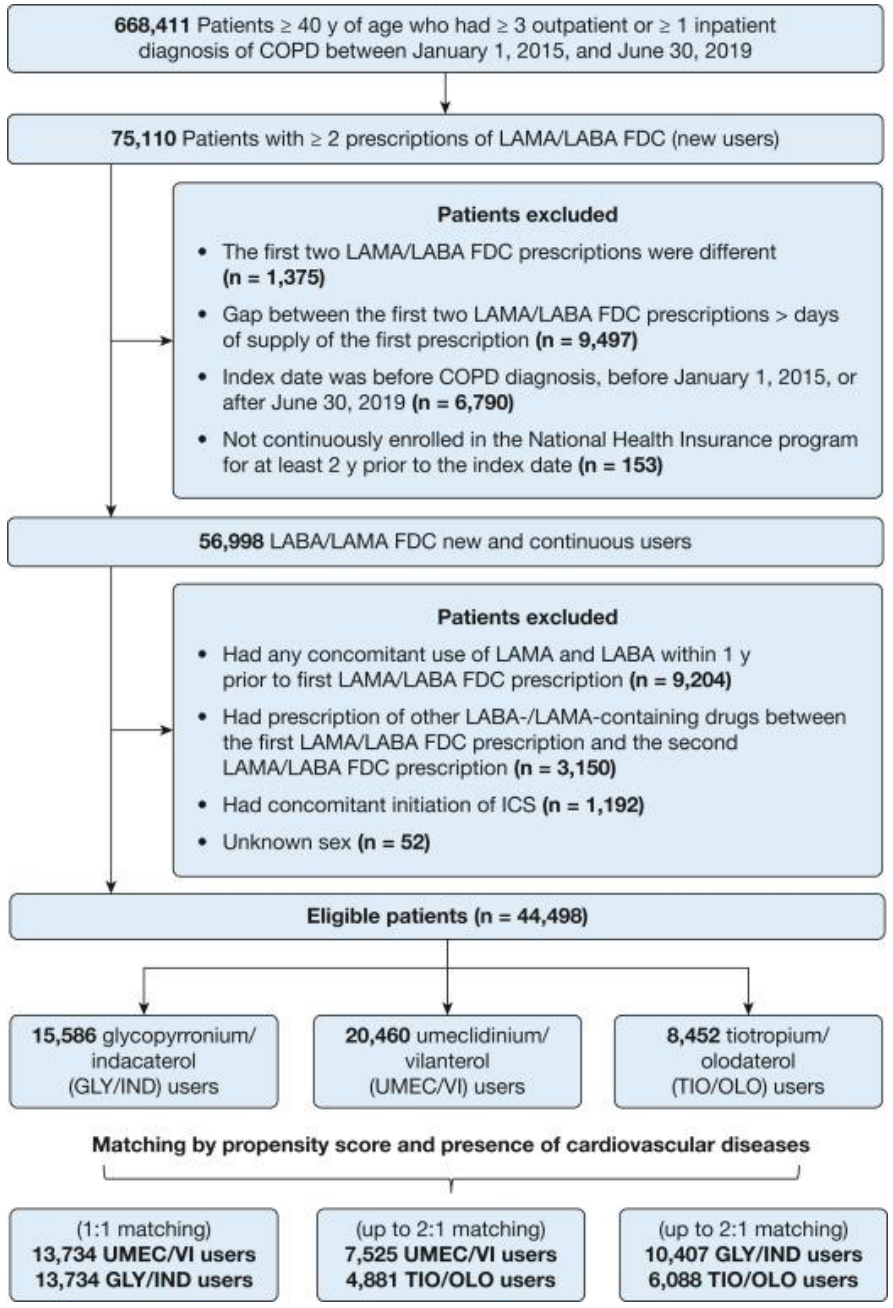


Table 3 Spirometry and FOT by MostGraph-01® after using each inhaler

	Gly/Ind	Ume/Vil	Tio/Olo	*P* value		
				Gly/Ind versus Ume/Vil	Gly/Ind versus Tio/Olo	Ume/Vil versus Tio/Olo
Spirometry						
IC (L)	2.02 ± 0.54	2.03 ± 0.57	2.04 ± 0.56	0.9939	0.9544	0.9812
FVC (L)	2.87 ± 0.74	2.88 ± 0.72	2.95 ± 0.75	0.9993	0.8137	0.8332
FEV1 (L)	1.52 ± 0.57	1.51 ± 0.56	1.52 ± 0.56	0.9969	0.9999	0.9977

1. Aziz, Mohamed Ismail Abdul, et al. IJCOPD, 2018, 3203-3231.
2. Kerwin, Edward, et al. Lung, 2017, 195: 739-747.
3. Muraki, Masato, et al. BMC Pulm Med, 2021, 21: 1-8.



Study design

- Retrospective cohort study used claims data in Taiwan
- ≥ 40y of age who received dual bronchodilator
- Three LAMA/LABA FDCs
  - UMEC/VI, GLY/IND, TIO/OLO

- Outcomes
  - Severe acute exacerbations
  - Cardiovascular events

1 : 1

1 : 2

1 : 2

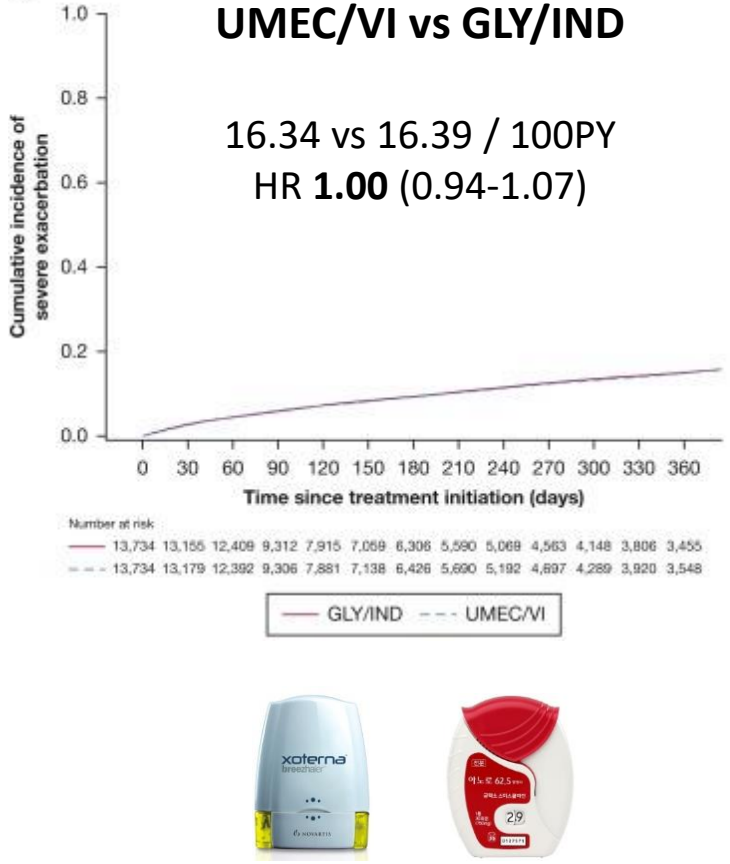
Weng, Ching-Fu, et al. Chest, 2023, 163.4: 799-814.

Severe exacerbation

A

UMEC/VI vs GLY/IND

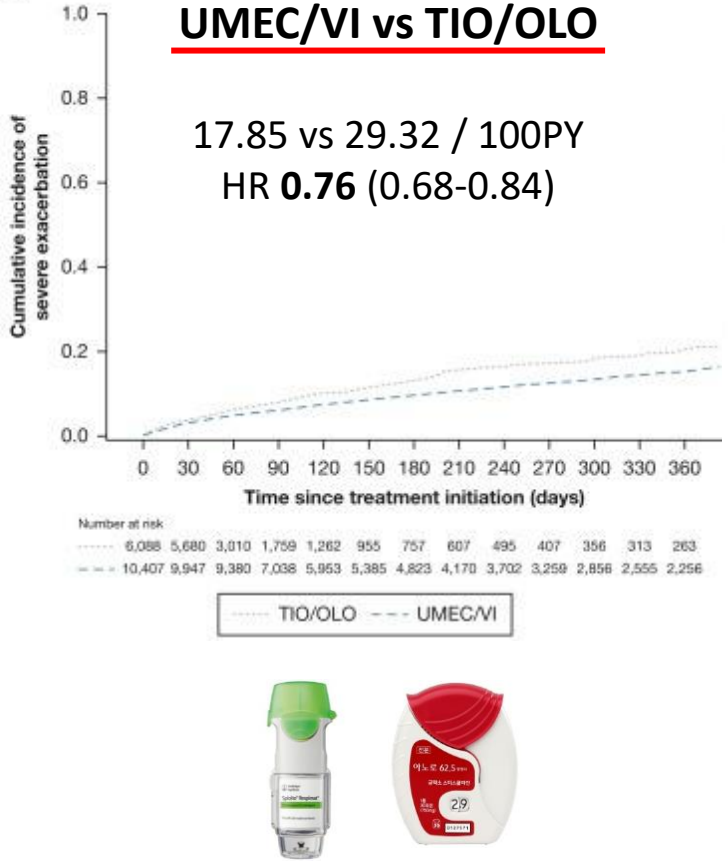
16.34 vs 16.39 / 100PY
HR **1.00** (0.94-1.07)



B

UMEC/VI vs TIO/OLO

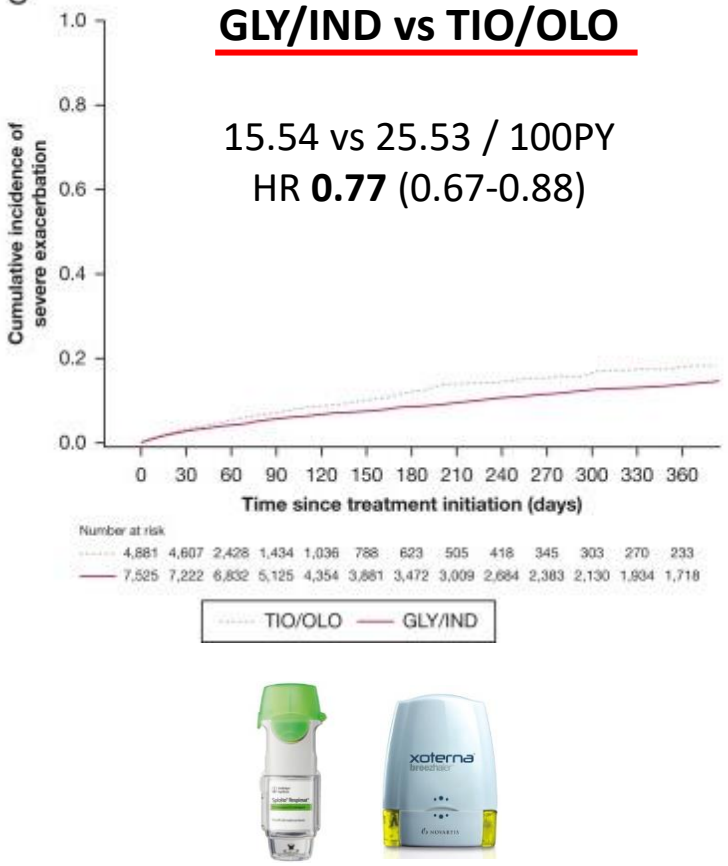
17.85 vs 29.32 / 100PY
HR **0.76** (0.68-0.84)



C

GLY/IND vs TIO/OLO

15.54 vs 25.53 / 100PY
HR **0.77** (0.67-0.88)



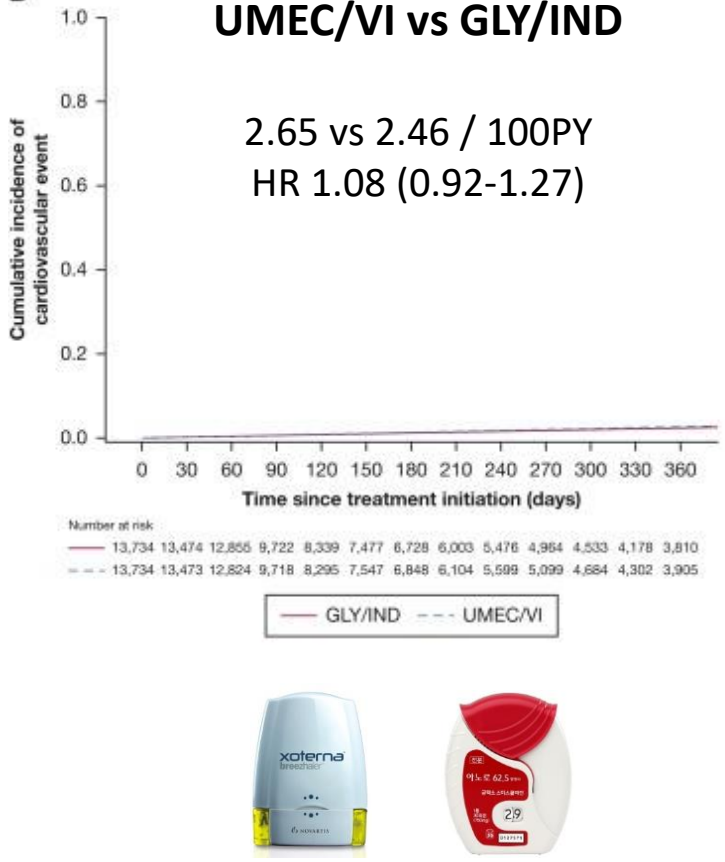
Weng, Ching-Fu, et al. Chest, 2023, 163.4: 799-814.

Cardiovascular event

D

UMEC/VI vs GLY/IND

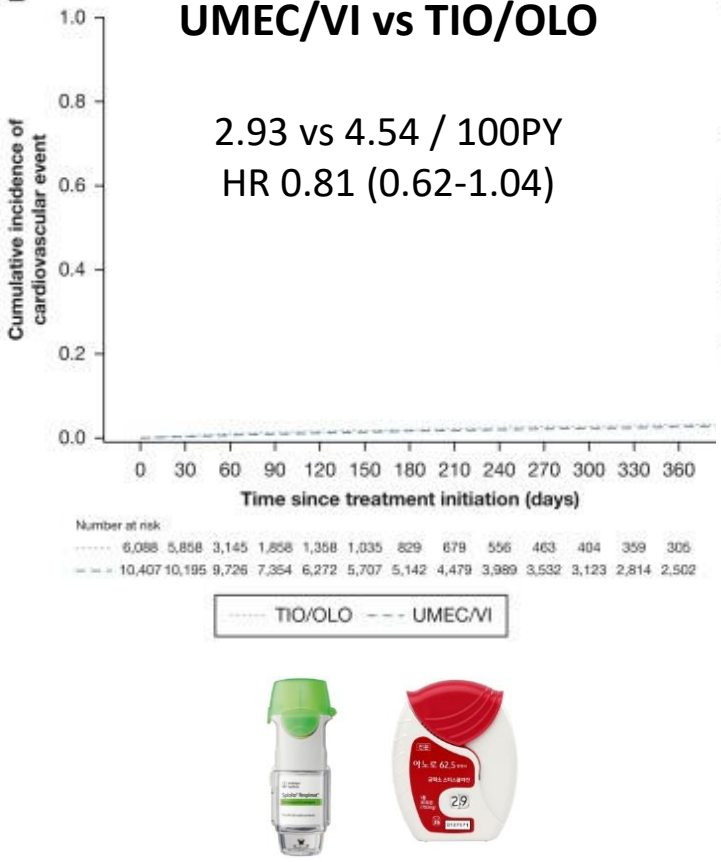
2.65 vs 2.46 / 100PY
HR 1.08 (0.92-1.27)



E

UMEC/VI vs TIO/OLO

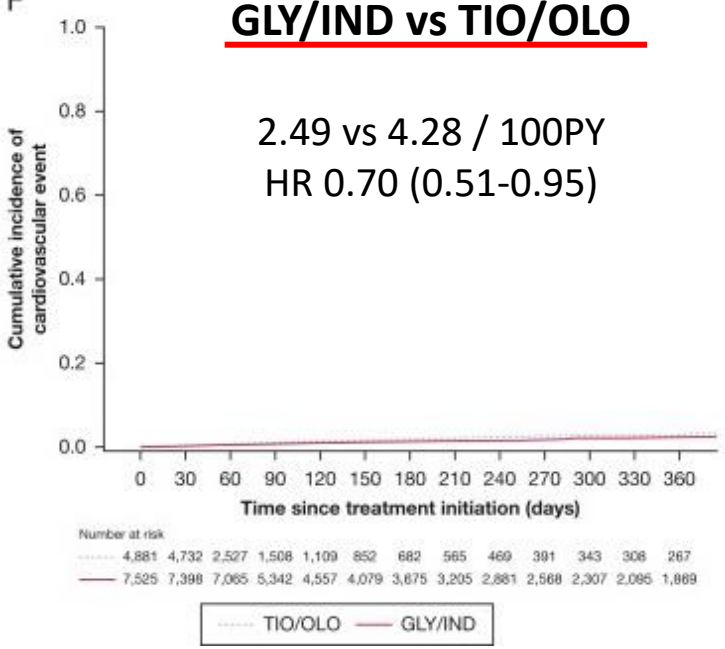
2.93 vs 4.54 / 100PY
HR 0.81 (0.62-1.04)



F

GLY/IND vs TIO/OLO

2.49 vs 4.28 / 100PY
HR 0.70 (0.51-0.95)



Weng, Ching-Fu, et al. Chest, 2023, 163.4: 799-814.

Restricting follow-up duration

TABLE 3] Sensitivity Analyses

Outcome/Analysis	UMEC/VI vs GLY/IND	UMEC/VI vs TIO/OLO	GLY/IND vs TIO/OLO
Severe AE as study outcome			
Main analysis (base case)	1.00 (0.94-1.07)	**0.76 (0.68-0.84)**	**0.77 (0.67-0.88)**
Including severe and moderate AE	1.01 (0.97-1.06)	**0.91 (0.85-0.98)**	**0.91 (0.84-0.99)**
Including severe AE and pneumonia event	0.99 (0.93-1.06)	**0.73 (0.67-0.81)**	**0.76 (0.67-0.85)**
Intention-to-treat analysis	1.00 (0.96-1.05)	**0.92 (0.86-0.98)**	**0.88 (0.82-0.96)**
Restricting follow-up duration			
6 mo	0.98 (0.90-1.07)	**0.75 (0.66-0.84)**	**0.75 (0.65-0.87)**
3 mo	1.00 (0.90-1.10)	**0.78 (0.69-0.89)**	**0.79 (0.67-0.92)**
2 mo	**0.79 (0.67-0.92)**	**0.79 (0.69-0.91)**	**0.78 (0.65-0.92)**
1 mo	0.94 (0.82-1.09)	0.94 (0.82-1.09)	0.85 (0.69-1.04)
Cardiovascular event as study outcome			
Main analysis (base case)	1.08 (0.92-1.27)	0.81 (0.62-1.04)	**0.70 (0.51-0.95)**
Intention-to-treat analysis	1.06 (0.95-1.17)	**0.84 (0.72-0.97)**	**0.78 (0.66-0.93)**
Restricting follow-up duration			
6 mo	0.82 (0.62-1.09)	0.93 (0.54-1.58)	1.03 (0.58-1.85)
3 mo	0.80 (0.56-1.14)	0.91 (0.49-1.67)	1.05 (0.53-2.08)
2 mo	0.79 (0.52-1.19)	0.86 (0.44-1.70)	0.96 (0.44-2.09)
1 mo	0.56 (0.29-1.08)	0.39 (0.14-1.09)	0.65 (0.23-1.84)

Weng, Ching-Fu, et al. Chest, 2023, 163.4: 799-814.

Study summary

- Incidence of severe AE: similar between UMEC/VI and GLY/IND.
- Risk of severe AE: UMEC/VI or GLY/IND < TIO/OLO
- Incidence of CV events: GLY/IND < TIO/OLO

Weng, Ching-Fu, et al. Chest, 2023, 163.4: 799-814.

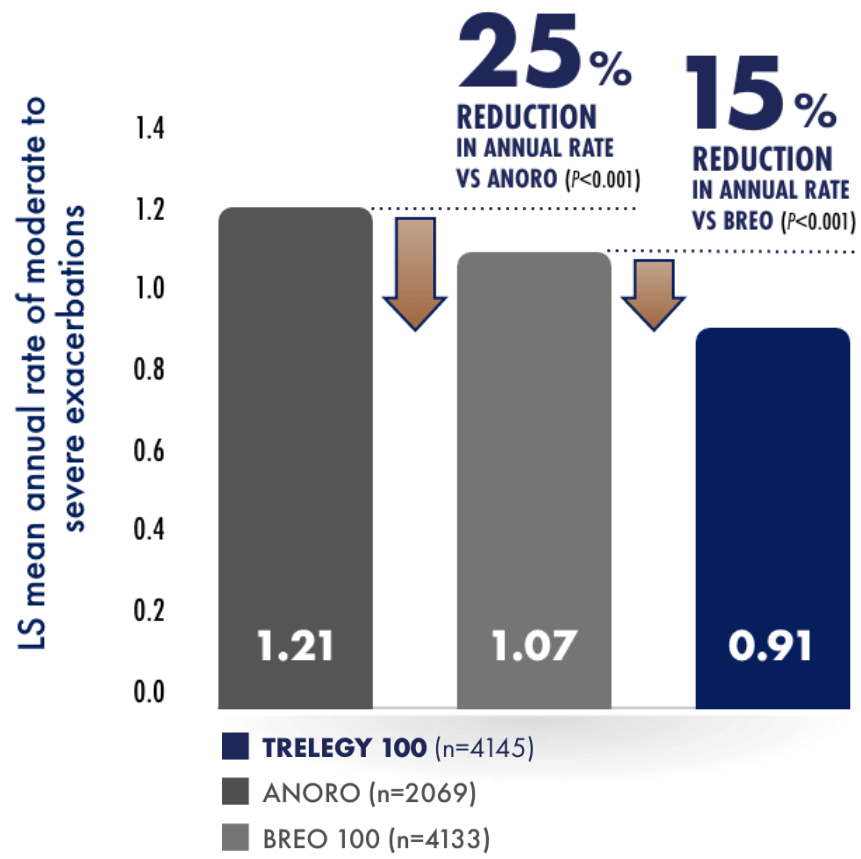
Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD

A Meta-analysis of 60 Randomized Controlled Trials

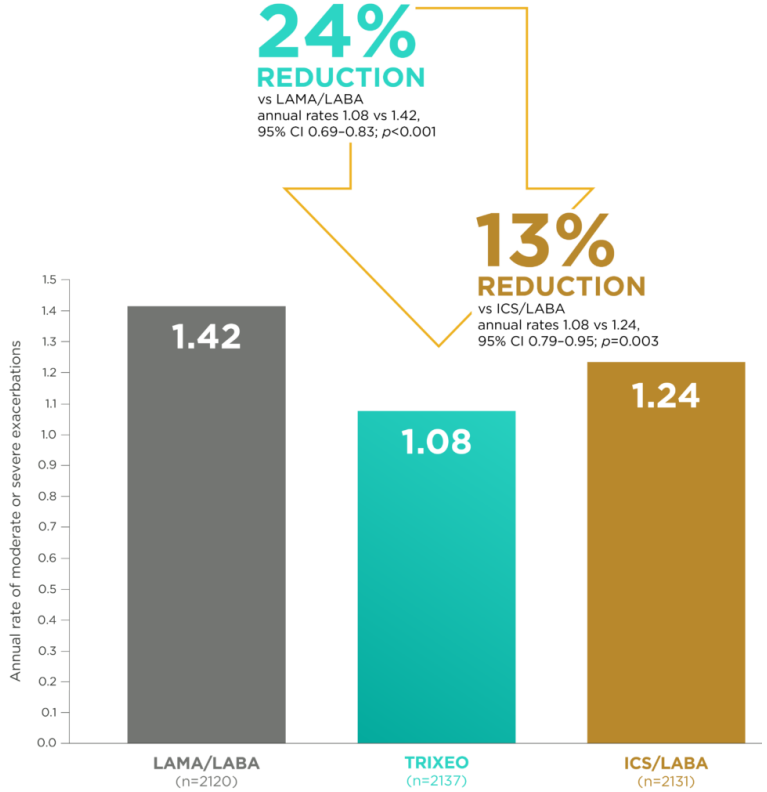
Hong Chen, MD; Zheng-Xu Deng, MD; Jian Sun, MD; Qiang Huang, MD; Lan Huang, MD; Yong-Hong He, MD; Chunlan Ma, MD; and Ke Wang, MD

IMPACT, ETHOS and exacerbation

IMPACT



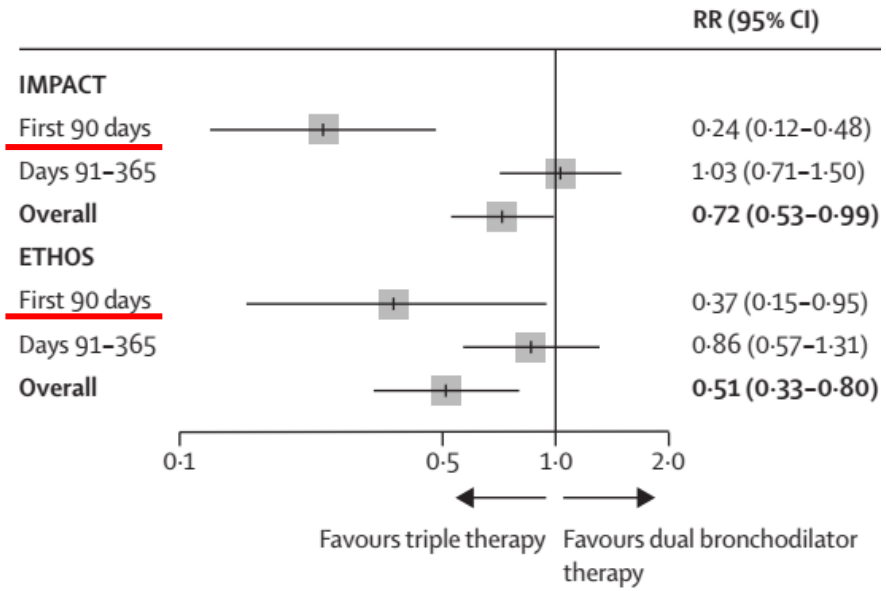
ETHOS



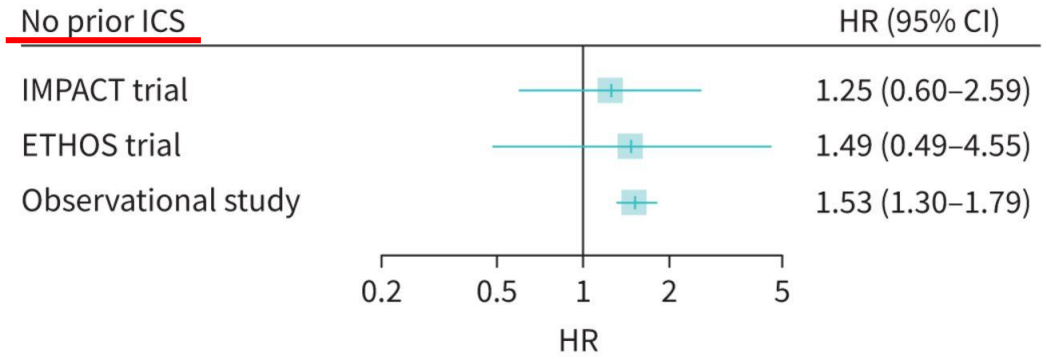
Lipson DA, et al. NEJM, 2018; 378: 1671–1680
Rabe KF, et al. NEJM, 2020; 383: 35–48.

Triple therapy and mortality

Mortality over time



All Cause Mortality (No prior ICS)

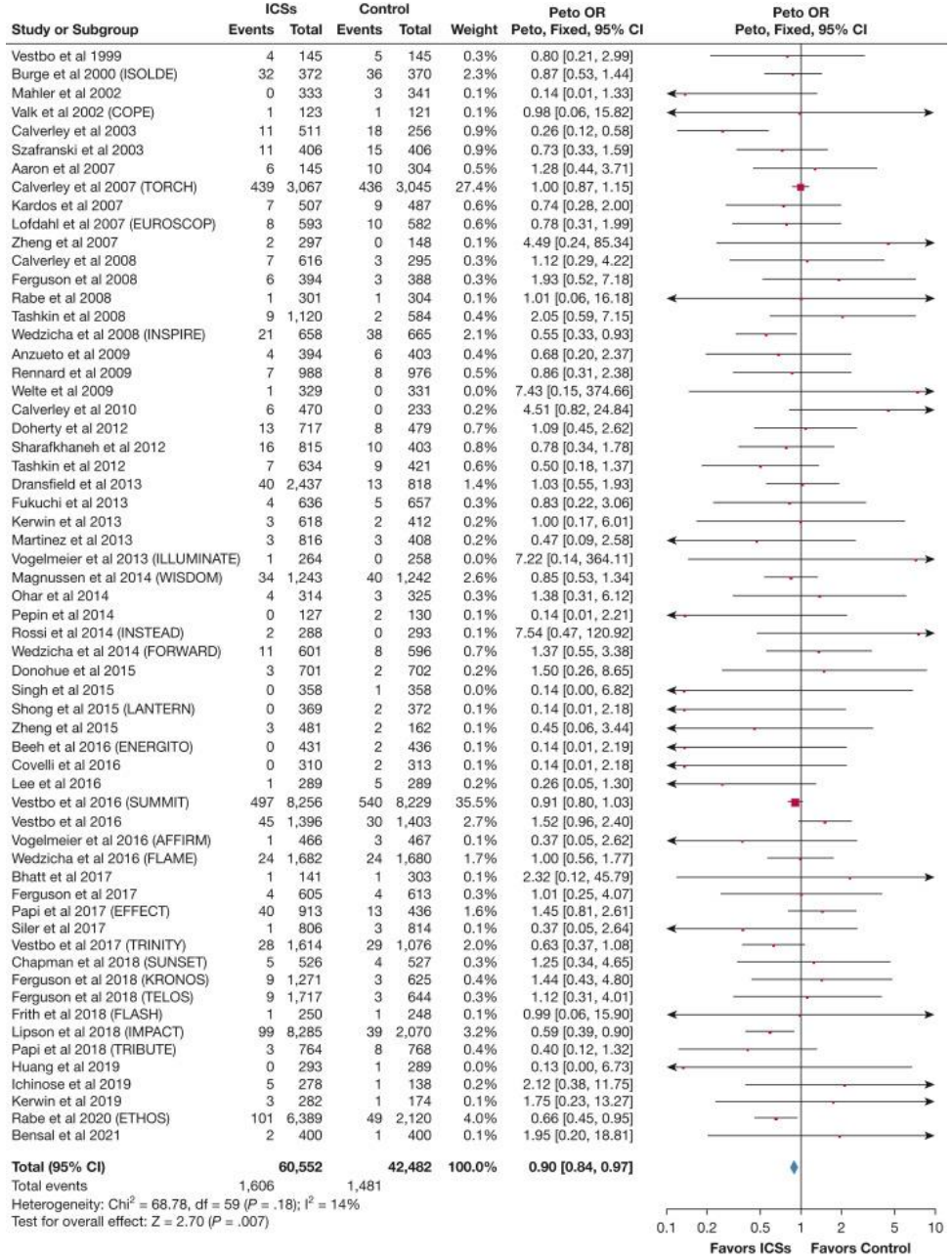


Suissa S. Lancet Resp Med, 2021 Jul 1;9(7):684-5.
Suissa, S. ERJ Open Research, 2023, 9.1.

ICSs and All-Cause Mortality Risk

- 60 RCTs enrolling 103,034 patients
- **Inhaled therapy containing ICSs**

  vs. without ICSs
  - Peto OR, **0.90**; 95% CI, 0.84-0.97



Study or Subgroup	ICSs Events	ICSs Total	Control Events	Control Total	Weight	Peto OR Peto, Fixed, 95% CI
Vestbo et al 1999	4	145	5	145	0.3%	0.80 [0.21, 2.99]
Burge et al 2000 (ISOLDE)	32	372	36	370	2.3%	0.87 [0.53, 1.44]
Mahler et al 2002	0	333	3	341	0.1%	0.14 [0.01, 1.33]
Valk et al 2002 (COPE)	1	123	1	121	0.1%	0.98 [0.06, 15.82]
Calverley et al 2003	11	511	18	256	0.9%	0.26 [0.12, 0.58]
Szafranski et al 2003	11	406	15	406	0.9%	0.73 [0.33, 1.59]
Aaron et al 2007	6	145	10	304	0.5%	1.28 [0.44, 3.71]
Calverley et al 2007 (TORCH)	439	3,067	436	3,045	27.4%	1.00 [0.87, 1.15]
Kardos et al 2007	7	507	9	487	0.6%	0.74 [0.28, 2.00]
Lofdahl et al 2007 (EUROSCOP)	8	593	10	582	0.6%	0.78 [0.31, 1.99]
Zheng et al 2007	2	297	0	148	0.1%	4.49 [0.24, 85.34]
Calverley et al 2008	7	616	3	295	0.3%	1.12 [0.29, 4.22]
Ferguson et al 2008	6	394	3	388	0.3%	1.93 [0.52, 7.18]
Rabe et al 2008	1	301	1	304	0.1%	1.01 [0.06, 16.18]
Tashkin et al 2008	9	1,120	2	584	0.4%	2.05 [0.59, 7.15]
Wedzicha et al 2008 (INSPIRE)	21	658	38	665	2.1%	0.55 [0.33, 0.93]
Anzueto et al 2009	4	394	6	403	0.4%	0.68 [0.20, 2.37]
Rennard et al 2009	7	988	8	976	0.5%	0.86 [0.31, 2.38]
Welte et al 2009	1	329	0	331	0.0%	7.43 [0.15, 374.66]
Calverley et al 2010	6	470	0	233	0.2%	4.51 [0.82, 24.84]
Doherty et al 2012	13	717	8	479	0.7%	1.09 [0.45, 2.62]
Sharafkhaneh et al 2012	16	815	10	403	0.8%	0.78 [0.34, 1.78]
Tashkin et al 2012	7	634	9	421	0.6%	0.50 [0.18, 1.37]
Dransfield et al 2013	40	2,437	13	818	1.4%	1.03 [0.55, 1.93]
Fukuchi et al 2013	4	636	5	657	0.3%	0.83 [0.22, 3.06]
Kerwin et al 2013	3	618	2	412	0.2%	1.00 [0.17, 6.01]
Martinez et al 2013	3	816	3	408	0.2%	0.47 [0.09, 2.58]
Vogelmeier et al 2013 (ILLUMINATE)	1	264	0	258	0.0%	7.22 [0.14, 364.11]
Magnussen et al 2014 (WISDOM)	34	1,243	40	1,242	2.6%	0.85 [0.53, 1.34]
Ohar et al 2014	4	314	3	325	0.3%	1.38 [0.31, 6.12]
Pepin et al 2014	0	127	2	130	0.1%	0.14 [0.01, 2.21]
Rossi et al 2014 (INSTEAD)	2	288	0	293	0.1%	7.54 [0.47, 120.92]
Wedzicha et al 2014 (FORWARD)	11	601	8	596	0.7%	1.37 [0.55, 3.38]
Donohue et al 2015	3	701	2	702	0.2%	1.50 [0.26, 8.65]
Singh et al 2015	0	358	1	358	0.0%	0.14 [0.00, 6.82]
Shong et al 2015 (LANTERN)	0	369	2	372	0.1%	0.14 [0.01, 2.18]
Zheng et al 2015	3	481	2	162	0.1%	0.45 [0.06, 3.44]
Beeh et al 2016 (ENERGITO)	0	431	2	436	0.1%	0.14 [0.01, 2.19]
Covelli et al 2016	0	310	2	313	0.1%	0.14 [0.01, 2.18]
Lee et al 2016	1	289	5	289	0.2%	0.26 [0.05, 1.30]
Vestbo et al 2016 (SUMMIT)	497	8,256	540	8,229	35.5%	0.91 [0.80, 1.03]
Vestbo et al 2016	45	1,396	30	1,403	2.7%	1.52 [0.96, 2.40]
Vogelmeier et al 2016 (AFFIRM)	1	466	3	467	0.1%	0.37 [0.05, 2.62]
Wedzicha et al 2016 (FLAME)	24	1,682	24	1,680	1.7%	1.00 [0.56, 1.77]
Bhatt et al 2017	1	141	1	303	0.1%	2.32 [0.12, 45.79]
Ferguson et al 2017	4	605	4	613	0.3%	1.01 [0.25, 4.07]
Papi et al 2017 (EFFECT)	40	913	13	436	1.6%	1.45 [0.81, 2.61]
Siler et al 2017	1	806	3	814	0.1%	0.37 [0.05, 2.64]
Vestbo et al 2017 (TRINITY)	28	1,614	29	1,076	2.0%	0.63 [0.37, 1.08]
Chapman et al 2018 (SUNSET)	5	526	4	527	0.3%	1.25 [0.34, 4.65]
Ferguson et al 2018 (KRONOS)	9	1,271	3	625	0.4%	1.44 [0.43, 4.80]
Ferguson et al 2018 (TELOS)	9	1,717	3	644	0.3%	1.12 [0.31, 4.01]
Frith et al 2018 (FLASH)	1	250	1	248	0.1%	0.99 [0.06, 15.90]
Lipson et al 2018 (IMPACT)	99	8,285	39	2,070	3.2%	0.59 [0.39, 0.90]
Papi et al 2018 (TRIBUTE)	3	764	8	768	0.4%	0.40 [0.12, 1.32]
Huang et al 2019	0	293	1	289	0.0%	0.13 [0.00, 6.73]
Ichinose et al 2019	5	278	1	138	0.2%	2.12 [0.38, 11.75]
Kerwin et al 2019	3	282	1	174	0.1%	1.75 [0.23, 13.27]
Rabe et al 2020 (ETHOS)	101	6,389	49	2,120	4.0%	0.66 [0.45, 0.95]
Bensal et al 2021	2	400	1	400	0.1%	1.95 [0.20, 18.81]
Total (95% CI)		**60,552**		**42,482**	**100.0%**	**0.90 [0.84, 0.97]**
Total events	1,606		1,481			

Heterogeneity: $Chi^2 = 68.78$, df = 59 ($P = .18$); $I^2 = 14\%$

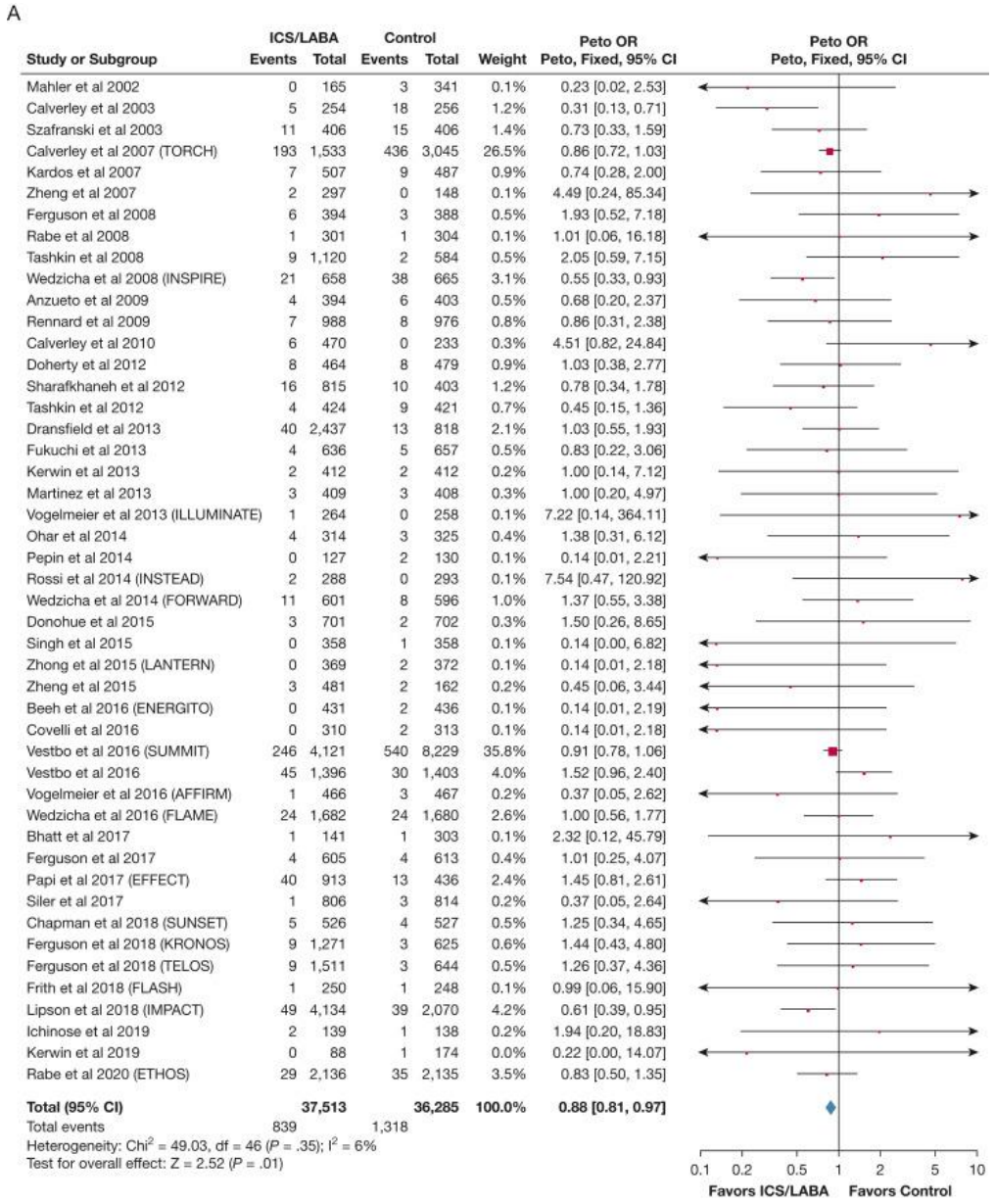
Test for overall effect: Z = 2.70 ($P = .007$)

Chen, Hong, et al. Chest, 2023, 163.1: 100-114.

ICSs and All-Cause Mortality Risk

ICS/LABA vs. without ICSs

- Peto OR, **0.88**; 95% CI, 0.81-0.97



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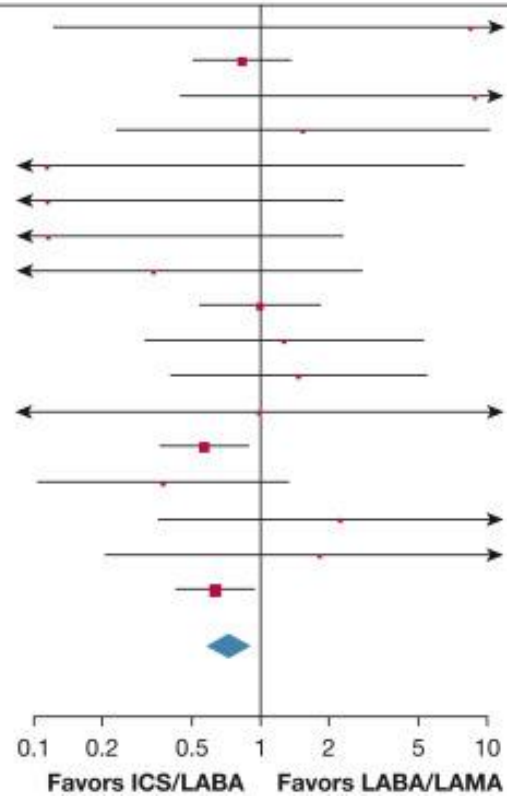
ICSs and All-Cause Mortality Risk

B

Study or Subgroup	ICS/LABA Events	ICS/LABA Total	LABA/LAMA Events	LABA/LAMA Total	Weight	Peto OR Peto, Fixed, 95% CI
Vogelmeir et al 2013 (ILLUMINATE)	1	264	0	258	0.3%	7.22 [0.14, 364.11]
Magnussen et al 2014 (WISDOM)	34	1,243	40	1,242	19.2%	0.85 [0.53, 1.34]
Rossi et al 2014 (INSTEAD)	2	288	0	293	0.5%	7.54 [0.47, 120.92]
Donohue et al 2015	3	701	2	702	1.3%	1.50 [0.26, 8.65]
Singh et al 2015	0	358	1	358	0.3%	0.14 [0.00, 6.82]
Zhong et al 2015 (LANTERN)	0	369	2	372	0.5%	0.14 [0.01, 2.18]
Beeh et al 2016 (ENERGITO)	0	431	2	436	0.5%	0.14 [0.01, 2.19]
Vogelmeier et al 2016 (AFFIRM)	1	466	3	467	1.1%	0.37 [0.05, 2.62]
Wedzicha et al 2016 (FLAME)	24	1,682	24	1,680	12.6%	1.00 [0.56, 1.77]
Chapman et al 2018 (SUNSET)	5	526	4	527	2.4%	1.25 [0.34, 4.65]
Ferguson et al 2018 (KRONOS)	9	1,271	3	625	2.8%	1.44 [0.43, 4.80]
Frith et al 2018 (FLASH)	1	250	1	248	0.5%	0.99 [0.06, 15.90]
Lipson et al 2018 (IMPACT)	99	8,285	39	2,070	23.2%	0.59 [0.39, 0.90]
Papi et al 2018 (TRIBUTE)	3	764	8	768	2.9%	0.40 [0.12, 1.32]
Ichinose et al 2019	5	278	1	138	1.4%	2.12 [0.38, 11.75]
Kerwin et al 2019	3	282	1	174	1.0%	1.75 [0.23, 13.27]
Rabe et al 2020 (ETHOS)	101	6,389	49	2,120	29.4%	0.66 [0.45, 0.95]
Total (95% CI)		**23,847**		**12,478**	**100.0%**	**0.75 [0.61, 0.92]**
Total events	291		180			

Heterogeneity: $Chi^2 = 16.52$, df = 16 ($P = .42$); $I^2 = 3\%$
Test for overall effect: Z = 2.80 ($P = .005$)



ICS/LABA vs. **LABA/LAMA**

Peto OR **0.75** [0.61, 0.92]

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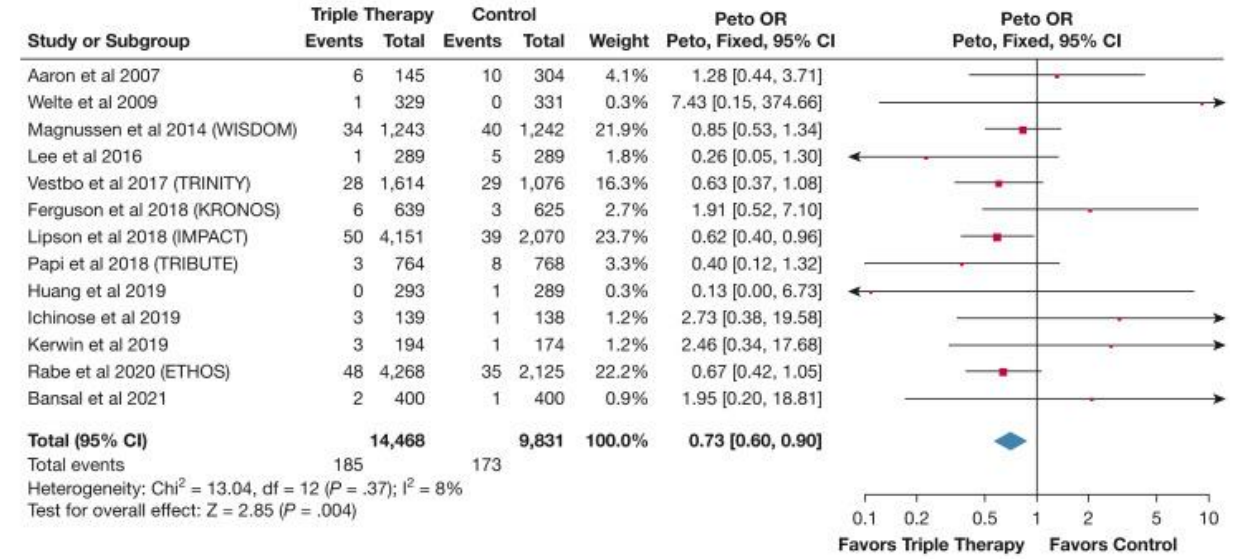
ICSs and All-Cause Mortality Risk

C



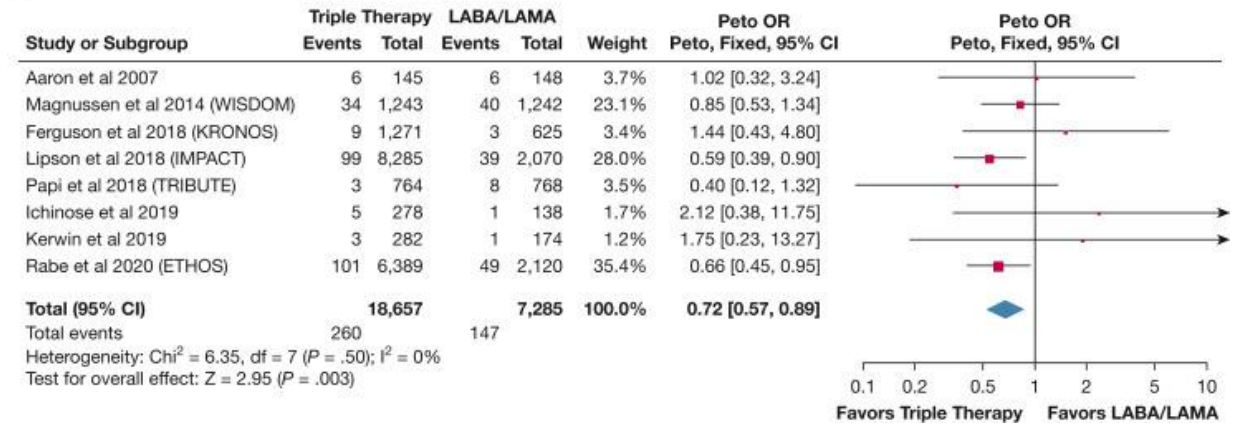
Study or Subgroup	Triple Therapy Events	Triple Therapy Total	Control Events	Control Total	Weight	Peto OR Peto, Fixed, 95% CI
Aaron et al 2007	6	145	10	304	4.1%	1.28 [0.44, 3.71]
Welte et al 2009	1	329	0	331	0.3%	7.43 [0.15, 374.66]
Magnussen et al 2014 (WISDOM)	34	1,243	40	1,242	21.9%	0.85 [0.53, 1.34]
Lee et al 2016	1	289	5	289	1.8%	0.26 [0.05, 1.30]
Vestbo et al 2017 (TRINITY)	28	1,614	29	1,076	16.3%	0.63 [0.37, 1.08]
Ferguson et al 2018 (KRONOS)	6	639	3	625	2.7%	1.91 [0.52, 7.10]
Lipson et al 2018 (IMPACT)	50	4,151	39	2,070	23.7%	0.62 [0.40, 0.96]
Papi et al 2018 (TRIBUTE)	3	764	8	768	3.3%	0.40 [0.12, 1.32]
Huang et al 2019	0	293	1	289	0.3%	0.13 [0.00, 6.73]
Ichinose et al 2019	3	139	1	138	1.2%	2.73 [0.38, 19.58]
Kerwin et al 2019	3	194	1	174	1.2%	2.46 [0.34, 17.68]
Rabe et al 2020 (ETHOS)	48	4,268	35	2,125	22.2%	0.67 [0.42, 1.05]
Bansal et al 2021	2	400	1	400	0.9%	1.95 [0.20, 18.81]
Total (95% CI)		**14,468**		**9,831**	**100.0%**	**0.73 [0.60, 0.90]**
Total events	185		173			

Heterogeneity: $Chi^2 = 13.04$, df = 12 ($P = .37$); $I^2 = 8\%$
Test for overall effect: Z = 2.85 ($P = .004$)

Triple vs. **without ICSs**

Peto OR **0.73** [0.60, 0.90]

D



Study or Subgroup	Triple Therapy Events	Triple Therapy Total	LABA/LAMA Events	LABA/LAMA Total	Weight	Peto OR Peto, Fixed, 95% CI
Aaron et al 2007	6	145	6	148	3.7%	1.02 [0.32, 3.24]
Magnussen et al 2014 (WISDOM)	34	1,243	40	1,242	23.1%	0.85 [0.53, 1.34]
Ferguson et al 2018 (KRONOS)	9	1,271	3	625	3.4%	1.44 [0.43, 4.80]
Lipson et al 2018 (IMPACT)	99	8,285	39	2,070	28.0%	0.59 [0.39, 0.90]
Papi et al 2018 (TRIBUTE)	3	764	8	768	3.5%	0.40 [0.12, 1.32]
Ichinose et al 2019	5	278	1	138	1.7%	2.12 [0.38, 11.75]
Kerwin et al 2019	3	282	1	174	1.2%	1.75 [0.23, 13.27]
Rabe et al 2020 (ETHOS)	101	6,389	49	2,120	35.4%	0.66 [0.45, 0.95]
Total (95% CI)		**18,657**		**7,285**	**100.0%**	**0.72 [0.57, 0.89]**
Total events	260		147			

Heterogeneity: $Chi^2 = 6.35$, df = 7 ($P = .50$); $I^2 = 0\%$
Test for overall effect: Z = 2.95 ($P = .003$)

Triple vs. **LABA/LAMA**

Peto OR **0.72** [0.57, 0.89]

Chen, Hong, et al. Chest, 2023, 163.1: 100-114.

Subgroups: medication, exacerbation

Results	No. of Patients (No. of Studies)	Inhaled Therapy Containing ICSs		Inhaled Therapy Without ICSs		Peto OR (95% CI)	I^2 Value (%)	Strength of Evidence[a]
		Events	Patients	Events	Patients			
Treatment duration stratified all-cause mortality risk								
≤ 6 mo	25,607 (30)	76	14,481	61	11,126	0.91 (0.64-1.29)	0	Moderate
> 6 mo	77,427 (30)	1,530	46,071	1,420	31,356	0.90 (0.83-0.97)	32	High
Dose-stratified all-cause mortality risk								
High dose[b]	31,945 (32)	651	15,455	689	16,490	0.95 (0.85-1.07)	16	Moderate
Medium dose[c]	23,695 (21)	133	12,663	151	11,032	0.71 (0.56-0.91)	29	High
Low dose[d]	51,038 (21)	756	28,588	757	22,450	0.88 (0.79-0.97)	33	High
Type-stratified all-cause mortality risk								
Fluticasone propionate	28,316 (24)	634	14,396	638	13,920	0.96 (0.86, 1.08)	0	High
Fluticasone furoate	39,535 (12)	694	24,073	638	15,462	0.91 (0.81, 1.01)	27	High
Budesonide	26,370 (18)	207	16,905	140	9,465	0.75 (0.59-0.94)	25	High
Beclomethasone dipropionate	5,884 (4)	44	3,211	45	2,673	0.75 (0.49-1.14)	48	Low
Mometasone furoate	3,162 (3)	27	1,967	20	1,195	0.84 (0.46-1.51)	0	Low
Exacerbation-stratified[e] all-cause mortality risk								
< 1	29,139 (14)	537	15,962	565	13,177	0.92 (0.81-1.03)	0	High
≥ 1 and < 2	23,620 (11)	596	13,252	539	10,368	0.99 (0.87-1.12)	17	Moderate
≥ 2	19,858 (3)	207	15,181	97	4,677	0.63 (0.49-0.83)	0	High

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Patient subgroups

Results	No. of Patients (No. of Studies)	Inhaled Therapy Containing ICSs		Inhaled Therapy Without ICSs		Peto OR (95% CI)	I^2 Value (%)	Strength of Evidence[a]
		Events	Patients	Events	Patients			
Baseline blood eosinophil counts-stratified all-cause mortality risk								
< 2%	1,806 (2)	32	935	28	871	1.06 (0.63-1.79)	72	Low
≥ 2%	6,503 (4)	47	3,489	63	3,014	0.61 (0.42-0.90)	0	High
< 200/μL	10,861 (3)	113	7,942	53	2,919	0.72 (0.51-1.03)	11	Moderate
≥ 200/μL	4,222 (2)	31	2,378	37	1,844	0.58 (0.36-0.95)	0	High
Lung function-stratified all-cause mortality risk								
GOLD stage I or II	32,545 (19)	579	17,214	617	15,331	0.91 (0.81-1.03)	0	High
≤ 6 mo	13,853 (15)	38	7,848	26	6,005	1.02 (0.61-1.69)	0	High
> 6 mo	18,692 (4)	541	9,366	591	9,326	0.91 (0.80-1.02)	0	High
GOLD stage III or IV	62,953 (36)	938	38,789	818	24,164	0.87 (0.78-0.96)	29	High
≤ 6 mo	12,391 (14)	37	6,976	35	5,415	0.81 (0.50-1.30)	6	High
> 6 mo	50,562 (22)	901	31,813	783	18,749	0.87 (0.79-0.97)	41	High
Age-stratified all-cause mortality risk								
< 65 y	52,399 (38)	449	31,663	348	20,736	0.81 (0.70-0.94)	2	High
≥ 65 y	49,355 (20)	1,150	28,245	1,129	21,110	0.93 (0.86-1.02)	29	High
BMI-stratified all-cause mortality risk								
< 25	4,941 (8)	53	2,701	56	2,240	0.86 (0.58-1.27)	0	Moderate
≥ 25	69,154 (27)	1,339	41,086	1,265	28,068	0.91 (0.84-0.99)	19	High

Chen, Hong, et al. Chest, 2023, 163.1: 100-114.

Study summary

- Inhaled therapy containing ICSs: reduction in all-cause mortality risk
- Subgroup analyses: treatment duration > 6 months, medium- and low-dose ICS, budesonide
- Strongest predictor: BEC ≥ 200/μL

Chen, Hong, et al. Chest, 2023, 163.1: 100-114.

Original research

Budesonide/formoterol maintenance and reliever therapy versus fluticasone/salmeterol fixed-dose treatment in patients with COPD

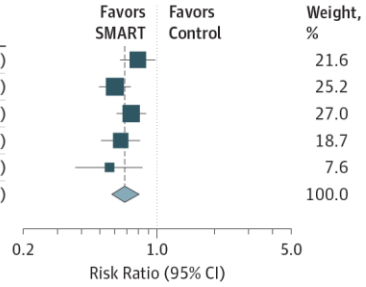
Susan Muiser ,[1,2] Kai Imkamp,[1,2] Dianne Seigers,[1] Nynke J Halbersma,[1] Judith M Vonk ,[2,3] Bart H D Luijk,[4] Gert-Jan Braunstahl,[5] Jan-Willem van den Berg,[6] Bart-Jan Kroesen,[7] Janwillem W H Kocks,[1,2,8,9] Irene H Heijink,[1,2,10] Helen K Reddel ,[11,12] Huib A M Kerstjens ,[1,2] Maarten van den Berge [1,2]

MART in asthma

MART vs. Same Dose ICS/LABA

Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
Vogelmeier et al,[23] 2012	1067	132	1076	167	-3.1 (-6.1 to -0.2)	0.80 (0.64 to 0.99)	21.6
Rabe et al,[25] 2006	1107	143	1138	245	-8.6 (-11.7 to -5.5)	0.60 (0.50 to 0.72)	25.2
Atienza et al,[24] 2013	1049	170	1042	229	-5.8 (-9.1 to -2.4)	0.74 (0.62 to 0.88)	27.0
Papi et al,[26] 2013	852	99	849	152	-6.3 (-9.6 to -2.9)	0.65 (0.51 to 0.82)	18.7
Patel et al,[27] 2013	151	28	152	50	-14.4 (-24.1 to -4.6)	0.56 (0.38 to 0.84)	7.6
Overall (random-effects model)	4226	572	4257	843	-6.4 (-10.2 to -2.6)	0.68 (0.58 to 0.80)	100.0

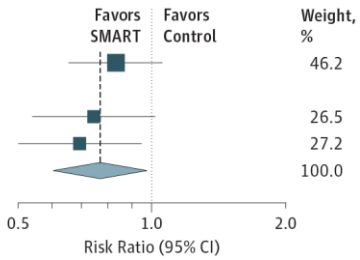
Heterogeneity: $I^2 = 29\%$, $P = .23$
Test for overall effect: $t_4 = -6.44$, $P < .001$



MART vs. Higher Dose ICS/LABA

Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)	46.2
Kuna et al,[33] 2007							
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)	26.5
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)	27.2
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)	100.0

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$



*Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits

Sobieraj, Diana M., et al. JAMA, 2018, 319.14: 1485-1496.

MART vs. fixed dose ICS

Single inhaler therapy compared to fixed dose ICS for asthma in adults not controlled on regular ICS

Patient or population: patients with asthma in adults not controlled on regular ICS
Settings: community
Intervention: Single inhaler therapy
Comparison: fixed dose ICS

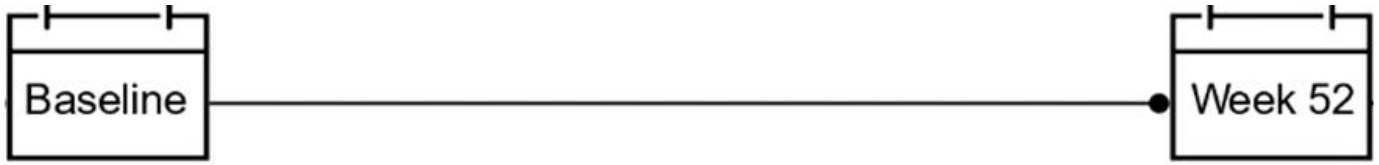
Outcomes	Illustrative comparative risks* (95% CI): Assumed risk	Illustrative comparative risks* (95% CI): Corresponding risk	Relative effect (95% CI)	No of Participants (studies)
	Fixed dose ICS	Single inhaler therapy		
Patients with exacerbations causing hospitalisation Follow-up: mean 11 months	**10 per 1000**	**6 per 1000** (3 to 11)	**OR 0.56** (0.28 to 1.09)	4209 (3 studies)
Patients with exacerbations treated with oral steroids Follow-up: mean 11 months	**181 per 1000**	**107 per 1000** (90 to 124)	**OR 0.54** (0.45 to 0.64)	4280 (4 studies)
Fatal serious adverse events Follow-up: mean 11 months	**1 per 1000**	**1 per 1000** (0 to 4)	**OR 0.37** (0.05 to 2.62)	4209 (3 studies)
Serious adverse events (non-fatal) Follow-up: mean 11 months	**48 per 1000**	**47 per 1000** (36 to 62)	**OR 0.97** (0.73 to 1.29)	4209 (3 studies)
Discontinuation due to adverse events Follow-up: mean 11 months	**36 per 1000**	**21 per 1000** (13 to 33)	**OR 0.57** (0.35 to 0.93)	2586 (2 studies)

Cates, Christopher J.; Karner, Charlotta. CDSR, 2013, 4.

Study design

An open-label, randomized, parallel-group, multicenter study to compare the efficacy and safety of budesonide/formoterol MART versus fixed-dose fluticasone/salmeterol in patients with moderate to severe COPD

2015.5 ~ 2019.6



Screening
N=300

Randomization
N=195

Treatment Period

MART Bud/Form 160/4.5 N=103

Fixed-dose FSC 500/50 N=92

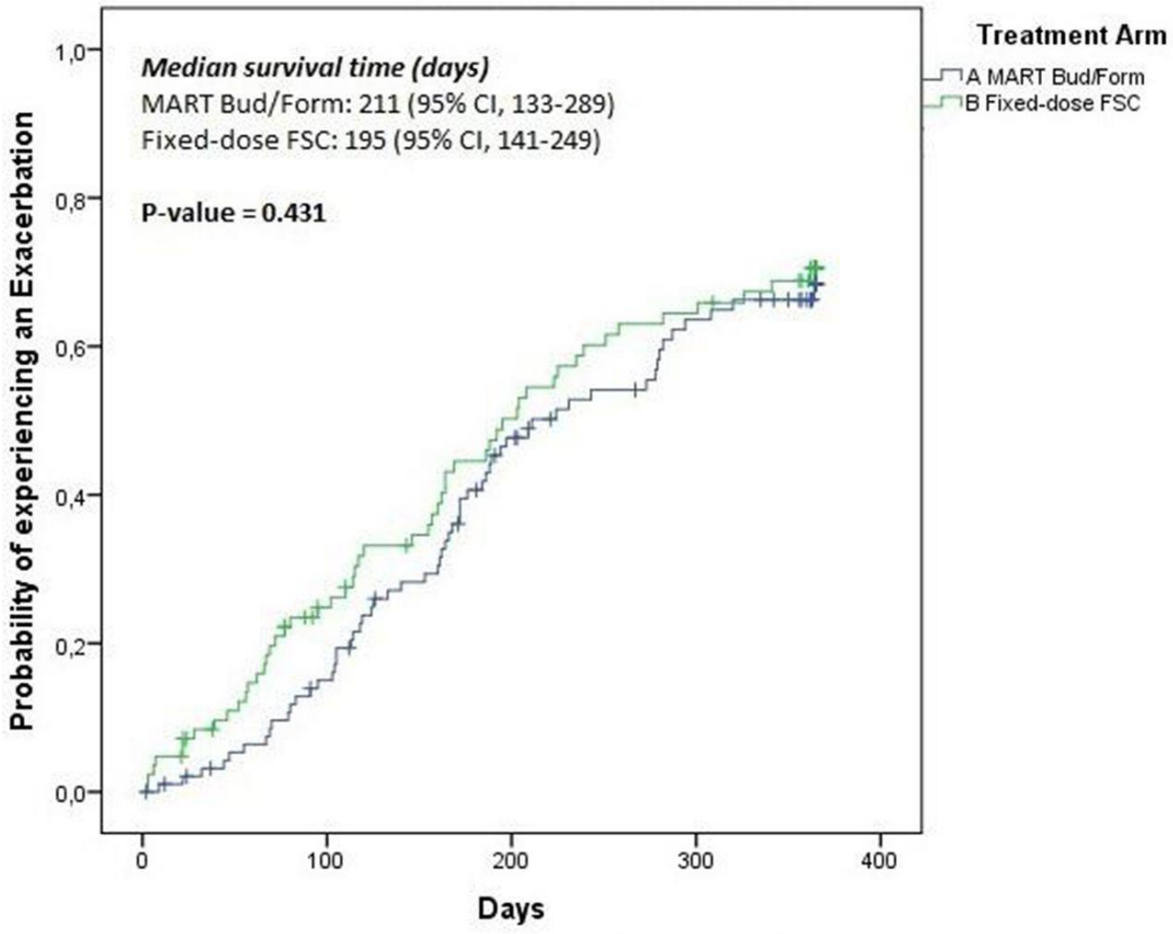
Follow-up

≥10 PY ever-smoker COPD
≥1 COPD exacerbation in previous 2 years

Visit 1: 0 months
Visit 2: 6 months
Visit 3: 12 months

Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

Primary outcome: exacerbation



<u>MART Bud/Form</u> vs **<u>Fixed-dose FSC</u>**

Primary Endpoint:
Moderate/Severe exacerbation rate

1.32 vs 1.32/year
Rate ratio 1.05 (95% CI 0.79 to 1.39)
P=0.741

Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

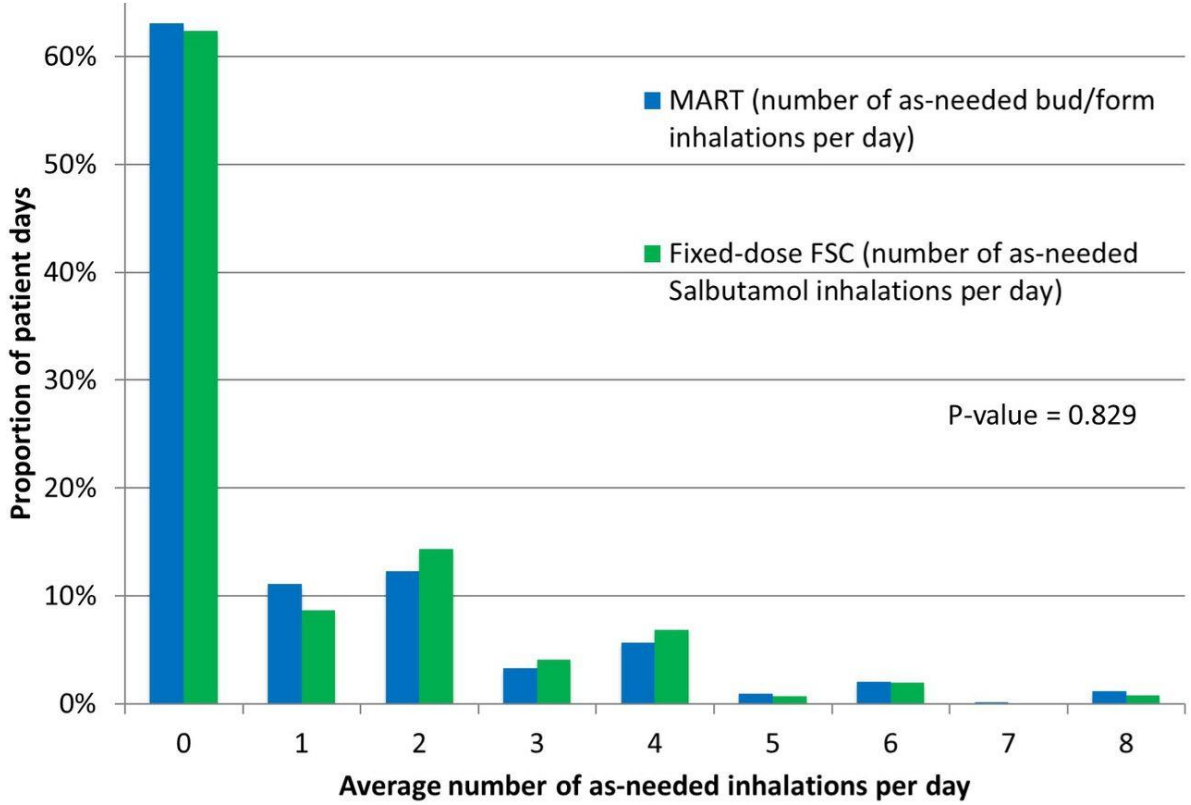
ICS exposure and as-needed medication use

MART Bud/Form vs **Fixed-dose FSC**

160/4.5 500/50

Total ICS per day
928µg/day vs 1747µg/day, P<0.001

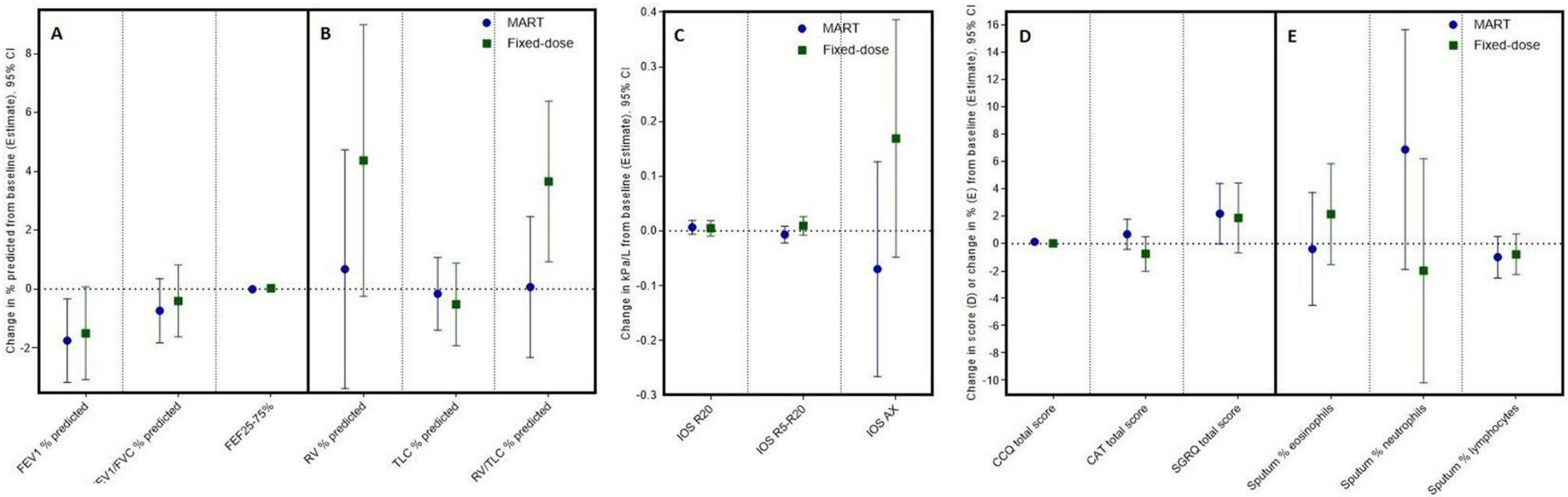
As-needed inhalation use; P=0.829



Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

Lung function and health status

Post-BD spirometry **IOS** **Questionnaires** **Induced sputum**



Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

Adverse events

Table 3 (Serious) adverse events and study discontinuation

Variable	MART Bud/Form n=103	Fixed-dose FSC n=92	P value
Patients with at least one adverse event, n*	75 (73%)	62 (67%)	0.408
Serious adverse events, n*	21 (20%)	17 (19%)	0.857
Hospitalisation due to exacerbation	8	9	
Hospitalisation due to pneumonia	5	0	
Other	8	8	
Patients with confirmed pneumonia (including on chest X-ray), n (%)¶			0.216†
0	98 (95%)	91 (99%)	
1	5 (5%)	1 (1%)	
Patients with confirmed or probable pneumonia, n*			0.068‡
0	96 (93%)	91 (99%)	
1	6 (6%)	1 (1%)	
2	1 (1%)	0	
ICS dosage/day µg/day budesonide equivalents	928 (798–1168)	1747 (1643–1877)	<0.001§
Premature discontinuation, n	31 (30%)	34 (37%)	0.31

Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

Study summary

- Budesonide/formoterol MART
  - Similarly effective and safe to fluticasone/salmeterol fixed-dose therapy
  - Much lower total daily standardised ICS dose with MART compared with fixed-dose therapy
- The potential successful treatment strategy, not only in asthma but also in patients with moderate to severe COPD

Muiser, Susan, et al. Thorax, 2023, 78.5: 451-458.

RESEARCH Open Access

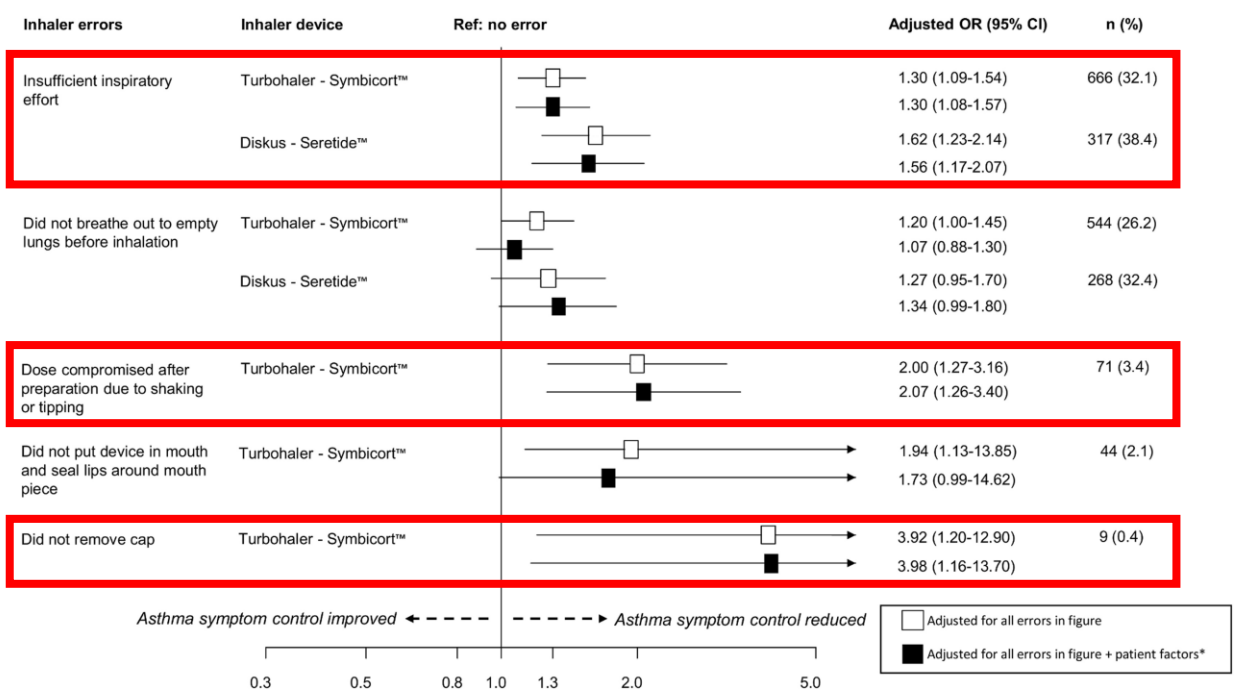
Identifying critical inhalation technique errors in Dry Powder Inhaler use in patients with COPD based on the association with health status and exacerbations: findings from the multi-country cross-sectional observational PIFotal study

Janwillem Kocks[1,2,3,4*], Sinthia Bosnic-Anticevich[5,6], Joyce van Cooten[1], Jaime Correia de Sousa[7], Biljana Cvetkovski[5], Richard Dekhuijzen[8], Lars Dijk[1], Marina Garcia Pardo[9], Asparuh Gardev[10], Radosław Gawlik[11], Iris van der Ham[1], Ymke Janse[1], Federico Lavorini[12], Tiago Maricoto[13], Jiska Meijer[1], Boyd Metz[1], David Price[3,14], Miguel Roman Rodriguez[9], Kirsten Schuttel[1], Nilouq Stoker[1], Ioanna Tsiligianni[15], Omar Usmani[16], Jaco Voorham[17] and Marika T. Leving[1]

Inhaler errors and uncontrolled asthma

Multicenter cross-sectional study of adult asthma (CRITIKAL Study)
>5,000 patients receiving ICS/LABA

DPIs



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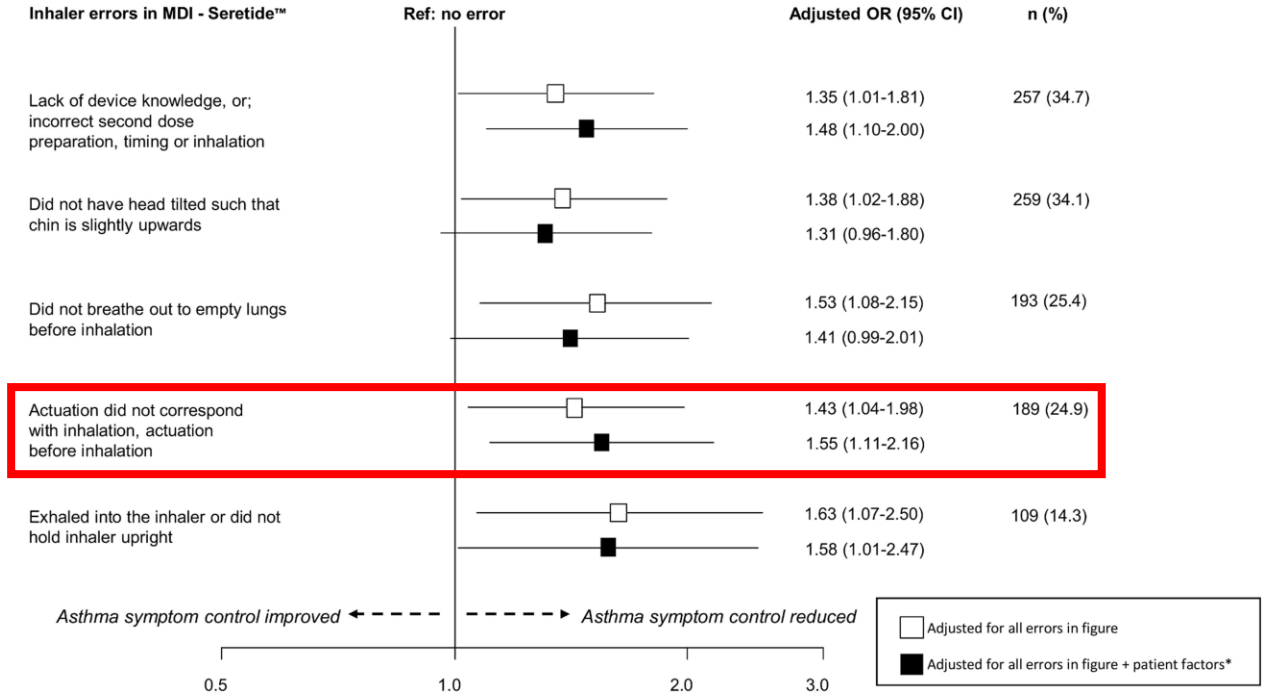
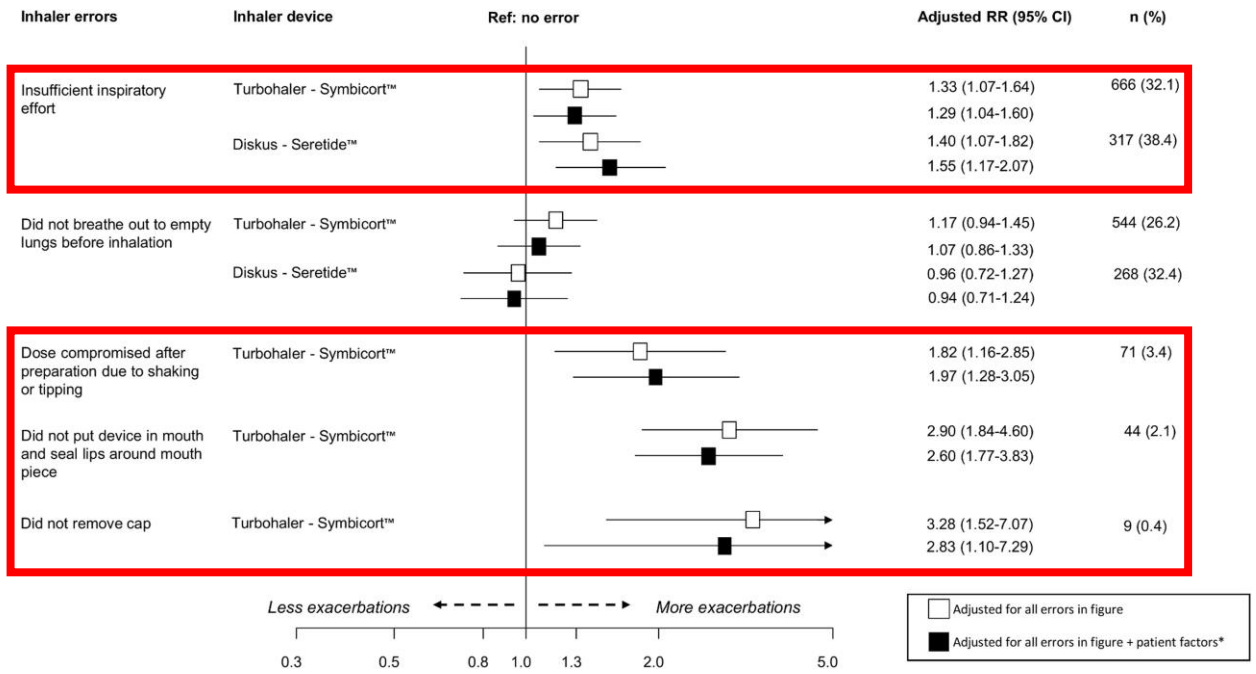


Price, David B., et al. JACI: In Practice, 2017, 5.4: 1071-1081. e9.

Inhaler errors and rate of exacerbations

Multicenter cross-sectional study of adult asthma (CRITIKAL Study)
>5,000 patients receiving ICS/LABA

DPIs



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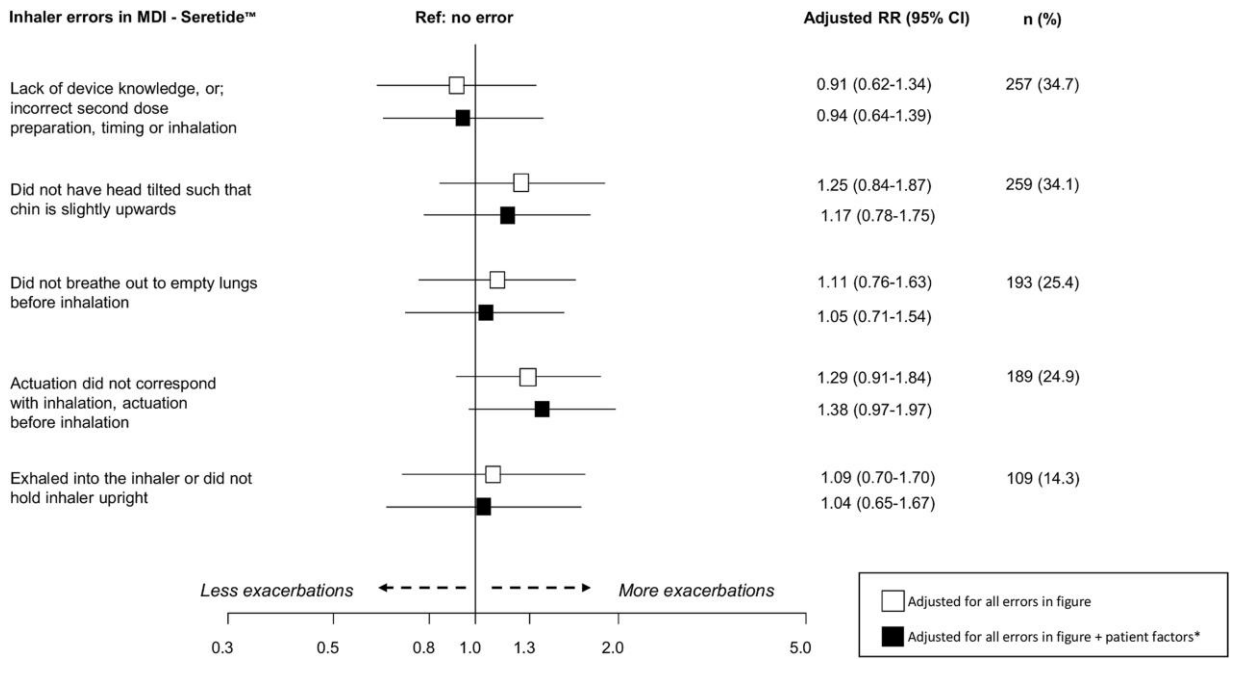


Price, David B., et al. JACI: In Practice, 2017, 5.4: 1071-1081. e9.

Inhaler handling and COPD exacerbation

2,935 patients with COPD visiting GPs and pulmonologists
Inhalation technique was rated by physicians
<40% of patients: perfect inhalation according instruction leaflet

TABLE 3 Critical error descriptions

	Breezhaler®	Diskus®	Handihaler®	pMDI	Respimat®	Turbuhaler®
Devices n	876	452	598	422	625	420
Dose preparation critical errors						
Lack of cartridge or no capsule in device prior to inhalation	3 (0.3)		5 (0.8)		35 (5.6)	
Inhalation despite dose counter at zero		20 (4.4)			37 (5.9)	16 (3.8)
Opening next blister when taking the capsule			34 (5.7)			
Activation error (not pressing button, twisting error, loading position error, not sliding lever, opening mouthpiece)	4 (0.5)	9 (2.0)	18 (3.0)		7 (1.1)	86 (20.5)
Total dose preparation critical error [95% CI]	7 (0.8) [0.3–1.6]	29 (6.4) [4.2–8.7]	48 (8.0) [5.8–10.2]	–	78 (12.5) [9.9–15.1]	100 (23.8) [19.7–27.9]
Dose delivery critical errors						
Expiration in powder device prior inhalation	87 (9.9)	60 (13.3)	60 (10.0)			36 (8.6)
No inspiration through the mouthpiece	21 (2.4)	15 (3.3)	22 (3.7)	7 (1.7)	11 (1.8)	14 (3.3)
Remaining powder in the capsule by the end	33 (3.8)		80 (13.4)			
Lack of synchronisation hand–lung with smoke emanation				181 (42.9)	246 (39.4)	
Total dose delivery critical error [95% CI]	131 (15.0) [12.6–17.3]	70 (15.5) [12.2–18.8]	149 (24.9) [21.4–28.4]	185 (43.8) [39.1–48.6]	249 (39.8) [36–43.7]	48 (11.4) [8.4–14.5]

TABLE 5 Determinants of severe exacerbation in the past 3 months among patients treated for at least 3 months (multiple binary logistic regression: final model)

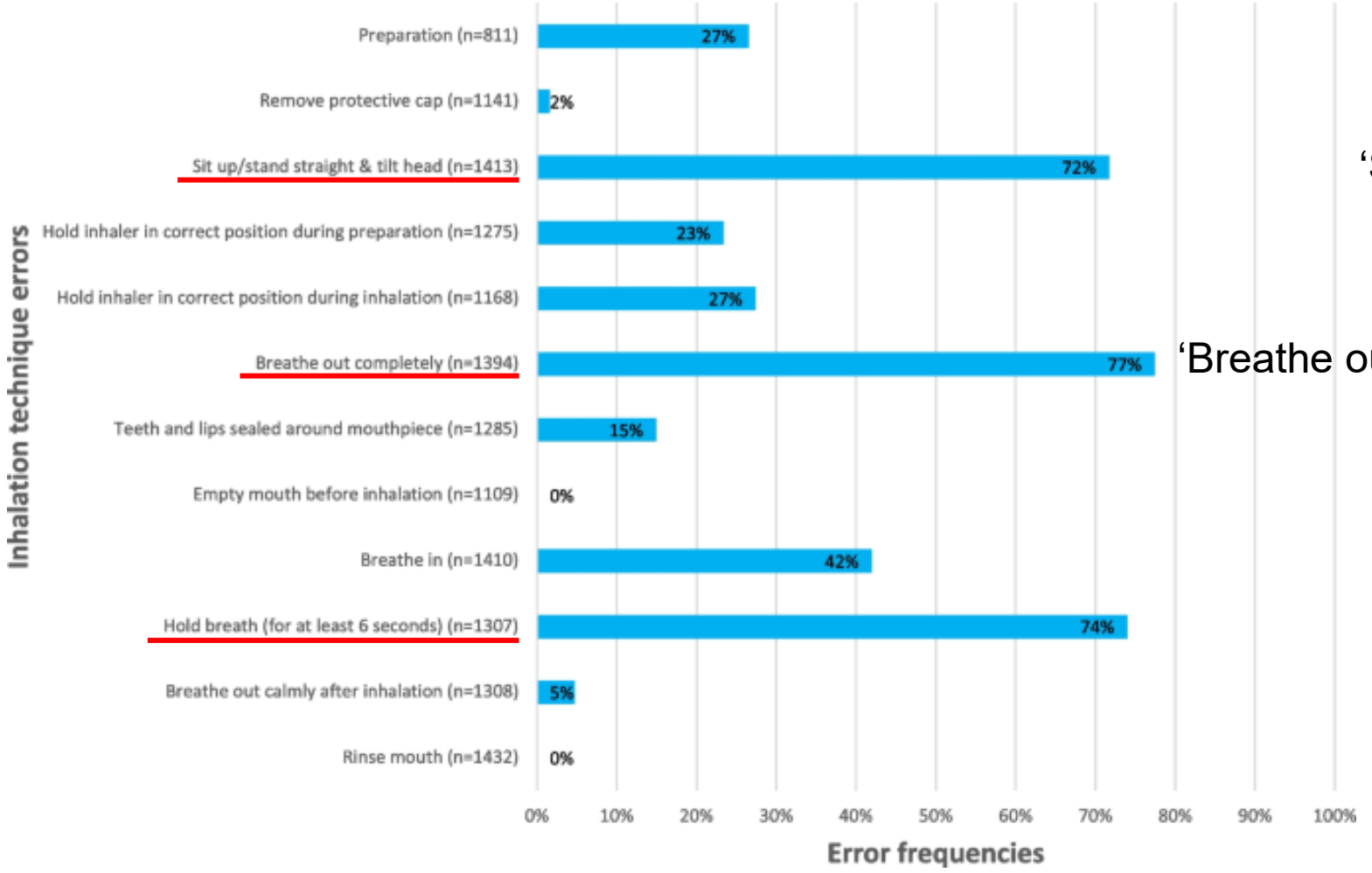
	Severe exacerbation in the past 3 months			
	No	Yes	OR (95% CI)#	p value
Subjects n	2775	146		
Error				0.0297
No error	767 (96.7)	26 (3.3)	1	
Non-critical error(s)	1100 (95.4)	53 (4.6)	1.29 (0.79–2.11)	
At least one critical error	908 (93.1)	67 (6.9)	1.86 (1.14–3.04)	
Age				0.0053
⩽70 years	1848 (96.3)	72 (3.7)	1	
>70 years	927 (92.6)	74 (7.4)	1.65 (1.16–2.36)	
Previous asthma				0.0034
No	2058 (95.7)	93 (4.3)	1	
Yes	717 (93.1)	53 (6.9)	1.72 (1.20–2.46)	
Duration of COPD				<0.0001
⩽5 years	891 (98.8)	11 (1.2)	1	
6–10 years	703 (95.1)	36 (4.9)	4.03 (2.03–8.01)	
>10 years	1181 (92.3)	99 (7.7)	5.77 (3.03–10.96)	
Poor adherence				0.0451
No	2550 (95.3)	127 (4.7)	1	
Yes	236 (92.9)	18 (7.2)	1.73 (1.01–2.97)	

Molimard, Mathieu, et al. ERJ, 2017, 49.2.

Methods

- *Post hoc* of PIFotal study
  - Association of peak inspiratory flow (PIF), inhalation technique and adherence with COPD outcomes
- Cross-sectional multi-country observational study in a primary care setting
- 1,434 COPD patients aged ≥ 40 years using a DPI for their maintenance therapy
- Inhalation technique: video recording and scoring by two independent researchers
- Outcome
  - Health status assessment; CCQ, CAT
  - The number of moderate and severe exacerbations in the past 12 months

Inhalation technique errors



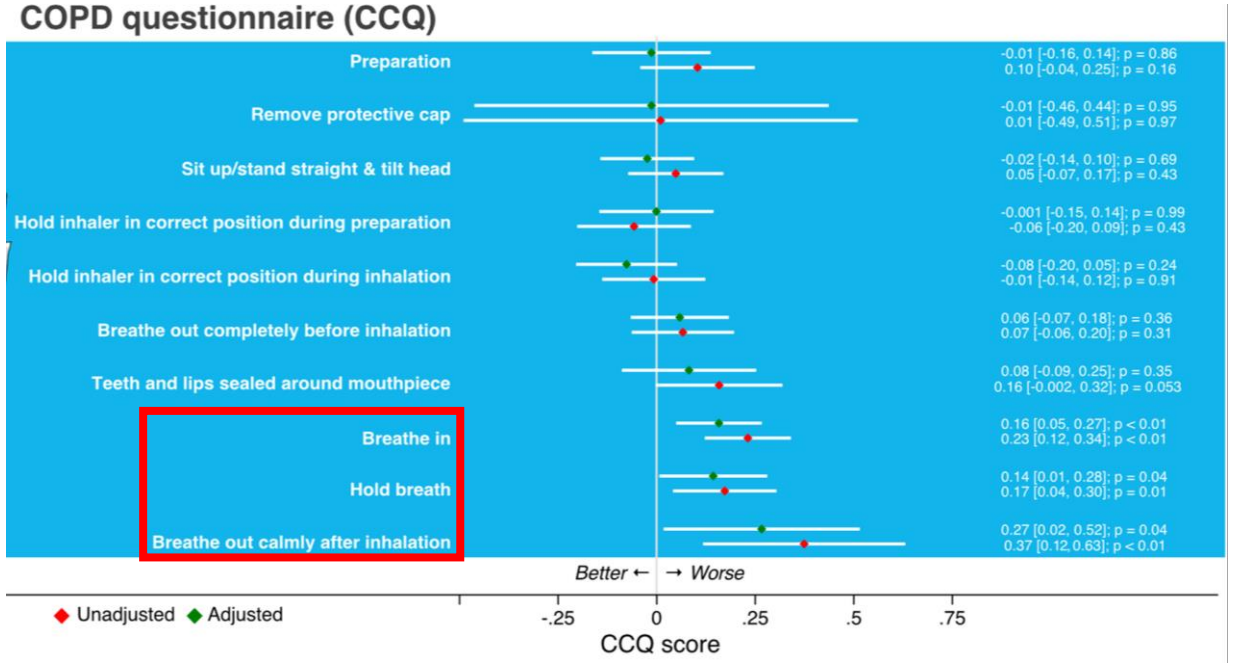
‘Sit up/stand straight & tilt head’

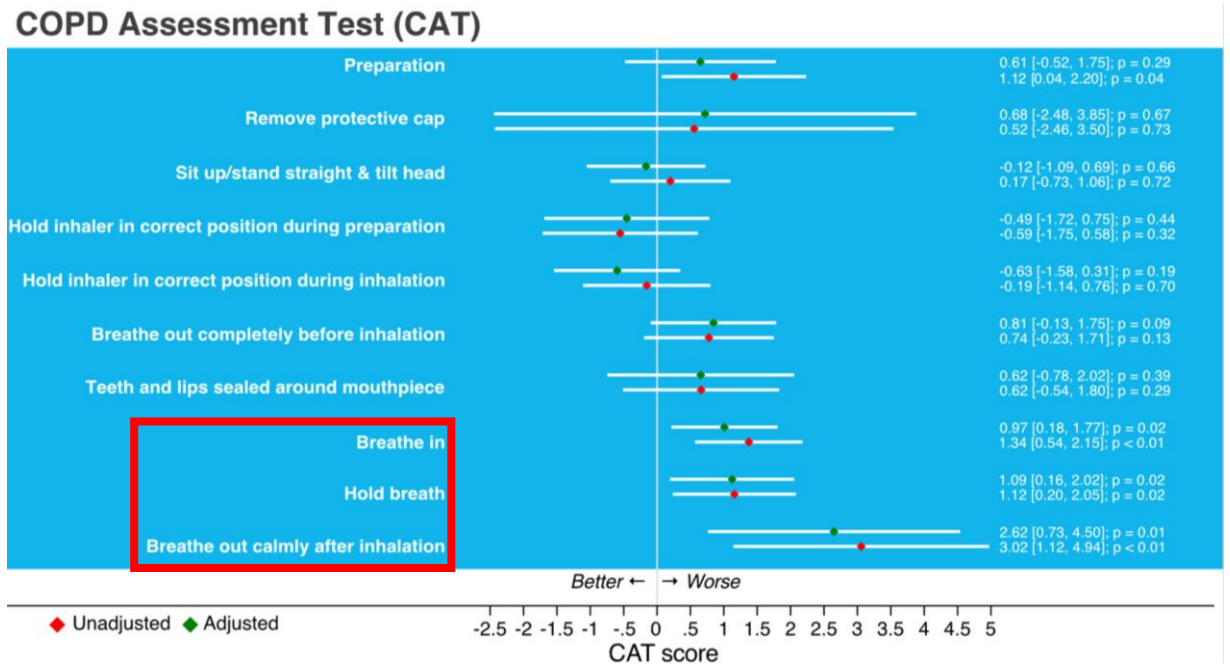
‘Breathe out completely before inhalation’

‘Hold breath (for at least 6 s)’

Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

Inhalation error and health status

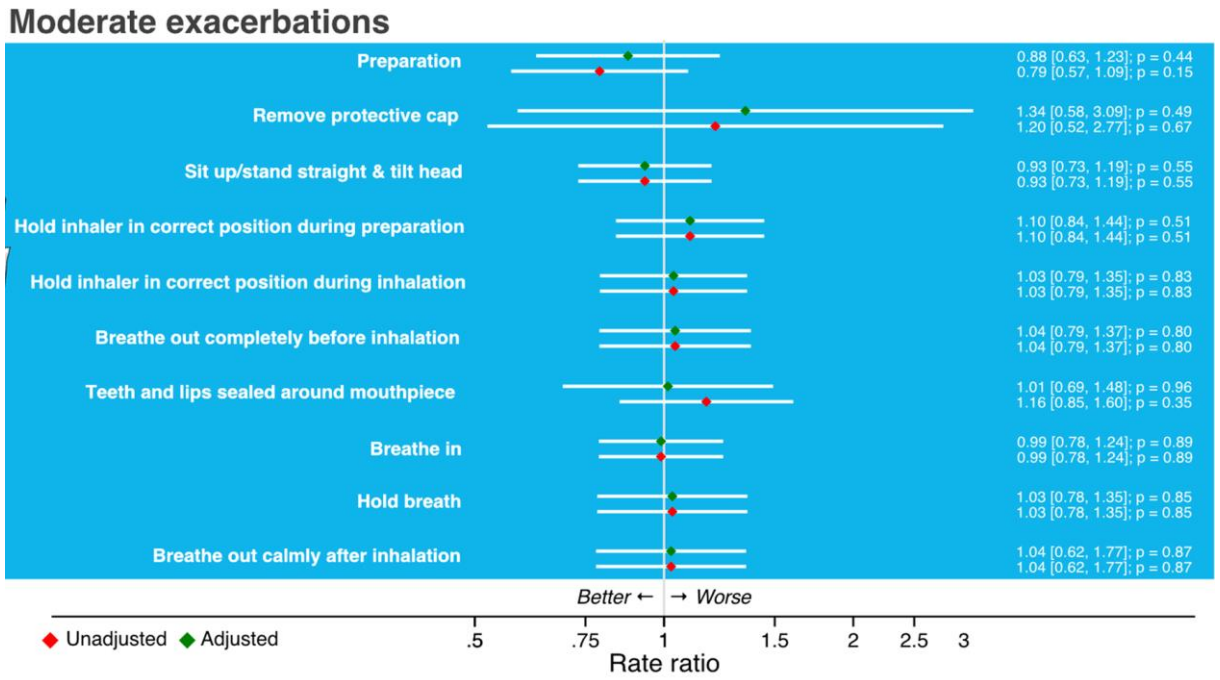


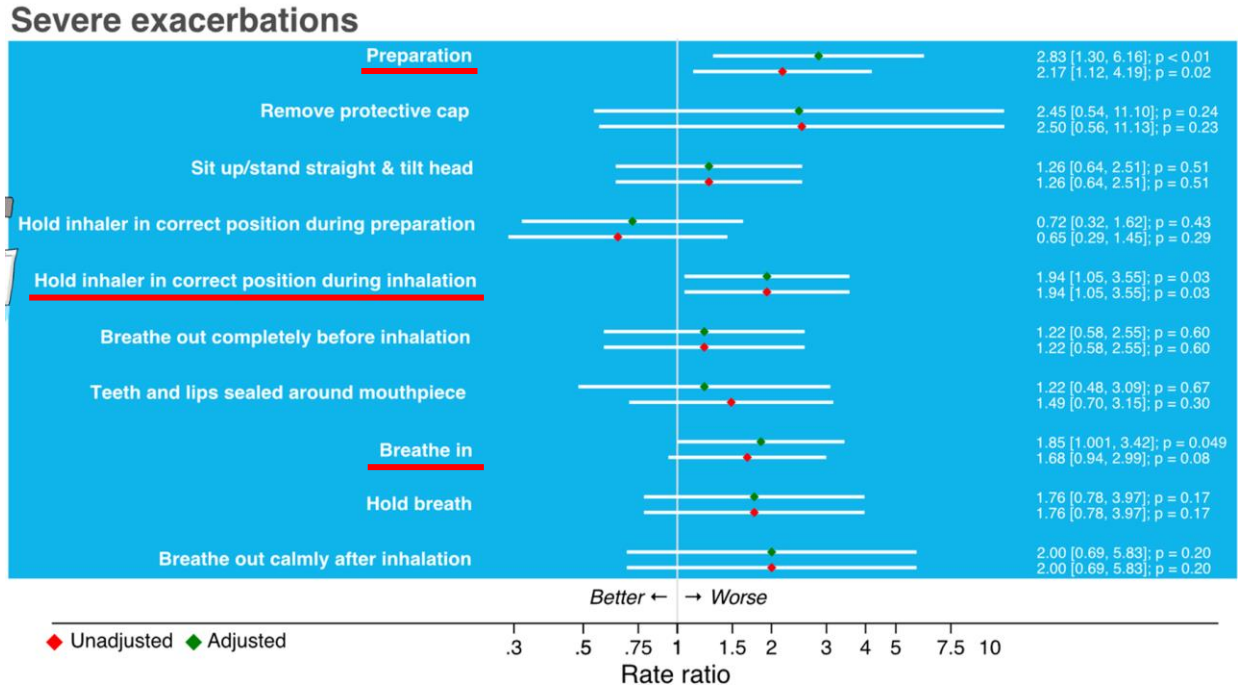


- Breathe in
- Hold breath
- Breathe out calmly after inhalation

Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

Inhalation error and exacerbations

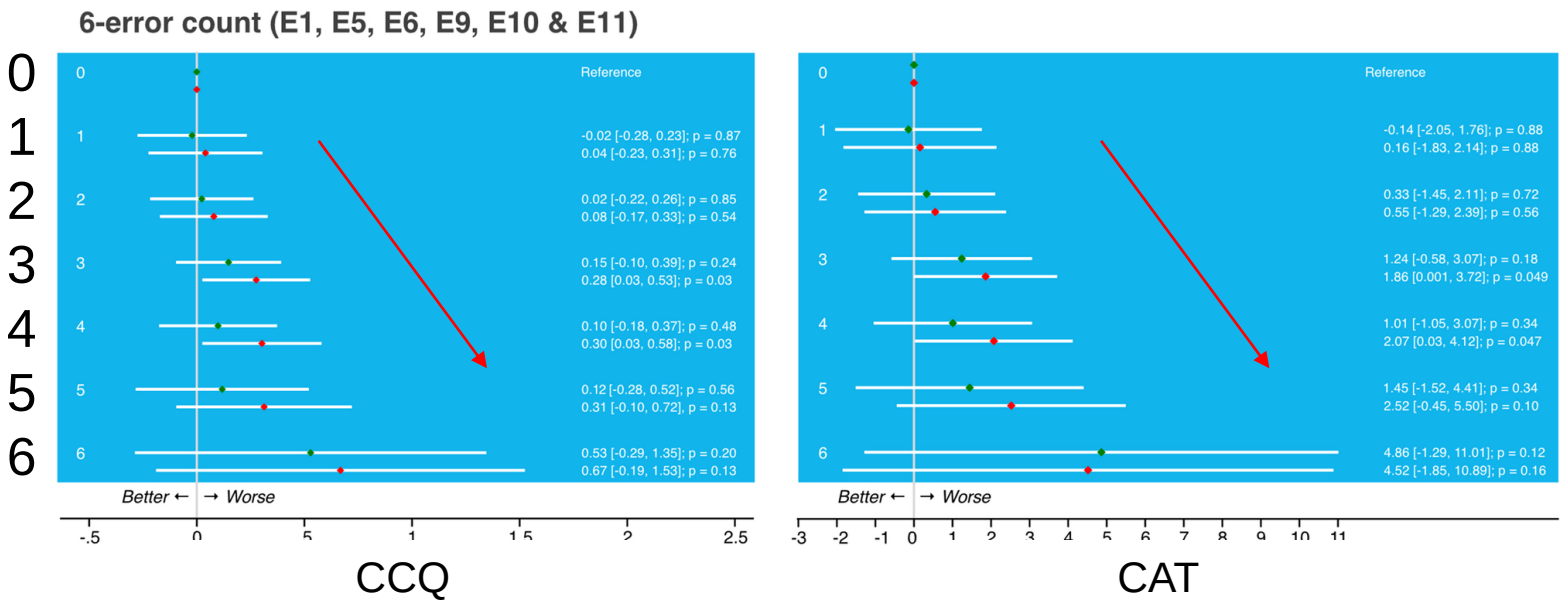




- Preparation
- Hold inhaler in correct position during inhalation
- Breath in

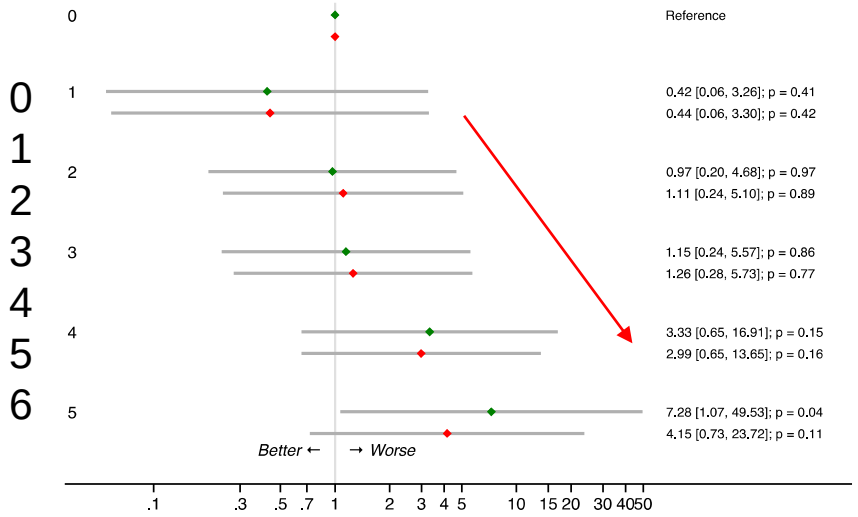
Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

Number of inhalation errors and health status, exacerbation



CCQ

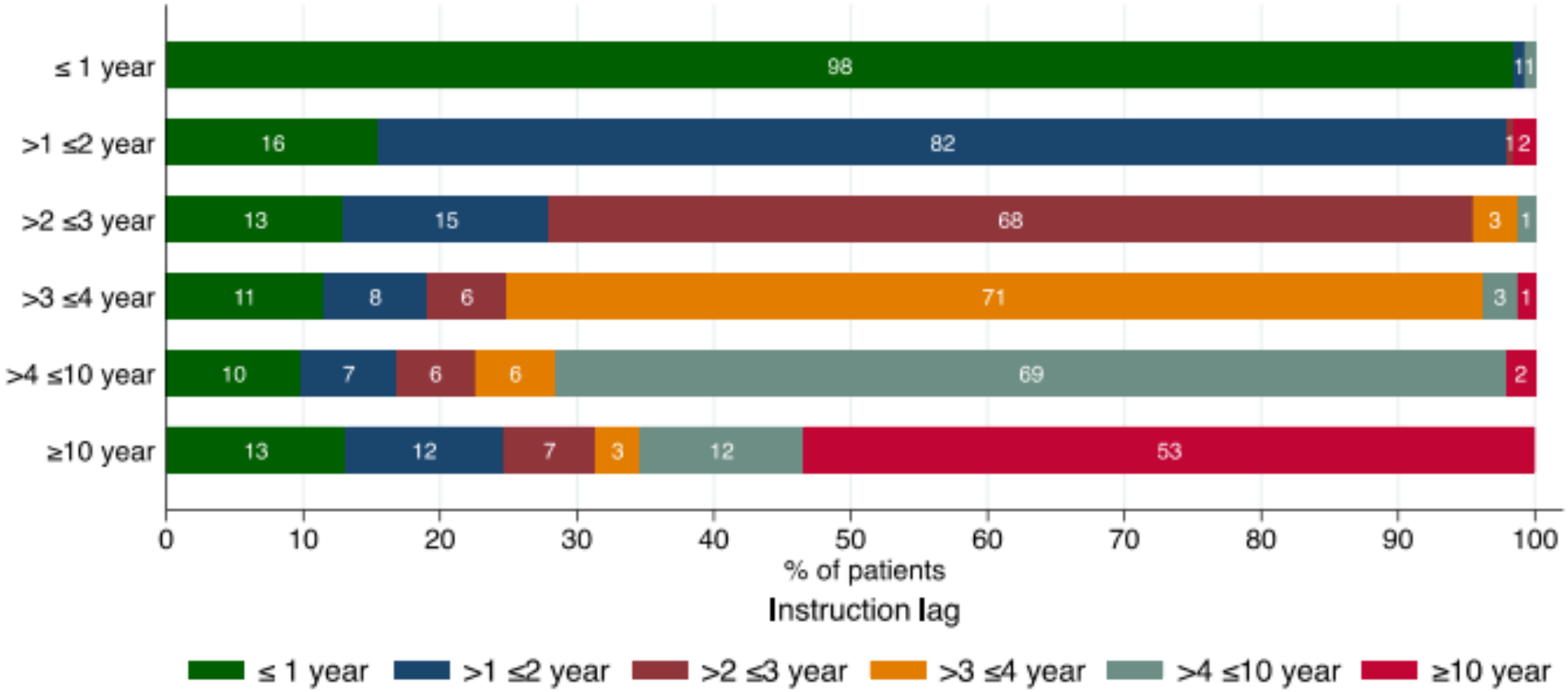
CAT



Severe exacerbation

Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

When was the last inhalation instruction?

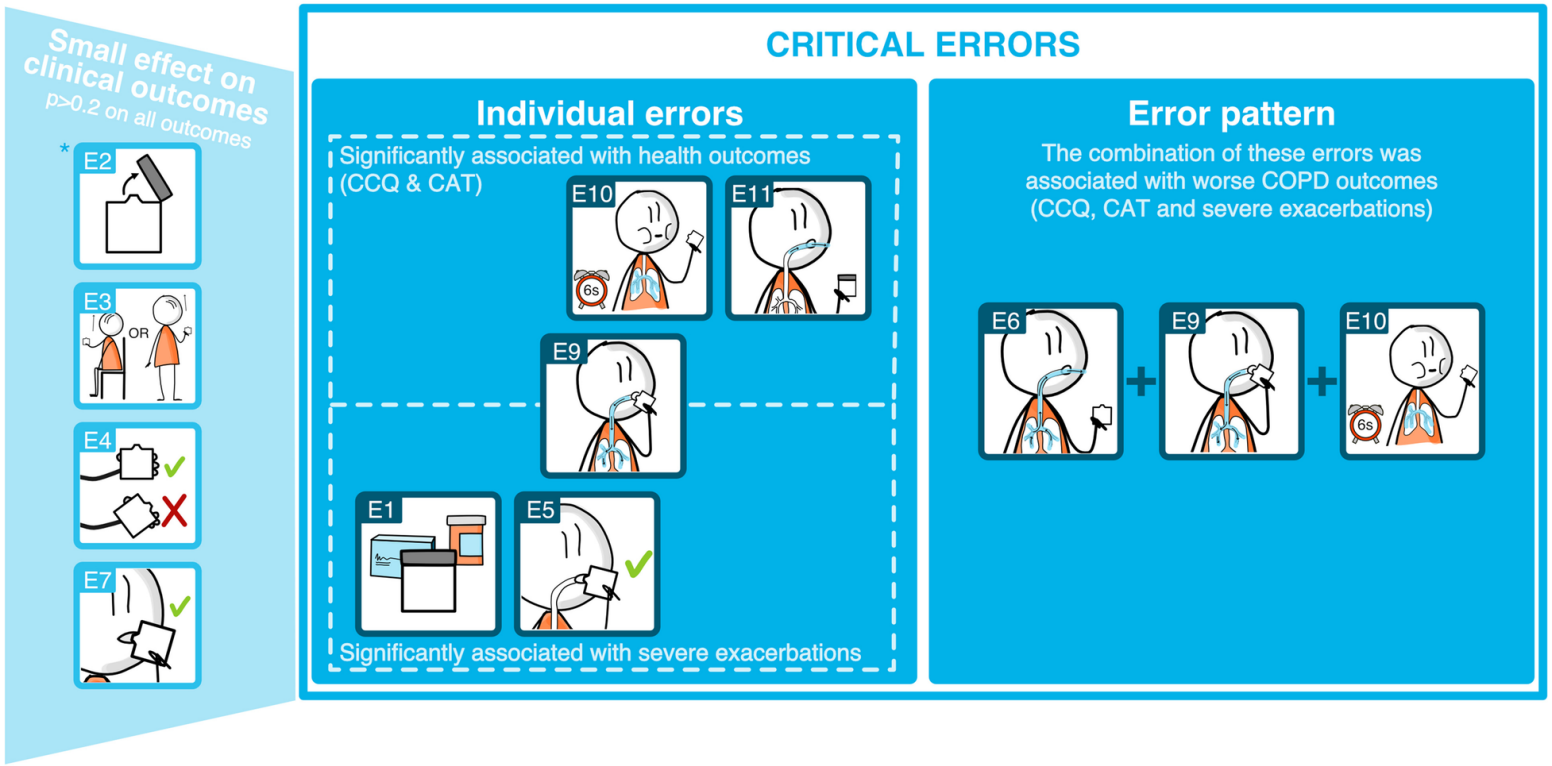


Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

Study summary

Critical inhalation technique errors associated with poor disease outcomes in patients with COPD on dry powder inhaler maintenance therapy

Error 1: Preparation; Error 2: Remove protective cap; Error 3: Sit up/stand straight & tilt head; Error 4: Hold inhaler in correct position during preparation; Error 5: Hold inhaler in correct position during inhalation; Error 6: Breathe out completely before inhalation; Error 7: Teeth and lips sealed around mouthpiece; Error 9: Breathe in; Error 10: Hold breath (for at least 6 seconds); Error 11: Breathe out calmly after inhalation



*An explanation for the small effect of this error could be the low prevalence of E2 (2%), resulting in limited statistical power to detect an association.

Kocks, Janwillem, et al. BMC pulm med, 2023, 23.1: 302.

Summary

- Anti-inflammatory agents in COPD
  - Previous studies: mixed results
  - Dupilumab in T2 high COPD: ↓Exacerbations, ↑FEV1, ↓ Sx, ↑ QoL
  - Nebulized PDE3/4 inhibitor: ↑FEV1
- CFTR potentiator in COPD: ↔ trough FEV1 (12 wk), ↑ trough FEV1 (24 wk)
- Severe AE risk: UMEC/VI, GLY/IND < TIO/OLO, CV event: GLY/IND < TIO/OLO
- ICSs containing inhaler, triple therapy: ↓ all-cause mortality
- MART in COPD: similarly effective fixed-dose FSC, lower daily ICS dosage
- Multiple critical inhalation technique error using DPIs: poorer outcomes