Triple Therapy for COPD

Main RCTs for Single Inhaler Triple Therapy

&

Real World Evidence for Triple Therapy

Current recommendation in managing stable COPD

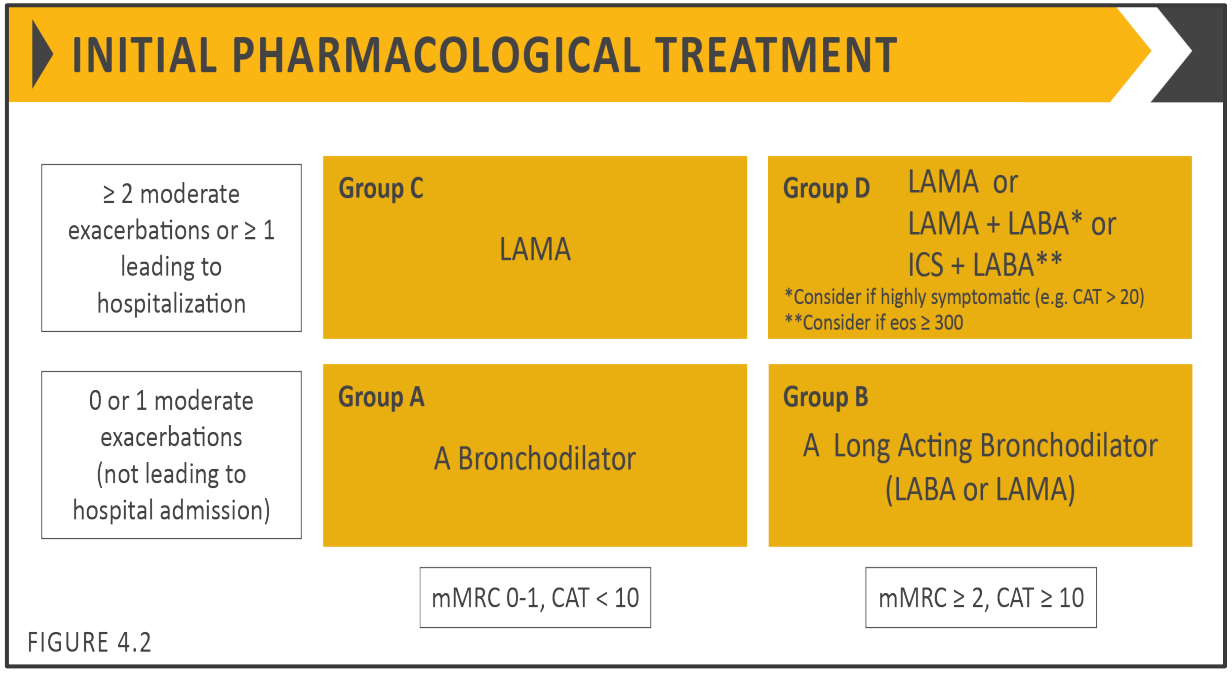
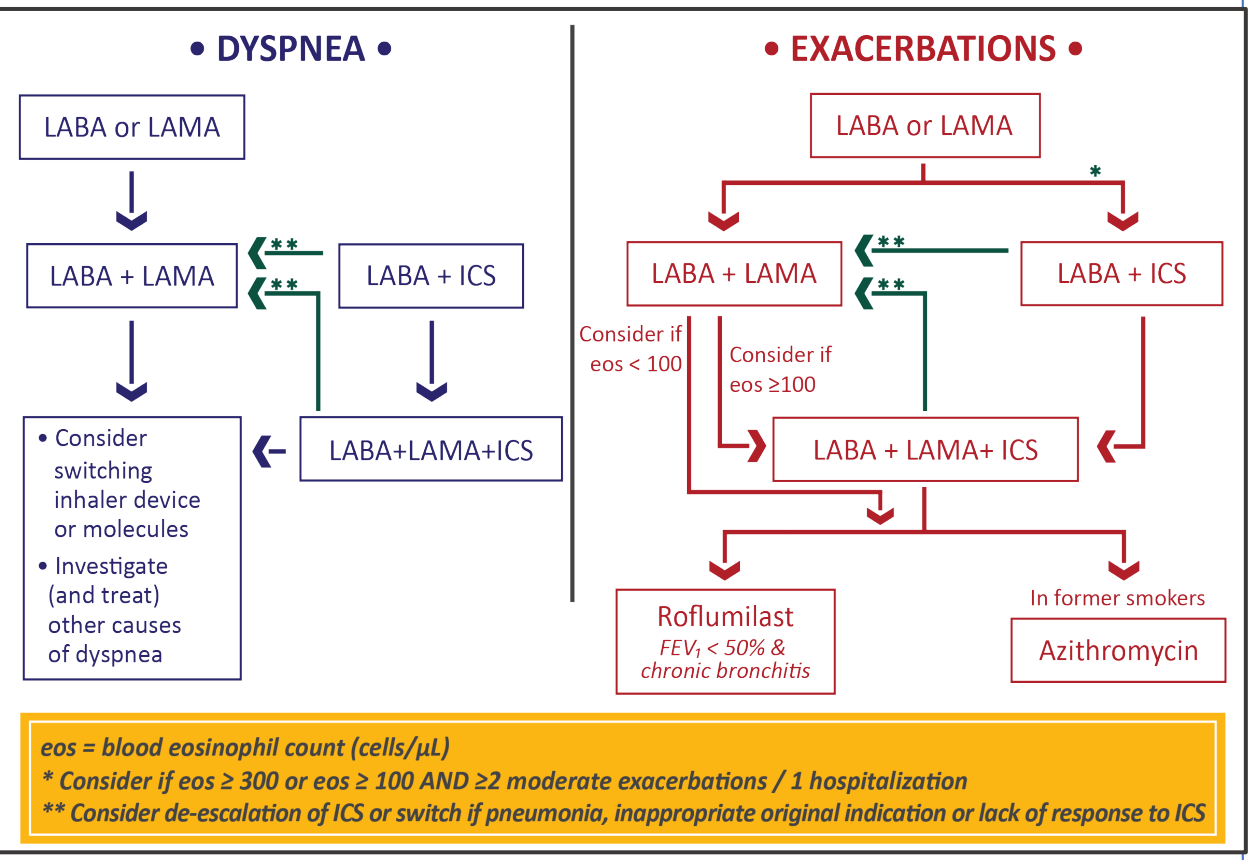


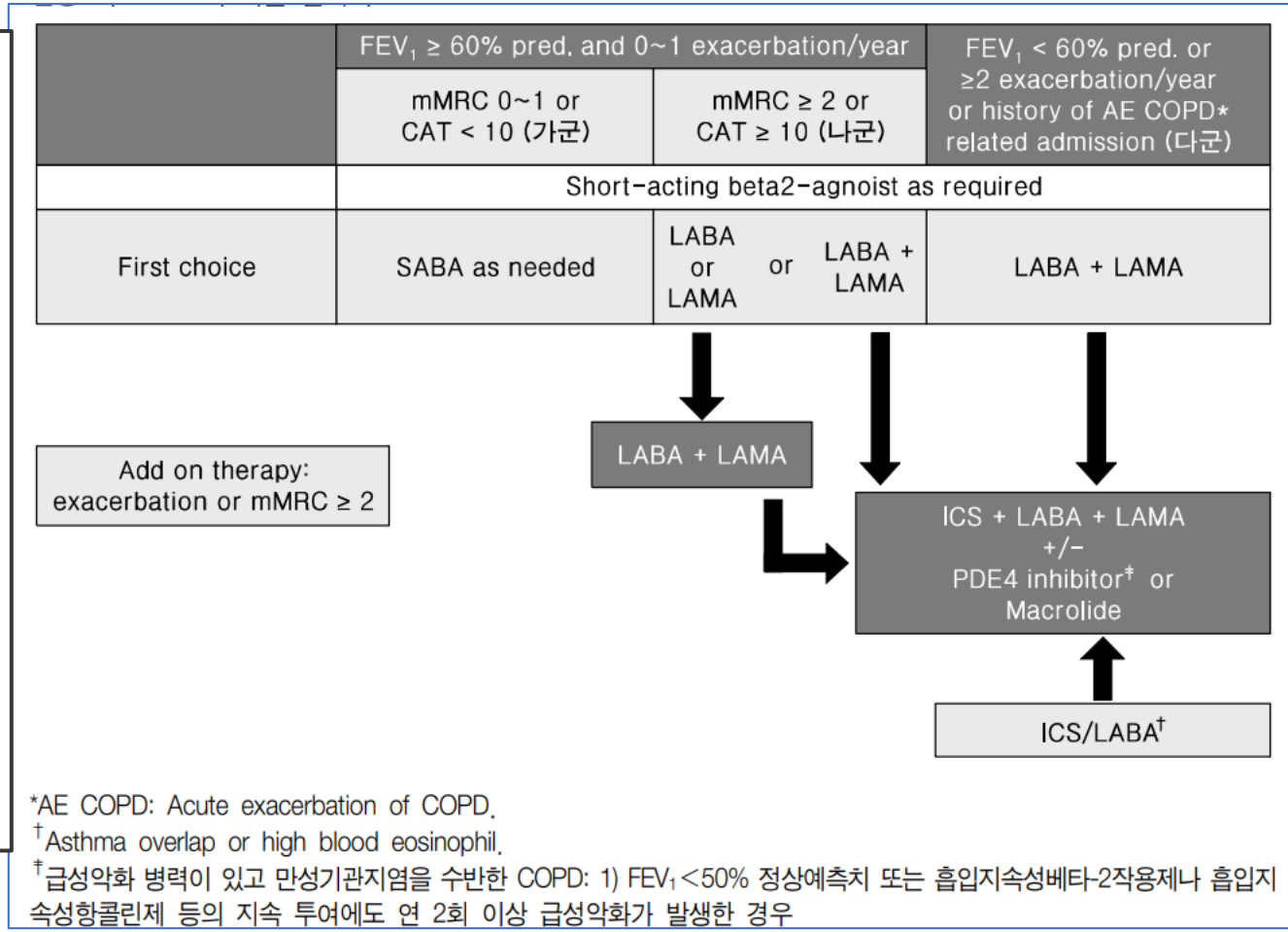
FIGURE 4.2

• 안정 시 COPD의 약물 단계치료

	FEV_1 ≥ 60% pred. and 0~1 exacerbation/year		FEV_1 < 60% pred. or ≥2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	SABA as needed	LABA or LAMA or LABA + LAMA	LABA + LAMA
			ICS/LABA†

Triple therapy in COPD Guidelines

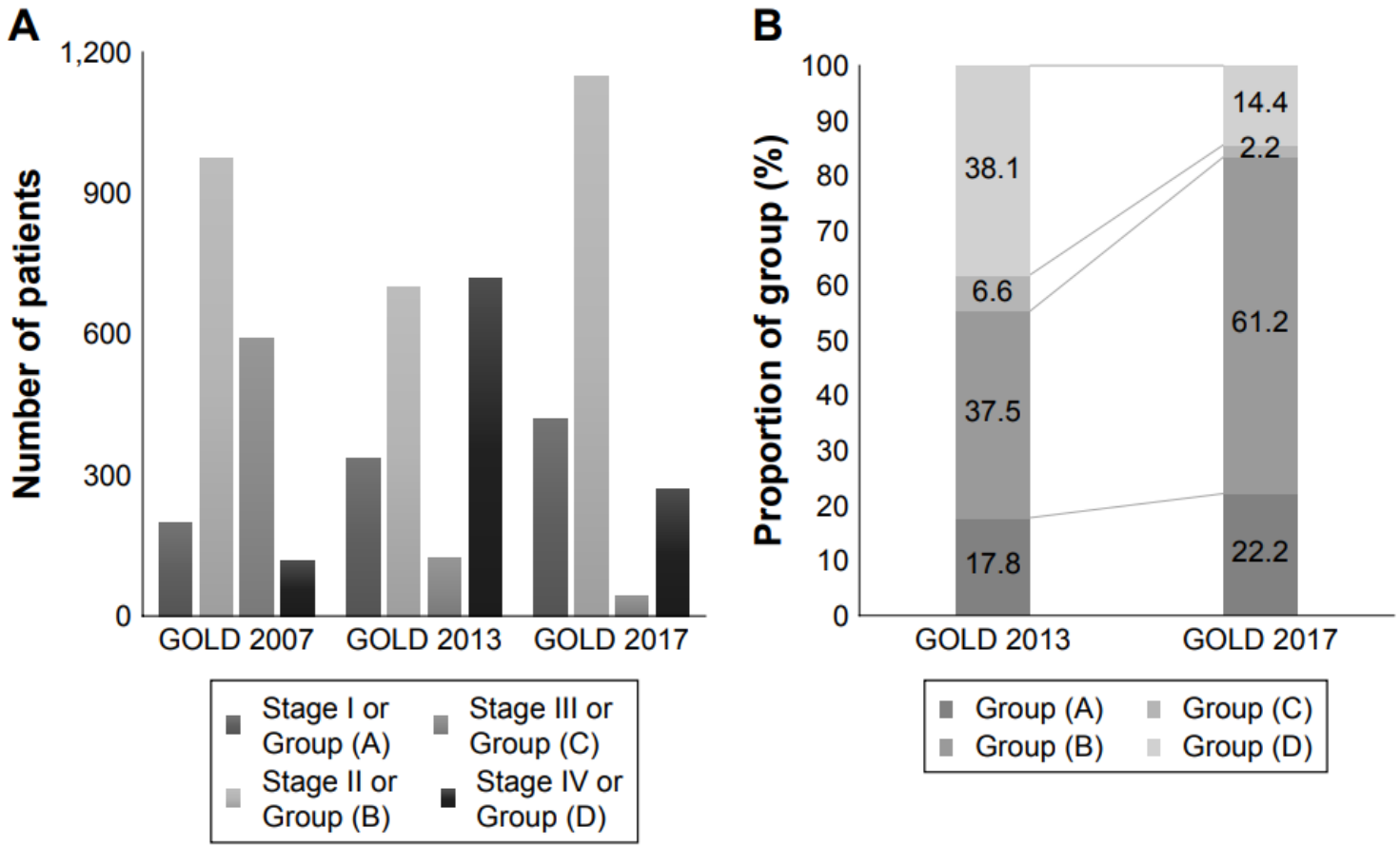




*AE COPD: Acute exacerbation of COPD.
†Asthma overlap or high blood eosinophil.
‡급성악화 병력이 있고 만성기관지염을 수반한 COPD: 1) FEV_1<50% 정상예측치 또는 흡입지속성베타-2작용제나 흡입지속성항콜린제 등의 지속 투여에도 연 2회 이상 급성악화가 발생한 경우

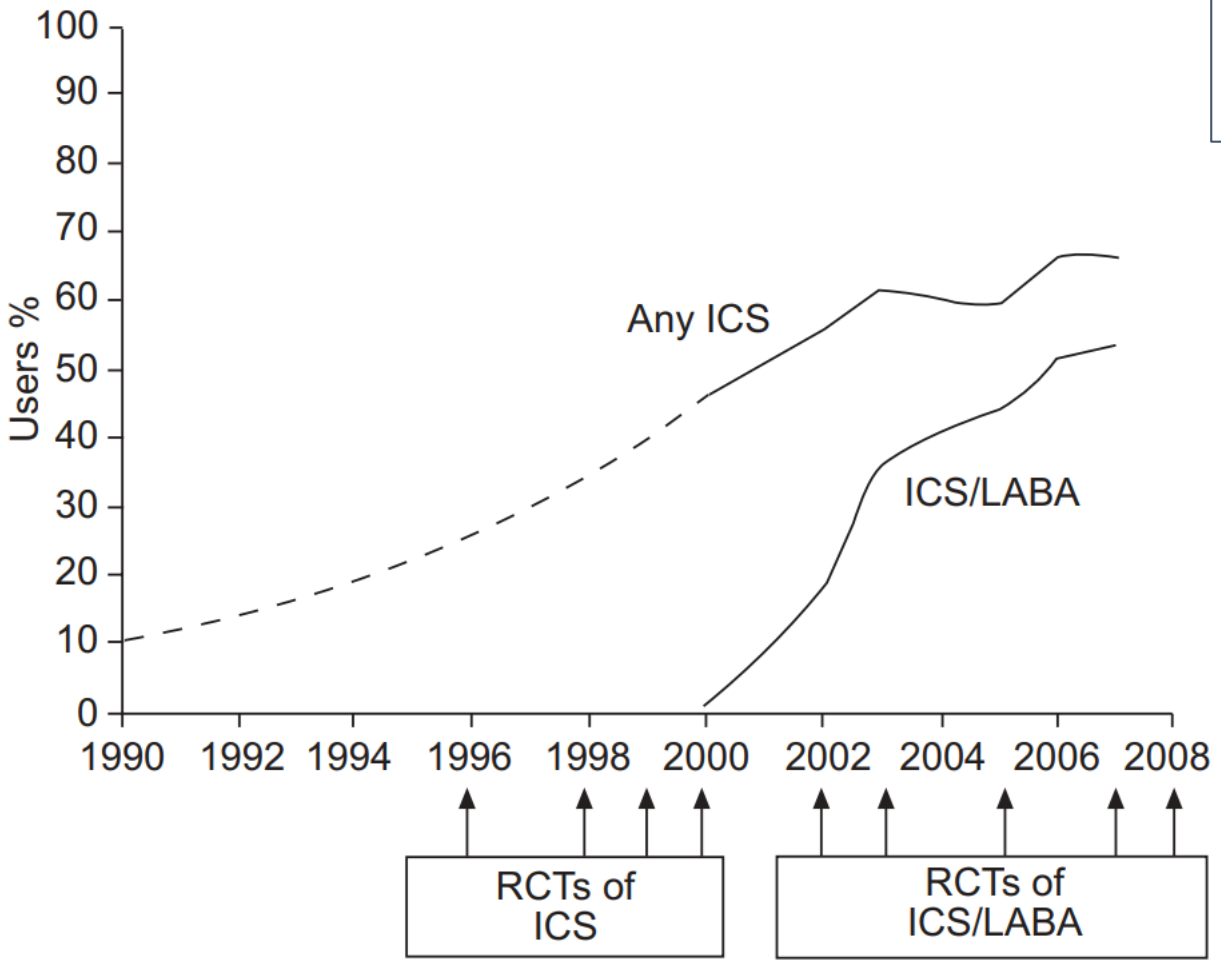
Q: 진료하시는 COPD환자 중 3제 흡입제 사용 환자 비율은?

1. 50% 이상
2. 40-50%
3. 30-40%
4. 20-30%
5. 20% 미만



International Journal of COPD 2018:13 3473–3484

Trends of ICS use in COPD



Papers

Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial

P S B
ISOL

BMJ: first published as 10.1136/bmj.320.7245.1297 on 12

Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial

*Peter Calverley, Romain Pauwels, Jørgen Vestbo, Paul Jones, Neil Pride, Amund Gulsvik, Julie Anderson, Claire Maden for the TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) study group**

Summary

Background Inhaled longacting $_2$ agonists improve lung function and health status in symptomatic chronic obstructive pulmonary disease (COPD), whereas inhaled corticosteroids reduce the frequency of acute episodes of symptom exacer
postula

this combination treatment should be considered for patients with COPD.

Lancet 2003; **361:** 449–56. Published online Jan 28, 2003 http://image.thelancet.com/extras/02art5284web.pdf

The NEW ENGLAND JOURNAL of MEDICINE

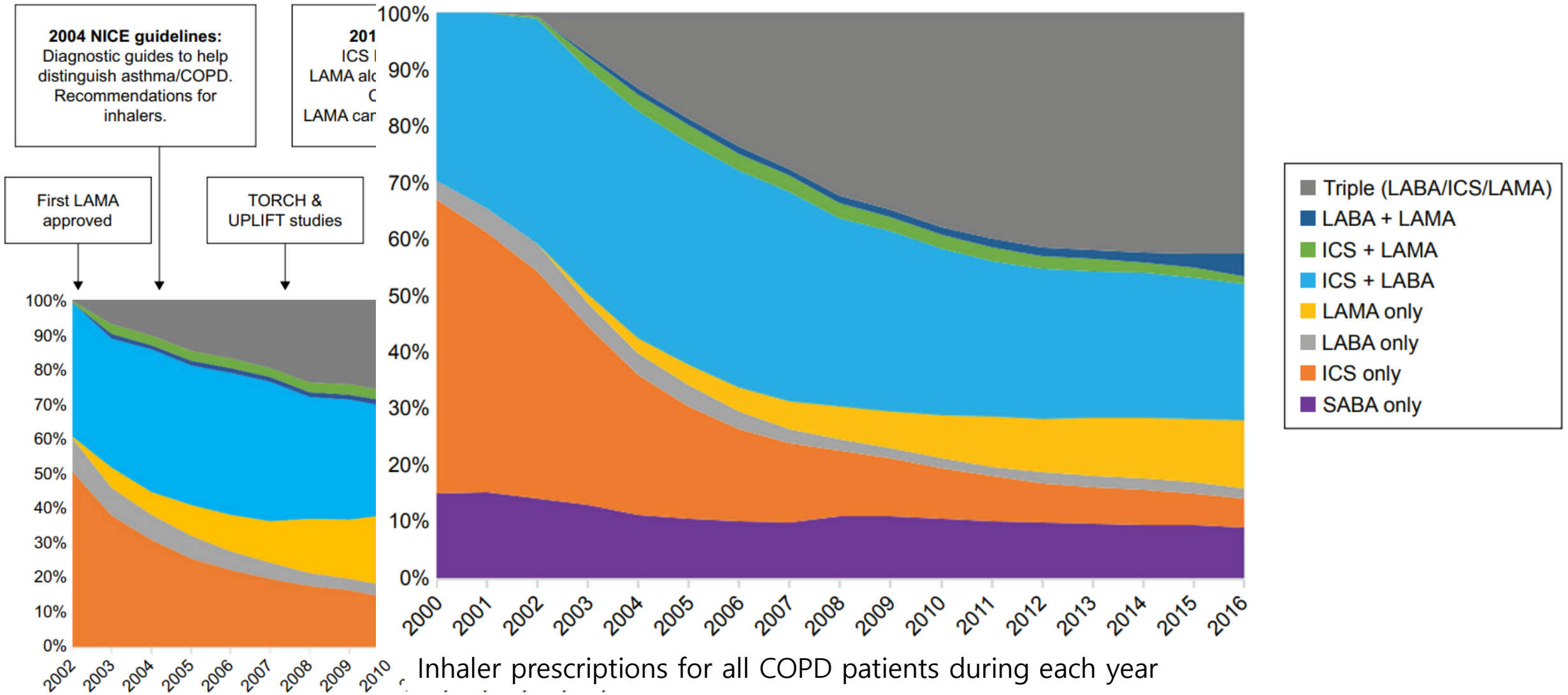
ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

ABSTRACT

Changes in COPD inhaler prescriptions



Inhaler prescriptions for all COPD patients during each year

Inhaler prescriptions for patients prescribed their first COPD maintenance inhalers

International Journal of COPD 2019:14

ICS use in Korean COPD

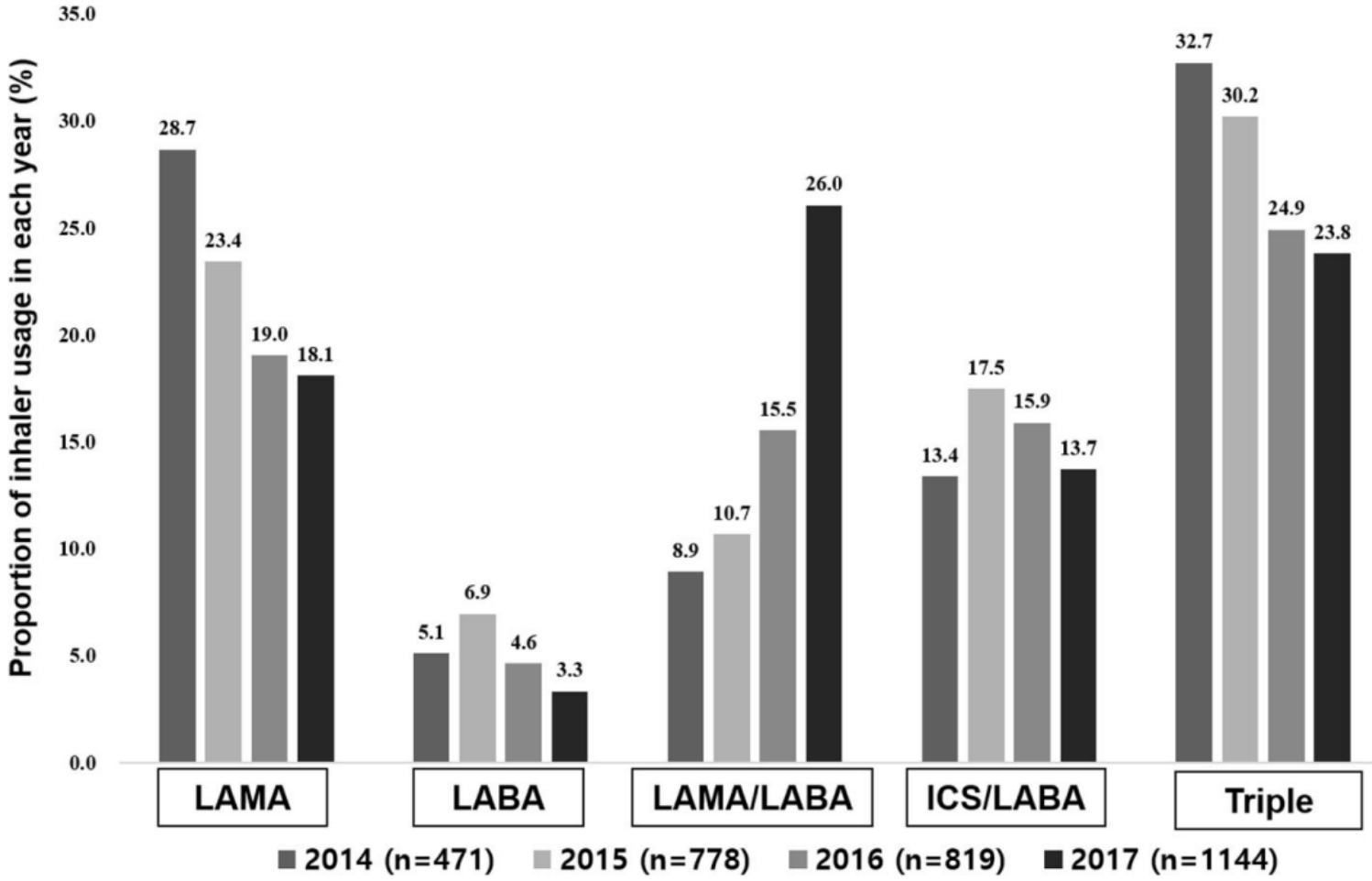


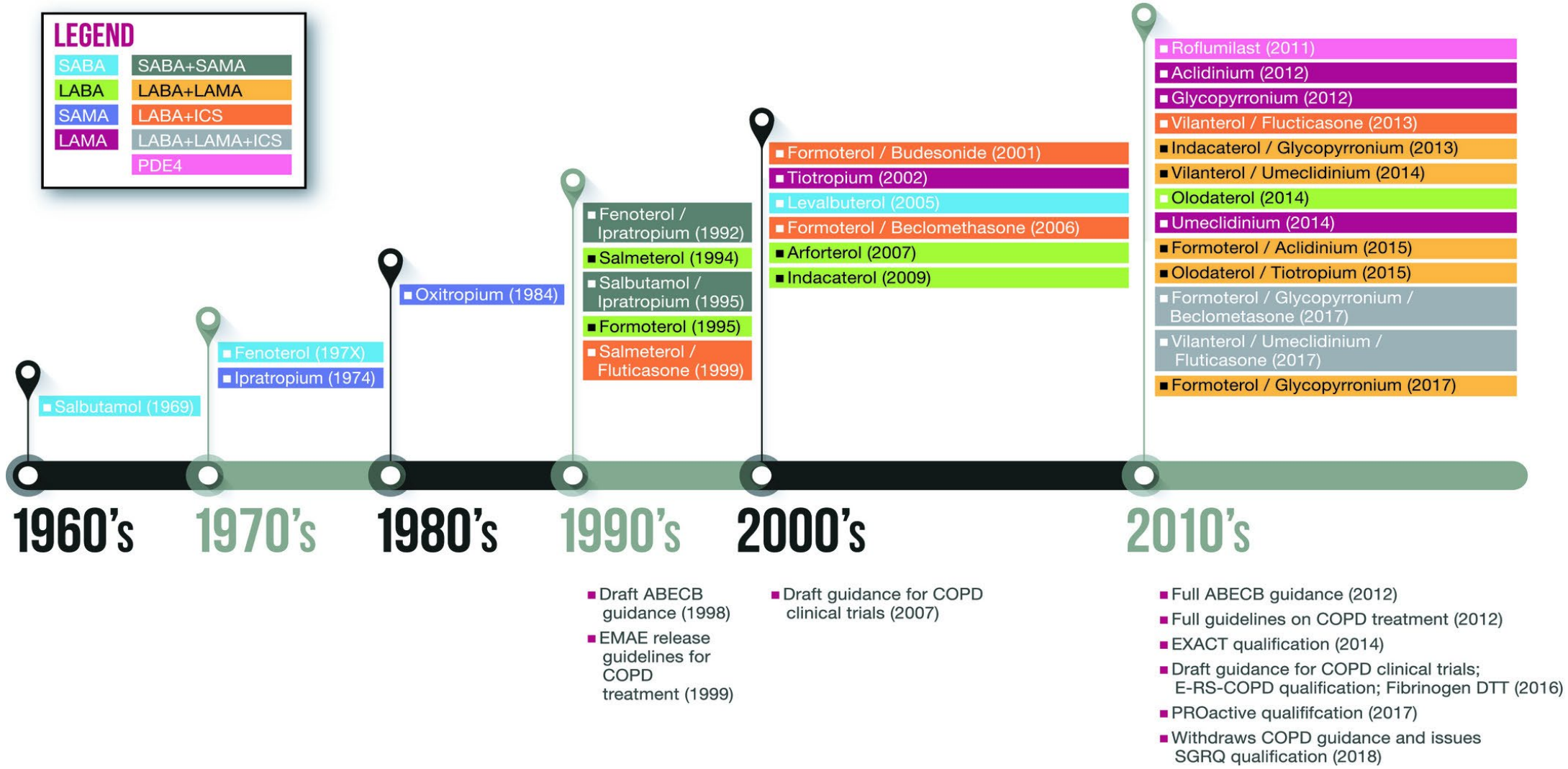
Fig. 2 Annual changes in inhaler usage. The medication possession ratio was defined such that inhalers used for more than 6 months were regarded as representative bronchodilators for each year. ICS = Inhaled corticosteroid; LAMA = long acting muscarinic antagonist; LABA = long

Lee et al. Respiratory Research (2019) 20:62

Q: 선생님께서 COPD환자에서 3제 흡입제를 사용하여 얻고자 하는 것은 무엇인가요?

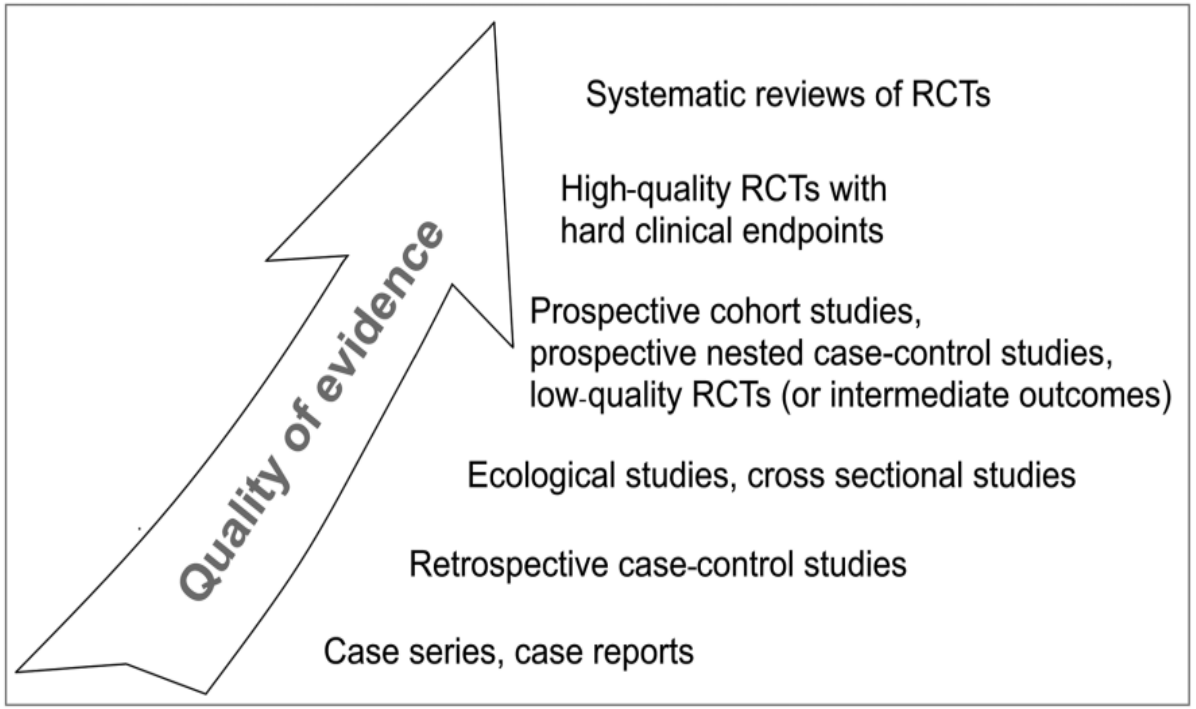
1. 사망률 저하
2. 급성악화 비율 감소
3. 삶의 질 개선
4. 폐기능 개선
5. 운동능력 향상

Drug Development & Validation of Their Efficacy



Clin Pharma and Therapeutics, Volume: 106, Issue: 6, Pages: 1222-1235,

Why RCT? - Evidence Based Medicine



Adv Nutr 2018;9:561–571

- only type of study able to establish causation
- ability to assign and administer treatment or intervention in a precise, controlled way.
- decreases selection bias and minimises confounding due to unequal distribution in a chosen population
- measurements can be chosen precisely making it easier to make observations consistently (especially parametric data)
- blinding is easier improving credibility
- decreasing patient or observer bias
- controlling of group allocations enhances similarity of baseline features so it is easier to form basis for statistical hypothesis
- can make trial large → may detect clinically relevant conclusions
- can have subgroup analysis enhancing usefulness for clinical practice
- a successful RCT with conclusive or inconclusive results is eminently publishable

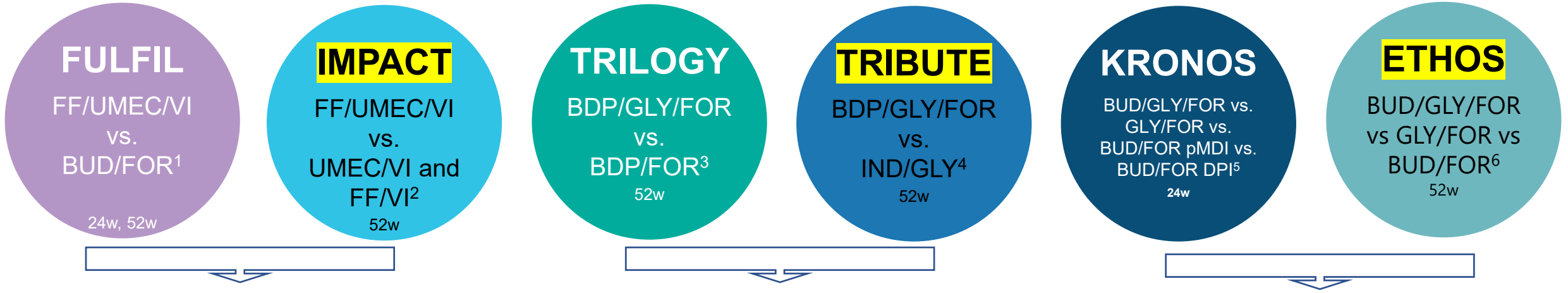
Medical Treatment for What?

- LAMA → (LABA/LAMA) → ICS/LABA/LAMA
- LABA →?(LABA/LAMA) → ICS/LABA/LAMA
- LABA/LAMA → ICS/LABA/LAMA

ICS/LABA →(LABA/LAMA) → ICS/LABA/LAMA

- ▼ Mortality
- ▼Exacerbation
- ▲Lung function
- ▼Dyspnea/ ▲QoL
- ▲ Exercise endurance

Triple therapy (ICS/LAMA/LABA) in Phase 3 large RCTs



1’ **FEV1/SGRQ** **Exacerbation** **FEV1/SGRQ** **Exacerbation** **FEV1/SGRQ** **Exacerbation**

1. Lipson DA et al. Am J Respir Crit Care Med 2017;196:438–446.
2. **Lipson DA et al. N Engl J Med 2018;378:1671–1680. IMPACT**
3. Singh D et al. Lancet 2016; 388:963–973.
4. **Papi A et al. Lancet 2018;39:1076–1084. TRIBUTE**
5. Ferguson GT et al. Lancet Respir Med 2018;6:747–758
6. **Rabe KF, et al. N Engl J Med. 2020;383(1)**:35-48. ETHOS

Efficacy of Triple Therapy in COPD

RCT

- **TRIBUTE**
- **IMPACT**
- **ETHOS**

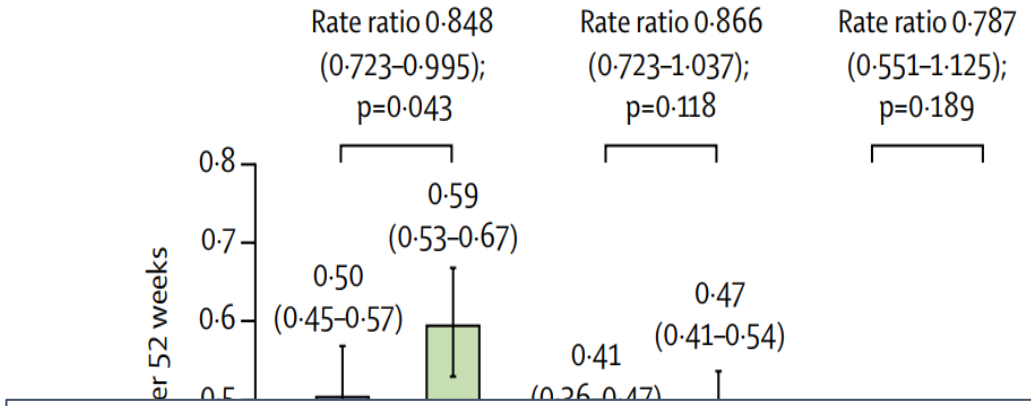
- **Lung function**
- **Dyspnea/QoL**
- **Exacerbation**
- **Mortality**
- **Adverse Events**

Target Population/Inclusion Criteria

Inclusion Criteria	TRIBUTE BDP/FOR/GLY bid vs. IND/GLY qd N=1,532	IMPACT FF/VI/UMEC vs. FF/VI vs. UMEC/VI qd N=10,355	ETHOS BUD/FOR/GLY (160,320) vs. BUD/FOR vs FOR/GLY bid N=8,509
FEV1	<50%	50-80%	25-65%
Exacerbation history - Moderate or severe exacerbation (last year)	≥1	≥1 (if FEV1 < 50%)or ≥2 moderate or one severe AE (if FEV1 of 50-80%)	≥1 (if FEV1 < 50%) or ≥2 moderate / 1 severe (if FEV1 ≥ 50%)
Symptom score	CAT ≥ 10	CAT ≥ 10	CAT ≥ 10
Baseline medication	ICS/LABA, ICS/LAMA or LABA/LAMA for ≥2 months	use LAMA, a LABA, or an ICS alone or in combination	At least two inhaled maintenance therapies at the time of screening
Run-in Period	2weeks IND/GLY (85/43ug)	Patients' own medications (LAMA, LABA, or ICS, alone or in combination)	1-4weeks Ipratropium bromide QID and patients' own ICS (if on an ICS at screening)
Exclusion of Asthma	Yes	No	Yes

Exacerbations

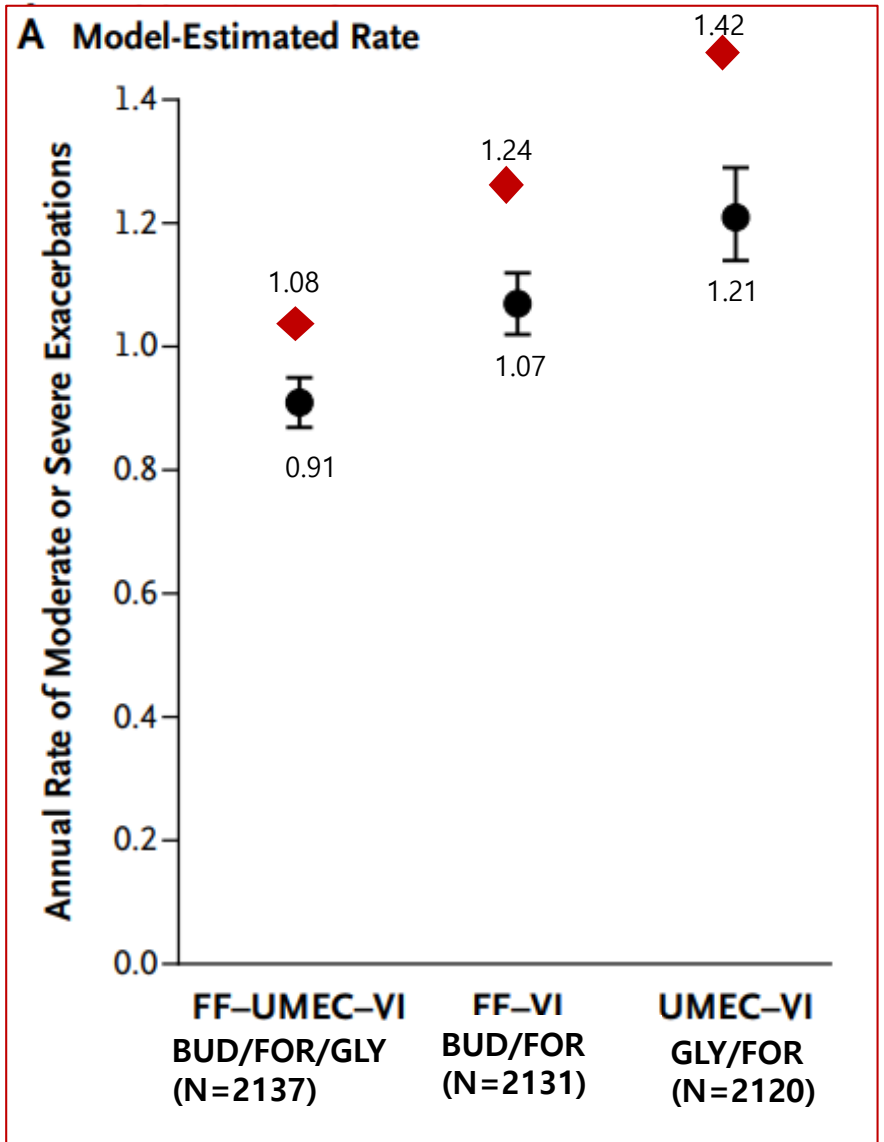
Exacerbation Rate



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	1.08	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

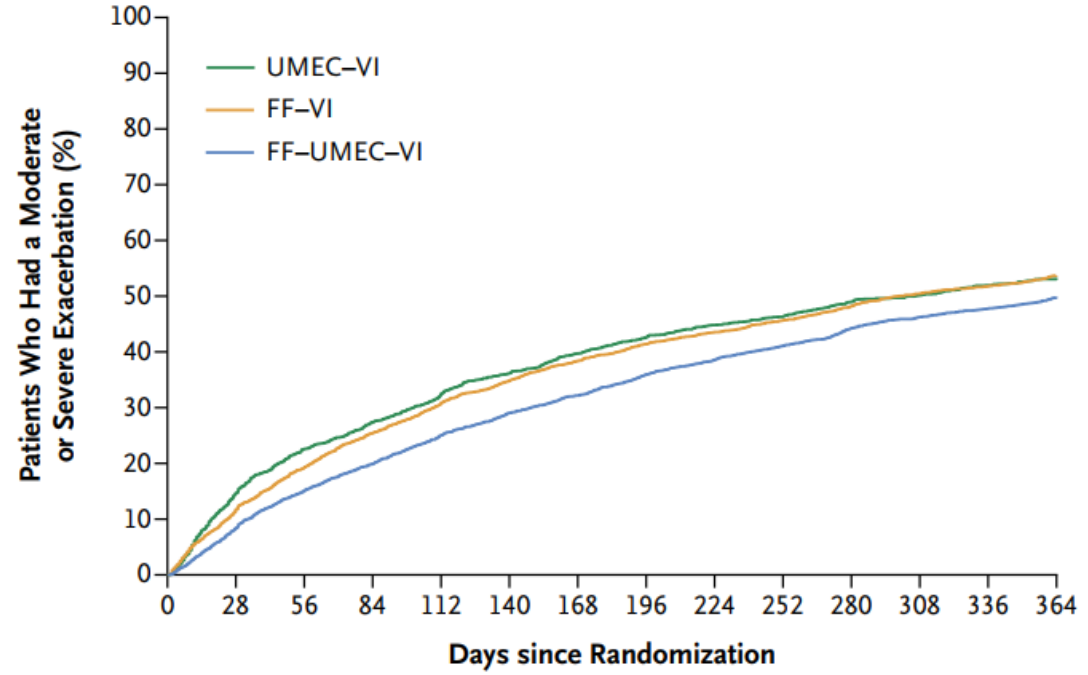
TRIBUTE

ETHOS



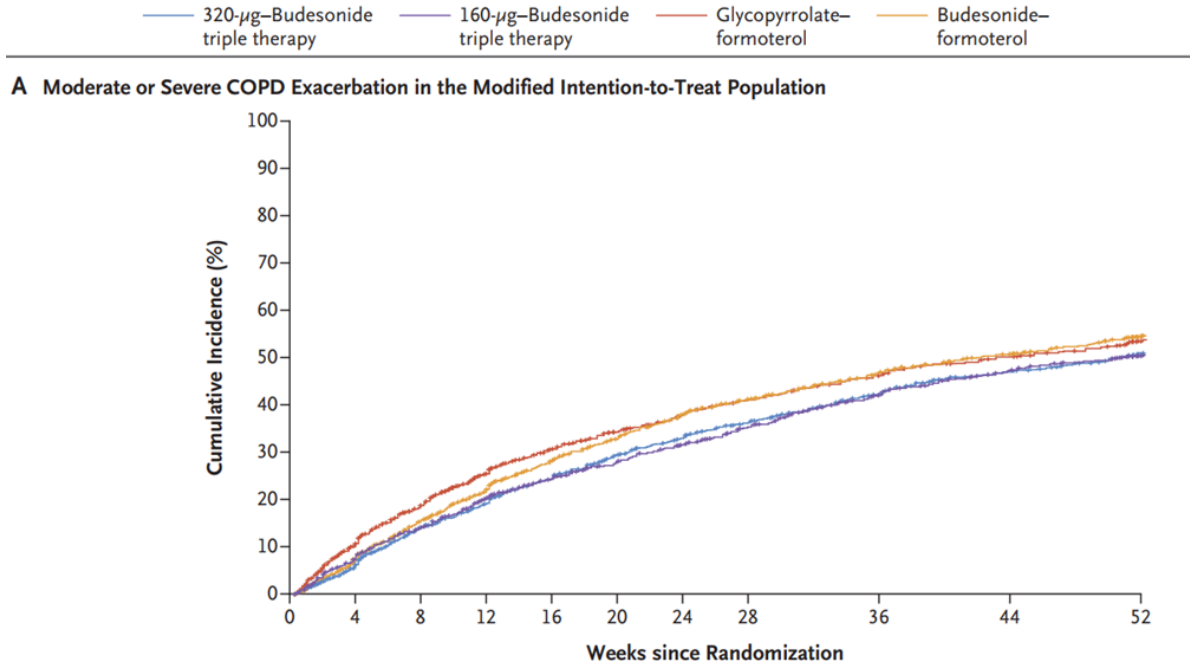
Cumulative incidence of exacerbation

B **Time-to-First-Event Analysis**



No. at Risk

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



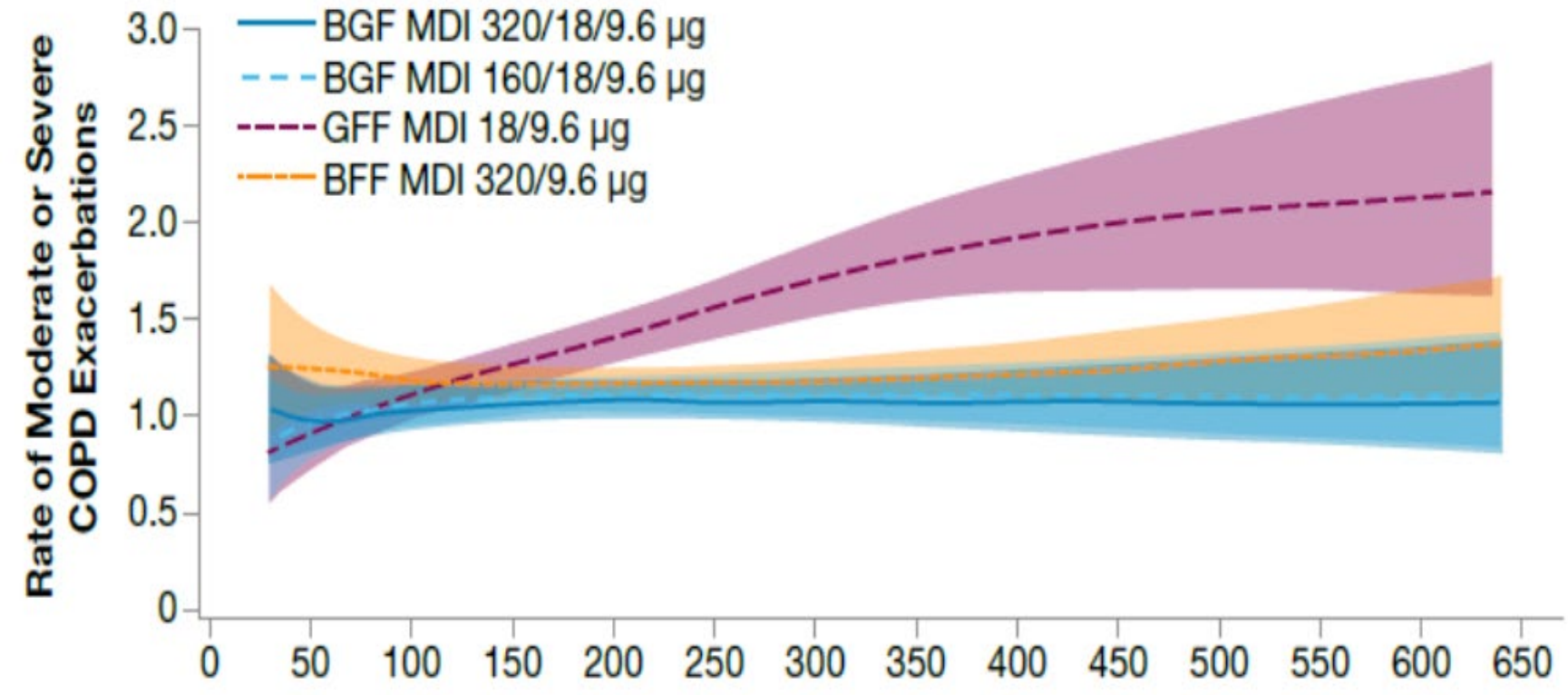
No. at Risk

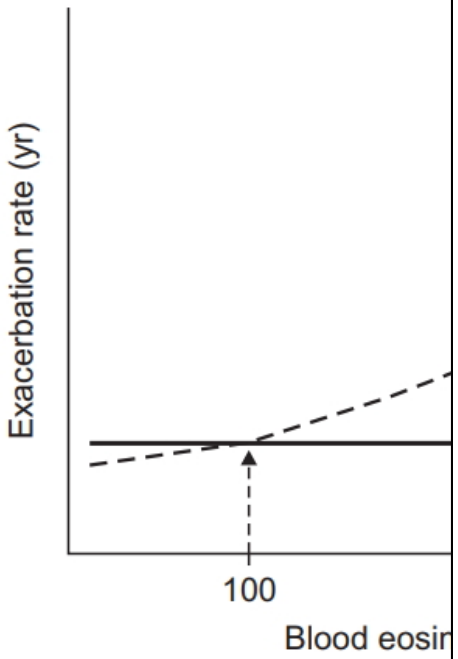
320-μg–Budesonide triple therapy	2137	1989	1776	1651	1523	1402	1318	1241	1106	996	760
160-μg–Budesonide triple therapy	2121	1936	1767	1623	1510	1426	1347	1259	1108	985	767
Glycopyrrolate–formoterol	2120	1849	1633	1466	1338	1251	1166	1096	988	907	692
Budesonide–formoterol	2131	1935	1721	1564	1410	1300	1196	1119	989	899	678

➔ RWE

Blood Eosinophil Counts in COPD
: A Biomarker of Inhaled Corticosteroid Effect

Figure S5. Rate of moderate or severe COPD exacerbations by blood eosinophil count (modified intent-to-treat population).





600

D. Singh, Lancet Respir Med 2019; 7: 745–56

Relationships among the explanatory clinical trials, observational study, and pragmatic clinical trials

Randomization
Comparability between patient groups

Continuum

Real-world evidence
Relative effectiveness of treatment in the real world

Prospective, blinded explanatory clinical trial

Pragmatic randomized clinical trial

Retrospective observational study

Cardiovasc Prev Pharmacother. 2020 Jul;2(3):85-98

Real world study of Triple therapy

	Open triple				
	Cohort study		Database study	Claim database study	
Country	China	Germany	UK	France	US
Source	12 hospital from China	500 centers from Germany	Optimum Patient Care Research Database (OPCRD) & Clinical Practice Research Datalink (CPRD)	General Sample of Beneficiaries (EGB) database : individual anonymous information from primary and secondary care	IBM® MarketScan® Commercial, Medicare Supplemental, and Multi-State Medicaid Research Databases
Definition of COPD	postFEV1/FVC <0.7	postFEV1/FVC <0.7	• COPD diagnostic read codes in CPRD	ICD10 codes: J41, J42, J44, or J96.1 and J96.0 only when J43 or J44 in associated diagnoses	ICD-9: 491.xx-492.xx, 494.xx, 496.xx; ICD-10: J41.0, J41.1, J41.8, J42, J43.0-J43.2, J43.8-J44.1, J44.9, J47.0, J47.1, J47.9
Other Inclusion	> 40 years of age CAT ≥10 ± mMRC≥2	Age ≥ 40 years; BDR (-)	+ medication of interest (triple or dual etc)	+ medication of interest (triple or dual etc)	+ medication of interest (triple or dual etc)
Exclusion	AECOPD, BA, BE, ILD, current malignancy, severe heart, liver, kidney diseases	Participating in asthma Disease Management Program, or other RCT			

Real world study of Triple therapy

	Closed triple			
	Retrospective study	Prospective study		Claim database study
Country	China	Austria	Italy	US
Source	Single center study	Multi -center study	Single center study	IQVIA PharMetrics Plus healthcare claims databa
Definition of COPD	postFEV1/FVC <0.7	postFEV1/FVC <0.7	postFEV1/FVC <0.7	COPD exacerbation diagnosis code in the primary position
Other Inclusion	• Over 40years of age • Step-up to triple therapy from mono or dual	Moderate to severe COPD	regularly treated with either LAMA/LABA or ICS/LABA combinations	at least one dispensing/administration of a systemic corticosteroid or guideline-recommended antibiotic within 5 days following, or prior to, the visit
Exclusion	Already on closed triple	AECOPD, allergy to medication		

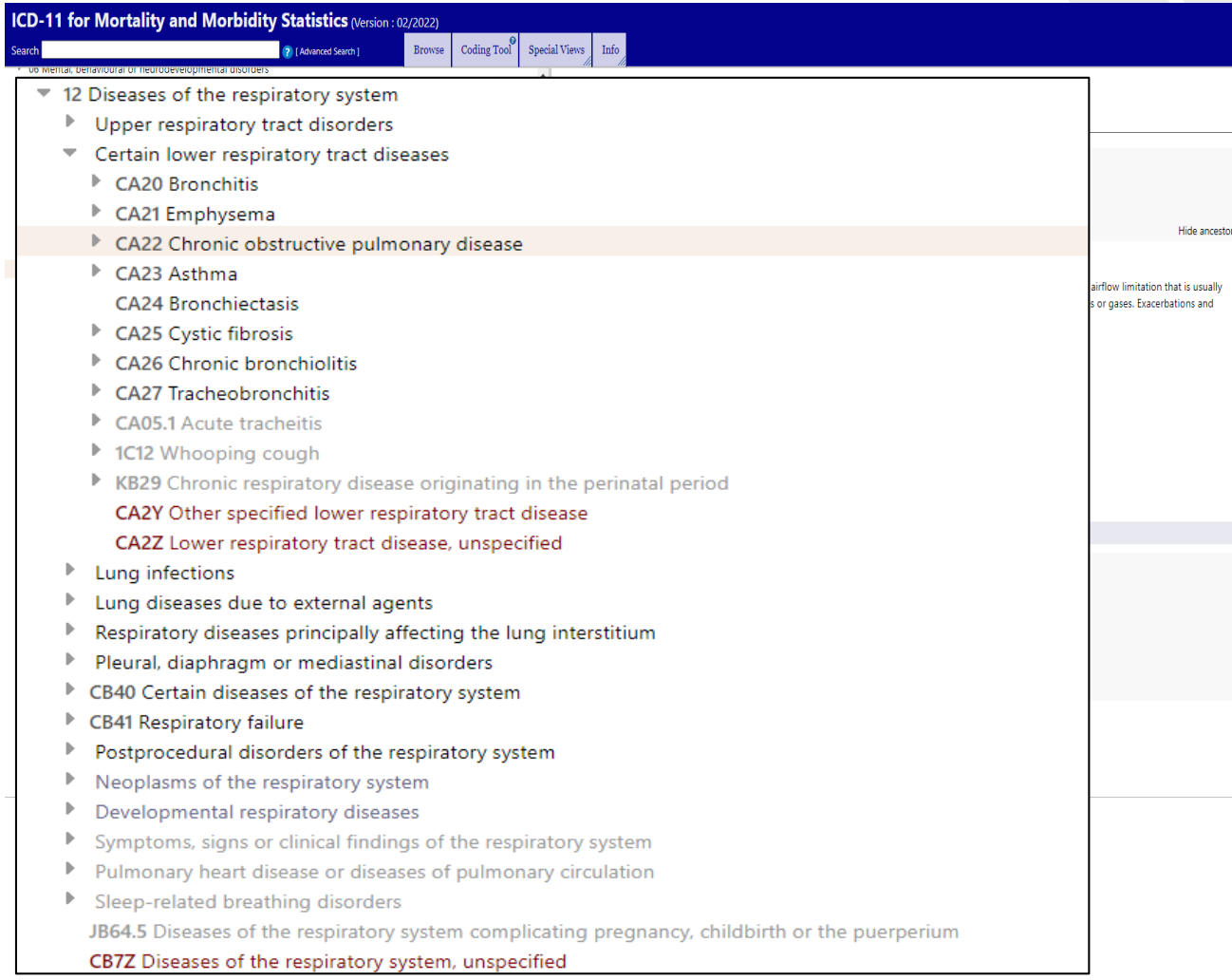
COPD 적정성 평가

마. 대상상병

○ 한국표준질병사인분류(Korean Standard Classification of Diseases, KCD) Ver 8.0 기준

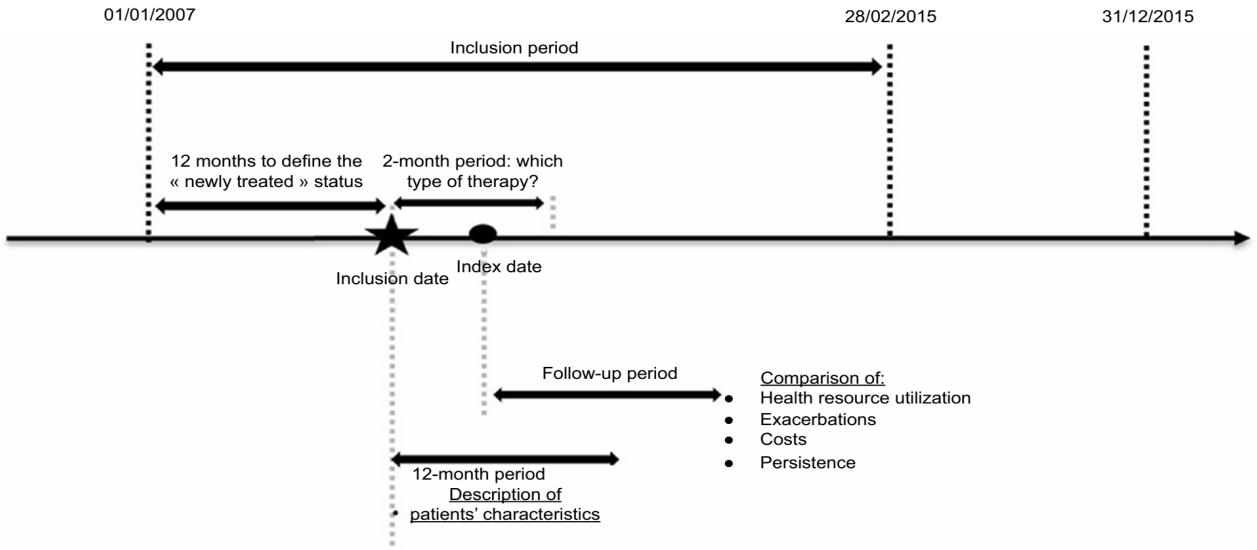
상병코드		상병명
J43 (폐기종)	J43.1	범소엽성 폐기종
	J43.2	중심소엽성 폐기종
	J43.8	기타 폐기종
	J43.9	상세불명의 폐기종
J44 (기타 만성 폐쇄성 폐질환)	J44.0	급성 하기도감염을 동반한 만성 폐쇄성 폐질환
	J44.1	급성 악화를 동반한 상세불명의 만성 폐쇄성 폐질환
	J44.8	기타 명시된 만성 폐쇄성 폐질환
	J44.9	상세불명의 만성 폐쇄성 폐질환

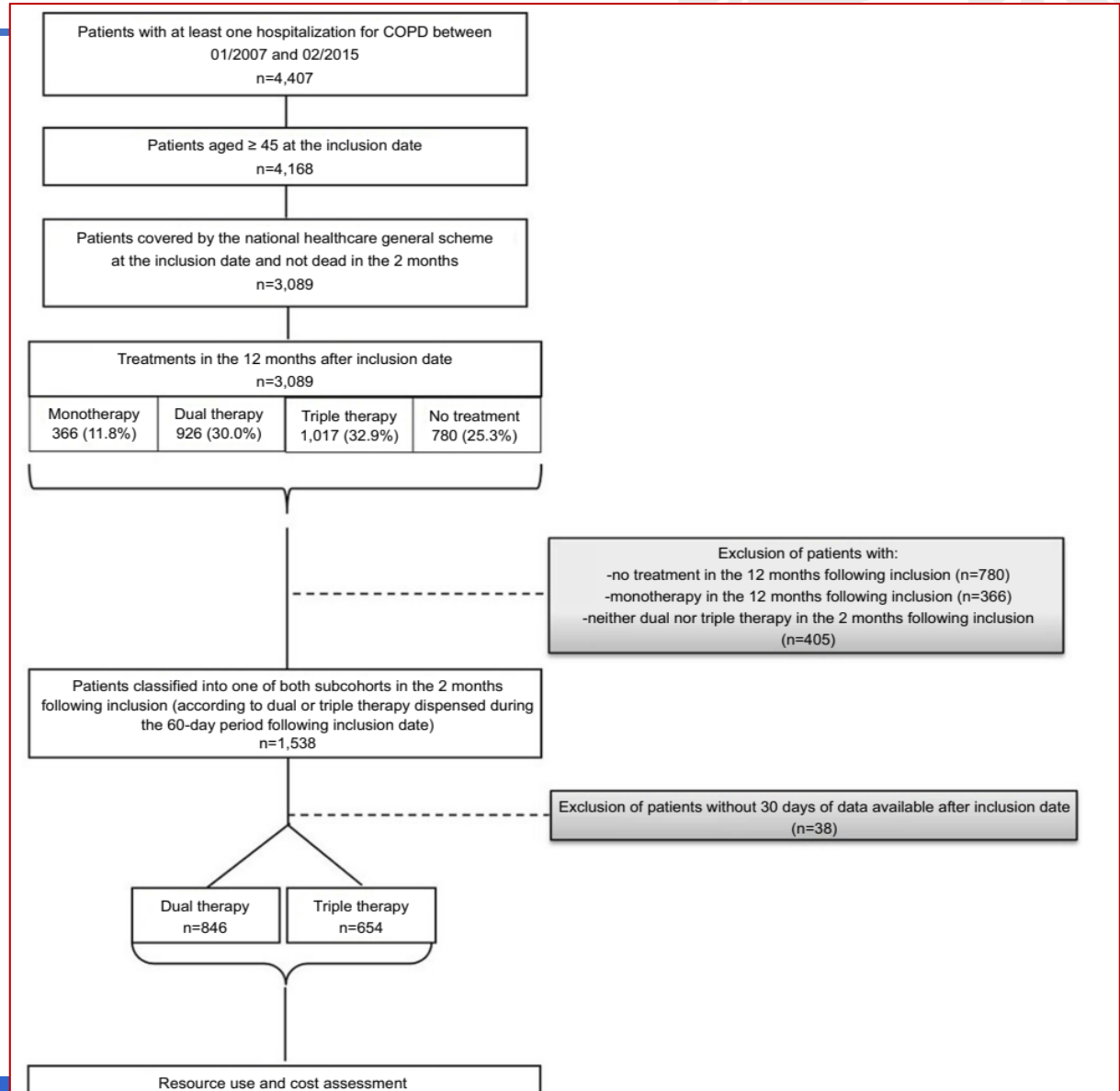
주 1. J43.0(맥로드 증후군)은 희귀성 질환으로 대상상병에서 제외
2. '16.1.1.부터 J44.0~J44.9에 중증도 표기(0: 경도, 1: 중등도, 2: 중증, 9: 상세불명)



Example of Study design and Flowchart of claim database study (1)

- **A French study using General Sample of Beneficiaries (EGB) database**





- Inclusion date : the date of discharge from the first hospitalization – meeting the inclusion criteria – recorded during the study period.
- Index date was defined as the date of the last dispensing within the 60-day period following the inclusion date.

IJCOPD 2019;14:1839-1854

Example of Study design and Flowchart of claim database study (2)

- **An UK study using Optimum Patient Care Research Database & Clinical Practice Research Datalink**

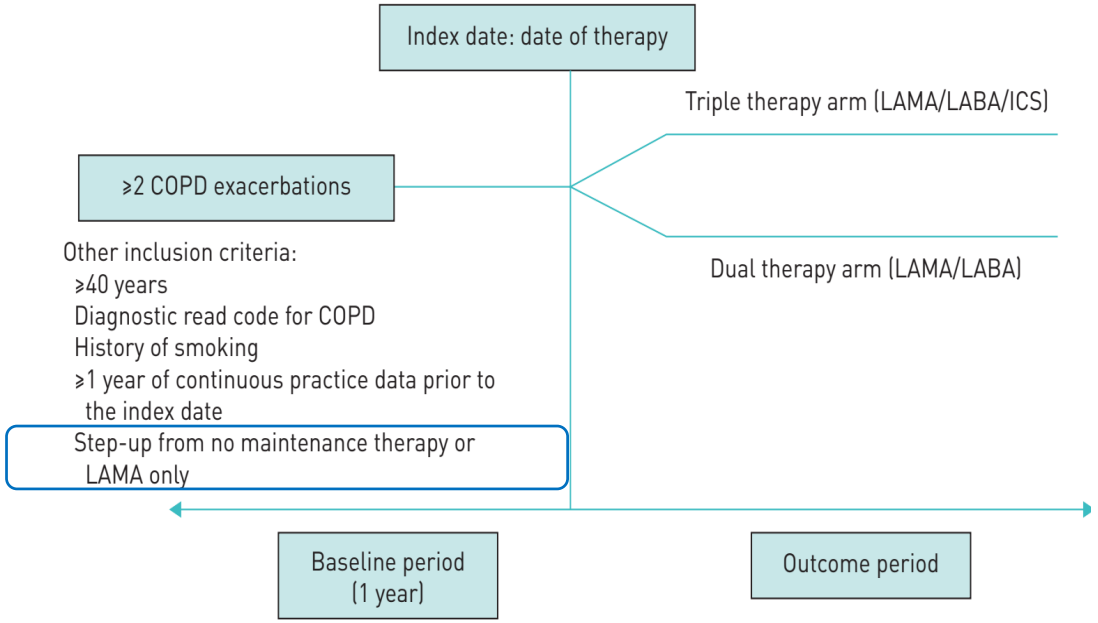
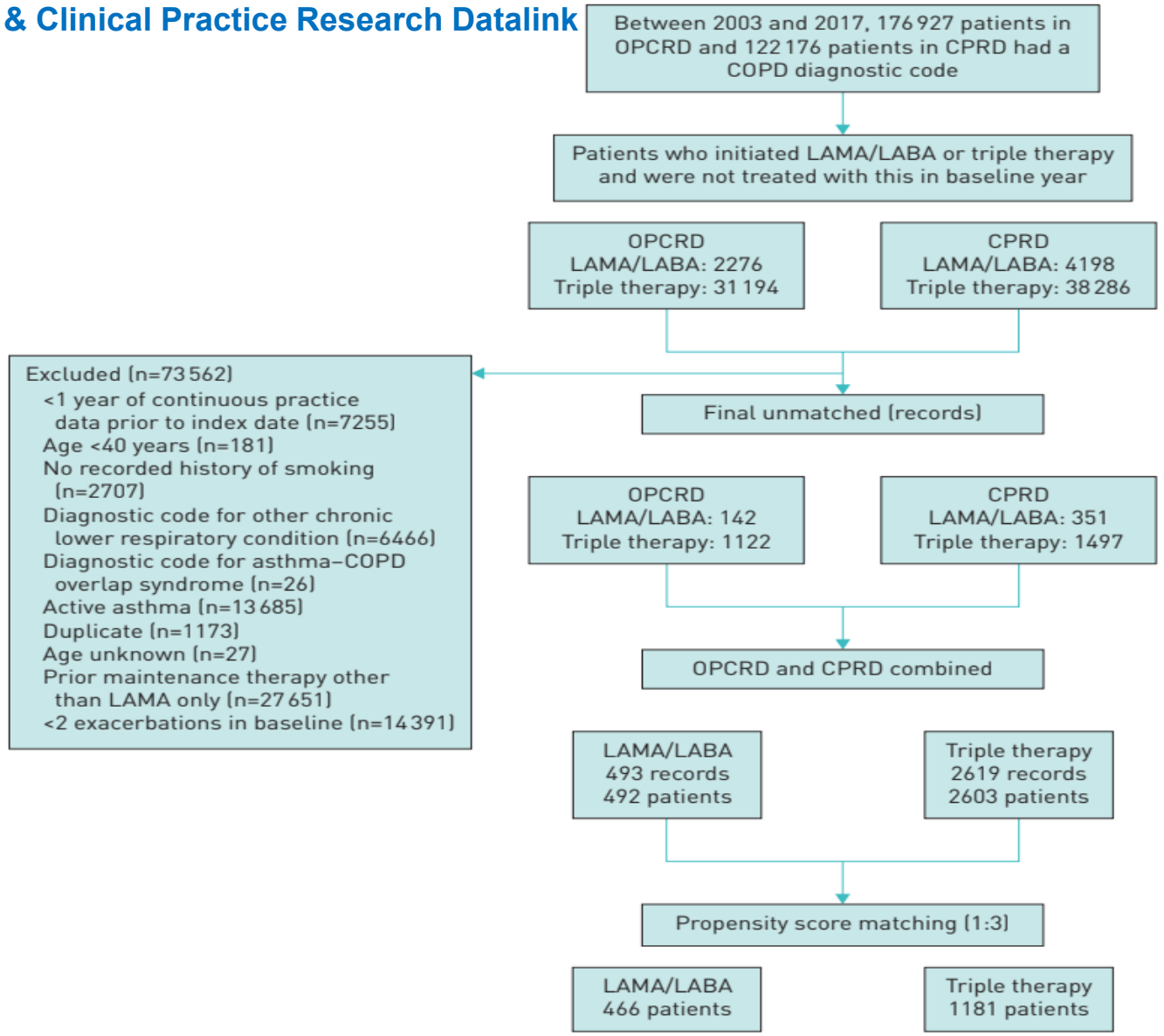


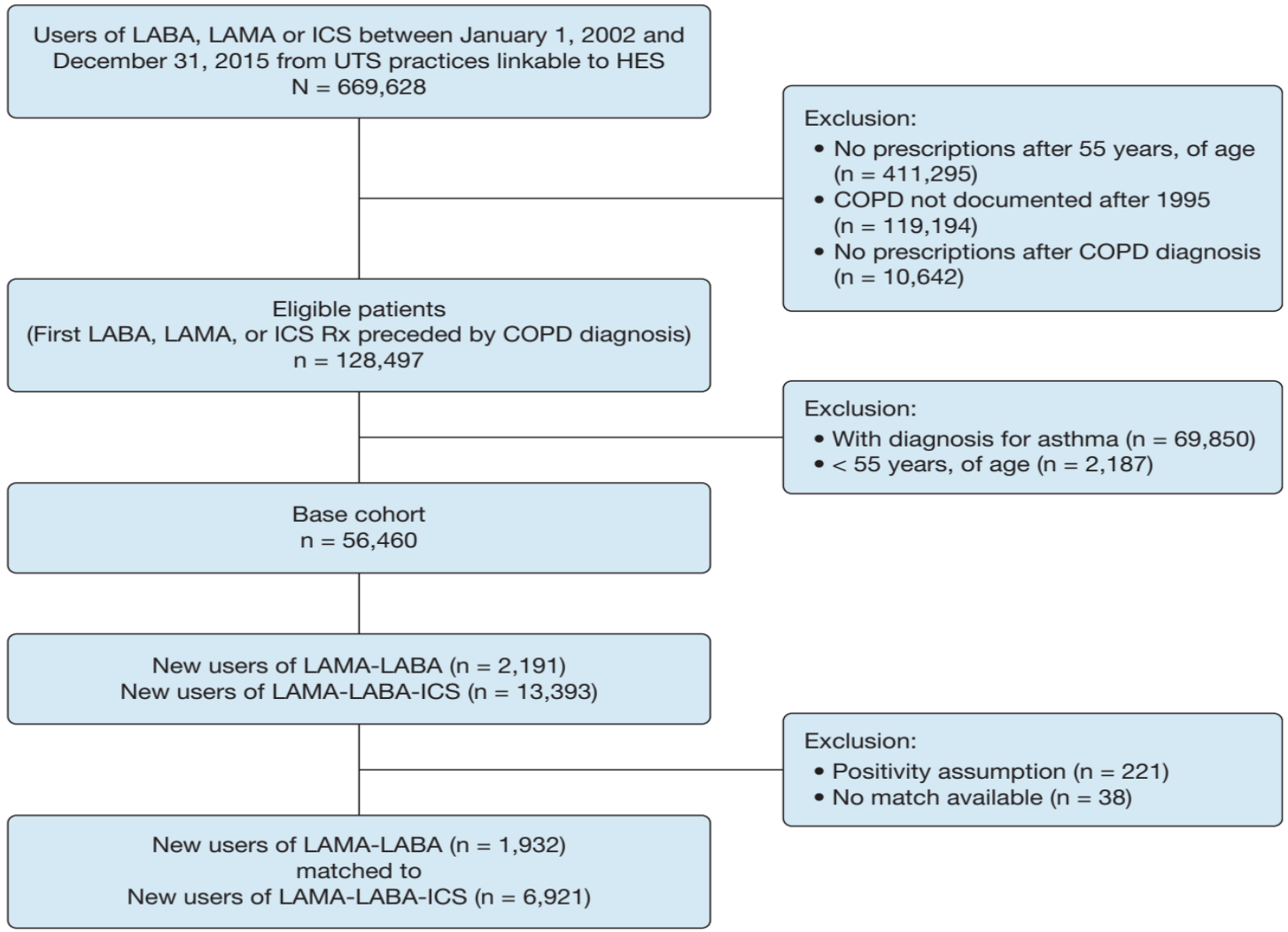
FIGURE 1 Study design. ICS: inhaled corticosteroid; LABA: long-acting inhaled ß-agonist; LAMA: long-act muscarinic antagonist.



ERJ Open Res 2019; 5: 00106-2019

Example of Study design and Flowchart of claim database study (3)

- **An UK study using Clinical Practice Research Datalink**



CHEST 2020;157:846-855

LABA/LAMA had as high incidence of severe exacerbations than patients treated with ICS/LABA/LAMA

- **A multicenter prospective longitudinal cohort study from China**

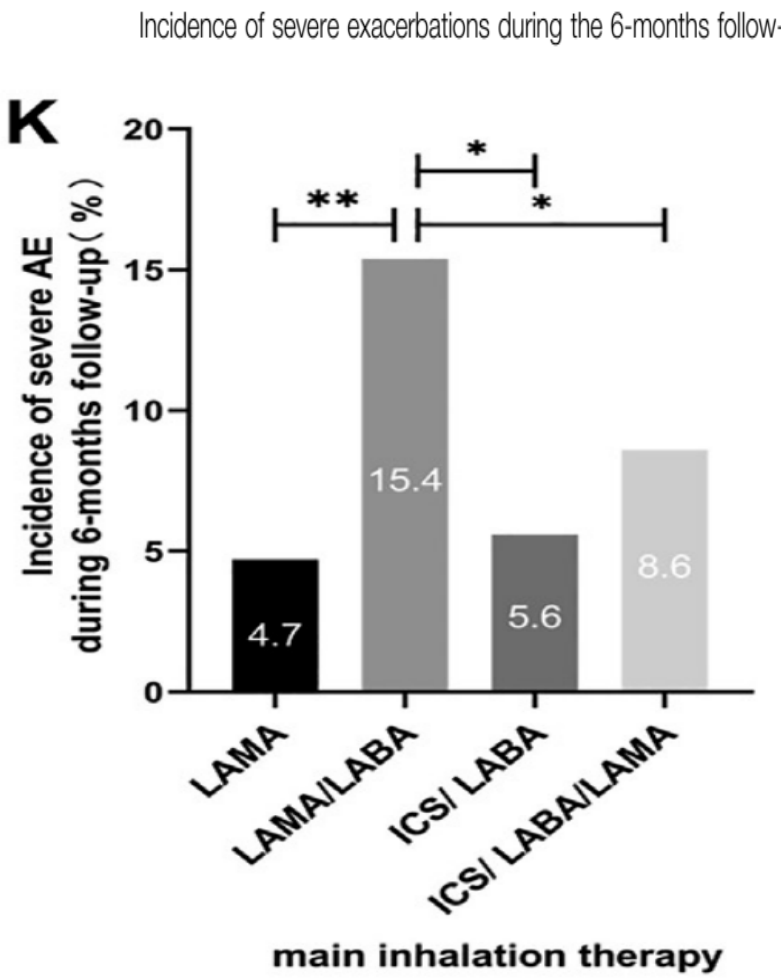


TABLE 5 | Multiple logistic regression for factors correlated with the incidence of severe exacerbation during 6 months follow-up.

Characteristics (*N* = 695)	aOR	a95%IC	*p*-value
Inhalation therapy			
ICS/LABA/LAMA	Reference		
LAMA	0.53	0.23–1.23	0.138
LAMA/LABA	1.95	1.04–3.66	**0.038**
ICS/LABA	0.63	0.21–1.89	0.408
Others	0.76	0.25–0.31	0.631

Note: *Factors in the logistic model: sex, age, treatment status at baseline, exacerbation in the past 1 year, severe exacerbation in the past 1 year, CAT score, mMRC score, Gold stage, group B/D, inhalation therapy; the bold p-values indicate statistical significance.*

Abbreviations: *CAT, COPD assessment test; mMRC, modified medical research council dyspnea scale; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; aOR, adjusted odds ratio; a95% CI, adjusted 95% confidence interval.*

Front Pharmacol. 2021;12:753653

Number of moderate and severe exacerbation

- **TRICOP study: A multicenter prospective open label non-interventional study from Austria**

  to evaluate the effectiveness of the fixed-dose triple therapy (BDP/DD/G)

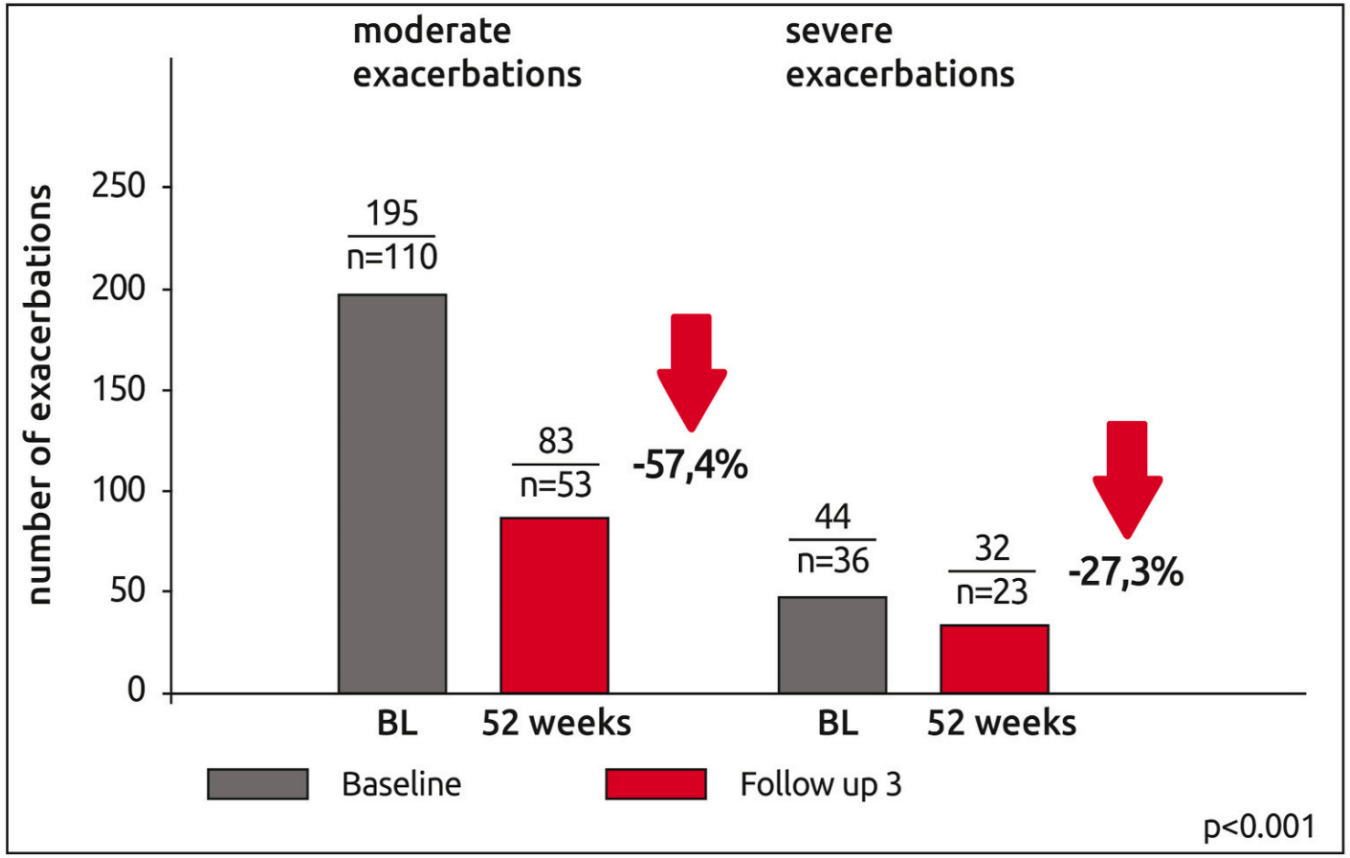


Fig. 4. Number of moderate and severe exacerbations experienced by COPD patients over the past 12 months at baseline and after 52 weeks of treatment with fixed-dose extrafine BDP/FF/G.

Respir Med 2021;182:106398

Effects of triple therapy c/w dual bronchodilators

- **An UK study using Optimum Patient Care Research Database & Clinical Practice Research Datalink**

TABLE 5 Unadjusted and adjusted effects of triple therapy compared with dual bronchodilation (baseline) on outcomes of interest during the outcome period

Outcome	Patients	Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
First exacerbation	1647	0.90 (0.79–1.02)	0.111	0.87 (0.76–0.99)	0.040
First acute respiratory event	1647	0.79 (0.70–0.88)	<0.001*	0.74 (0.66–0.84)	<0.001*
Treatment failure	1647	0.86 (0.76–0.98)	0.020	0.83 (0.73–0.95)	0.005*
First acute OCS course	1647	0.95 (0.82–1.09)	0.437	0.93 (0.80–1.07)	0.298
First antibiotics course	1647	0.91 (0.79–1.04)	0.171	0.89 (0.77–1.04)	0.138
Pneumonia diagnosis	1647	1.26 (0.80–1.98)	0.325	0.71 (0.21–2.38)	0.573
		RR (95% CI)	p-value	RR (95% CI)	p-value
Exacerbation rate	1138	0.85 (0.73–1.00)	0.056	0.86 (0.73–1.01)	0.068
Acute OCS courses rate	1138	0.83 (0.68–1.01)	0.067	0.80 (0.66–0.98)	0.030
Antibiotics courses rate	1138	0.88 (0.72–1.06)	0.183	0.91 (0.75–1.10)	0.332
Acute respiratory events rate	1138	0.80 (0.70–0.90)	<0.001	0.79 (0.70–0.90)	<0.001*
		OR (95% CI)	p-value	RR (95% CI)	p-value
mMRC ⩾2	885	1.20 (0.86–1.68)	0.293	1.12 (0.76–1.66)	0.566

HR: hazard ratio; OCS: oral corticosteroid; mMRC: modified Medical Research Council dyspnoea scale; RR: rate ratio. *: p<0.05 after controlling for 10 statistical tests for secondary outcomes performed following Holm's method [22].

ERJ Open Res 2019; 5: 00106-2019

First exacerbation stratified by blood eosinophil count & prior exacerbation numbers

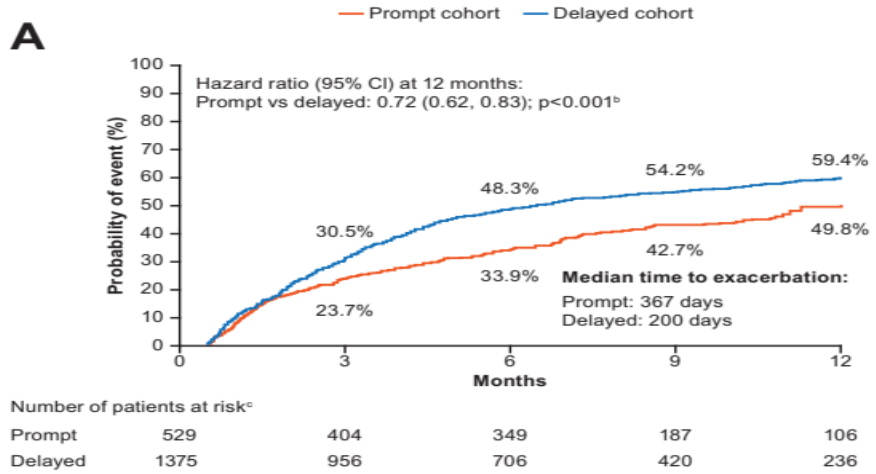
- **An UK study using Clinical Practice Research Datalink**

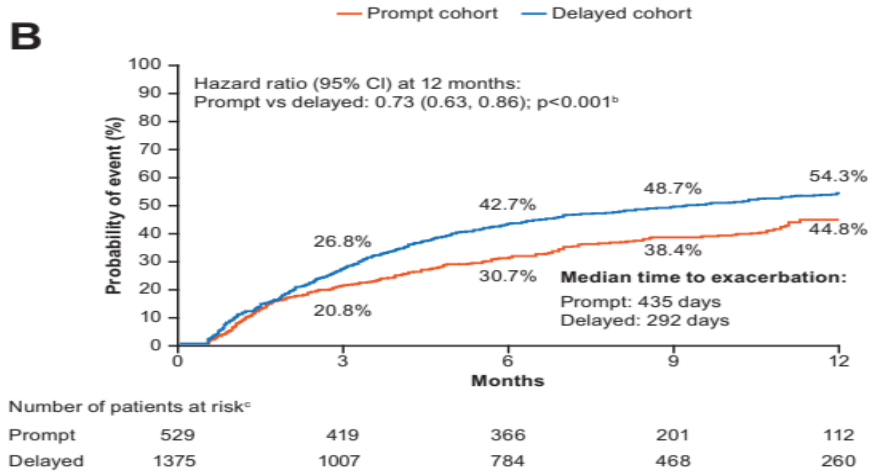
Treatment Group	No. of Patients	No. With Events	Person-Years	Rate per 100 per Year	Crude[a] HR	Adjusted[b] HR (95% CI)
Moderate or severe exacerbation						
LAMA-LABA-ICS	5,776	1,615	2,040	79.2	1.06	0.97 (0.86-1.09)
LAMA-LABA	1,598	355	457	77.7	1.00	1.00 (Reference)
Stratified by eosinophil count						
< 2%						
LAMA-LABA-ICS	1,984	590	695	84.8	1.09	1.01 (0.83-1.23)
LAMA-LABA	537	125	156	80.2	1.00	1.00 (Reference)
2%-4%						
LAMA-LABA-ICS	2,392	637	861	74.0	1.10	1.01 (0.84-1.21)
LAMA-LABA	672	136	193	70.5	1.00	1.00 (Reference)
4%-6%						
LAMA-LABA-ICS	898	248	312	79.5	1.10	1.01 (0.75-1.36)
LAMA-LABA	259	56	76	73.9	1.00	1.00 (Reference)
> 6%						
LAMA-LABA-ICS	502	140	171	81.8	0.74	0.66 (0.46-0.94)
LAMA-LABA	130	38	32	117.5	1.00	1.00 (Reference)
Prior COPD exacerbations in baseline year						
0						
LAMA-LABA-ICS	3,827	583	1,568	37.2	1.01	0.97 (0.80-1.17)
LAMA-LABA	1,145	138	372	37.1	1.00	1.00 (Reference)
1						
LAMA-LABA-ICS	1,656	523	560	93.5	1.07	1.09 (0.88-1.35)
LAMA-LABA	426	103	115	89.8	1.00	1.00 (Reference)
≥ 2						
LAMA-LABA-ICS	1,438	830	360	230.8	0.82	0.83 (0.70-0.98)
LAMA-LABA	361	177	55	320.1	1.00	1.00 (Reference)

CHEST 2020;157:846-855

Time to first COPD exacerbation

- **A US study using IQVIA PharMetrics Plus healthcare claims database**
  to investigate the impact of prompt versus delayed initiation of single inhaler of FF/UMEC/VI





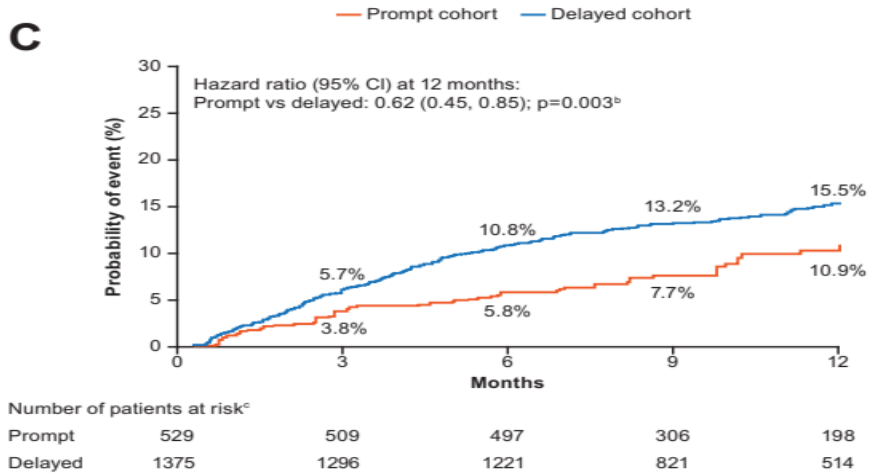


Figure 3 Time-to-first COPD exacerbation for (**A**) overall exacerbations, (**B**) moderate exacerbations, and (**C**) severe exacerbations (weighted analysis)[a].
Notes: [a] Prompt and delayed patients were weighted using the inverse probability of treatment weighting approach based on the propensity score. Variables used in the propensity score calculation included the following: age, sex, year/quarter of index date, US region, type of insurance plan (ie, PPO, HMO, POS, and other types), Quan-CCI score (categories of 0, 1, 2, and 3+), asthma diagnosis, type of COPD-related exacerbation on the index date, patients with multiple events in the index exacerbation, respiratory medication use, all-cause and COPD-related HRU and medical costs, and comorbidities (those with ≥5% prevalence in either cohort). [b] Hazard ratios, including CIs and p-values, were calculated using Cox proportional hazards models. [c] The number of patients still observed at each timepoint.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HMO, health maintenance organization; HRU, healthcare resource utilization; PPO, preferred provider organization; POS, point-of-service; Quan-CCI, Quan-Charlson comorbidity index.

IJCOPD 2022;17:491-504

COPD exacerbation rates

- **A US study using IQVIA PharMetrics Plus healthcare claims database**
  to investigate the impact of prompt versus delayed initiation of single inhaler of FF/UMEC/VI

Table 2 Rates of COPD Exacerbations Among Weighted Prompt and Delayed Cohorts

COPD Exacerbations	Number of Events		Rate (PPY)		Rate Ratio[a] (95% CI)[b] [A]/[B]	p-value[b]
	Prompt (N = 529)	Delayed (N = 1375)	Prompt [A]	Delayed [B]		
Observation period[c], mean (SD)	358.0 (137.4)	369.4 (140.7)				
Overall exacerbations	506	1708	0.98	1.23	0.79 (0.65, 0.94)	0.004
Moderate exacerbations[d]	447	1430	0.86	1.03	0.84 (0.69, 0.99)	0.038
Severe exacerbations[e]	59	278	0.11	0.20	0.57 (0.37, 0.79)	0.002

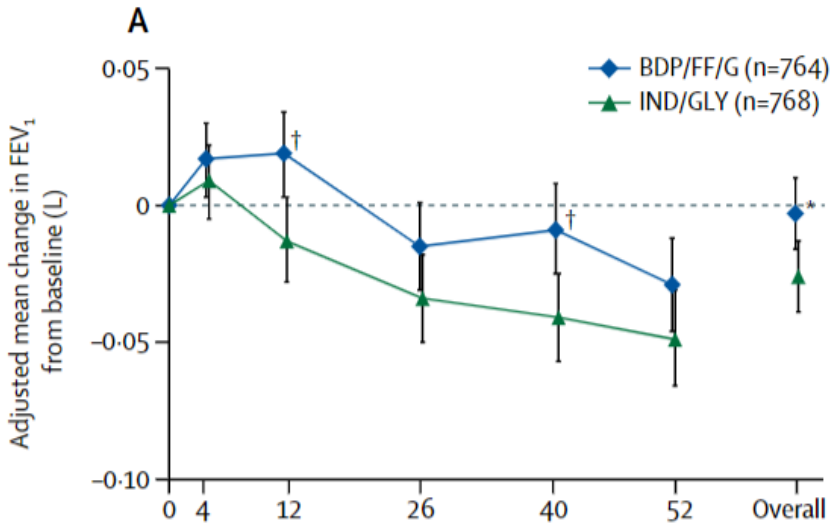
Notes: Prompt and delayed patients were weighted using the inverse probability of treatment weighting approach based on the propensity score. Variables used in the propensity score calculation included the following: age, sex, year/quarter of index date, US region, type of insurance plan (ie, PPO, HMO, POS, and other types), Quan-CCI score (categories of 0, 1, 2, and 3+), asthma diagnosis, type of COPD-related exacerbation on the index date, patients with multiple events in the index exacerbation, respiratory medication use, all-cause and COPD-related HRU and medical costs, and comorbidities (those with ≥5% prevalence in either cohort). [a] Rate ratios were calculated from Poisson regression models with log-link. [b] CIs and p-values were calculated using non-parametric bootstrap procedures with 999 replications. [c] The observation period spanned from the index date until the earliest of health plan disenrollment or end of data availability. [d] Moderate COPD exacerbations were defined as an outpatient or ER visit with a COPD exacerbation diagnosis code in the primary position and at least one dispensing/administration of a systemic corticosteroid or guideline-recommended antibiotic within 5 days following, or prior to, the visit. [e] Severe COPD exacerbations were defined as an inpatient hospitalization with a diagnosis code for COPD exacerbation in the primary position.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HMO, health maintenance organization; HRU, healthcare resource utilization; POS, point-of-service; PPO, preferred provider organization; PPY, per person-year; Quan-CCI, Quan-Charlson comorbidity index; SD, standard deviation.

IJCOPD 2022;17:491-504

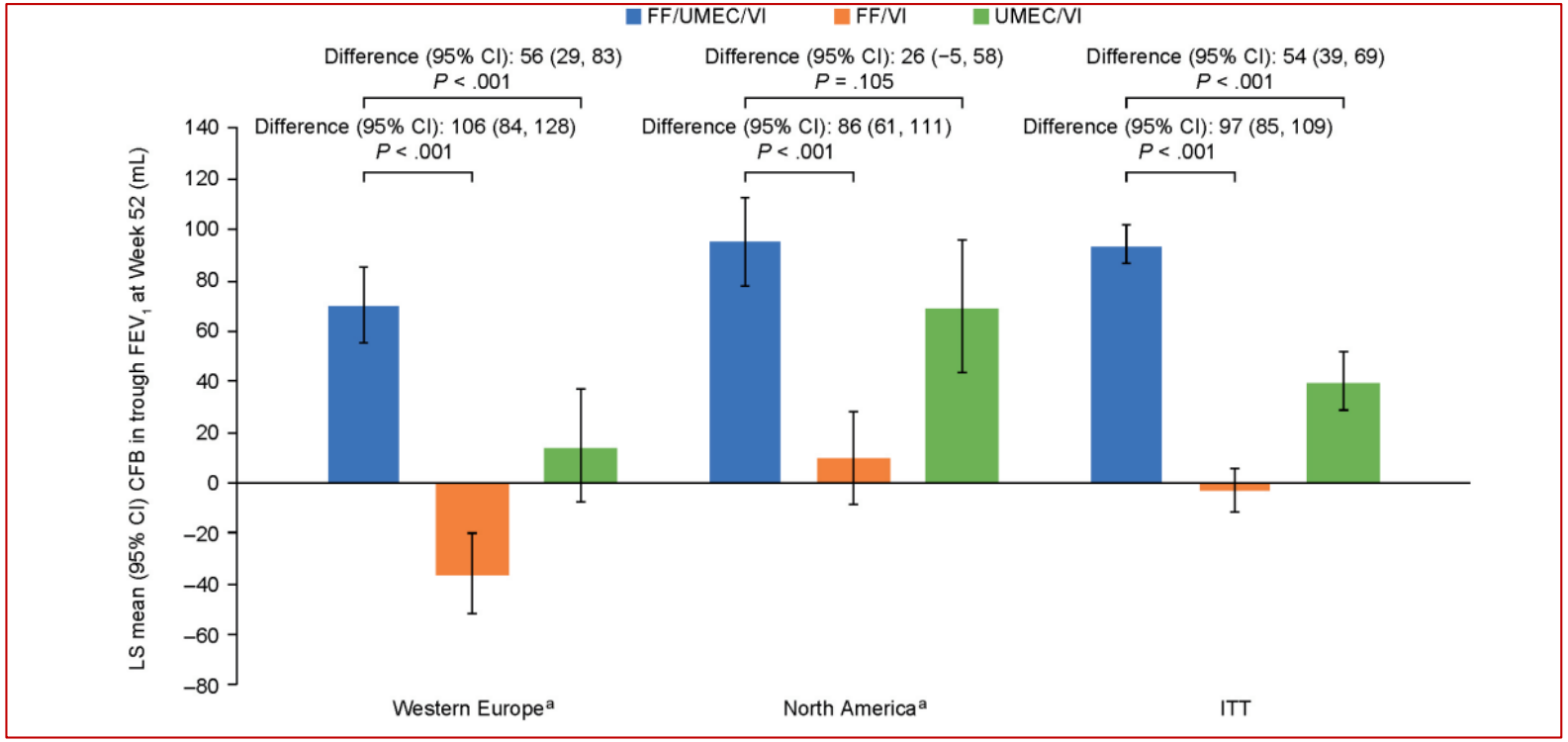
Lung function

Trough FEV1 change (TRIBUTE, IMPACT)



Adjusted mean difference between treatments (mL)						
	8	32	20	32	19	22
Number with available measurements						
BDP/FF/G	761 754	737	718	694	688	757
IND/GLY	767 758	742	712	677	652	760

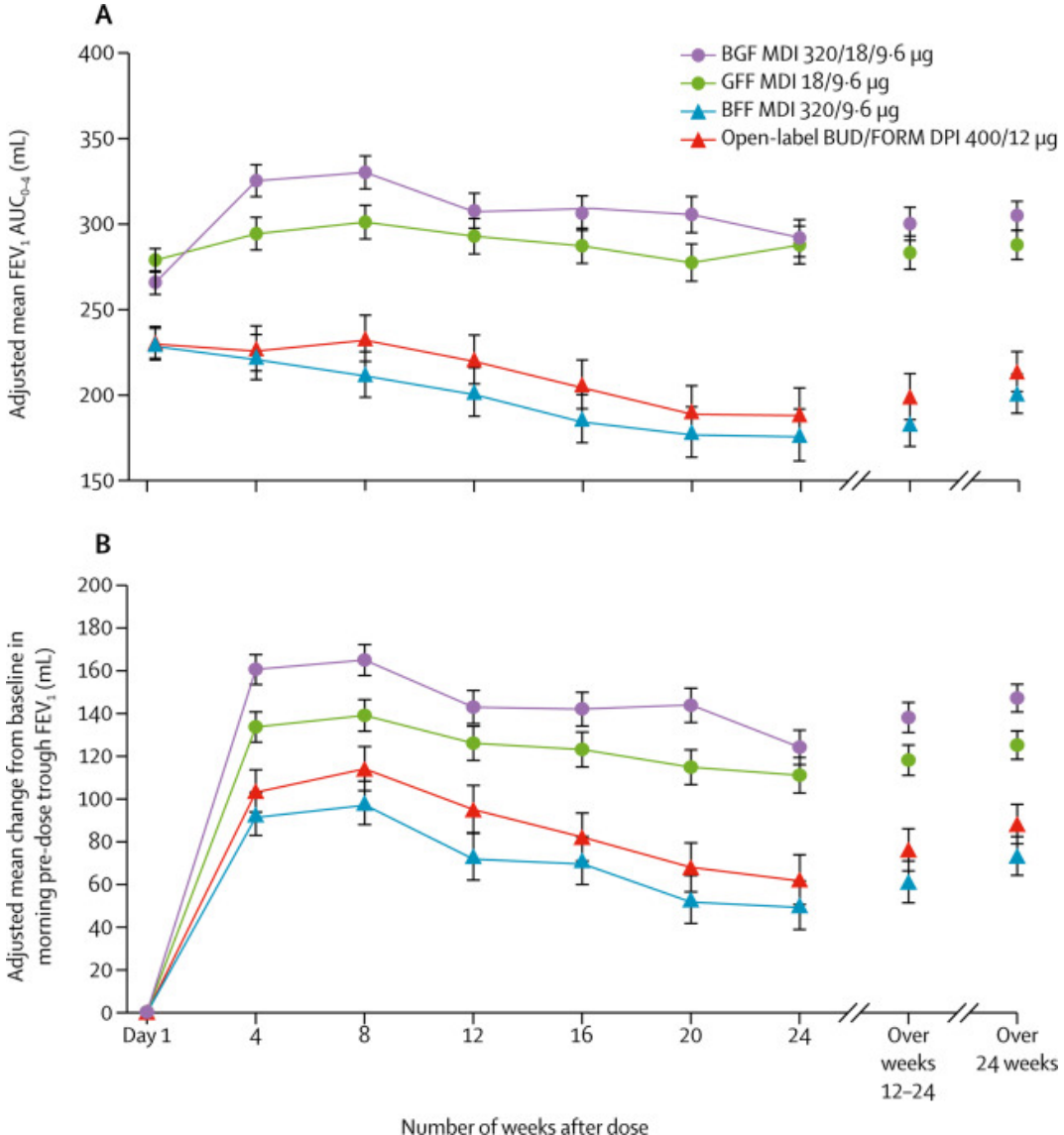
Outcome	Triple Therapy (N=4151)	Fluticasone Furoate–Vilanterol (N=4134)	Umeclidinium–Vilanterol (N=2070)
Trough FEV_1			
No. of patients evaluated	3366	3060	1490
Mean at wk 52 (95% CI) — ml	1274 (1265 to 1282)	1177 (1168 to 1185)	1220 (1208 to 1232)
Mean change from baseline (95% CI) — ml	94 (86 to 102)	−3 (−12 to 6)	40 (28 to 52)
Difference between triple therapy and dual-therapy comparator (95% CI) — ml	—	97 (85 to 109)†	54 (39 to 69)†



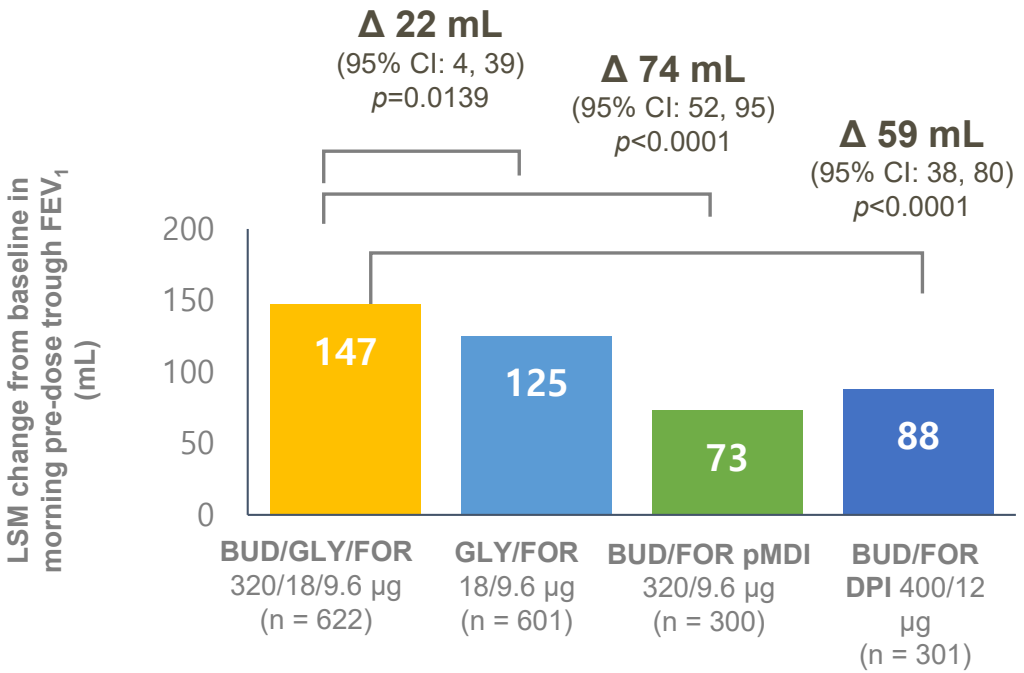
	Patients with a response		Odds ratio (95% CI)	p value
	BDP/FF/G (n=764)	IND/GLY (n=768)		
Pre-dose FEV_1*				
Week 26	176 (23%)	156 (20%)	1·18 (0·92–1·50)	0·194
Week 52	145 (19%)	125 (16%)	1·19 (0·91–1·55)	0·198

Adjusted mean change from baseline in pre-dose FEV1

RCTs on lung function (KRONOS)

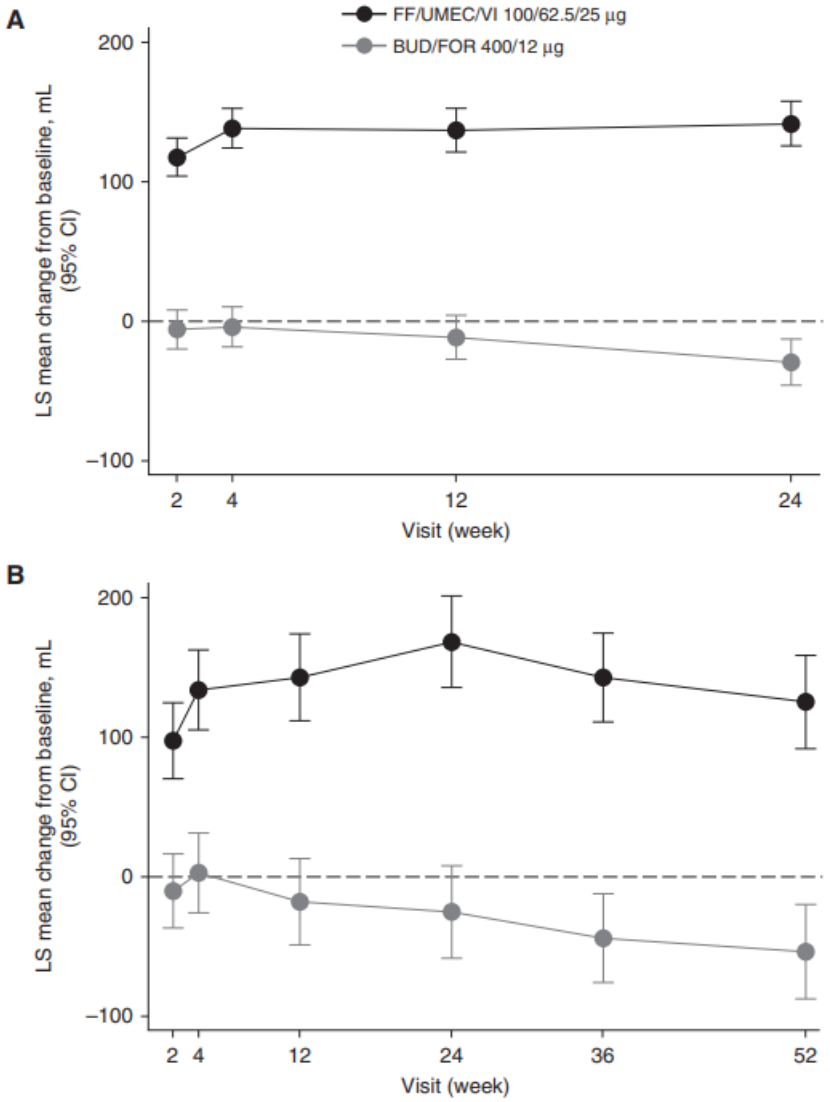


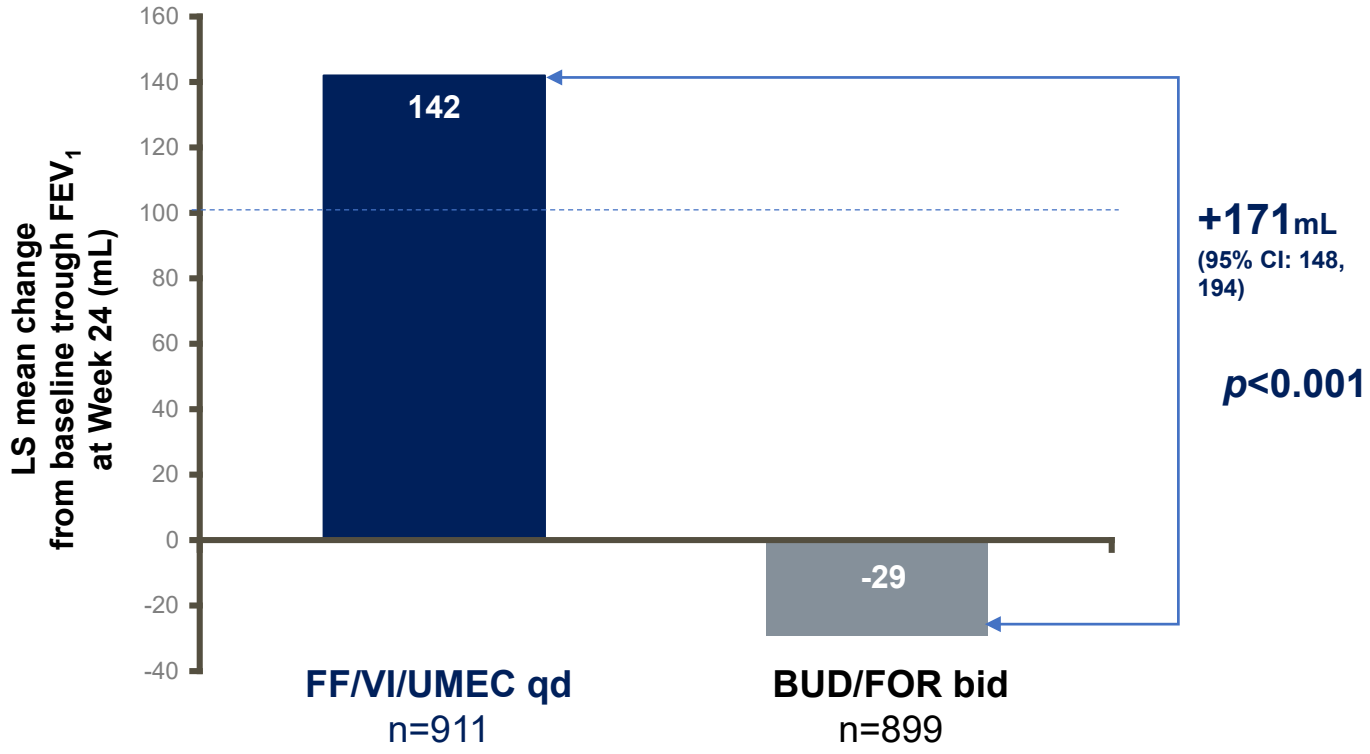
Change from baseline in morning pre-dose trough FEV_1 over 24 weeks



Lancet Respiratory Medicine, 2018 Oct;6(10):747-758

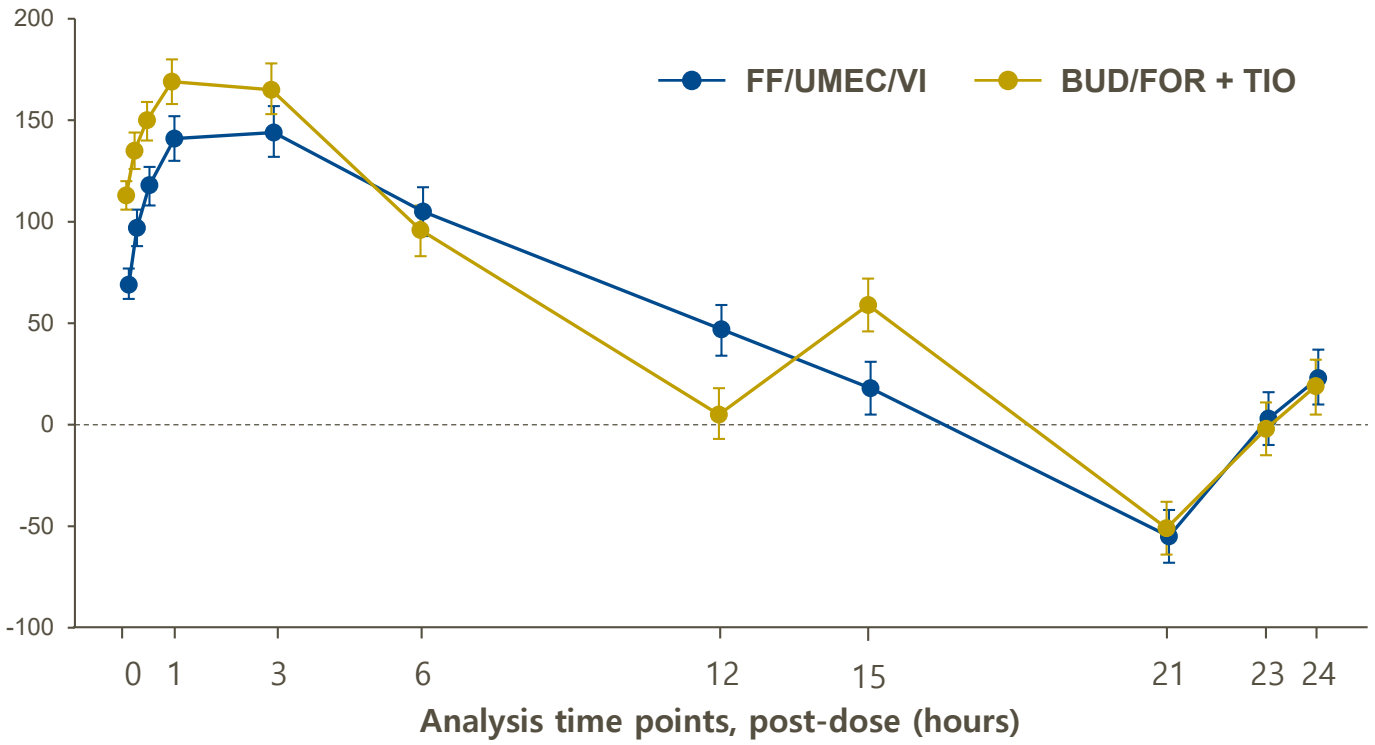
FULFIL trial (FF/VI/UMEC vs. BUD/FOR)

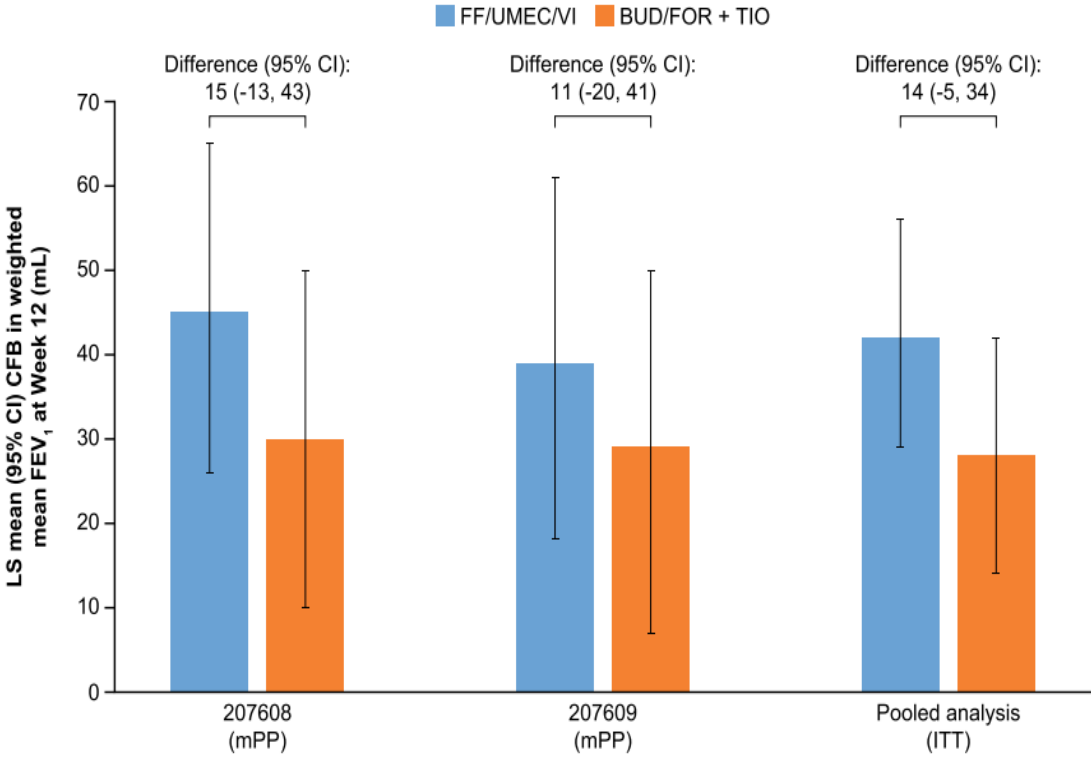




➔ RWE

FF/UMEC/VI vs. BUD/FOR + TIO

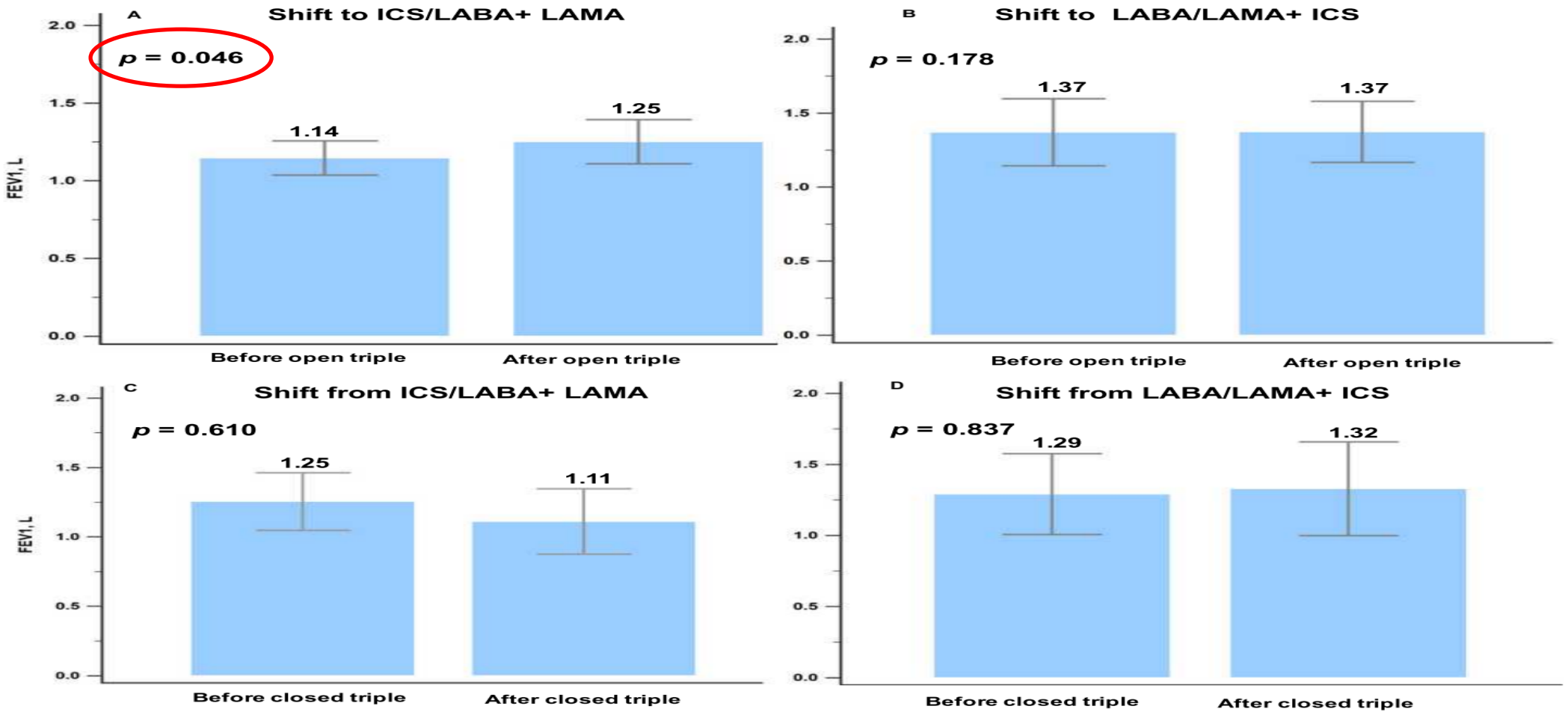




Ferguson et al. Respiratory Research (2020) 21:131

Change of FEV_1 before and after Triple Therapy

- A single center retrospective study from China



IJCOPD 2021:16:1555-1568

Change of FEV1 & FVC in patients with severe airflow limitation

- **TRICOP study: A multicenter prospective open label non-interventional study from Austria**

  to evaluate the effectiveness of the fixed-dose triple therapy (BDP/DD/G)

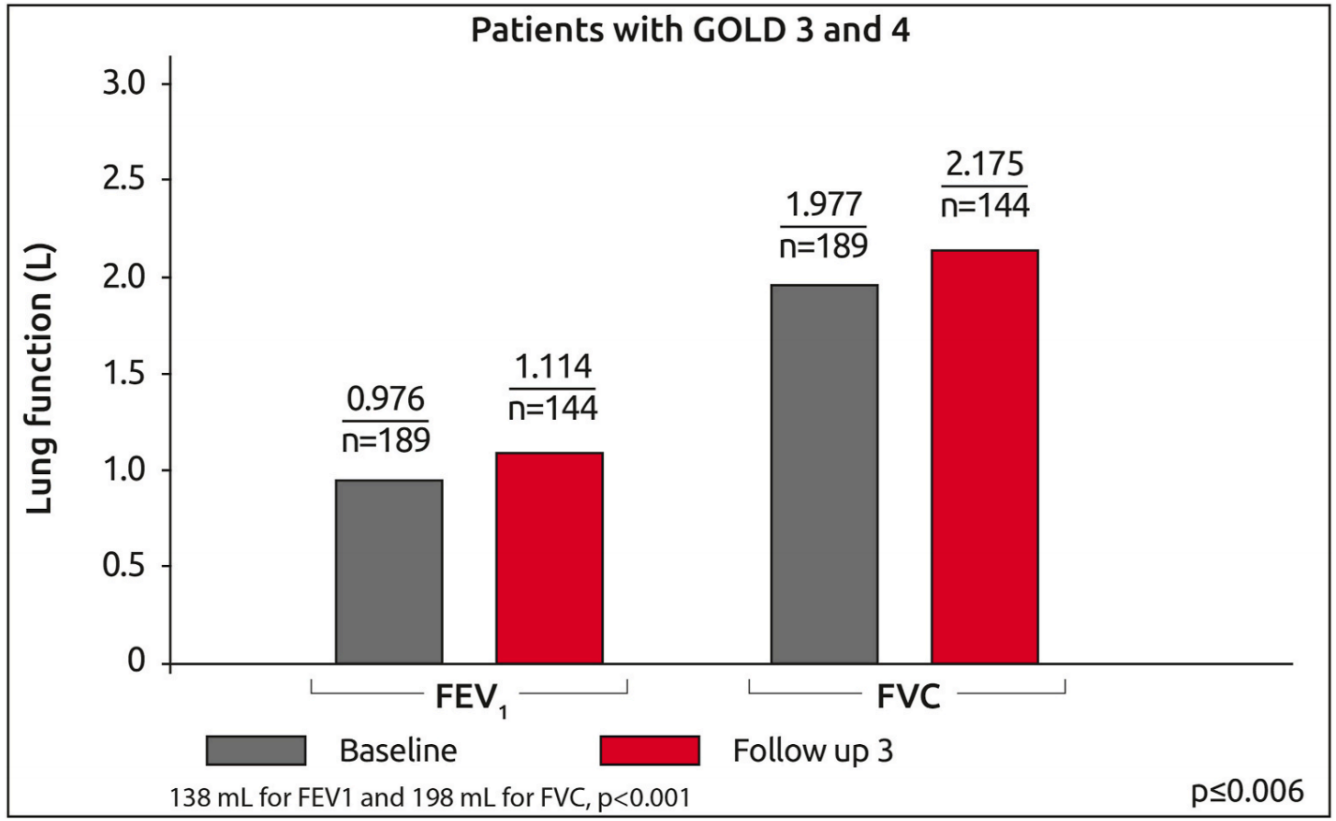
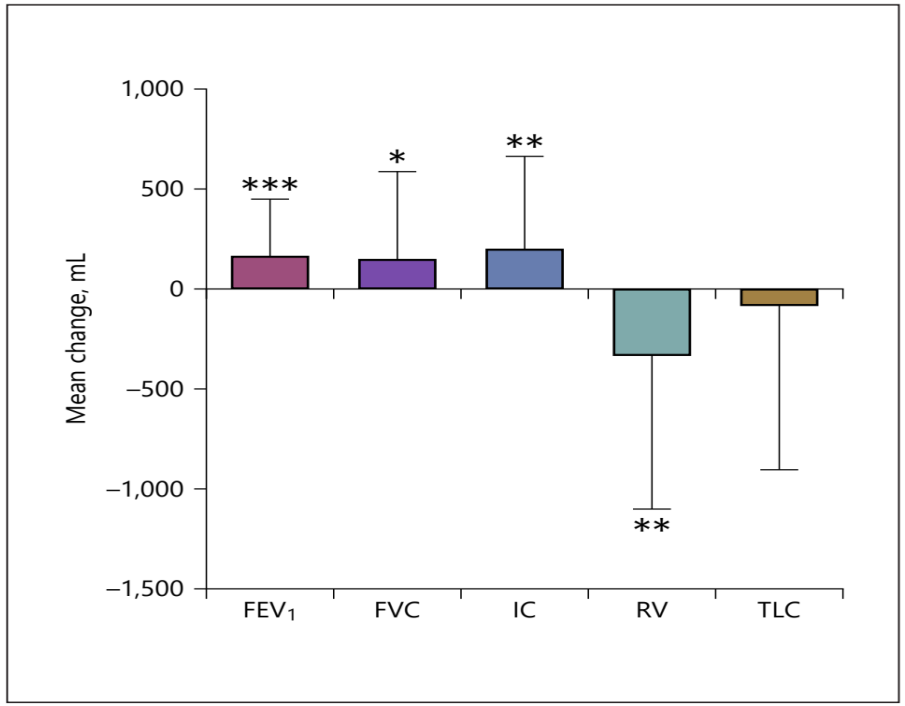


Fig. 1. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) in patients with GOLD 3 and 4 as determined at baseline and during follow up 3 after 52 weeks of treatment with a fixed-dose extrafine beclometasone, formoterol and glycopyrronium.

Respir Med 2021;182:106398

Change of lung function before and after Closed Triple Therapy

- **A 24 weeks single center study from Italy**
  to assess the effect single inhaler of FF/UMEC/VI



Color version available online

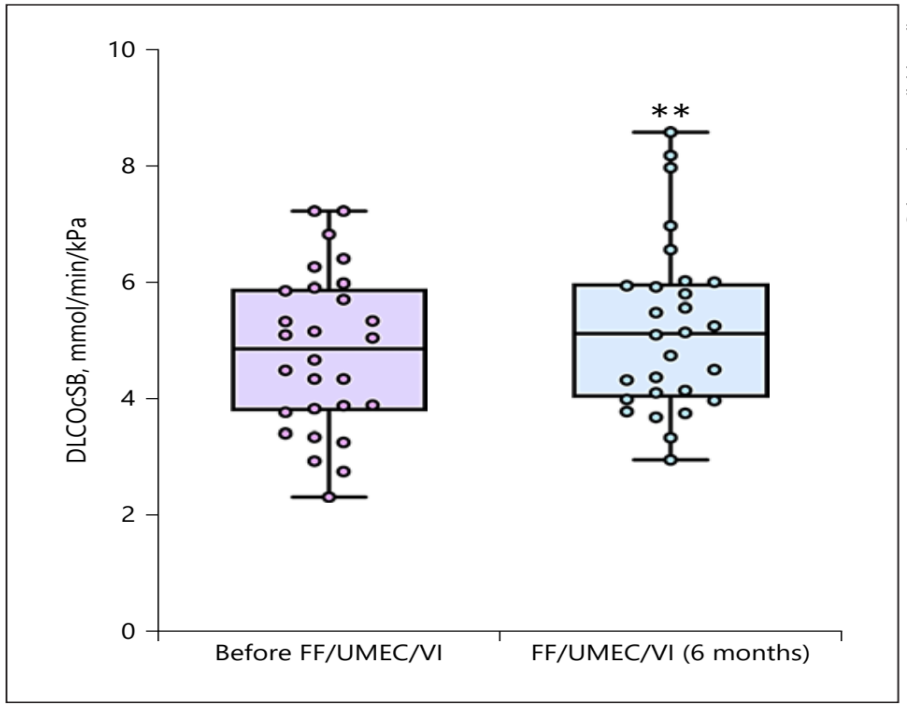


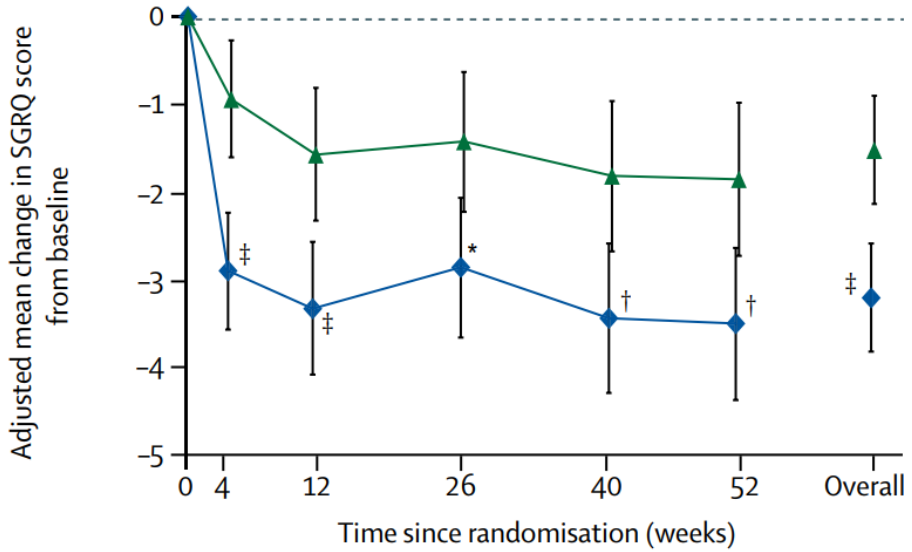
Fig. 1. Mean changes of FEV_1, FVC, IC, RV, and TLC after 24 weeks of combined triple inhaled therapy (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; RV, residual volume.

Fig. 2. Effect of FF/UMEC/VI on DLCOcSB. In regard to the 28 patients who satisfactorily performed DLCOcSB, test values significantly increased after 24 weeks of combined triple inhaled therapy (**$p < 0.01$). FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; DLCOcSB, corrected single-breath diffusion lung capacity for carbon monoxide.

Respiration 2021:100:127-134

Dyspnea/QoL

QoL (SGRQ total score)

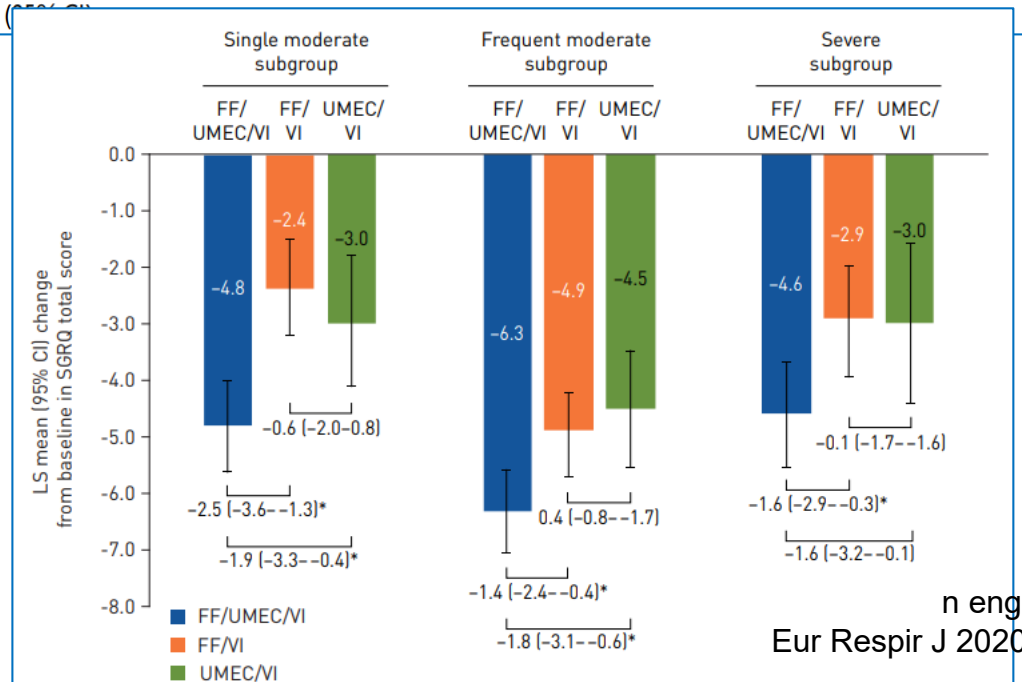


Adjusted mean difference between treatments						
	−1·96	−1·75	−1·43	−1·62	−1·64	−1·68
Number with available measurements						
BDP/FF/G	763	757	740	722	695	667	760
IND/GLY	768	762	744	716	679	654	763

	Patients with a response		Odds ratio (95% CI)	p value
	BDP/FF/G (n=764)	IND/GLY (n=768)		
SGRQ total score†				
Week 26	310 (41%)	292 (38%)	1·13 (0·92–1·40)	0·255
Week 52	311 (41%)	279 (36%)	1·22 (0·99–1·51)	0·068

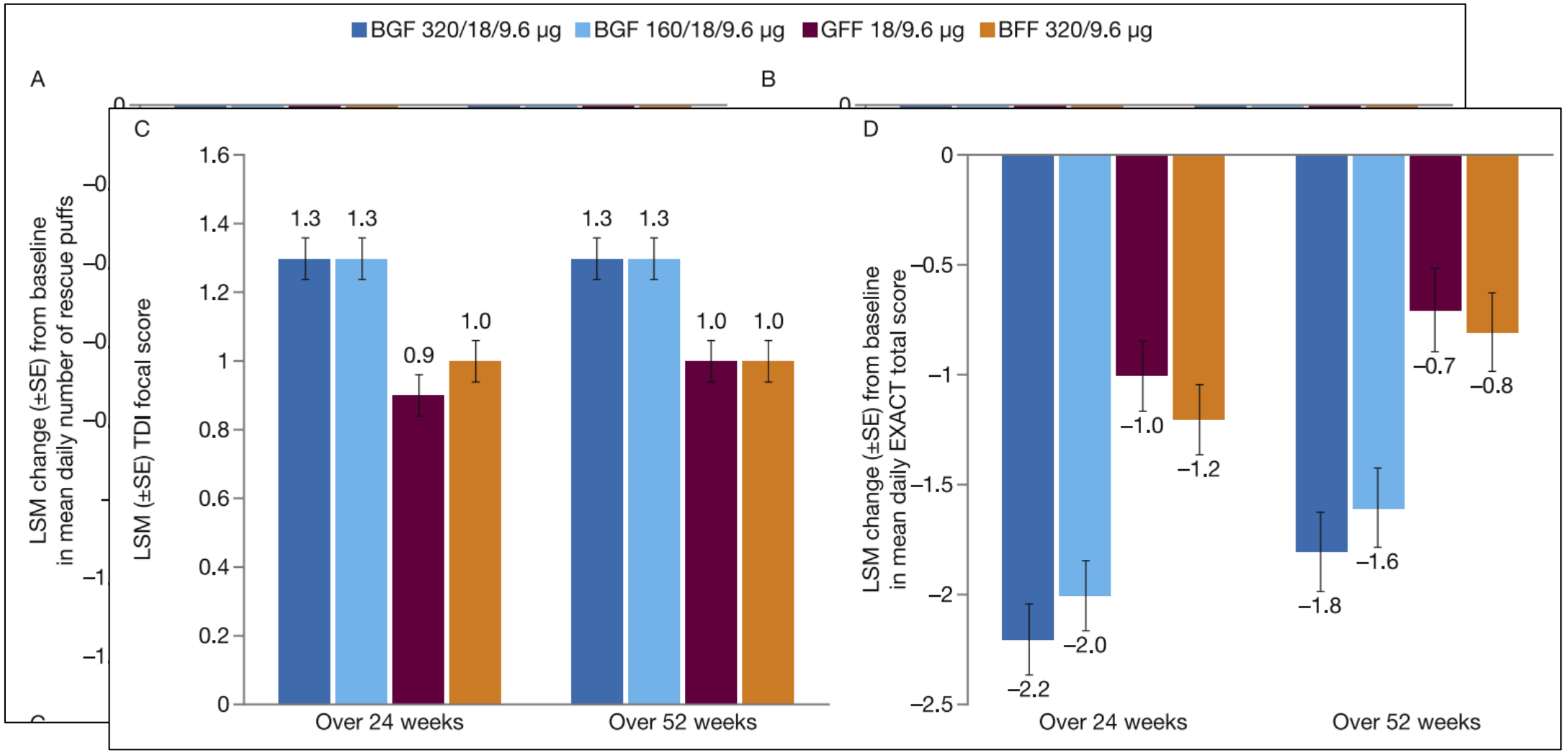
Lancet 2018; 391: 1076–84

Outcome	Triple Therapy (N=4151)	Fluticasone Furoate–Vilanterol (N=4134)	Umeclidinium–Vilanterol (N=2070)
SGRQ total score‡			
No. of patients evaluated	3318	3026	1470
Mean at wk 52 (95% CI)	45.0 (44.5 to 45.4)	46.8 (46.3 to 47.2)	46.8 (46.1 to 47.4)
Mean change from baseline (95% CI)	−5.5 (−5.9 to −5.0)	−3.7 (−4.2 to −3.2)	−3.7 (−4.4 to −3.0)
Difference between triple therapy and dual-therapy comparator (95% CI)	—	−1.8 (−2.4 to −1.1)†	−1.8 (−2.6 to −1.0)†
Response according to SGRQ total score at wk 52 — no. (%)§	1723 (42)	1390 (34)	696 (34)
Odds ratio for triple therapy vs. dual-therapy comparator (	—	1.41 (1.29 to 1.55)†	1.41 (1.26 to 1.57)†



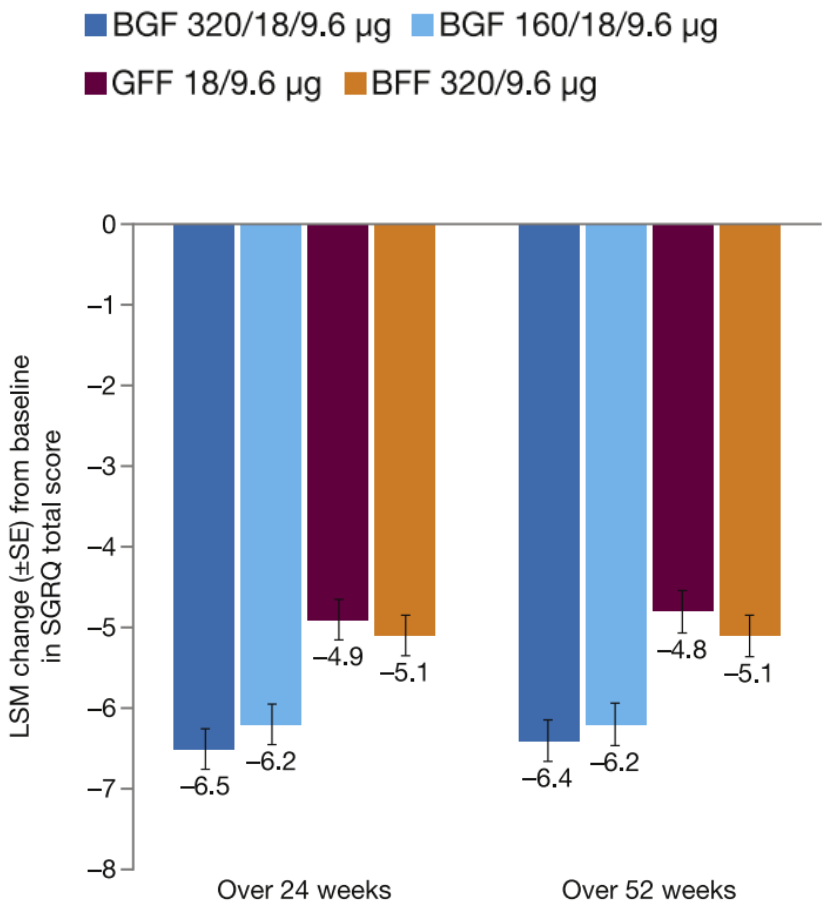
n engl j med 378;18
Eur Respir J 2020; 55: 1901921

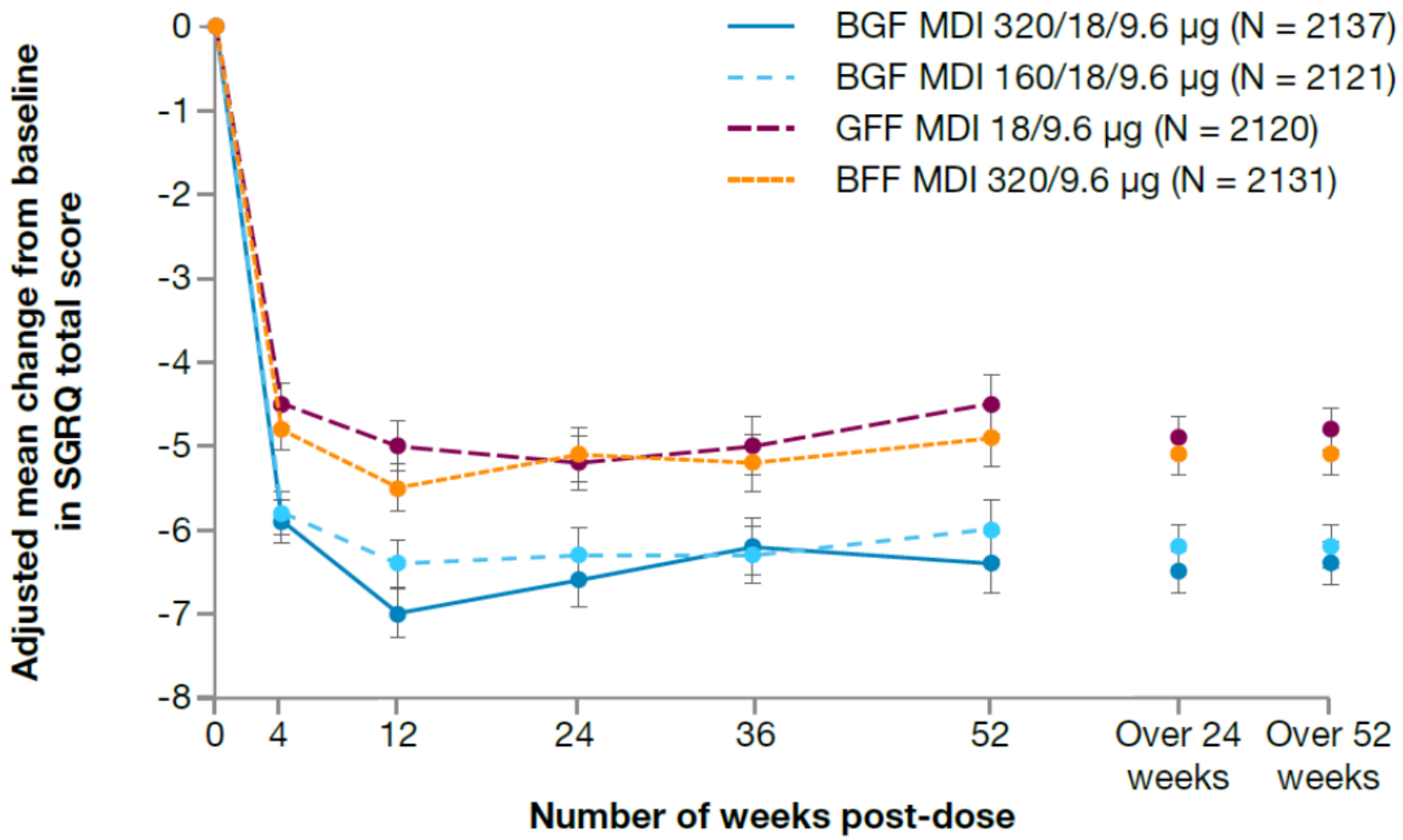
Benefits of BGF on symptoms and quality of life in patients with COPD in the ETHOS trial



Respiratory Medicine 185 (2021) 106509

Change from baseline in SGRQ total score (ETHOS trial)





ICS/LABA/LAMA is more likely to attain MCID than patients treated with LAMA

- **A multicenter prospective longitudinal cohort study from China**

TABLE 4 | Multiple logistic regression for factors correlated with the response rate of MCID.

Characteristics (*N* = 695)	cOR	c95%IC	*p*-value	aOR	a95%IC	*p*-value
Sex			**0.005**			**0.024**
male	Reference			Reference		
female	2.18	1.27–3.73		1.93	1.09–3.42	
Inhalation therapy			<**0.001**			
LAMA	Reference			Reference		
LAMA/LABA	4.09	2.56–6.54	<**0.001**	3.97	2.48–6.35	<**0.001**
ICS/LABA	1.00	0.55–1.81	0.999	0.90	0.49–1.64	0.726
ICS/LABA/LAMA	3.36	2.23–5.08	<**0.001**	3.17	2.09–4.80	<**0.001**
Others	0.77	0.40–1.49	0.446	0.78	0.41–1.51	0.462

Note: *Factors in the logistic model: sex, age, smoking status, treatment status at baseline, exacerbation history in the past 1 year, Gold stage, group B/D, Inhalation therapy; the bold p-values indicate statistical significance.*

Abbreviations: *MCID, minimum clinically important difference; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; cOR, crude odds ratio; c95% CI, crude 95% confidence interval; aOR, adjusted odds ratio; a95% CI, adjusted 95% confidence interval.*

Front Pharmacol. 2021;12:753653

Effectiveness of switching to Triple Therapy

- **A single center retrospective study from China**

	To open triple			To closed triple		
	Before	After	P-value	Before	After	P-value
Annualized rate of moderate/severe exacerbation	0.47	0.45	0.787	**0.38**	**0.25**	**0.047**
CAT						
ICS/LABA + LAMA	10.01	9.61	0.325	9.36*	10.66*	0.019
LABA/LAMA + ICS	9.16	9.56	0.613	9.57§	10.61§	0.351
mMRC						
ICS/LABA + LAMA	1.98	1.98	1.00	1.88*	1.94*	0.055
LABA/LAMA + ICS	1.60	1.96	0.107	2.00§	1.90§	0.162
FEV1						
ICS/LABA + LAMA	1.14L	1.25L	0.046	1.25*	1.11*	0.610
LABA/LAMA + ICS	1.37L	1.37L	0.178	1.29§	1.32§	0.837

*: from ICS/LABA + LAMA to closed triple
§: from LABA/LAMA + ICS to closed triple

IJCOPD 2021:16:1555-1568

Change of CAT score

- **TRICOP study: A multicenter prospective open label non-interventional study from Austria**

  to evaluate the effectiveness of the fixed-dose triple therapy (BDP/DD/G)

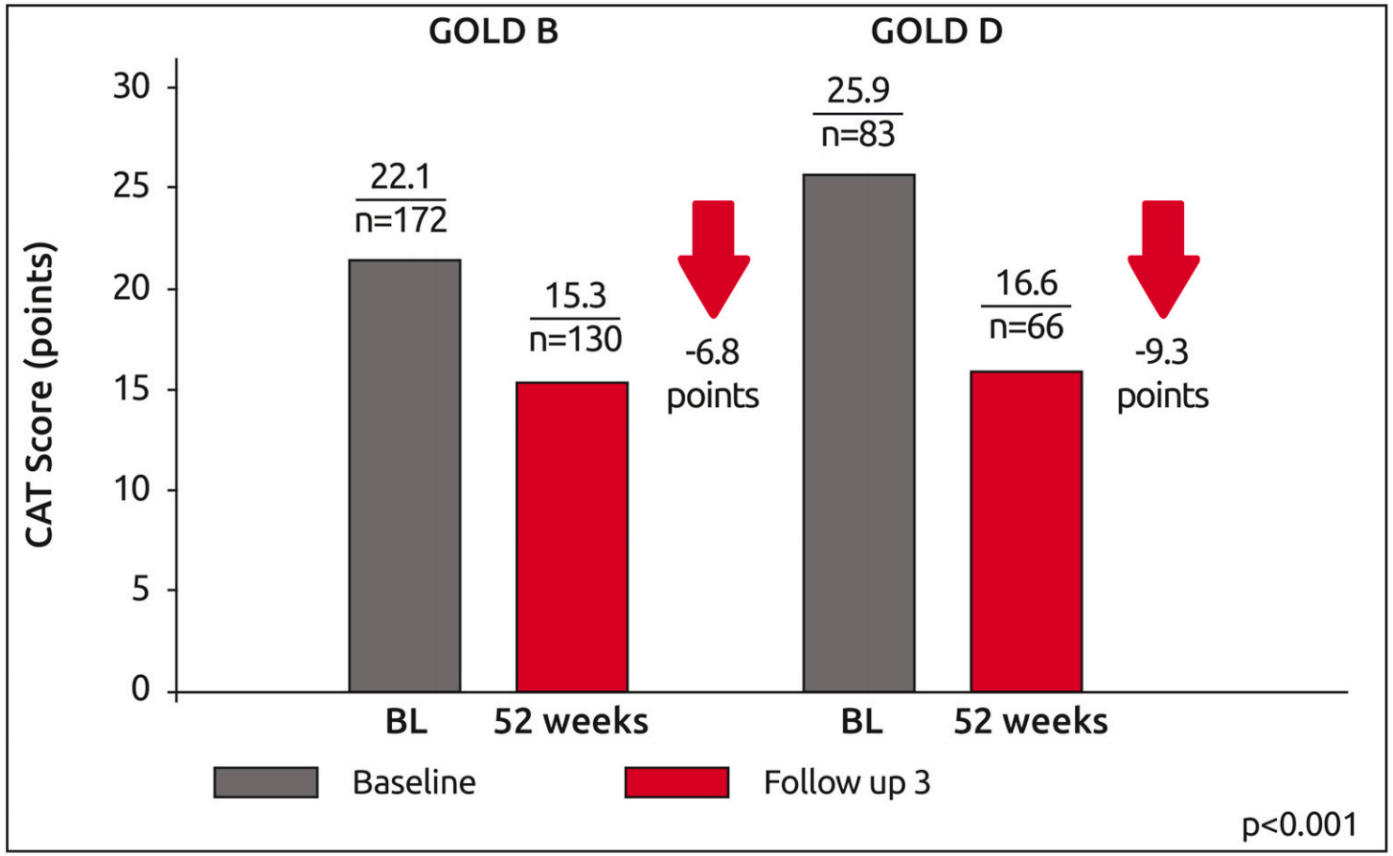
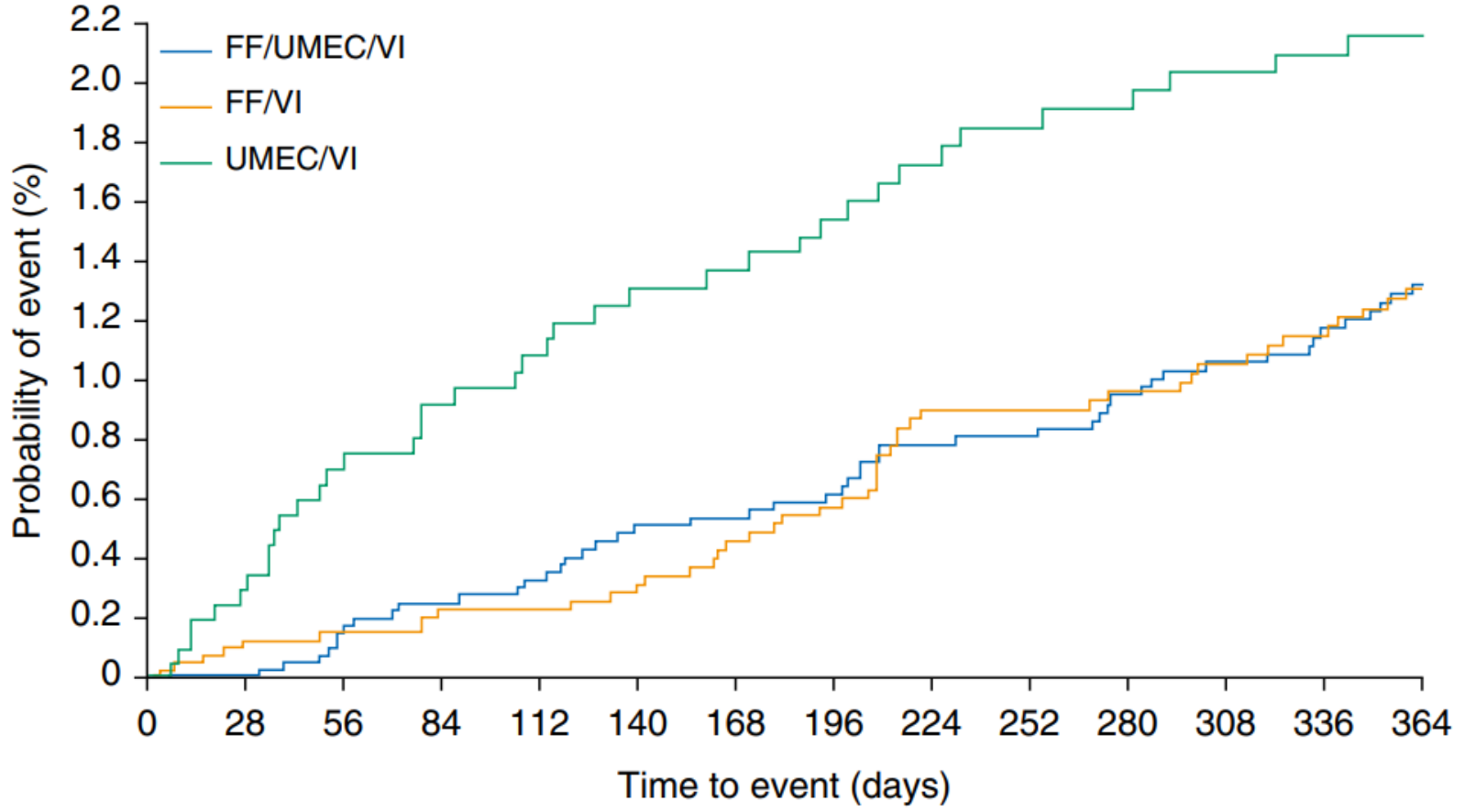


Fig. 3. COPD Assessment Test (CAT) score of patients with GOLD B and D at baseline and after 52 weeks of treatment with fixed-dose extrafine BDP/FF/G.

Respir Med 2021;182:106398

Mortality

Time to all-cause mortality for on-treatment deaths



FF/UMEC/VI	4,151	4,082	3,968	3,898	3,838	3,752	3,714	3,690	3,613	3,581	3,545	3,486	3,454	3,346
FF/VI	4,134	3,984	3,798	3,694	3,619	3,496	3,443	3,391	3,291	3,258	3,230	3,182	3,152	3,044
UMEC/VI	2,070	1,993	1,880	1,820	1,769	1,713	1,685	1,656	1,612	1,595	1,578	1,548	1,531	1,485

Relative reduction in risk

Triple vs. UMEC/VI: 42%

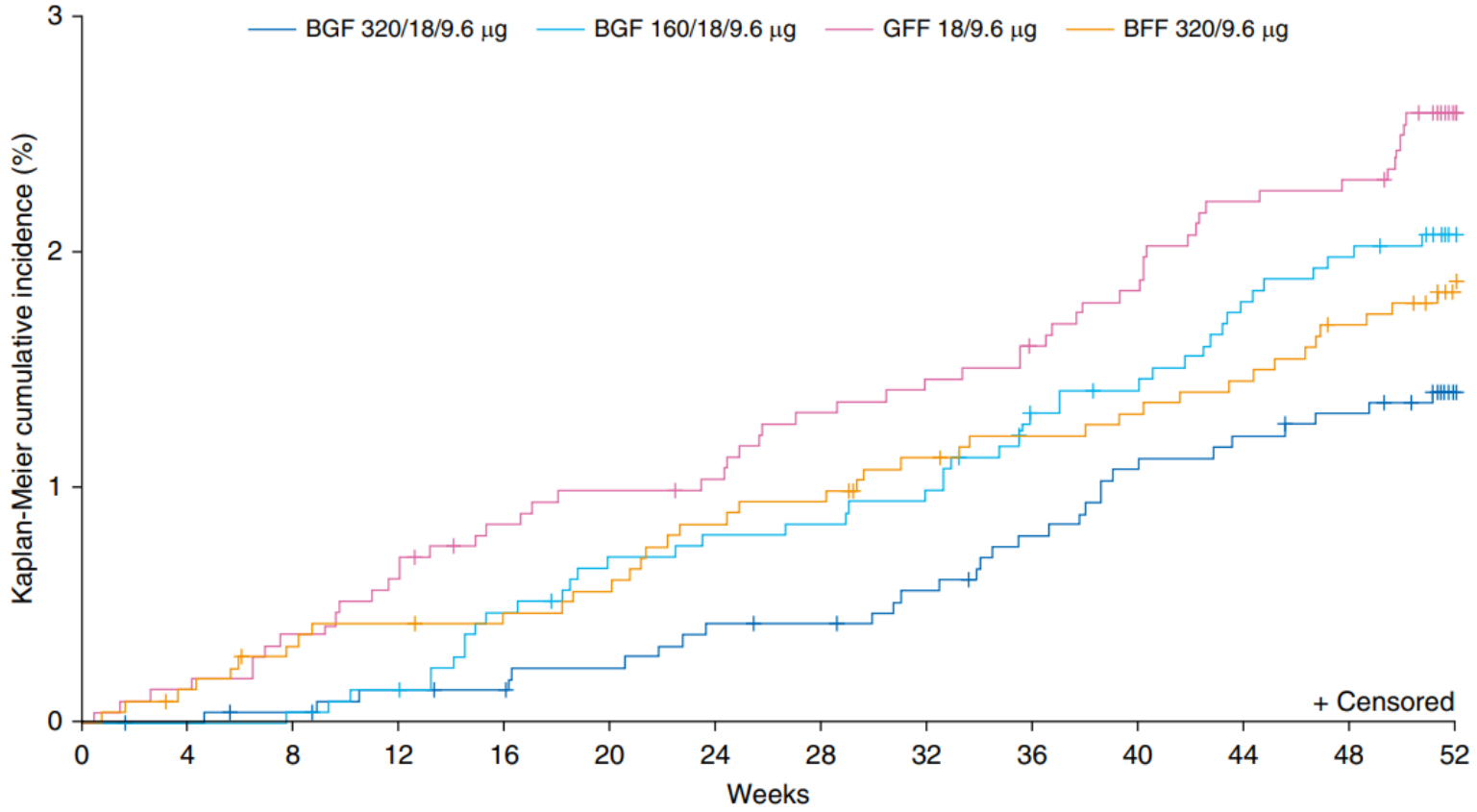
(95% CI: 12, 62); *p*=0.011

FF/VI vs. UMEC/VI: 39%

(95% CI: 7, 60); *p*=0.022

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

Mortality in ETHOS trial

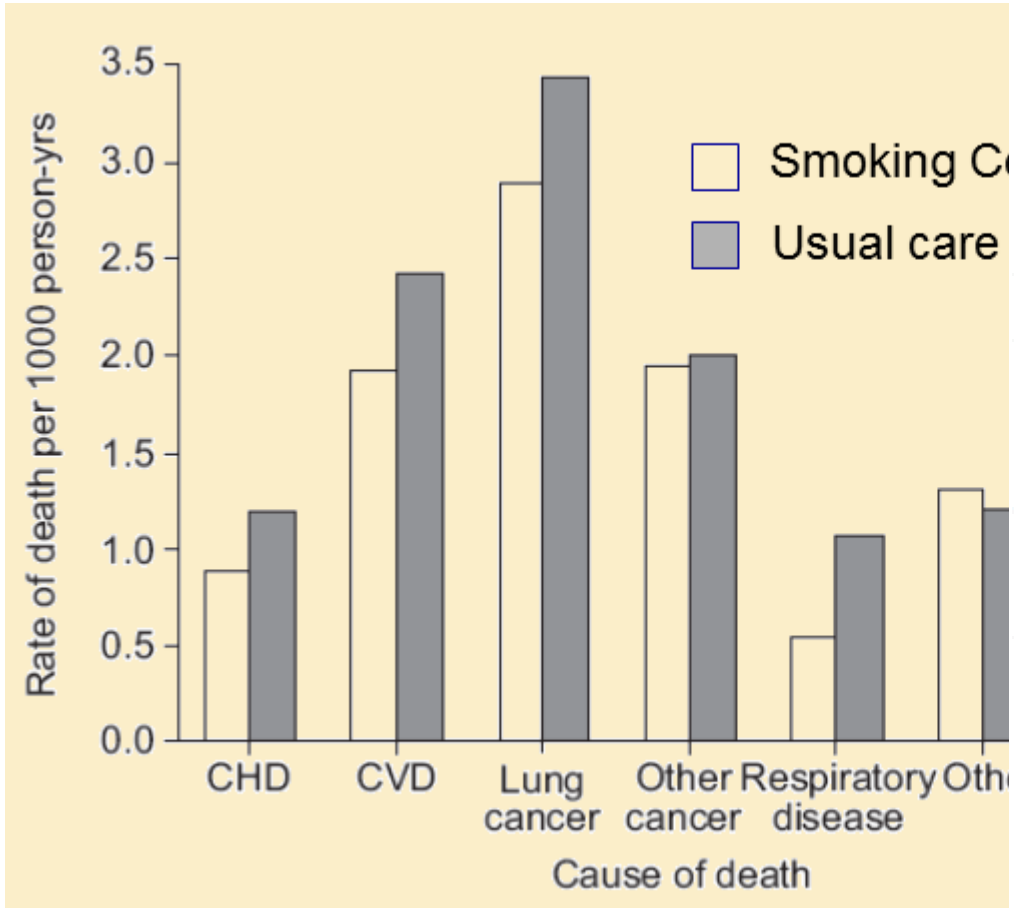


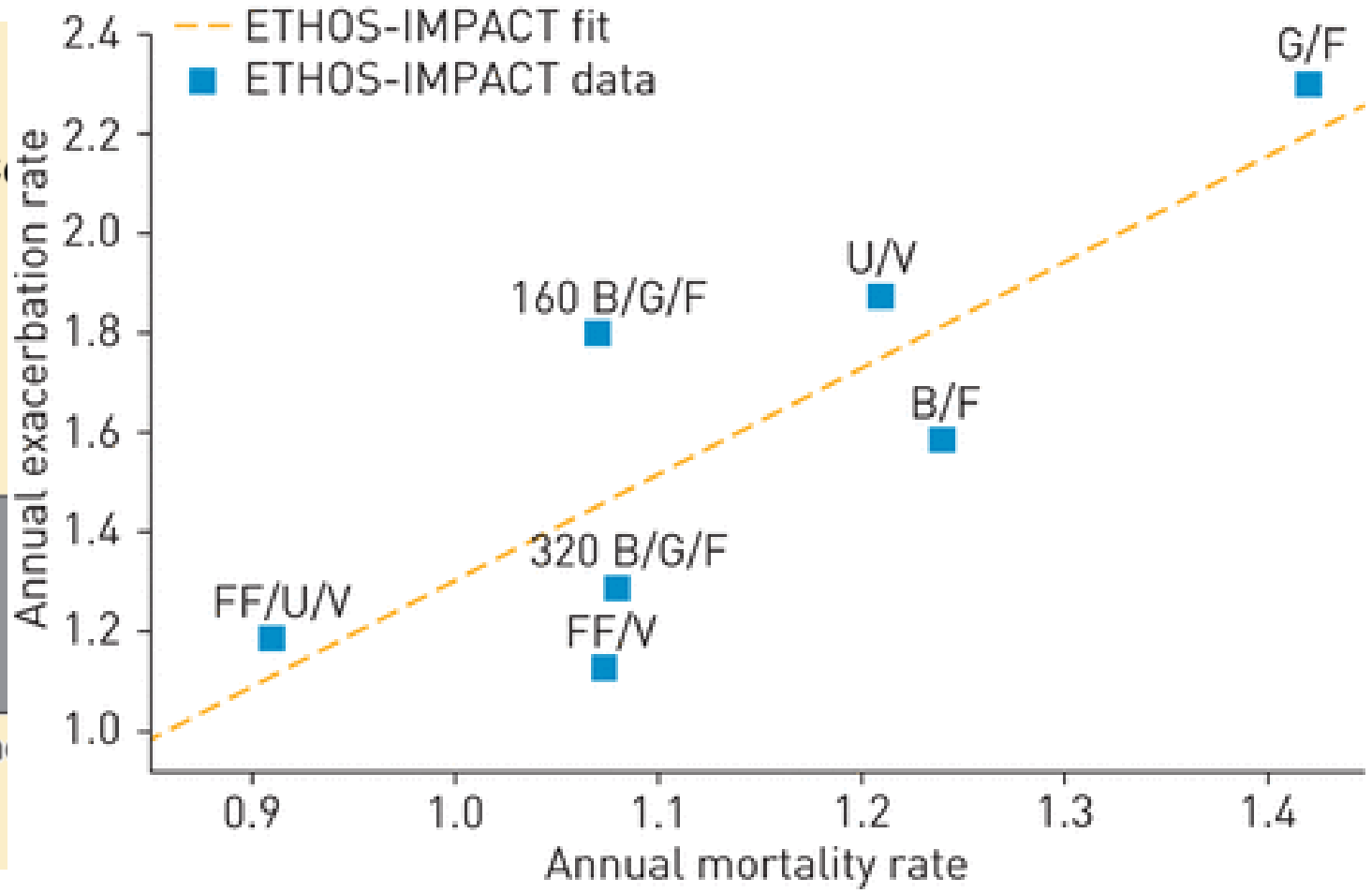
Patients at risk														
BGF 320/18/9.6 µg	2,137	2,136	2,134	2,131	2,130	2,127	2,123	2,122	2,118	2,112	2,106	2,103	2,100	2,075
BGF 160/18/9.6 µg	2,121	2,121	2,120	2,118	2,110	2,104	2,102	2,101	2,098	2,087	2,084	2,076	2,072	2,062
GFF 18/9.6 µg	2,120	2,117	2,112	2,106	2,100	2,097	2,095	2,089	2,086	2,082	2,077	2,069	2,067	2,045
BFF 320/9.6 µg	2,131	2,127	2,122	2,120	2,118	2,116	2,110	2,108	2,102	2,099	2,097	2,094	2,088	2,075

Figure 2. Kaplan-Meier plot for time to all-cause death (final retrieved dataset; intent-to-treat population). BFF = budesonide/formoterol fumarate; BGF = budesonide/glycopyrrolate/formoterol fumarate; GFF = glycopyrrolate/formoterol fumarate.

AJRCCM 2021, 203(5):553-564

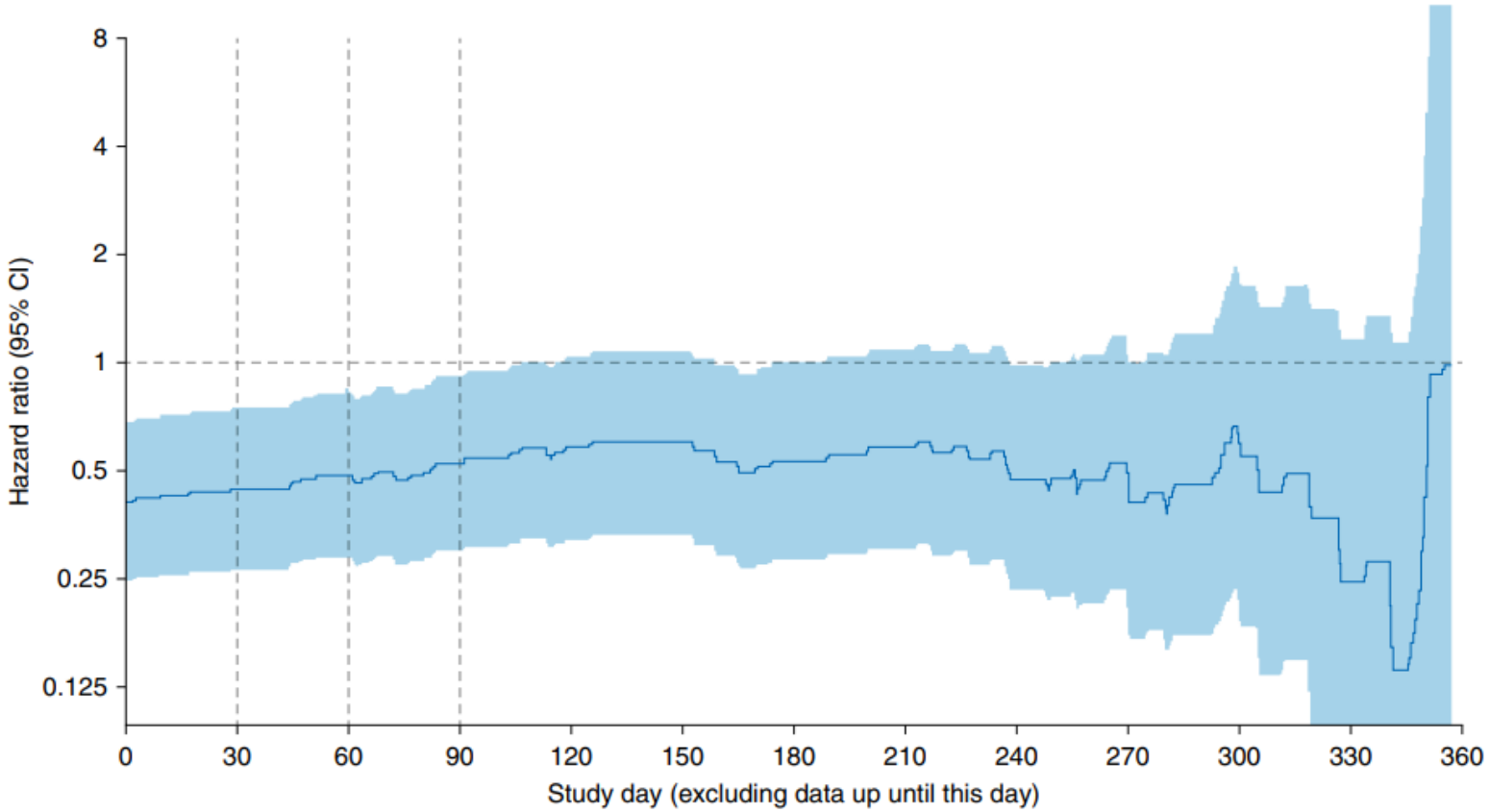
Exacerbation & Mortality in IMPACT-ETHOS trials





Antonisen et al Ann Intern Med 2005;142:233
McGarvey Thorax 2007
Andreas S, Taube C, ERJ Open Research 2020 6: 00634-2020

Hazard ratio for time to all-cause death for BGF(320ug) vs. GFF over the study period

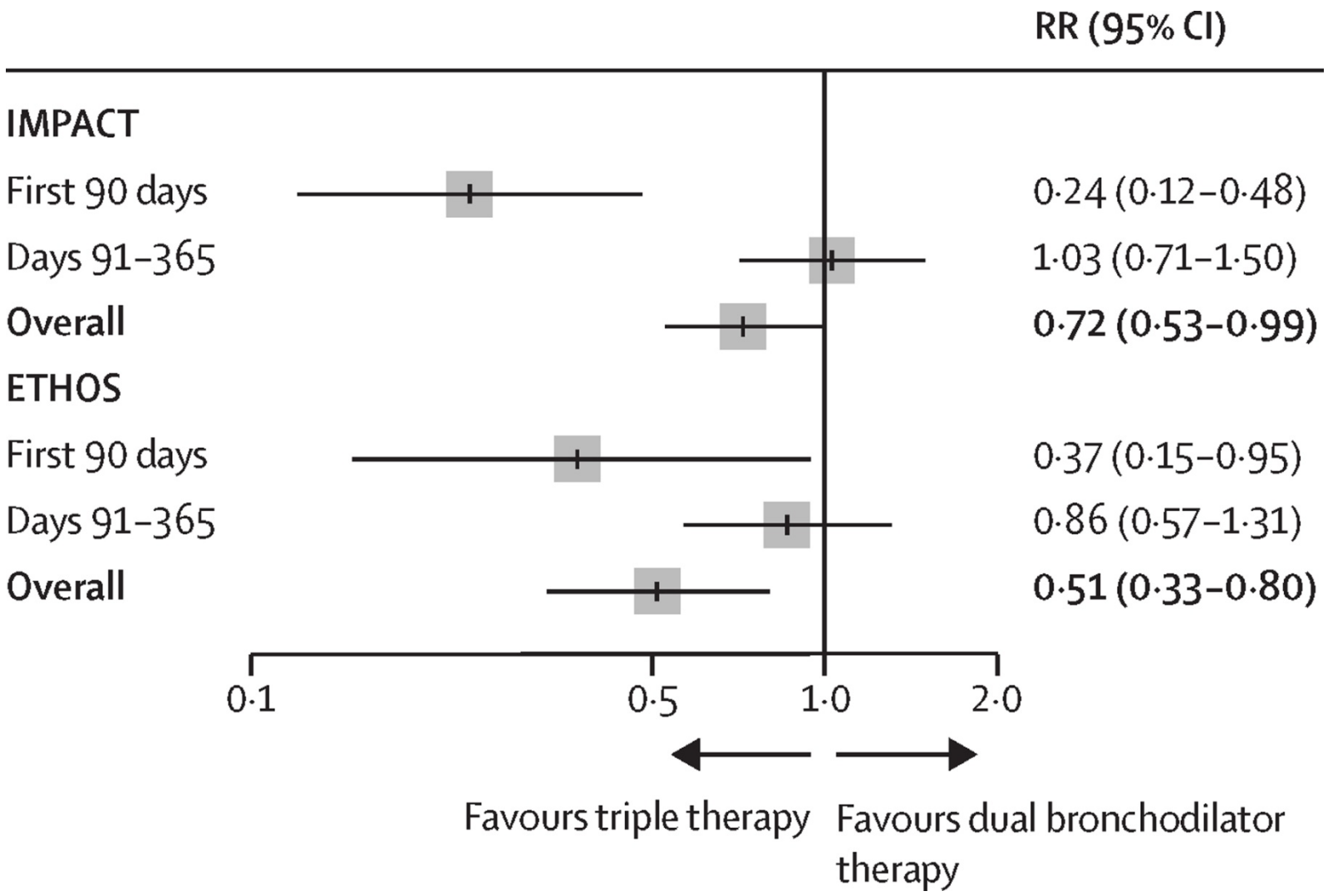


Patients at risk													
BGF 320/18/9.6 µg	1,696	1,695	1,694	1,691	1,689	1,689	1,685	1,685	1,681	1,676	1,674	1,671	1,665
GFF 18/9.6 µg	1,698	1,694	1,690	1,683	1,678	1,677	1,675	1,673	1,670	1,664	1,656	1,655	1,644

Figure 6. Hazard ratio for time to all-cause death for 320/18/9.6 µg BGF versus GFF over the study period, excluding all previous data, in patients using inhaled corticosteroids at study entry (final retrieved dataset; intent-to-treat population). BGF = budesonide/glycopyrrolate/formoterol fumarate; CI = confidence interval; GFF = glycopyrrolate/formoterol fumarate.

Martinez, Rabe, Ferguson, et al. Am J Respir Crit Care Med 2021;203(5):553–564

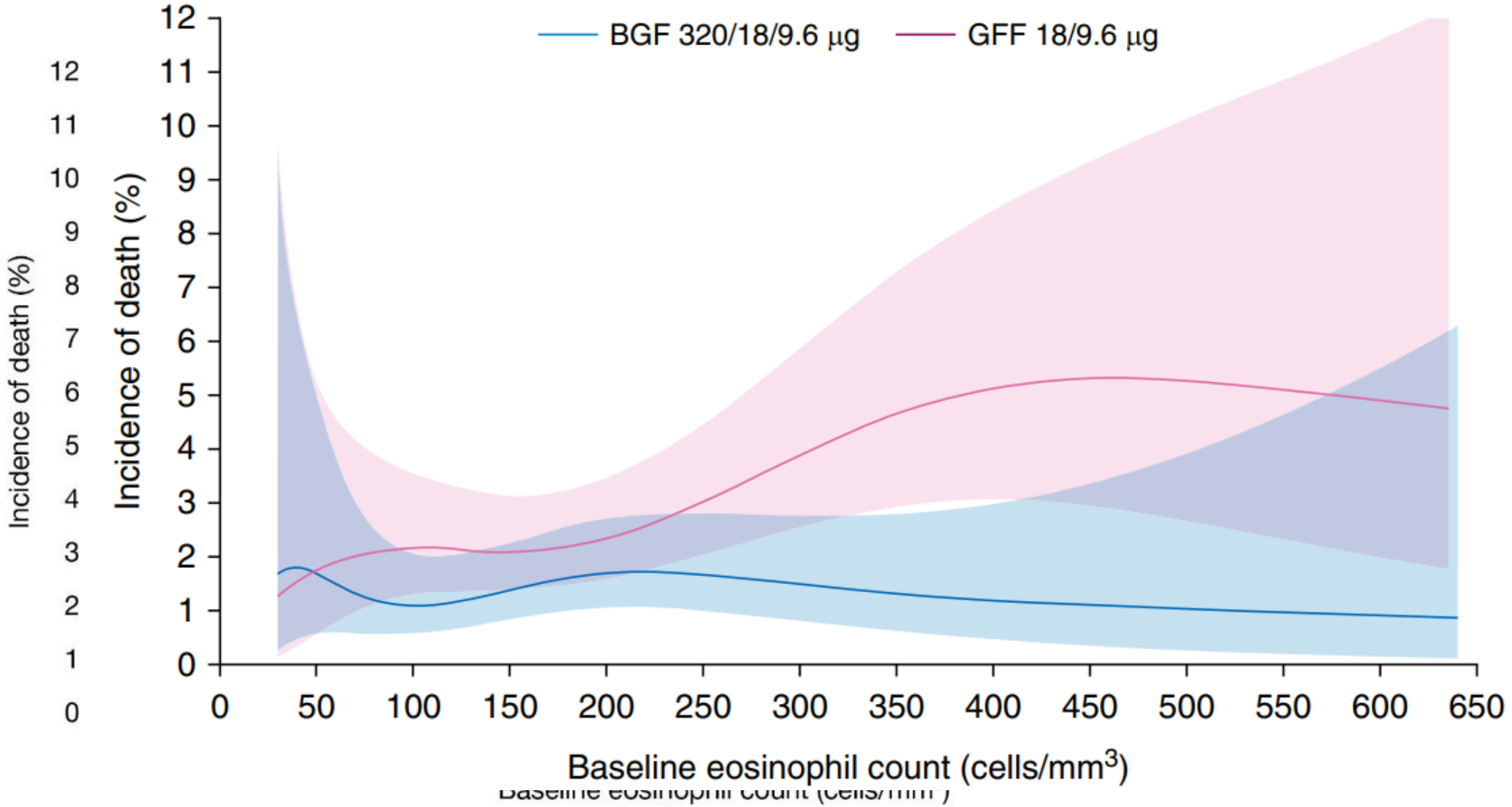
Triple Therapy and Mortality over time



Lancet Resp Med 2021;9(7):684-685

Incidence of death by baseline blood eosinophil count for BGF(320) versus GFF

➔ RWE



3(5):553–564

COPD. 2022 Dec;19(1):1-9. doi: 10.1080/15412555.2021.1977789. Epub 2021 Sep 21.

Triple Inhaler versus Dual Bronchodilator Therapy in COPD: Real-World Effectiveness on Mortality

Samy Suissa [1 2], Sophie Dell'Aniello [1 2], Pierre Ernst [1 2]

Affiliations + expand

PMID: 34544314 DOI: 10.1080/15412555.2021.1977789

Abstract

Randomized trials of triple therapy including an inhaled corticosteroid (ICS) for chronic obstructive pulmonary disease (COPD) reported remarkable benefits on mortality compared with dual bronchodilators, likely resulting from ICS withdrawal at randomization. We compared triple therapy with dual bronchodilator combinations on major COPD outcomes in a real-world clinical practice setting. We identified a cohort of COPD patients, age 50 or older, treated during 2002-2018, from the United Kingdom's Clinical Practice Research Datalink. Patients initiating treatment with a long-acting

The adjusted hazard ratio (HR) of all-cause mortality with LAMA-LABA-ICS compared with LAMA-LABA was 1.17 (95% CI: 1.04-1.31) while for severe exacerbation and pneumonia it was 1.19 (1.08-1.32) and 1.29 (1.16-1.45) respectively. However, mortality was not elevated with triple therapy among patients with asthma diagnosis (HR 0.99; 95% CI: 0.74-1.34), with two or more prior exacerbations (HR 0.88; 95% CI: 0.70-1.11), and with FEV_1 percent predicted >30%. In a real-world setting of COPD treatment, triple therapy initiation was not more effective than dual bronchodilators at preventing all-cause mortality and severe COPD exacerbations. Triple therapy may be unsafe among patients without prior exacerbations, in whom ICS are not recommended, with no asthma diagnosis and with very severe airflow obstruction.Supplemental data for this article is available online at

prior exacerbations, in whom ICS are not recommended, with no asthma diagnosis and with very severe airflow obstruction.Supplemental data for this article is available online at https://doi.org/10.1080/15412555.2021.1977789 .

Keywords: New-user cohort design; exacerbations; inhaled coticosteroids; long-acting bronchodilators; observational research; pneumonia; real-world evidence.

Q; COPD 환자에서 Triple therapy 적용 시 가장 우려하시는 부분은 무엇입니까?

1. Pneumonia
2. Oral thrush
3. Cardiovascular events
4. Cost
5. None

Medical cost or Health care utilization

Hospitalization and medical cost btw matched cohort

- A French study using General Sample of Beneficiaries (EGB) database

Table 5 Health care resource use in patients receiving dual therapy versus triple therapy

Health care resource use	Dual therapy (n=530)		Triple therapy (n=530)		Comparison number of patients *p*-value*	Comparison number of care *p*-value**
	Number of patients (%)	Mean number of care (Std)	Number of patients (%)	Mean number of care (Std)		
Hospitalizations						
Hospitalizations for all causes	296 (55.8%)	2.5 (5.5)	355 (67.0%)	3.0 (7.8)	0.0001	0.0849
COPD-related hospitalizations	133 (25.1%)	0.6 (1.7)	187 (35.3%)	0.8 (2.0)	0.0002	0.0821

Table 6 Comparison of total costs (in €) associated with health care resource use between matched patients under dual therapy and those under triple therapy, over the study period, using Wilcoxon test

Costs	Dual therapy (n=530)	Triple therapy (n=530)	*p*-value
	Mean cost (ET)	Mean cost (ET)	
Drug costs	727.8 (673.8)	981.5 (822.7)	<0.0001
Costs not related to drugs	1,856.9 (3063.6)	1,798.8 (2267.6)	0.8896
Hospitalizations	7,240.4 (17,825.8)	9,096.9 (20,304.2)	0.0086
Total	9,825.1 (18,665.1)	11,877.1 (20,951.2)	0.0087

IJCOPD 2019;14:1839-1854

Prompt initiation of SITT after exacerbation had significantly lower costs

- **A US study using IQVIA PharMetrics Plus healthcare claims database**
  to investigate the impact of prompt versus delayed initiation of single inhaler of FF/UMEC/VI

- *Prompt initiator : initiated FF/UMEC/VI within 30 days following the index date*
- *Delayed initiator : initiated FF/UMEC/VI within 31–180 days following the index date*

Table 3 Healthcare Costs Among Weighted Prompt and Delayed Cohorts

Healthcare Costs	Prompt [A] N = 529	Delayed [B] N = 1375	Cost Difference (95% CI)[a]	p-value[a]
Observation period[b], mean (SD)	358.0 (137.4)	369.4 (140.7)		
Healthcare costs[c], $US 2019 PPY, mean (SD)				
All-cause				
Total costs (medical + pharmacy)	$26,107 ($44,967)	$32,400 ($61,154)	−6293 (−11,698, −1170)	0.014
Total medical costs	$18,870 ($43,079)	$24,360 ($59,083)	−5489 (−10,383, −644)	0.026
Hospitalization costs	$6201 ($25,063)	$9346 ($42,669)	−3145 (−6297, −238)	0.032
Outpatient visit costs	$12,250 ($30,776)	$14,517 ($35,814)	−2267 (−5629, 1697)	0.204
ER visit costs	$419 ($1354)	$496 ($1743)	−77 (−251, 126)	0.426
Pharmacy costs	$7237 ($9556)	$8040 ($11,000)	−803 (−1935, 479)	0.180
COPD-related[d]				
Total costs (medical + pharmacy)	$12,694 ($26,740)	$17,640 ($45,377)	−4946 (−8288, −1832)	0.002
Total medical costs	$8919 ($26,065)	$13,286 ($45,277)	−4367 (−7656, −1307)	0.004
Hospitalization costs	$5499 ($24,430)	$8075 ($41,160)	−2576 (−5658, 173)	0.066
Outpatient visit costs	$3223 ($7107)	$4909 ($15,827)	−1686 (−2873, −302)	0.018
ER visit costs	$197 ($898)	$303 ($1520)	−105 (−241, 38)	0.138
Pharmacy costs	$3775 ($2881)	$4353 ($3239)	−579 (−929, −222)	0.004

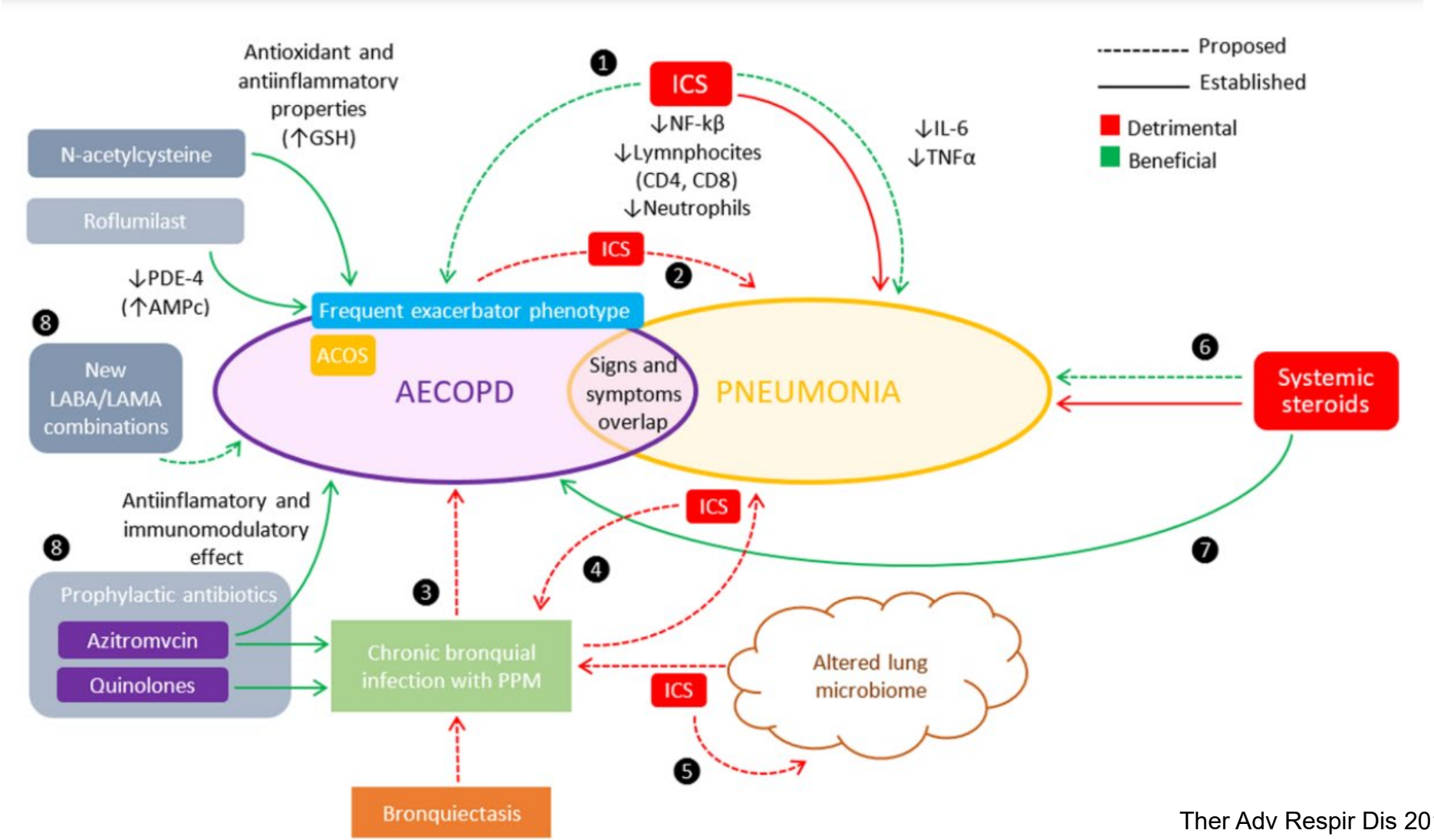
Notes: Prompt and delayed patients were weighted using the inverse probability of treatment weighting approach based on the propensity score. Variables used in the propensity score calculation included the following: age, sex, year/quarter of index date, US region, type of insurance plan (ie, PPO, HMO, POS, and other types), Quan-CCI score (categories of 0, 1, 2, and 3+), asthma diagnosis, type of COPD-related exacerbation on the index date, patients with multiple events in the index exacerbation, respiratory medication use, all-cause and COPD-related HRU and medical costs, and comorbidities (those with ≥5% prevalence in either cohort). [a] CIs and p-values were calculated using non-parametric bootstrap procedures with 999 replications. [b] The observation period spanned from the index date to the earliest of health plan disenrollment or end of data availability. [c] All costs were inflation-adjusted to 2019 US dollars based on the medical care component of the Consumer Price Index. [d] A claim was considered COPD-related if it was associated with a primary or secondary diagnosis of COPD.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HMO, health maintenance organization; HRU, healthcare resource utilization; POS, point-of-service; PPO, preferred provider organization; PPY, per person-year; Quan-CCI, Quan-Charlson comorbidity index; SD, standard deviation.

IJCOPD 2022;17:491-504

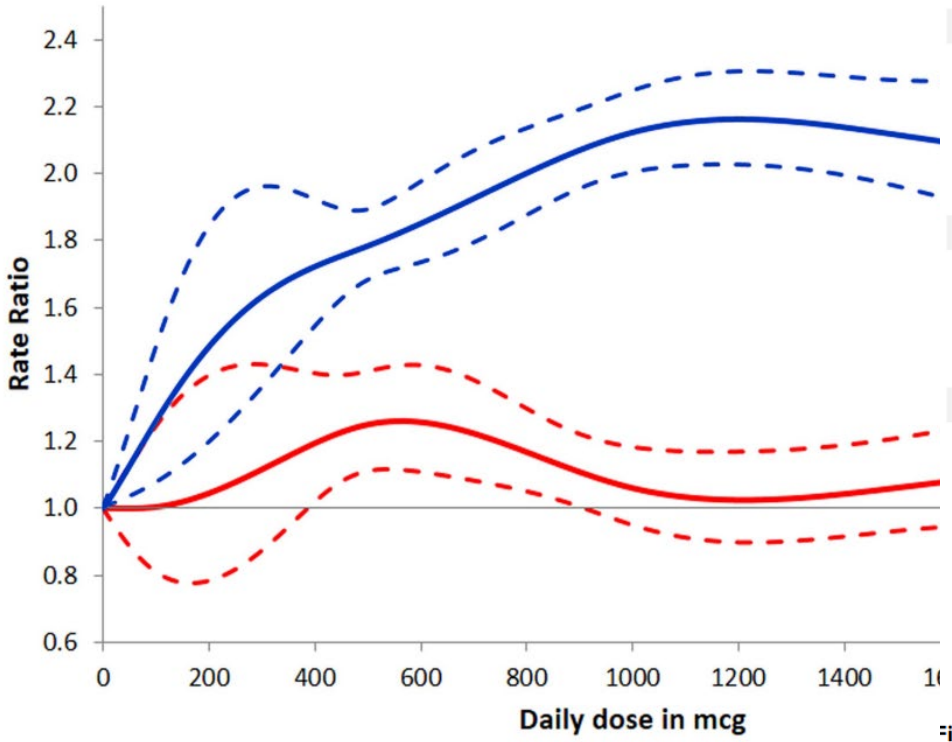
Adverse Events

ICS, Friend or Foe in COPD?



Ther Adv Respir Dis 2016, Vol. 10(3) 235–255

Dose–response curves for risk of pneumonia with ICS



Suissa S, et al. Thorax 2013;68:1029–1036.

Variables			Hazard Ratio (95% CI)	p-value
Treatment group				
	ICS Non-user	1.00		
	ICS User	1.62 (1.54-1.70)		<.0001
ICS cumulative dose				
	0	1.00		
	1-15000	1.35 (1.27-1.43)		<.0001
	15001-30720	1.51 (1.42-1.60)		<.0001
	30721-107160	1.96 (1.85-2.09)		<.0001
	>107160	2.03 (1.89-2.18)		<.0001
ICS dose				
	No	1.00		
	Low	1.59 (1.51-1.68)		<.0001
	Medium	1.67 (1.59-1.77)		<.0001
	High	1.55 (1.40-1.71)		<.0001
Type of ICS				
	No	1.00		
	Fluticasone propionate	1.79 (1.70-1.89)		<.0001
	Budesonide	1.44 (1.35-1.54)		<.0001
	Beclomethasone	1.52 (1.38-1.68)		<.0001
	Ciclesonide	1.29 (1.14-1.45)		<.0001
	Fluticasone furoate	1.80 (1.61-2.01)		<.0001

Figure 3 Hazard ratios of pneumonia according to the use of inhaled corticosteroid (ICS) and subtype of ICS users.

International Journal of Chronic Obstructive Pulmonary Disease 2020:15 3397–3406

IMPACT trial

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

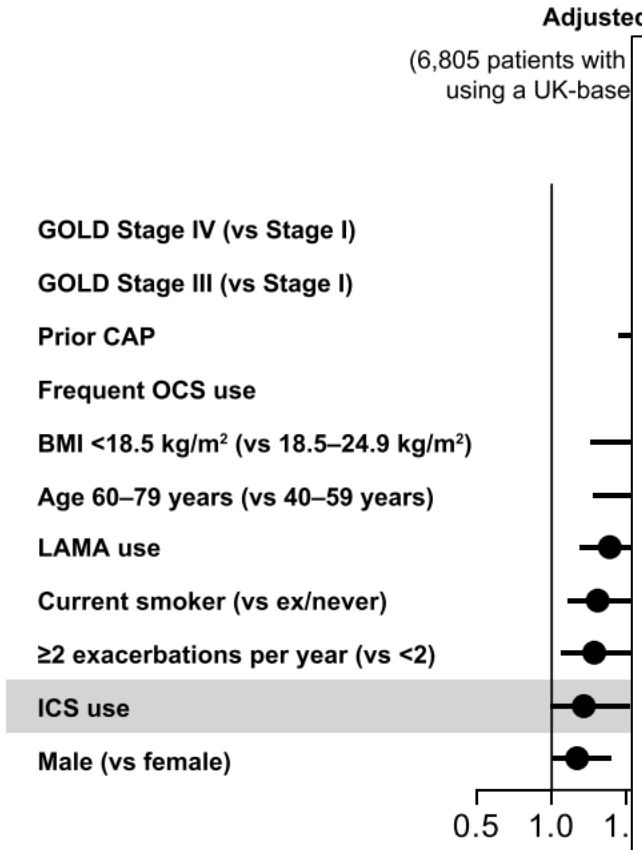
Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

ETHOS trial

Table 3. Adverse Events during the 52-Week Treatment Period (Safety Population).*

Event	320-μg–Budesonide Triple Therapy (N=2144)		160-μg–Budesonide Triple Therapy (N=2124)		Glycopyrrolate–Formoterol (N=2125)		Budesonide–Formoterol (N=2136)	
	no. of patients (%)	*no. of events (no. per 1000 patient-yr)*	*no. of patients (%)*	*no. of events (no. per 1000 patient-yr)*	*no. of patients (%)*	*no. of events (no. per 1000 patient-yr)*	*no. of patients (%)*	*no. of events (no. per 1000 patient-yr)*
Any adverse event	1368 (63.8)	4527 (2388.4)	1356 (63.8)	4382 (2318.7)	1312 (61.7)	4074 (2301.7)	1377 (64.5)	4746 (2587.0)
Serious adverse events	426 (19.9)	664 (350.3)	445 (21.0)	681 (360.3)	433 (20.4)	639 (361.0)	440 (20.6)	653 (355.9)
Adverse events that led to early discontinuation	119 (5.6)	150 (79.1)	112 (5.3)	146 (77.3)	146 (6.9)	187 (105.7)	140 (6.6)	160 (87.2)
Confirmed major adverse cardiovascular event†	31 (1.4)	32 (16.9)	30 (1.4)	31 (16.4)	44 (2.1)	47 (26.6)	23 (1.1)	24 (13.1)
Confirmed pneumonia†	90 (4.2)	93 (49.1)	75 (3.5)	78 (41.3)	48 (2.3)	51 (28.8)	96 (4.5)	106 (57.8)
Deaths from any cause during treatment period	20 (0.9)	19 (10.0)‡	28 (1.3)	28 (14.8)	35 (1.6)	35 (19.8)	29 (1.4)	29 (15.8)
Adverse events that occurred in ≥3% of patients overall								
Nasopharyngitis	227 (10.6)	290 (153.0)	239 (11.3)	315 (166.7)	199 (9.4)	255 (144.1)	234 (11.0)	331 (180.4)
COPD	203 (9.5)	256 (135.1)	221 (10.4)	263 (139.2)	219 (10.3)	268 (151.4)	242 (11.3)	300 (163.5)
Upper respiratory tract infection	123 (5.7)	149 (78.6)	137 (6.5)	176 (93.1)	102 (4.8)	129 (72.9)	115 (5.4)	154 (83.9)
Pneumonia	98 (4.6)	101 (53.3)	85 (4.0)	93 (49.2)	61 (2.9)	66 (37.3)	107 (5.0)	117 (63.8)
Bronchitis	66 (3.1)	74 (39.0)	68 (3.2)	76 (40.2)	76 (3.6)	81 (45.8)	69 (3.2)	83 (45.2)

Overall benefit/risk ratio



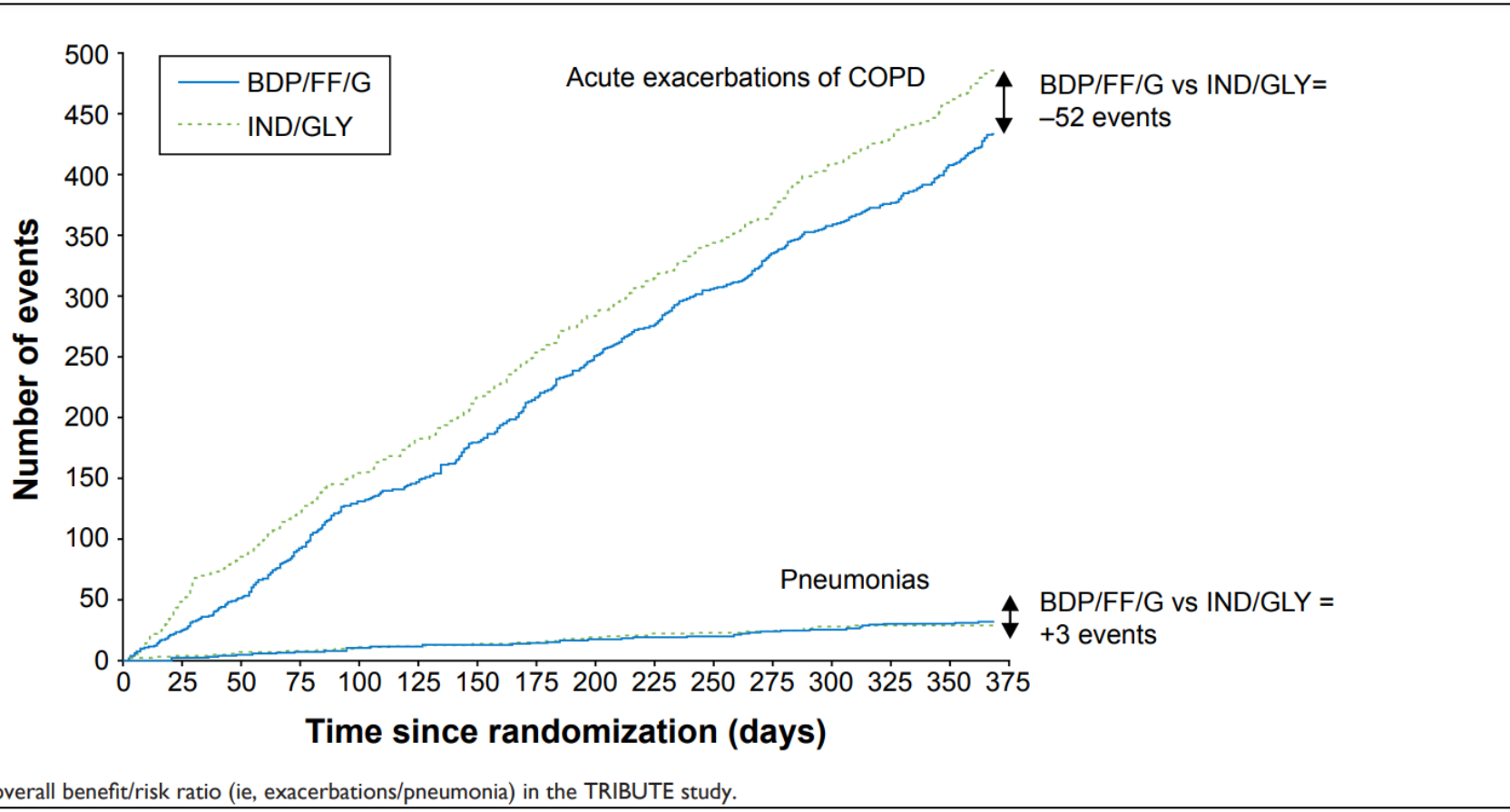


Figure 1 The overall benefit/risk ratio (ie, exacerbations/pneumonia) in the TRIBUTE study.

Figure 1 Disease severity and exacerbation history are strongly correlated with pneumonia risk whereas ICS only adds a small additional risk.

Int J Chron Obstruct Pulmon Dis 2018:13 3971–3981
Int J Chron Obstruct Pulmon Dis. 2021;16:499–517

Day *et al. Respiratory Research* (2020) 21:139
https://doi.org/10.1186/s12931-020-01398-w

Respiratory Research

RESEARCH Open Access

Triple Therapy & MACE

Single-inhaler triple therapy fluticasone

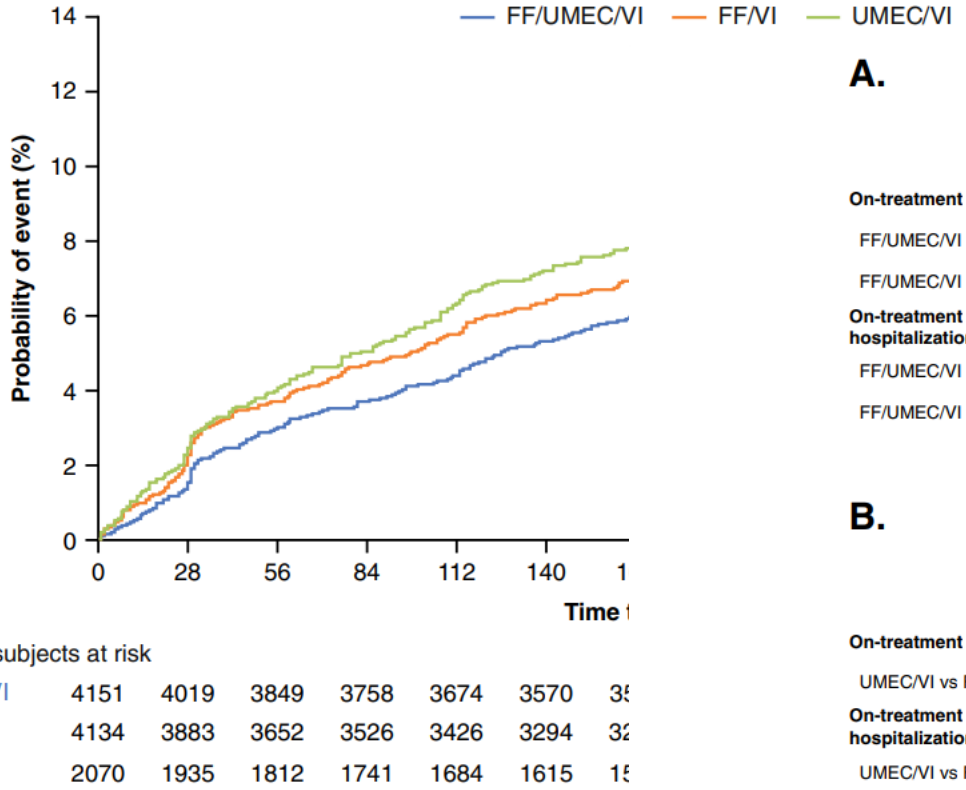


Fig. 1 Kaplan–Meier plot of TTF on-treatment CVAESI. CVAESI, cardiovascular first; UMEC, umeclidinium; VI, vilanterol

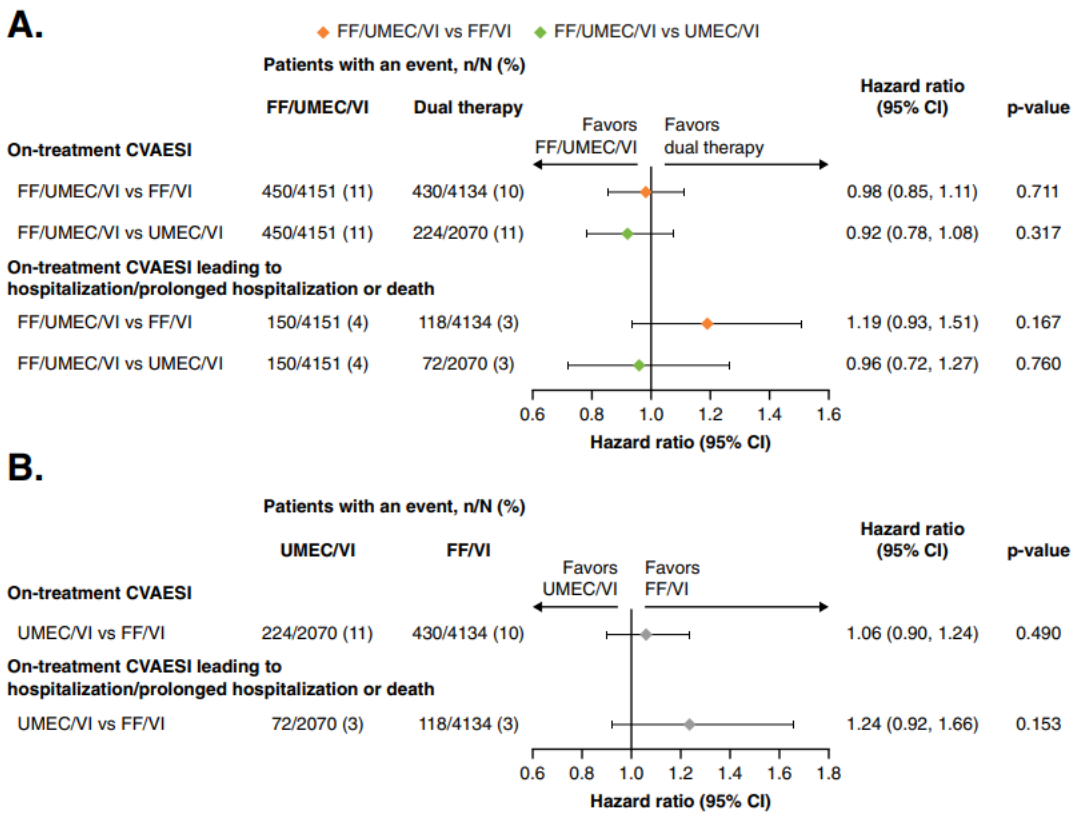


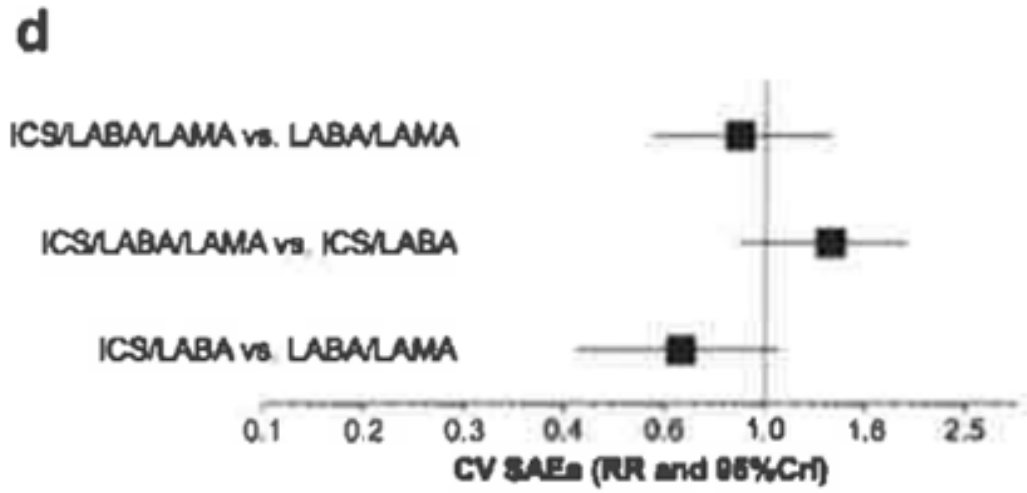
Fig. 2 TTF on-treatment CVAESI and hospitalized or fatal CVAESI. **a**. FF/UMEC/VI versus FF/VI and UMEC/VI. **b**. UMEC/VI versus FF/VI. Hospitalized or fatal CVAESI refers to any CVAESI that resulted in hospitalization/prolonged hospitalization or death. CI, confidence interval; CVAESI,

Adverse events of special interest of Cardiovascular effects (CVAESI)

Day et al. Respiratory Research (2020) 21:139

Incidence of MACE and pneumonia adverse events (ETHOS trial)

	Budesonide/ glycopyrrolate/ formoterol 320/18/9.6 µg (N = 2144)	Budesonide/ glycopyrrolate/ formoterol 160/18/9.6 µg (N = 2124)	Glycopyrrolate/ formoterol 18/9.6 µg (N = 2125)	Budesonide/ formoterol 320/9.6 µg (N = 2136)	All patients (N = 8529)
MACE					
Patients with events submitted to CEC	54 (2.5)	55 (2.6)	64 (3.0)	53 (2.5)	226 (2.6)
Number of events submitted to CEC	57	56	70	56	239
Patients with confirmed MACE	31 (1.4)	30 (1.4)	44 (2.1)	23 (1.1)	128 (1.5)
Non-fatal MI	9 (0.4)	13 (0.6)	17 (0.8)	8 (0.4)	47 (0.6)
Non-fatal stroke	12 (0.6)	6 (0.3)	6 (0.3)	6 (0.3)	30 (0.4)
Cardiovascular death	10 (0.5)	11 (0.5)	22 (1.0)	10 (0.5)	53 (0.6)



Pneumonia development

- **An UK study using Clinical Practice Research Datalink**

TABLE 2] First Exacerbation and Pneumonia: Crude and Adjusted HRs of a First COPD Exacerbation and Severe Pneumonia Comparing LAMA-LABA-ICS Initiation With LAMA-LABA Initiation in Patients With COPD in the First Year After Treatment Initiation, From the As-Treated Analysis

Treatment Group	No. of Patients	No. With Events	Person-Years	Rate per 100 per Year	Crude[a] HR	Adjusted[b] HR (95% CI)
Moderate or severe exacerbation						
LAMA-LABA-ICS	6,921	1,936	2,487	77.8	1.06	0.97 (0.87-1.08)
LAMA-LABA	1,932	418	542	77.2	1.00	1.00 (Reference)
Severe exacerbation						
LAMA-LABA-ICS	6,921	356	3,074	11.6	1.25	1.04 (0.79-1.37)
LAMA-LABA	1,932	60	630	9.5	1.00	1.00 (Reference)
First severe pneumonia						
LAMA-LABA-ICS	6,921	280	3,099	9.0	1.57	1.46 (1.03-2.06)
LAMA-LABA	1,932	37	634	5.8	1.00	1.00 (Reference)

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

[a]Crude, after matching on high-dimensional propensity scores, sex, prior severe exacerbation, and prior maintenance treatment.

[b]After matching on high-dimensional propensity scores, sex, prior severe exacerbation, and prior maintenance treatment, adjusted further for percent predicted FEV_1.

CHEST 2020;157:846-855

Q; Triple therapy 를 적용하는 환자들에게서 ICS withdrawal 에 대해서 어떻게 생각하십니까?

1. 부작용의 위험이 있으므로 반드시 withdrawal 해야 된다.
2. 큰 문제가 없었다면 withdrawal 할 필요 없다.
3. 잘 모르겠다.
4. 기타

ICS withdrawal

ICS withdrawal

- Is it necessary to withdrawal of ICS in COPD?
- Who are the preferred cases for withdrawal of ICS in patients under triple therapy?
- With withdrawal of ICS in COPD, will it decrease the incidence of pneumonia in COPD?

WISDOM trial

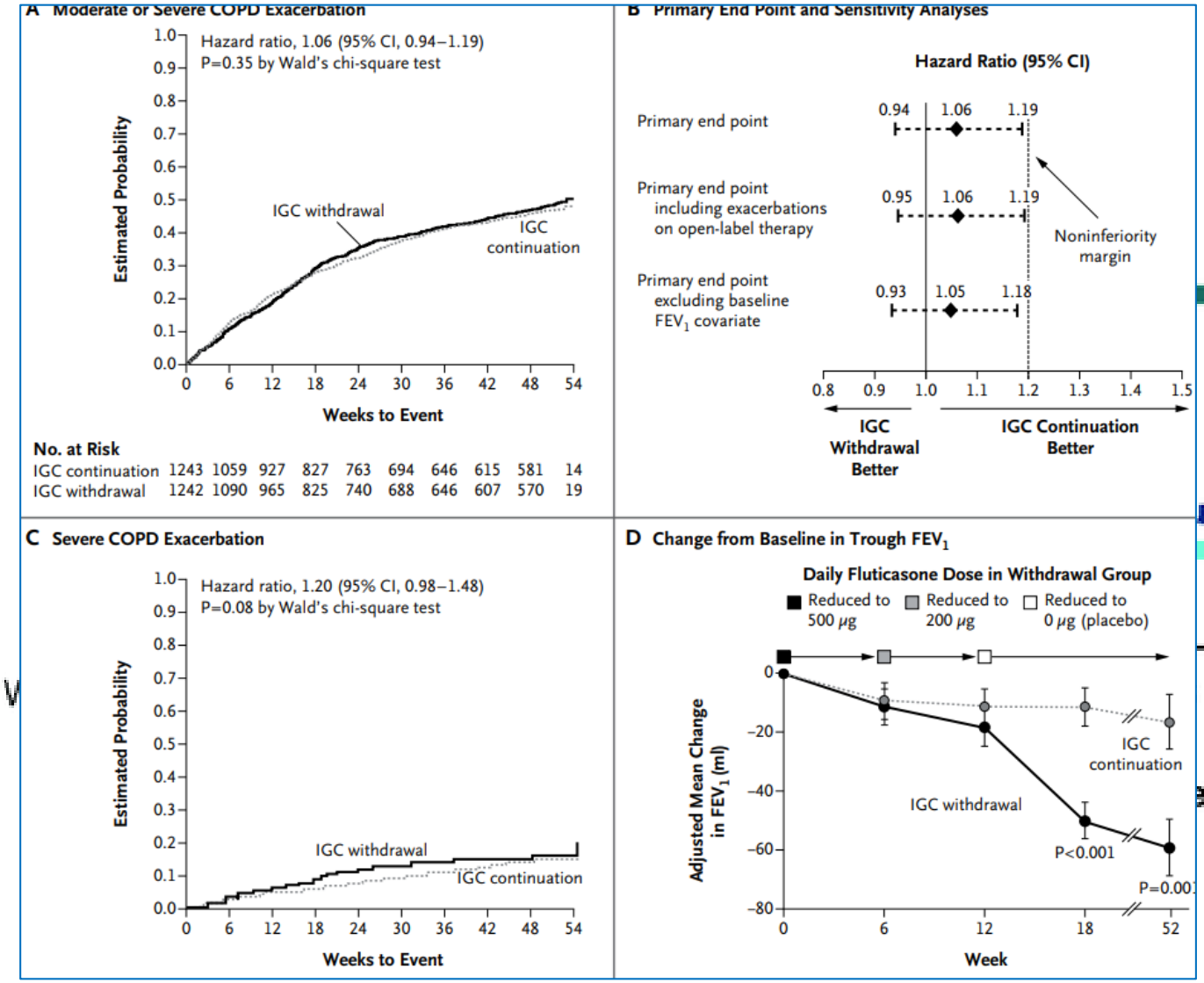
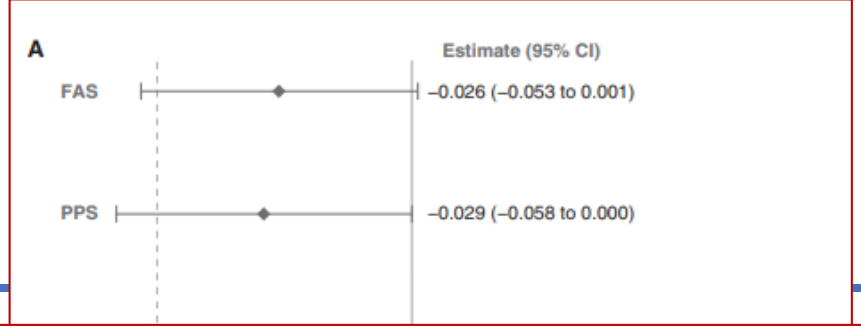


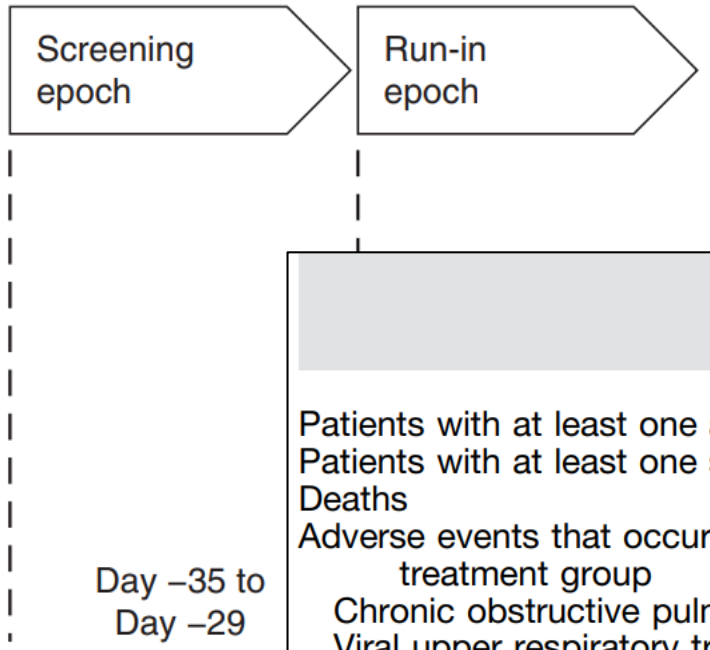
Table 2. Adverse Events.*

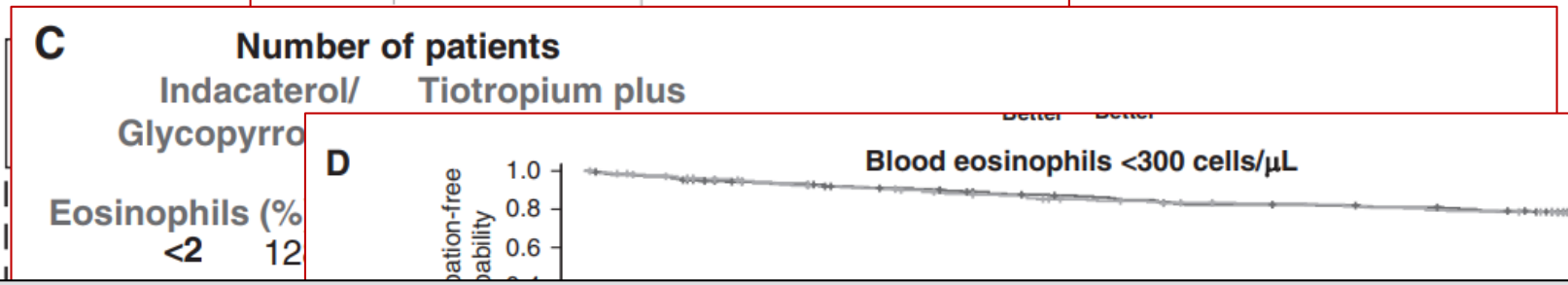
Variable	Glucocorticoid Continuation (N=1243)	Glucocorticoid Withdrawal (N=1242)
	no. of patients (%)	
Adverse events		
Any	880 (70.8)	890 (71.7)
Leading to discontinuation of study drug	115 (9.3)	127 (10.2)
Serious adverse events		
Any	292 (23.5)	300 (24.2)
Death		
During study period	34 (2.7)	40 (3.2)
Including vital-status follow-up	38 (3.1)	43 (3.5)
Requiring hospitalization	273 (22.0)	271 (21.8)
Adverse events of special interest†		
Pneumonia	72 (5.8)	68 (5.5)
Major adverse cardiac event		
Any	25 (2.0)	27 (2.2)
Fatal	14 (1.1)	19 (1.5)
Stroke	9 (0.7)	6 (0.5)

SUNSET trial

→ RWE





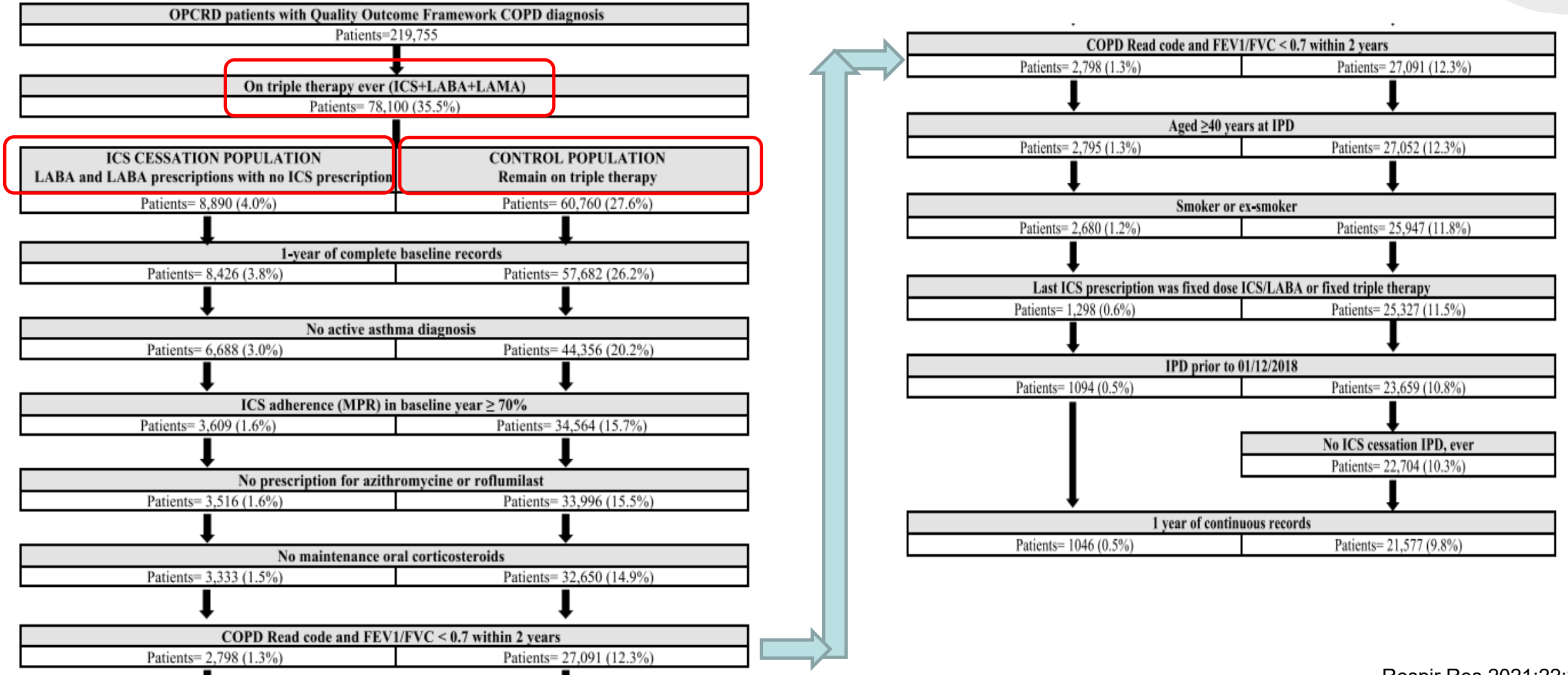


	Indacaterol/Glycopyrronium (*n* = 527)	Tiotropium Plus Salmeterol/Fluticasone (*n* = 526)
Patients with at least one adverse event	426 (80.8)	434 (82.5)
Patients with at least one serious adverse event	32 (6.1)	34 (6.5)
Deaths	4 (0.8)	5 (1.0)
Adverse events that occurred in ⩾1% of either treatment group		
Chronic obstructive pulmonary disease	372 (70.6)	358 (68.1)
Viral upper respiratory tract infection	57 (10.8)	59 (11.2)
Blood creatinine increased*	26 (4.9)	24 (4.6)
Cough	24 (4.6)	15 (2.9)
Oral candidiasis	12 (2.3)	18 (3.4)
Bronchitis	13 (2.5)	5 (1.0)
Oropharyngeal candidiasis	6 (1.1)	7 (1.3)
Influenza	6 (1.1)	6 (1.1)
Back pain	8 (1.5)	9 (1.7)
Headache	7 (1.3)	13 (2.5)
Oropharyngeal pain	7 (1.3)	7 (1.3)
Hypertension	7 (1.3)	10 (1.9)
Pneumonia	6 (1.1)	9 (1.7)

Figure 1. SUNSET
up visits at clinic afte
and 182). Safety fol
corticosteroids.

Patients' flow chart

- An UK study using Optimum Patient Care Research Database to evaluate the effect of ICS cessation versus continuation of triple therapy in COPD patients



Respir Res 2021;22:25

Cessation of ICS was not associated with an increased risk of having an exacerbation in the outcome year

- **An UK study using Optimum Patient Care Research Database to evaluate the effect of ICS cessation versus continuation of triple therapy in COPD patients**

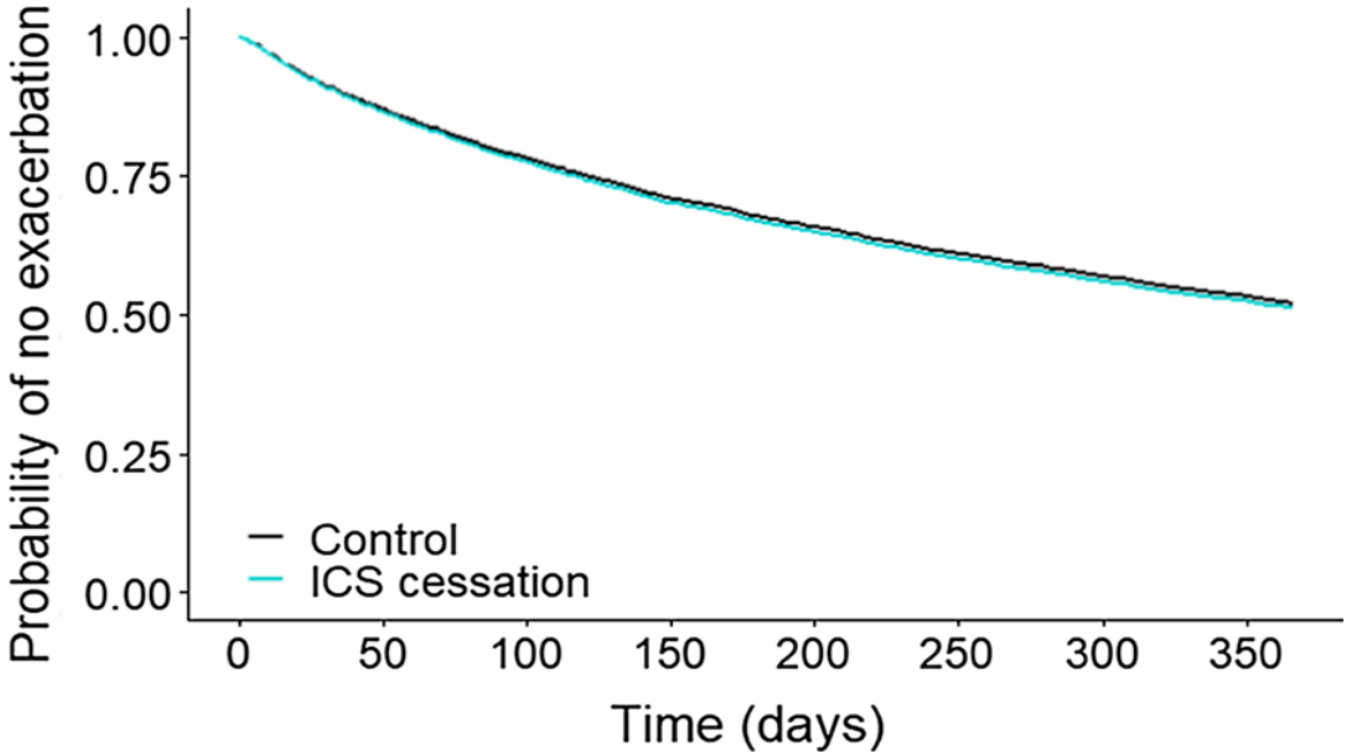


Fig. 2 Plot of multivariate Cox proportional hazards model of time to first exacerbation in the 1-year outcome period. HR = 1.04 (95% CI 0.94–1.15; p = 0.441)

Respir Res 2021;22:25

Cessation of ICS was associated with a non-significantly reduced risk of having a consultation coded for pneumonia in the outcome year

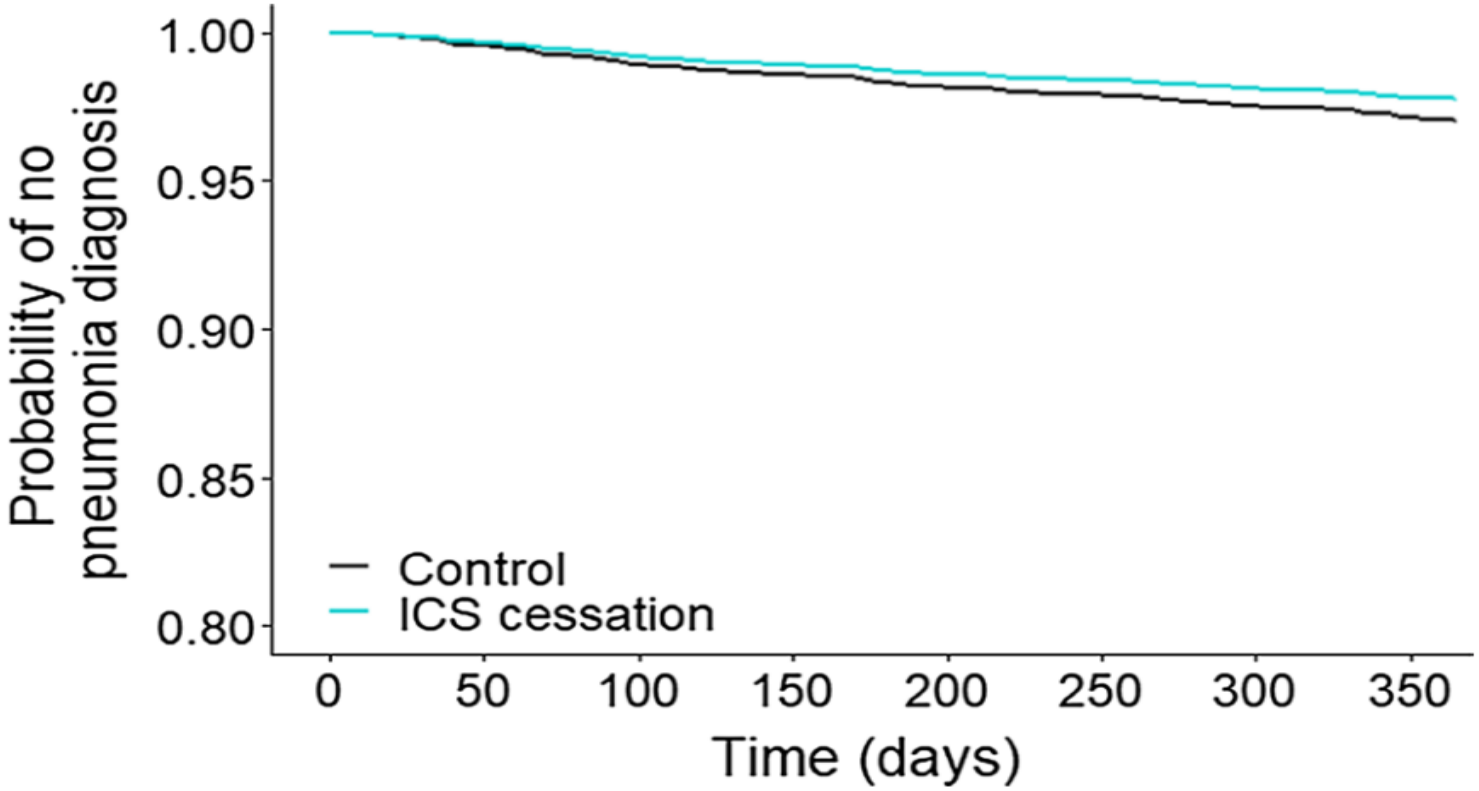


Fig. 3 Plot of multivariate Cox proportional hazards model of time to first consultation for pneumonia in the 1-year outcome period. HR = 0.69 (95% CI 0.45 to 1.08; p = 0.108)

Respir Res 2021;22:25

Decreased the odds of successful ICS withdrawal was observed in patients with blood Eo count≥0.3 or prescriptions of OCS in baseline year

- An UK study using Optimum Patient Care Research Database to evaluate the effect of ICS cessation versus continuation of triple therapy in COPD patients

Table 6 Determinants of successful ICS cessation

Variable	Total	Event	Univariate analysis			Multivariate analysis		
			HR	95% CI	p-value	HR	95% CI	p-value
Asthma diagnosis pre-baseline								
No	899	223 (24.8%)		Ref				
Yes	147	24 (16.3%)	0.59	0.37 to 0.94	0.026			
Blood eosinophil count								
<0.1	99	27 (27.2%)		Ref				
≥0.1 to <0.3	608	145 (23.8%)	0.84	0.52 to 1.35	0.462	0.76	0.47 to 1.27	0.282
≥0.3	182	31 (17.0%)	0.55	0.30 to 0.99	0.044	0.50	0.27 to 0.91	0.023
Exacerbations managed in primary care in baseline year								
0	535	171 (31.9%)		Ref				
1	258	55 (21.3%)	0.58	0.41 to 0.82	0.002			
2	119	12 (10.1%)	0.24	0.13 to 0.45	<0.001			
3+	134	9 (6.7%)	0.15	0.08 to 0.31	<0.001			
Antibiotic prescriptions in baseline year								
0	553	175 (31.6%)		Ref				
1	243	51 (20.9%)	0.57	0.40 to 0.82	0.002			
2	107	9 (8.4%)	0.20	0.10 to 0.40	<0.001			
3+	143	12 (8.4%)	0.20	0.11 to 0.37	<0.001			
OCS prescriptions in baseline year								
0	476	155 (32.5%)		Ref				
1	183	46 (25.1%)	0.70	0.47 to 1.02	0.064	0.70	0.45 to 1.05	0.090
2	116	13 (11.2%)	0.26	0.14 to 0.48	<0.001	0.23	0.11 to 0.44	<0.001
3+	271	33 (12.2%)	0.29	0.19 to 0.43	<0.001	0.31	0.19 to 0.47	<0.001

Respir Res 2021;22:25

ICS withdrawal in ATS & ERS guideline

AMERICAN THORACIC SOCIETY DOCUMENTS

Pharmacologic Management of Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Gui

Linda Nici, Manoj J. Mammen, Edward Charbek, Paul E. Alexander, David H. Au, Cynth
Gavin C. Donaldson, Michael Dreher, Vincent S. Fan, Andrea S. Gershon, MeiLan K. Ha
Fernando J. Martinez, Paula M. Meek, Michael Morgan, Michael I. Polkey, Milo A. Puha
Don D. Sin, George R. Washko, Jadwiga A. Wedzicha, and Shawn D. Aaron; on behalf
Society Assembly on Clinical Problems

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY FEBRUARY 2020

PICO Question	Recommendation
3. In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), should the ICS be withdrawn?	In patients with COPD who are receiving tripl (ICS/LABA/LAMA), we suggest that the ICS withdrawn if the patient has had no exacer the past year.

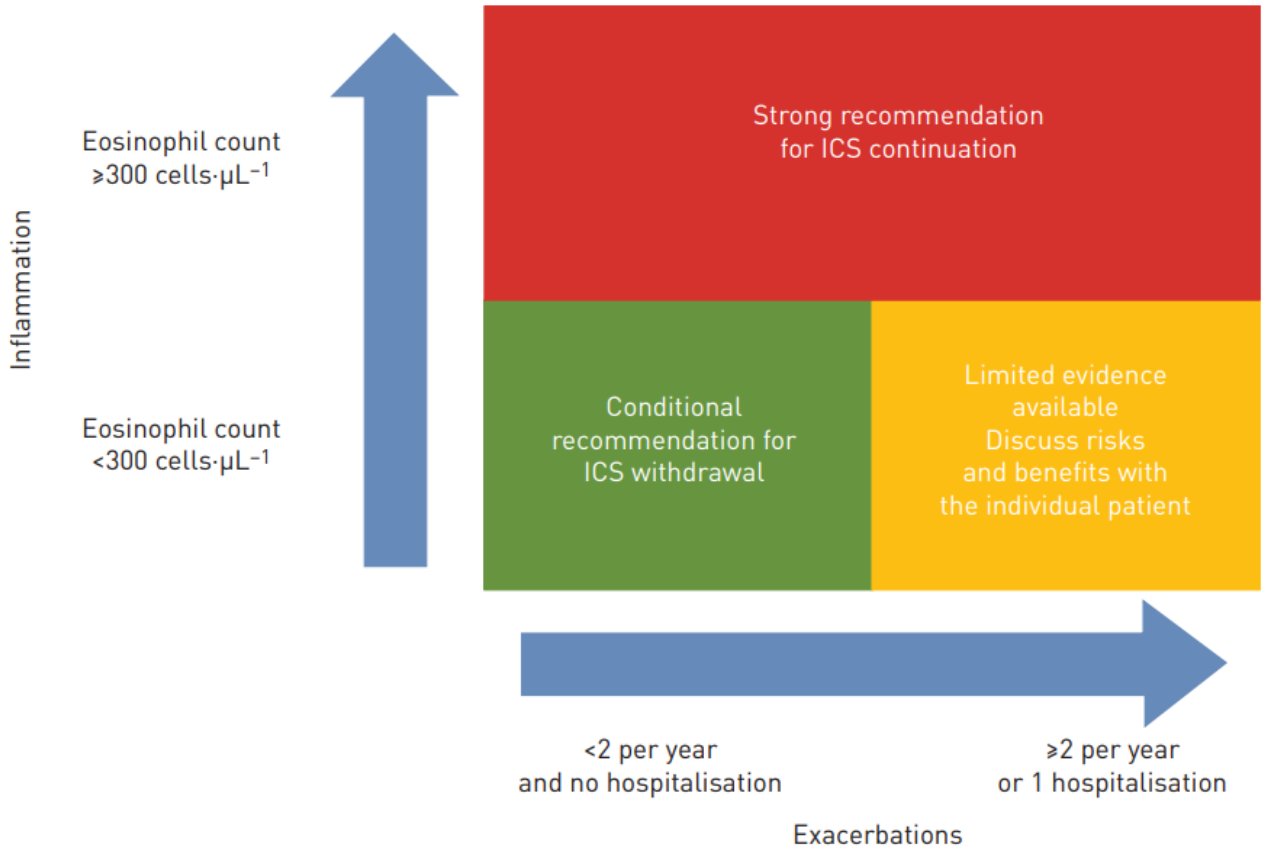


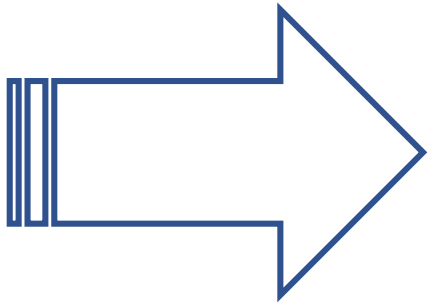
FIGURE 1 Summary of the guideline recommendations. ICS: inhaled corticosteroid. We recommend taking account of prior exacerbation history and blood eosinophil counts. Patients with a high rate of exacerbations and eosinophil counts >300 cells·μL^{-1} should not be considered for ICS withdrawal. Patients not meeting these criteria may be candidates for ICS withdrawal.

Am J Respir Crit Care Med. 2020;201(9):e56–e6, Eur Respir J. 2020;55(6):2000351

Summary
- Proven Efficacy of Single Inhaler Triple Therapy in RCTs

RCT

- TRIBUTE
- IMPACT
- ETHOS



Single Inhaler Triple Therapy

vs	LABA/LAMA	ICS/LABA
Exacerbation	⇩	⇩
Mortality (secondary)	⇩	⇔
Dyspnea/QoL (MCID?)	⇩	⇩
Lung function (MCID?)	⇧	⇧
Pneumonia	⇧	⇔

Summary

- Real world studies of Triple inhaled therapy for COPD support the findings of pivotal RCTs showing
  - Decreased exacerbation
  - Improved symptoms and quality of life
  - Reduced medical cost

Discussion

Pharmacologic Management of Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Guideline

Table 2. Recommendations for the Pharmacologic Treatment of Stable Chronic Obstructive Pulmonary Disease

PICO Question	Recommendation	Strength of Recommendation	Certainty of Evidence
1. In patients with COPD who complain of dyspnea or exercise intolerance, is LABA/LAMA combination therapy more effective than and as safe as LABA or LAMA monotherapy?	In patients with COPD who complain of dyspnea or exercise intolerance, we recommend LABA/LAMA combination therapy over LABA or LAMA monotherapy.	Strong	Moderate certainty
2. In patients with COPD who complain of dyspnea or exercise intolerance despite the use of dual therapy with LABA/LAMA, is triple therapy with ICS/LABA/LAMA more effective than and as safe as dual therapy with LABA/LAMA?	In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, we suggest the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization.	Conditional	Moderate certainty
3. In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), should the ICS be withdrawn?	In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), we suggest that the ICS can be withdrawn if the patient has had no exacerbations in the past year.	Conditional	Moderate certainty
	requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy.		
5. In patients with COPD who have a history of severe and frequent exacerbations despite otherwise optimal therapy, is maintenance oral steroid therapy more effective than and as safe as no maintenance oral steroid therapy?	In patients with COPD and a history of severe and frequent exacerbations despite otherwise optimal therapy, we advise against the use of maintenance oral corticosteroid therapy.	Conditional	Low certainty
6. In patients with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, is opioid-based therapy more effective than and as safe as no additional therapy?	In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management, within a personalized shared decision-making approach.	Conditional	Very low certainty

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; PICO = Population, Intervention, Comparator, and Outcomes.

Am J Respir Crit Care Med 2020;201: e56–e69

Suggested indication for triple therapy

Table 3 When to Prefer Triple Therapy FDCs Over Dual Bronchodilation

Immediate choice in

- Patients who present for the first time, and have severe airway obstruction (FEV_1 <50%) and are symptomatic
- Patients who have had frequent (≥2) moderate or severe exacerbations (≥1 hospitalisation) in the previous year
- Patients who have peripheral eosinophilia (>300 cells $\cdot \mu L^{-1}$)
- Patients with significant lung function decline
- Patients discharged from hospital after a COPD exacerbation.

[229] 만성폐쇄성폐질환 흡입용 치료제	허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함. - 아 래 - 가. 중등도 이상의 만성폐쇄성폐질환[FEV1 (1초 강제호기량) 값이 예상 정상치의 80% 미만] 환자의 유지요법 나. FEV1(1초 강제호기량) 값이 예상 정상치의 80% 이상인 만성폐쇄성폐질환 환자 중, 호흡곤란 등의 증상이 적절히 조절되지 않는 경우 유지요법 ※ 대상 약제: [단일제] . Aclidinium bromide 흡입제 . Indacaterol maleate 흡입제 . Umeclidinium 흡입제 [복합제] . Formoterol fumarate + Aclidinium bromide 흡입제 . Indacaterol maleate + Glycopyrronium bromide 흡입제 . Olodaterol + Tiotropium 흡입제 . Vilanterol + Umeclidinium 흡입제 보건복지부 고시 제2022-56호 (2022.3.1.)

[229] Vilanterol trifenatate + Fluticasone furoate + Umeclidinium 흡입제 (품명:트렐리지엘립타)	허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함. - 아 래 - ○ 중등도 이상의 성인(만 18세 이상) 만성폐쇄성폐질환 가. 지속성 베타2-효능약과 지속성 무스카린 수용체 길항제 복합요법에도 불구하고 다음의 조건을 만족할 경우 - 다 음 - 1) FEV1 값이 예상 정상치의 60% 미만인 경우 또는 2) 연 2회 이상 급성악화가 발생한 경우(투여소견서 참조하여 인정) ※ 급성악화는 호흡곤란의 악화, 기침의 증가, 가래양의 증가 또는 가래색의 변화 등으로 약제의 변경 또는 추가(항생제·스테로이드제 등)가 필요한 경우를 말함. 나. 지속성 베타2-효능약과 흡입용 코르티코스테로이드 복합요법에도 불구하고 호흡곤란 등의 증상이 적절히 조절되지 않는 경우 다. 각 개별고시를 만족하여 동 약제와 동일 함량인 Vilanterol trifenatate + Fluticasone furoate 흡입제, Umeclidinium 흡입제를 동시에 투여 중인 환자가 동 약제의 허가사항에 부합하여 동 약제로 전환하고자 할 경우 보건복지부 고시 제2021-152호(2021.6.1.)

Q & A

Supplementary slides

Taylor & Francis

Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

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

Luigino Calzetta, Beatrice Ludovica Ritondo, Patrizia de Marco, Mario Cazzola & Paola Rogliani

To cite this article: Luigino Calzetta, Beatrice Ludovica Ritondo, Patrizia de Marco, Mario Cazzola & Paola Rogliani (2021) Evaluating triple ICS/LABA/LAMA therapies for COPD patients: a network

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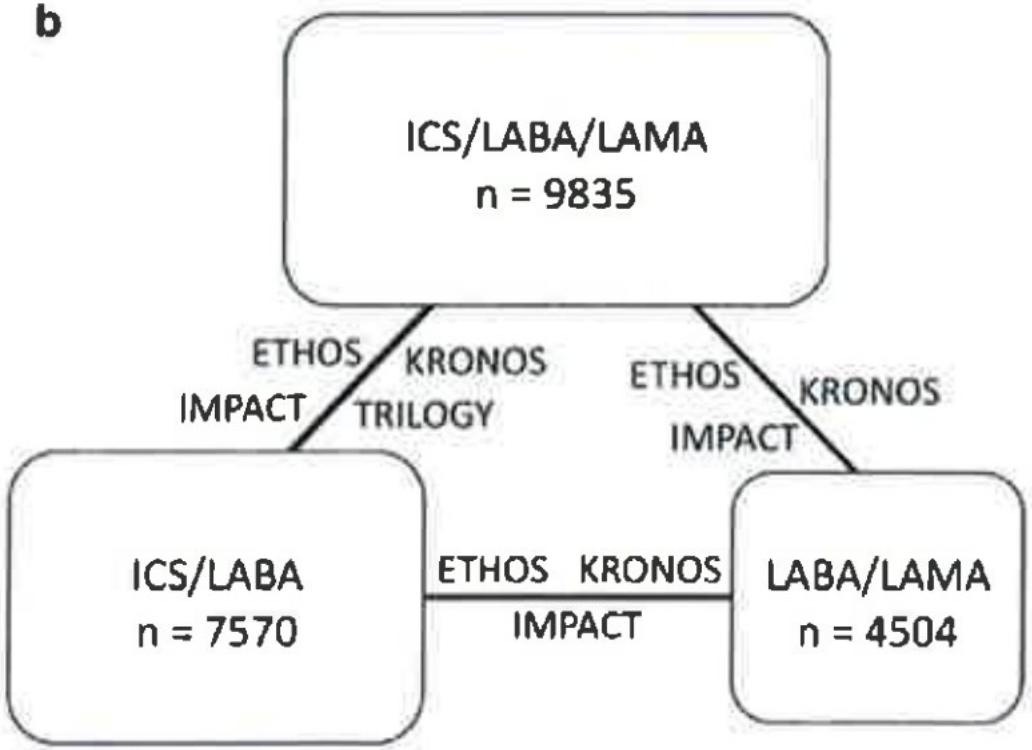
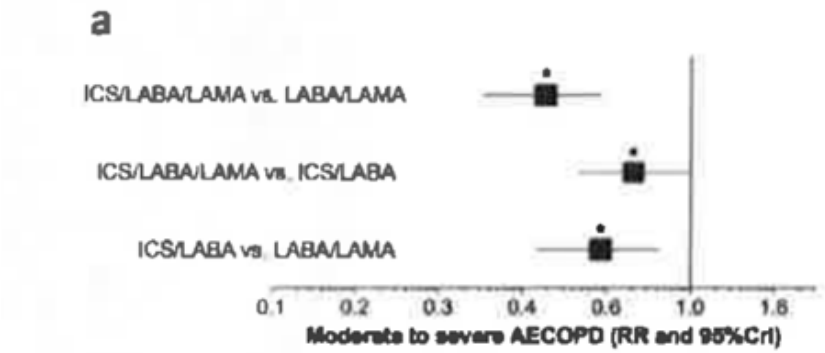
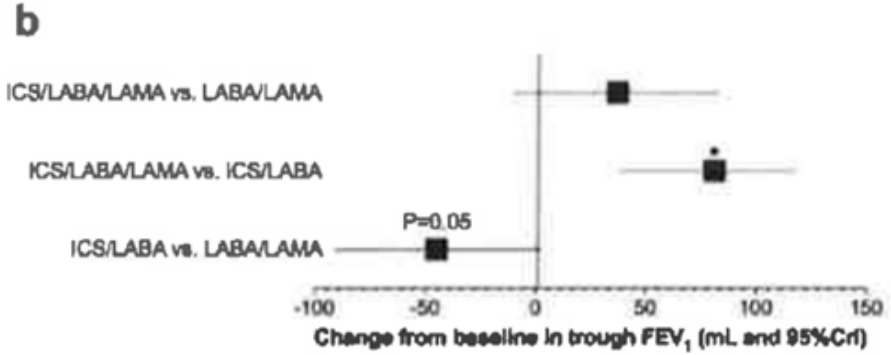


Expert Rev Respir Med. 2021;15(1):143–152

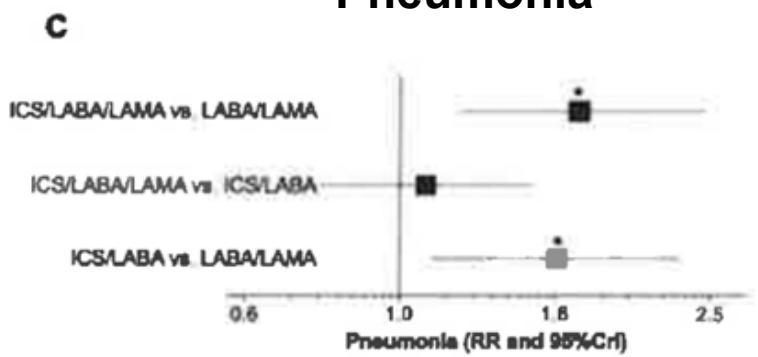
Mod to Severe Exacerbation



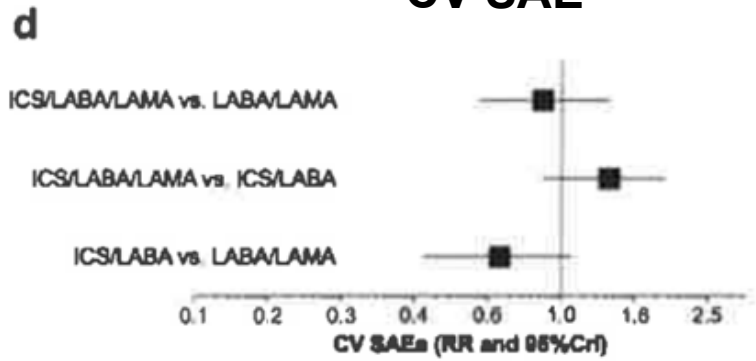
Trough FEV1



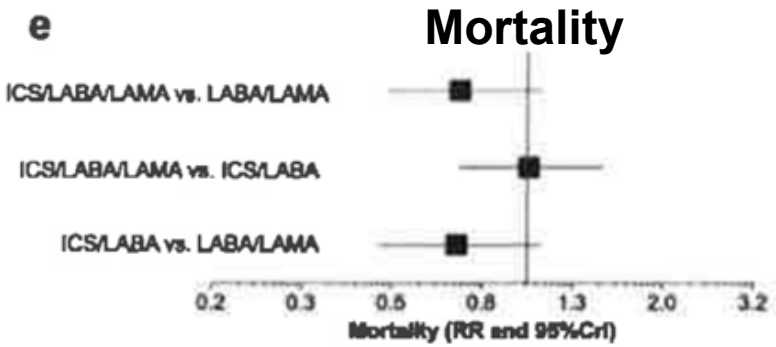
Pneumonia



CV SAE



Mortality



Expert Rev Respir Med. 2021;15(1):143–152

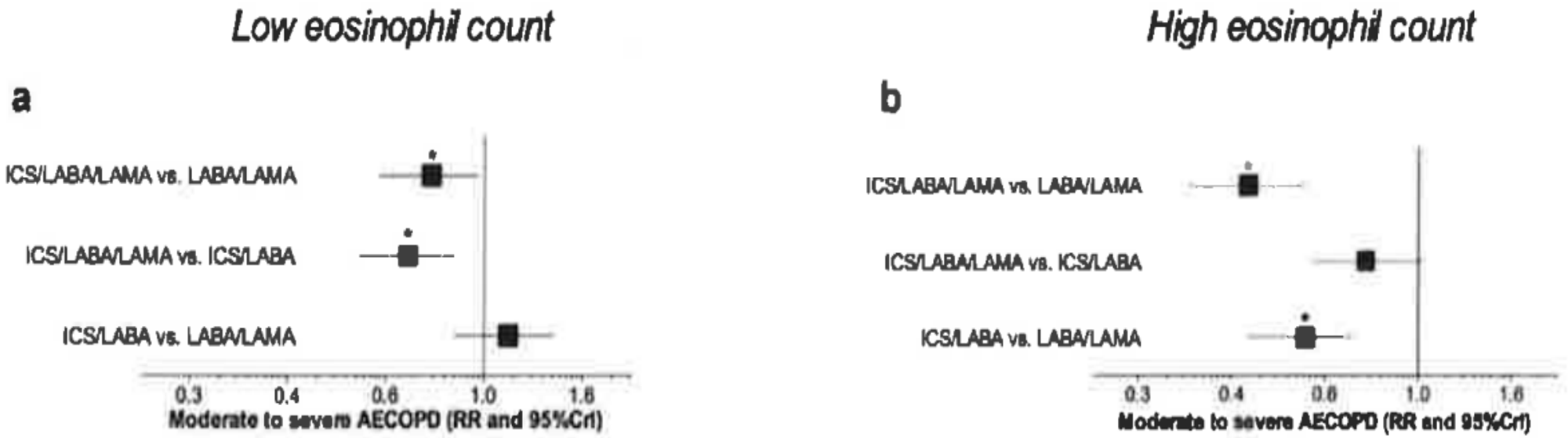


Figure 3. Forest plot of the subset NMA performed in patients with low and high eosinophil count at baseline (A and B, respectively) comparing the impact of ICS/LABA/LAMA, LABA/LAMA, and ICS/LABA FDCs on the risk of moderate to severe AECOPD. *P < 0.05 vs. comparator. AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; CrI: credible interval; ICS: inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; NMA: network meta-analysis; RR: relative risk.

Expert Rev Respir Med. 2021;15(1):143–152

Rank probability of best therapy	Moderate to severe AECOPD			FEV_1	Pneumonia	Weighted efficacy/safety profile	
	Overall	Low eosinophil count	High eosinophil count	Overall	Overall	Low eosinophil count	High eosinophil count
1	ICS/LABA/LAMA (0.99)	ICS/LABA/LAMA (0.99)	ICS/LABA/LAMA (0.99)	ICS/LABA/LAMA (0.98)	LABA/LAMA (0.99)	ICS/LABA/LAMA (0.71)	ICS/LABA/LAMA (0.71)
2	ICS/LABA (0.51)	LABA/LAMA (0.43)	ICS/LABA (0.52)	LABA/LAMA (0.51)	ICS/LABA (0.36)	LABA/LAMA (0.64)	LABA/LAMA (0.50)
3	LABA/LAMA (0.01)	ICS/LABA (0.09)	LABA/LAMA (0.00)	ICS/LABA (0.02)	ICS/LABA/LAMA (0.15)	ICS/LABA (0.16)	ICS/LABA (0.30)

AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1st second; ICS: inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; SUCRA: surface under the cumulative ranking curve analysis.

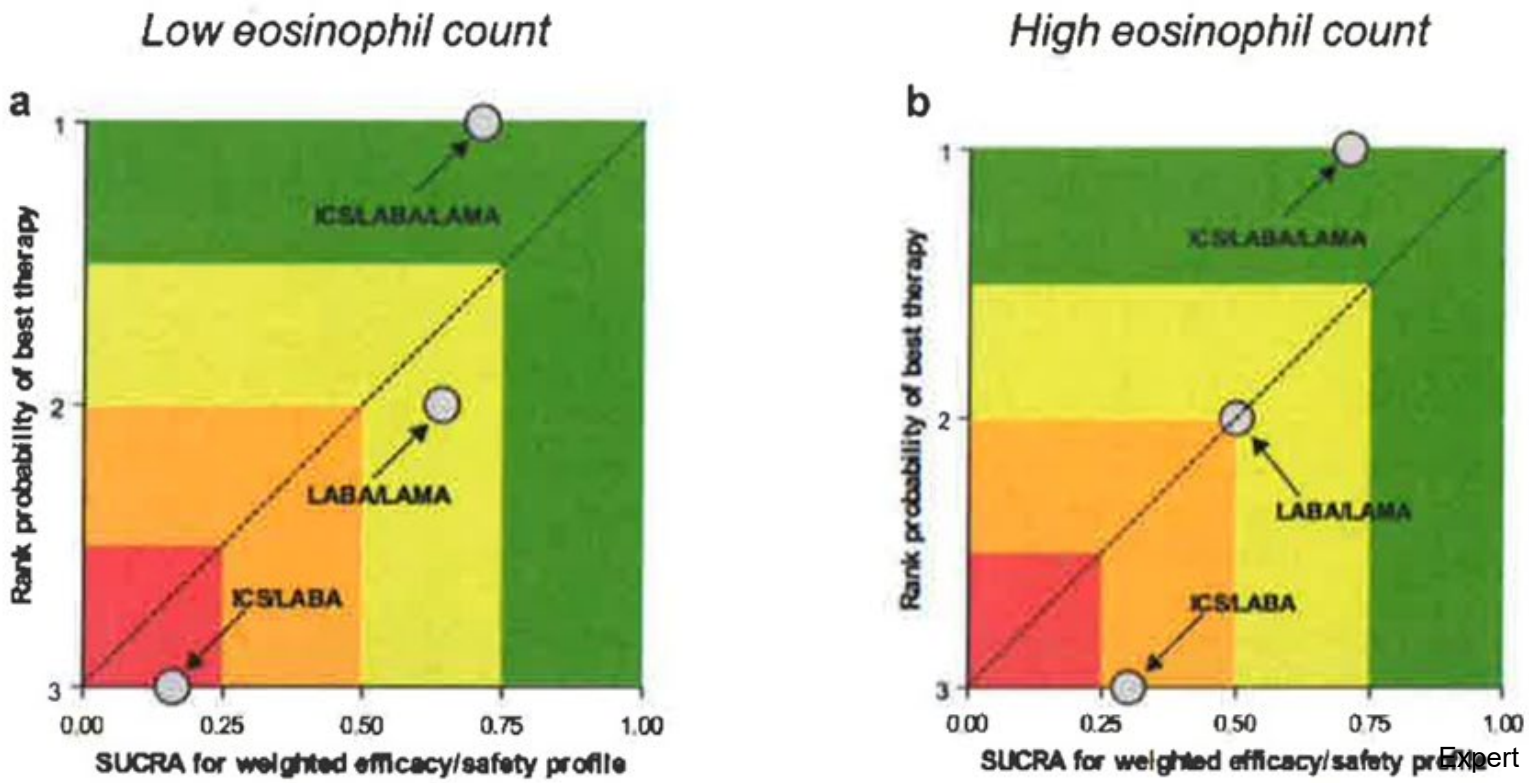


Table 2 Pharmacological Characteristics of the ICSs, LABAs and LAMAs Included in Triple Therapy FDCs Approved for Maintenance Treatment of COPD

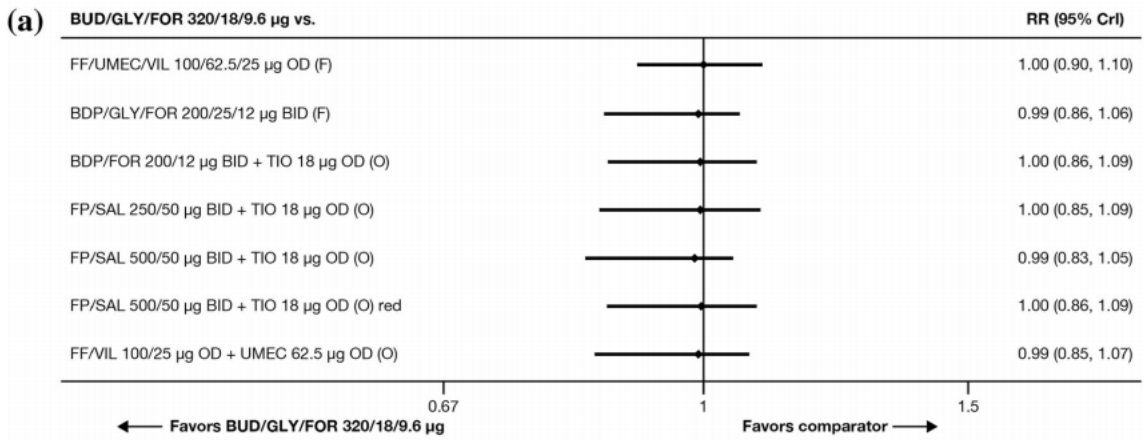
ICSs							
	Relative Glucocorticoid Receptor Binding Affinity*	Lipophilicity (log P**)	Aqueous Solubility (μg mL^{-1})	PPB (%)	Vss l	CL h^{-1}	F (%)
Beclomethasone dipropionate	53 (1345)	4.59 (3.27)	0.13 (15.5)	95.9	424	120	62^{CFC} 82^{HFA} 41^{oral}
Budesonide	935	2.32	16	91.4	180	84	39^{DPI} 11^{oral}
Fluticasone furoate	2989	4.17	0.03	99.7	608	65	15^{DPI} 1^{oral}

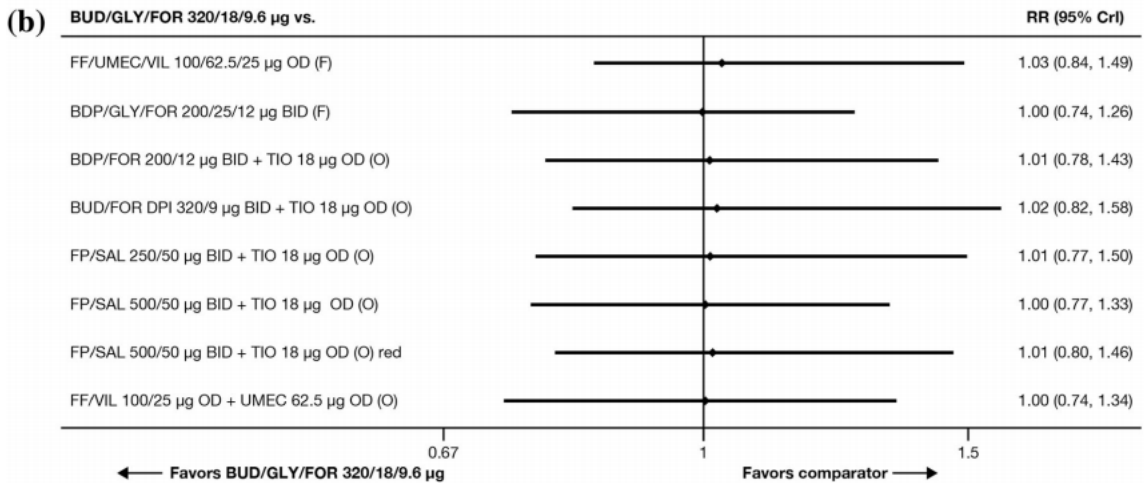
LABAs						
	β_2-AR				β_1-AR	β_2/β_1 ratio
	pKi	IA (% isoprenaline)	Onset of action ($t_{1/2}$, min)	Duration of action (h)		
Formoterol	8.06	95.0	5.9	0.93	6.10	130
Vilanterol	9.42	70.0	3.45	NA	NA	2400

LAMAs									
	M_3 mAChR				M_1 mAChR		M_2 mAChR		M_3/M_2 ratio
	pKi	K_{off} (h^{-1})	Onset of action ($t_{1/2}$, min)	Duration of action (h)	pKi	K_{off} (h^{-1})	pKi	K_{off} (h^{-1})	
Glycopyrronium	9.28	0.11	8.72	6.1	9.77	NA	9.09	1.84	16.5
Umeclidinium	9.80	0.53	9.0	1.37	9.80	NA	9.82	4.44	8.7

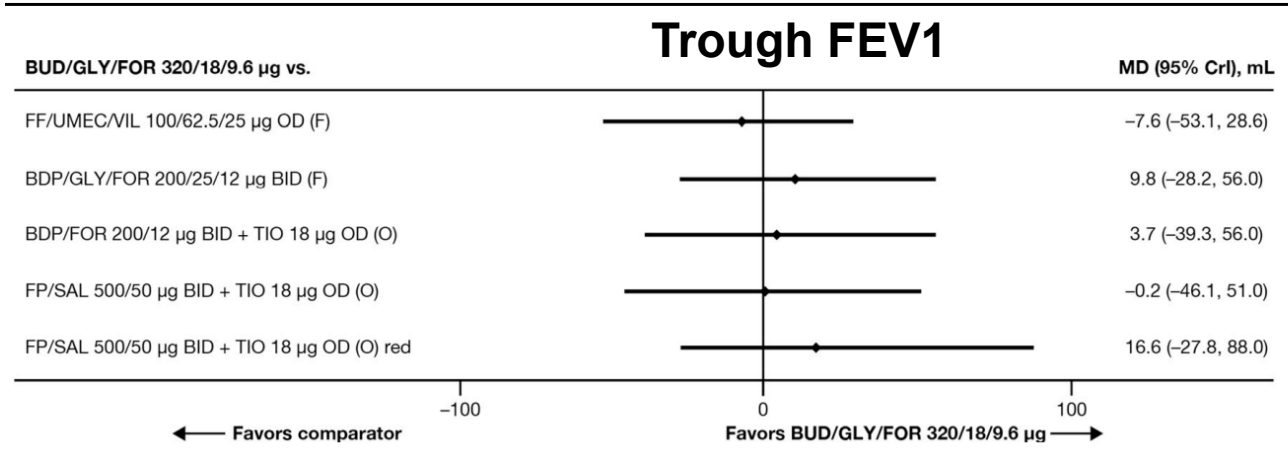
Notes: *Glucocorticoid receptor binding affinity is relative to dexamethasone with dexamethasone affinity = 100. **Log P values are defined as the $\log_{10}$ of the octanol/water partition coefficient. Sources[16] and [30].

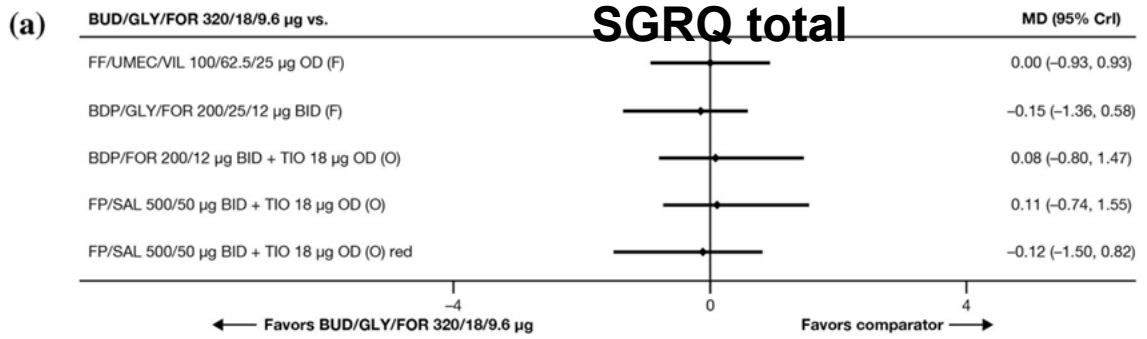
Abbreviations: CL, plasma clearance; F, absolute bioavailability determined in healthy subjects; IA, intrinsic activity; K_{off}, dissociation rate; NA, not available in human tissue; pKi, the negative logarithm to base 10 of the equilibrium dissociation constant of a ligand determined in inhibition studies; PPB, plasma protein binding; Vss, volume of distribution at steady state; $t_{1/2}$, residence half-life.

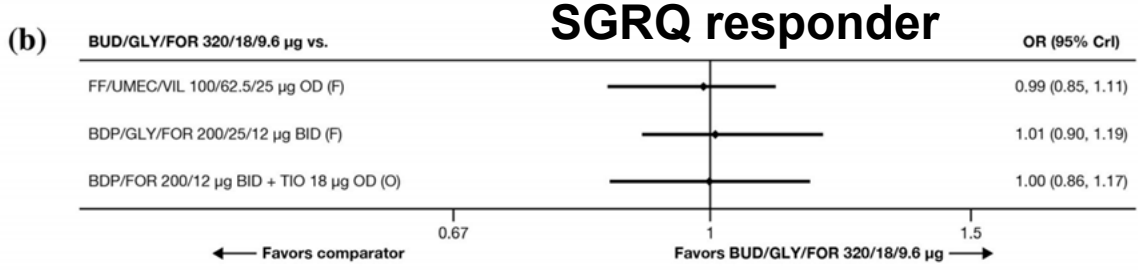


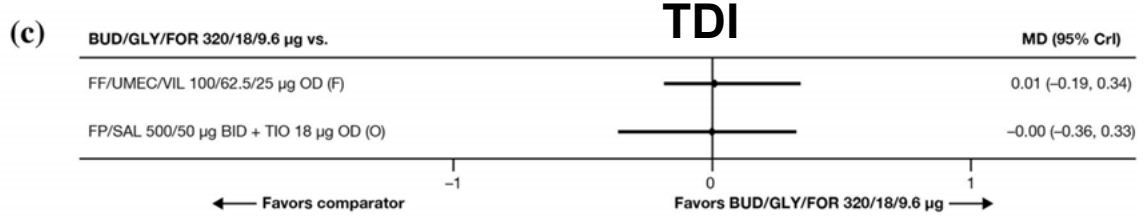


Mod to Severe Exacerbation Rate



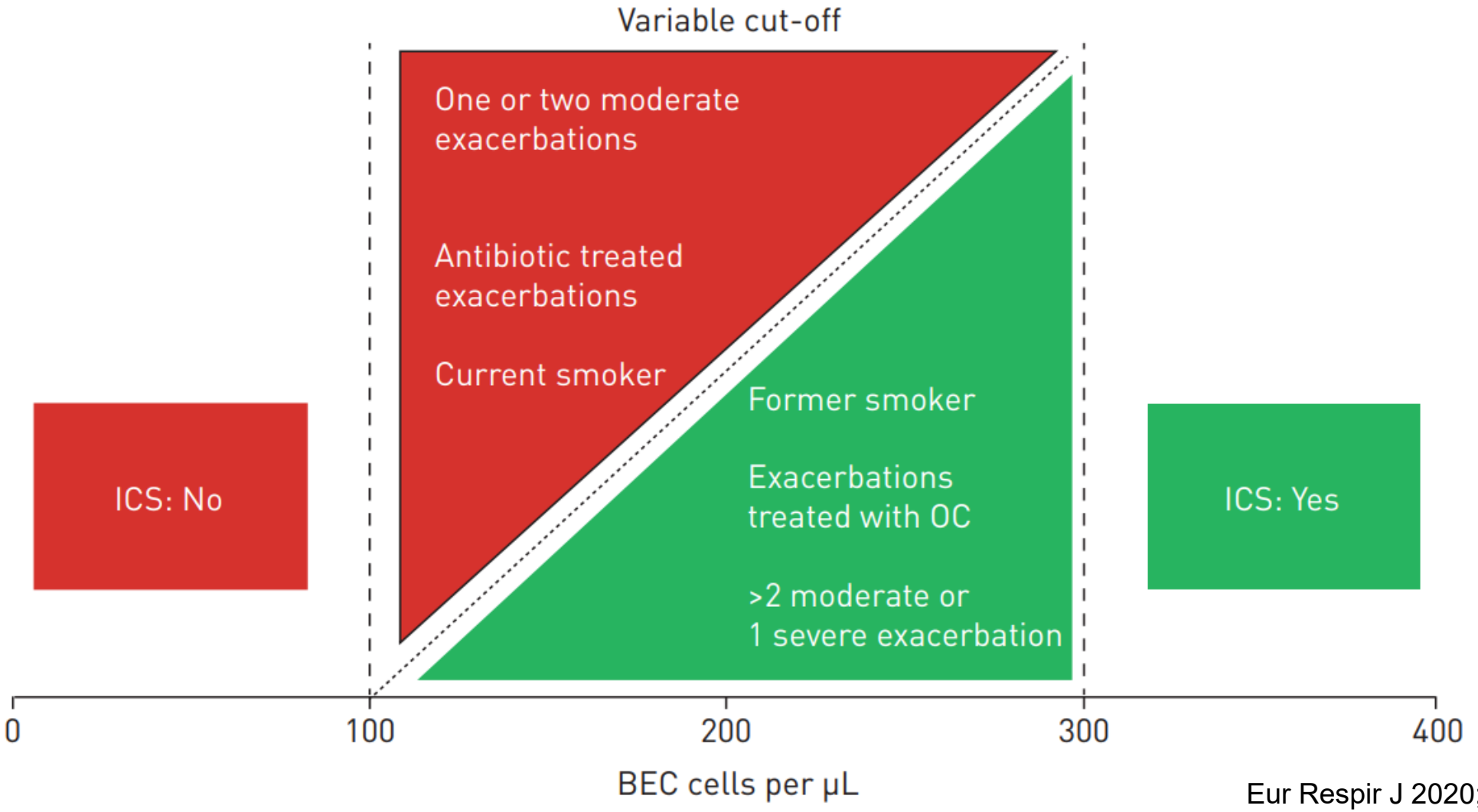




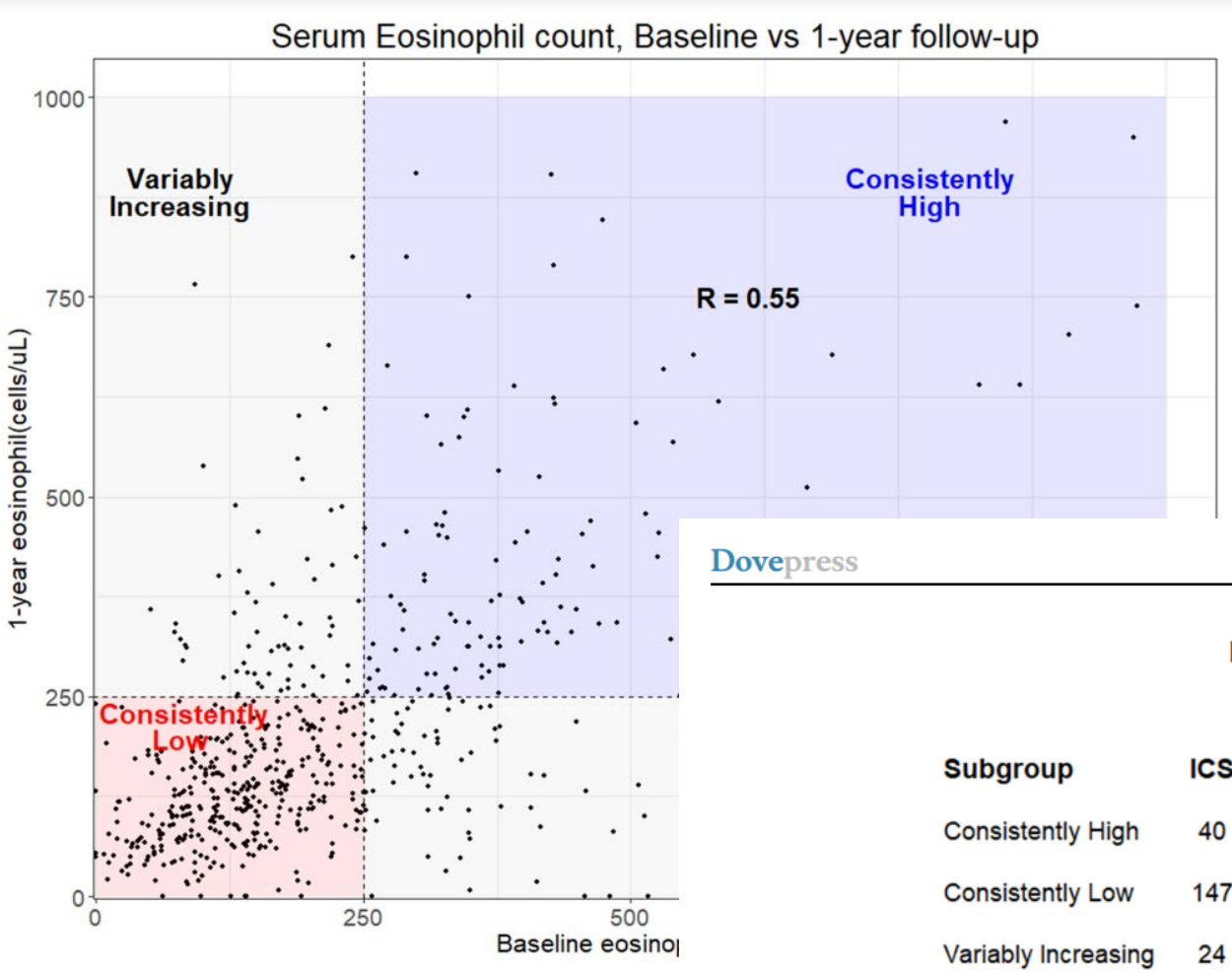


Adv Ther (2021) 38:3089–3112

Indication of ICS in COPD according to blood eosinophil counts and other factors.



Eur Respir J 2020; 55: 2000881



Consistently High (n=125) **20%**	Consistently Low (n=355) **57%**	Variably Increasing (n=63) **10%**	Variably Decreasing (n=75) **12%**

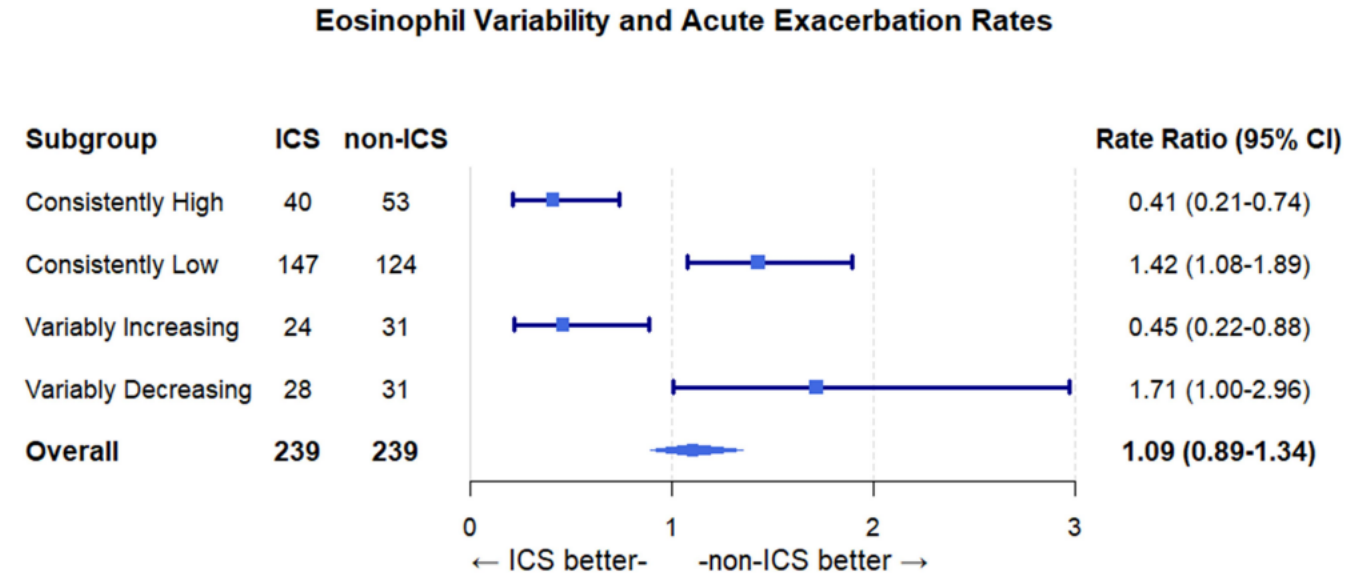


Figure 3 Eosinophil variability and the effect of ICS on acute exacerbation rate.
Abbreviation: CI, confidence interval.

HR for pneumonia

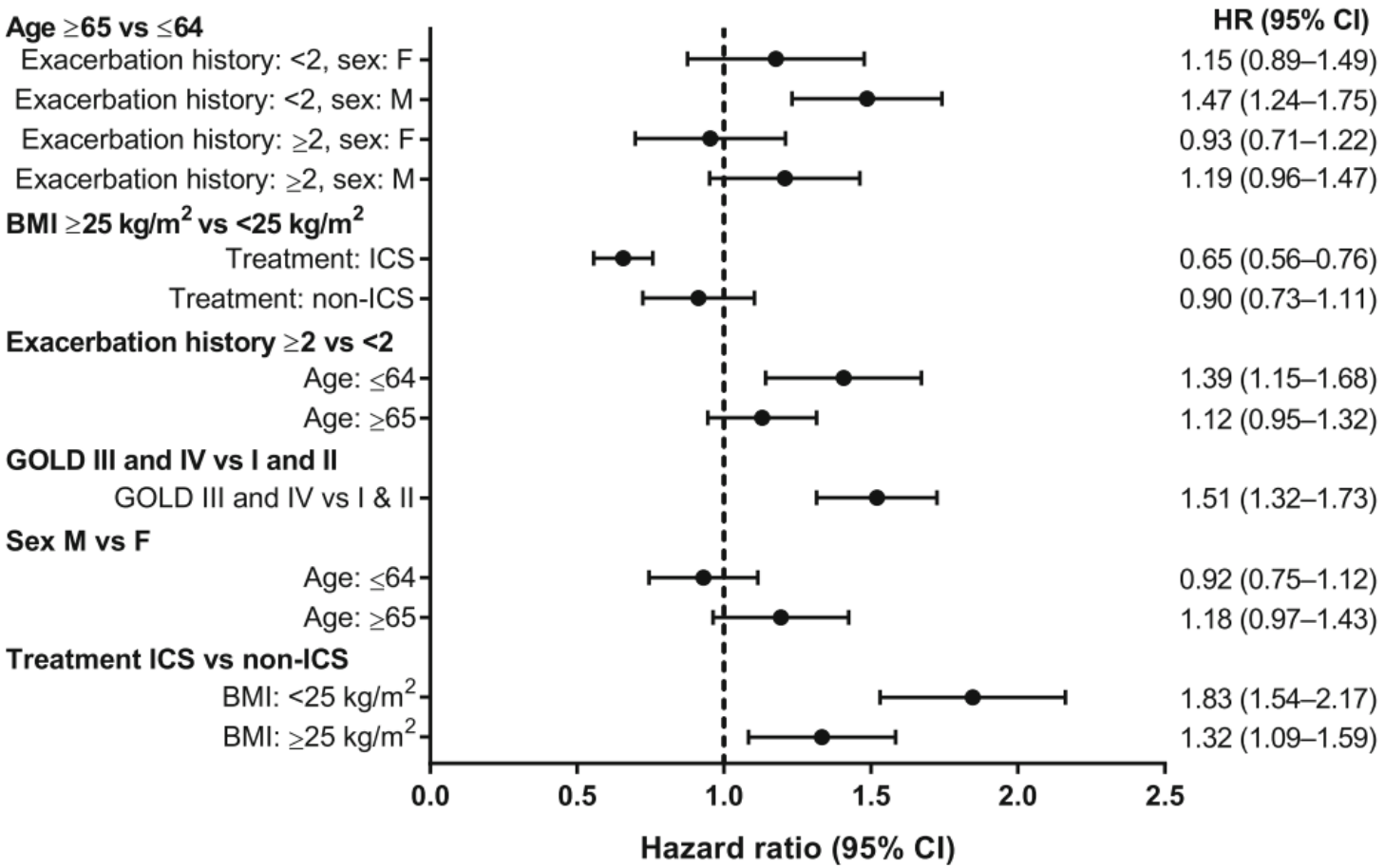


Fig. 1 Hazard ratios (95% confidence intervals [CIs]) for pneumonia from selected seven-covariate pneumonia model. *BMI* body mass index, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroids

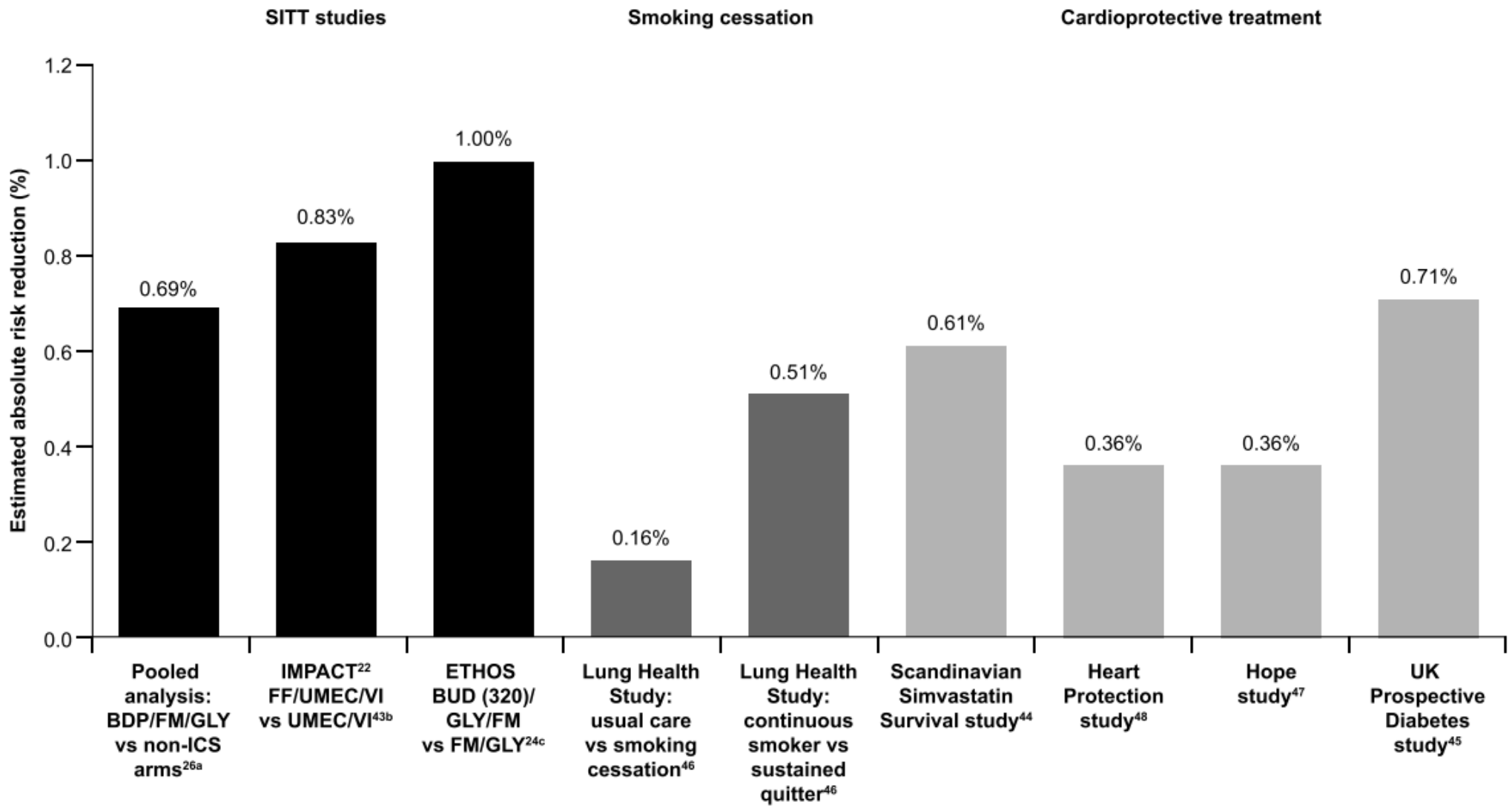


Figure 2 All-cause mortality benefits with SITT are similar to, or better than, smoking cessation and cardioprotective treatments. [a]Pooled analysis of AEs leading to a fatal

Am J Respir Crit Care Med Vol 203, Iss 6, pp 689–698, Mar 15, 2021

LHS (1994)
Active, n=1,961
Nonactive, n=1,962
Ipratropium Bromide

Copenhagen (1999)
Active, n=145
Nonactive, n=145
Budesonide

ISOLDE (2000)
Active, n=339
Nonactive, n=325
Fluticasone Propionate

LHS2 (2000)
Active, n=557
Nonactive, n=559
Triamcinolone

BRONCUS (2005)
Active, n=256
Nonactive, n=267
N-acetylcysteine

UPLIFT (2008)
Active, n=2,554
Nonactive, n=2,410
Tiotropium

TORCH (2008)
Active, n=4,082
Nonactive, n=1,261
TORCH Composite Active Arr

SUMMIT (2016)
Active, n=11,657
Nonactive, n=3,800
SUMMIT Composite Active Ar

Zhou (2017)
Active, n=388
Nonactive, n=383
Tiotropium

Overall
Active Therapy 5.0 mL/year (9

Table 1. Baseline Demographics and Characteristics of the Patients Included in the Systematic Review of Pharmacological Trials Lasting 12 Months or Longer in Patients with COPD

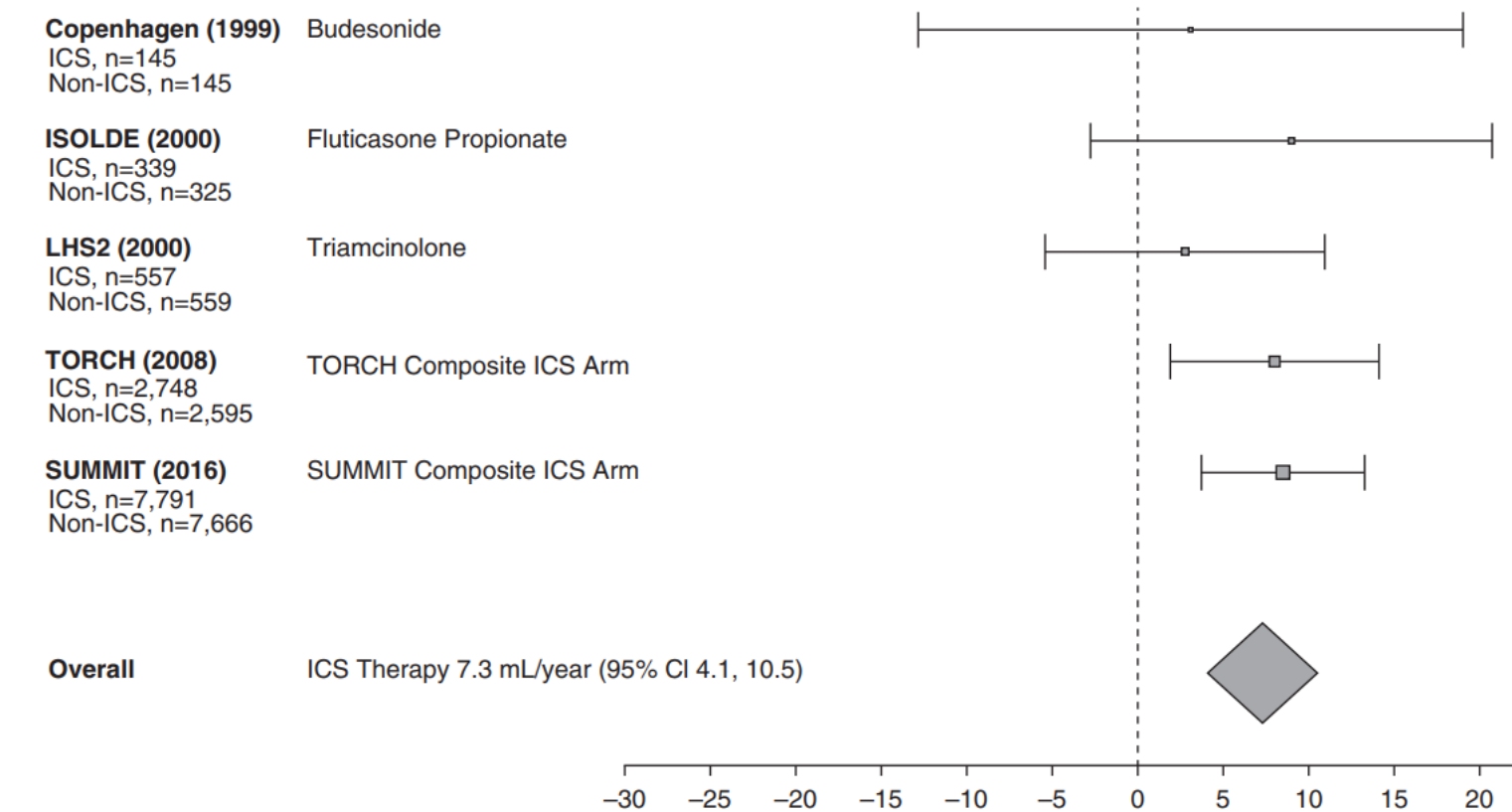
	(1997–2003)	(1992–1998)	(2000–2005) TORCH*	(2003–2008)	(1986–1994) Lung	(2011–2015)	(2011–2015) SUMMIT*	(1992–1994) Copenhagen	(1994–1999) Lung Health
Treatment arms: placebo/**active intervention(s)**									
Number of participar in study (*and in R analysis, if differer* (total) placebo/**tot active interventic**									
Age, mean, yr									
Sex, F, *n* (%)									
Smoking status current, %									
Previous year exacerbation hx,									
FEV_1, mean, L†									
FEV_1, mean, % predicted									
Study duration									
Number of spirometric assessments									
Completion of the study placebo/**tot active interventic**									

Definition of abbr
Obstructive Lung
in COPD Health;
Statements and r
*Date is start of r
†Post-bronchodila
‡Study was event-driven average treatmer
§Variable follow-up.
‖15,457 contributed an average of seven
¶Every 6 months during follow-up.
**Completed fifth year of spirometry.

Table 2. Impact of Therapy on FEV_1, in the Studies Included in This Systematic Review

Treatment arms: placebo/**active intervention**	FEV_1 decline in placebo/active (SE), ml	Treatment difference for each active arm vs. plac (SE) [95% CI], ml

Definition of abbr
Steroids in Obstr
UPLIFT = Underst
The table present
*Date is start of r



Study designs and populations

	FULFIL[1]	IMPACT[2]	KRONOS[3]
Size	1,810 patients	10,355 patients	1,896 patients
Prior history of asthma	Permitted	Permitted	Permitted
Duration	24 weeks (52-week extension arm†)	52 weeks	24 weeks (52 week extension)
Run-in medication	Current COPD medications	Current COPD medications	Ipratropium QID; ICS use allowed if the patient was on a stable ICS dose 4 weeks prior to screening‡
Treatment arms	FF/UMEC/VI vs BUD/FOR	FF/UMEC/VI vs FF/VI vs UMEC/VI	BUD/GLY/FOR vs GLY/FOR vs BUD/FOR pMDI vs BUD/FOR DPI§
Delivery of SITT	ELLIPTA DPI	ELLIPTA DPI	Aerosphere pMDI
Primary endpoint(s)	FEV_1 and SGRQ co-primary endpoints	Annual rate of moderate/severe exacerbations	Lung function (FEV_1) co-primary endpoints
Population **Asian ethnicity**	-	-	**45%**
Exacerbation history	**Required if FEV_1 ≥50 to <80%#** **(35% of patients had no exacerbations in the prior year)**	**Required** **(Inclusion criteria: ≥1 exacerbation in the prior year)**	**Not required** **(74% of patients had no exacerbations in the prior year)**
ICS at study entry	**66%**	**71%**	**72%**
Safety assessments	Pre-defined AESIs, imaging required for pneumonia events	Pre-defined AESIs, imaging required for pneumonia	Standardised definition of pneumonia (required imaging)**

As there are currently no head-to-head studies available, direct comparisons between TRELEGY Ellipta and BUD/GLY/FOR cannot be made and no definitive conclusions can be drawn regarding any differences in study results

Inhaled corticosteroids in COPD: Friend or foe?

Benefits and risks of ICS use in COPD management

Factors to consider when *initiating* ICS treatment (in combination with long-acting bronchodilators) in COPD patients

• STRONG SUPPORT	• CONSIDER USE	• AVOID USE
• Hx. of hospitalization(s) for ECOPD*		• Repeated pneumonia events
• ≥2 moderate ECOPD/year*	• 1 moderate ECOPD/year*	•
• Blood eosinophils >300 cells/μL	• Blood eosinophils 100–300 cells/μL	• Blood eosinophils <100 cells/μL
• Hx. of, or concomitant, asthma		• Hx. of mycobacterial infection

GOLD 2021 supports ICS use in patients meeting certain criteria, thorough patient characterization is essential

* despite appropriate long-acting bronchodilator maintenance therapy

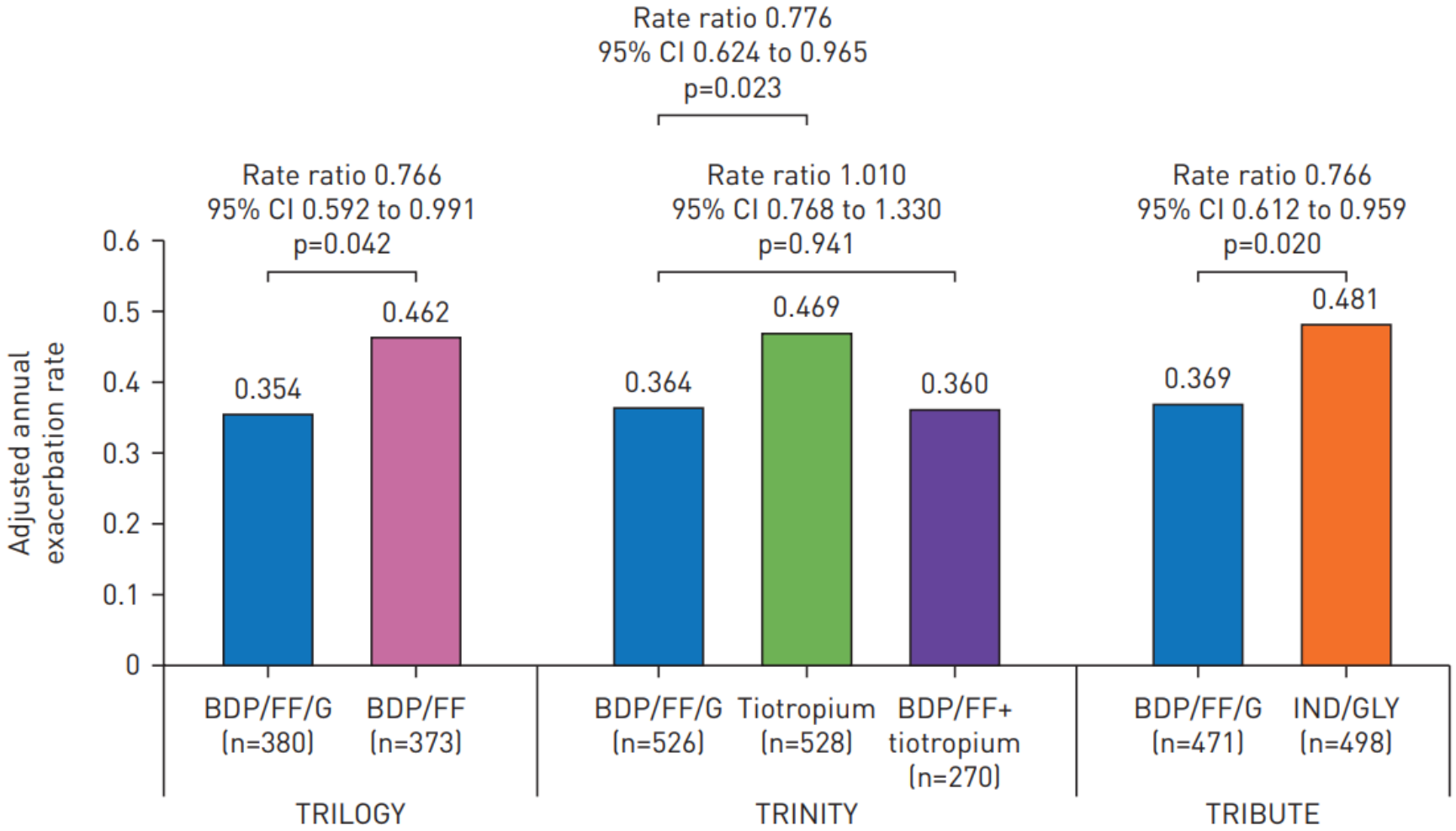
Table 2 Number (%) of patients with a CID overall and by individual component

Endpoint	TRILOGY			TRINITY					TRIBUTE		
	BDP/FF/G (N=687)	BDP/FF (N=680)	HR time to first event (95% CI)	BDP/FF/G (N=1,077)	Tiotropium (N=1,074)	BDP/FF + tiotropium (N=538)	HR time to first event (95% CI)		BDP/FF/G (N=764)	IND/GLY (N=768)	HR time to first event (95% CI)
							BDP/FF/G vs tiotropium	BDP/FF/G vs BDP/FF + tiotropium			
FEV_1[a]	276 (40.2)	402 (59.1)	0.55 (0.47, 0.64); $P<0.001$	483 (44.8)	598 (55.7)	225 (41.8)	0.69 (0.62, 0.78); $P<0.001$	1.11 (0.95, 1.30); $P=0.197$	448 (58.6)	460 (59.9)	0.98 (0.86, 1.12); $P=0.748$
SGRQ total score[b]	279 (40.6)	317 (46.6)	0.78 (0.67, 0.92); $P=0.003$	426 (39.6)	523 (48.7)	208 (38.7)	0.72 (0.63, 0.82); $P<0.001$	1.04 (0.88, 1.23); $P=0.610$	369 (48.3)	418 (54.4)	0.81 (0.71, 0.93); $P=0.003$
TDI focal score[c]	175 (25.5)	204 (30.0)	0.81 (0.66, 0.99); $P=0.040$	–	–	–	–	–	–	–	–
COPD exacerbation[d]	214 (31.1)	240 (35.3)	0.80 (0.67, 0.97); $P=0.020$	351 (32.6)	383 (35.7)	167 (31.0)	0.84 (0.72, 0.97); $P=0.015$	1.06 (0.88, 1.27); $P=0.569$	273 (35.7)	288 (37.5)	0.90 (0.76, 1.06); $P=0.219$
Death	14 (2.0)	16 (2.4)	0.88 (0.43, 1.81); $P=0.728$	20 (1.9)	28 (2.6)	8 (1.5)	0.66 (0.37, 1.18); $P=0.163$	1.25 (0.55, 2.84); $P=0.592$	16 (2.1)	20 (2.6)	0.76 (0.39, 1.46); $P=0.409$
Composite, any event (excluding TDI)	**480 (69.9)**	**569 (83.7)**	**0.61 (0.54, 0.70); *P*,0.001**	**800 (74.3)**	**883 (82.2)**	**394 (73.2)**	**0.72 (0.65, 0.79); *P*,0.001**	**1.06 (0.94, 1.20); *P*=0.326**	**623 (81.5)**	**668 (87.0)**	**0.82 (0.73, 0.91); *P*,0.001**
Composite, any event (including TDI)	**506 (73.7)**	**592 (87.1)**	**0.62 (0.55, 0.70); *P*,0.001**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**–**

Notes: [a]Patients with decrease from baseline ≥100 mL; [b]patients with deterioration (ie, increase from baseline) ≥4 units; [c]patients with TDI focal score ≤−1 unit; [d]patients with a moderate/severe exacerbation. The composite CID was based on the occurrence of any of the following: decrease of ≥100 mL from baseline in FEV_1; increase of ≥4 units from baseline in SGRQ total score; TDI focal score ≤−1 unit (TRILOGY definition that included TDI only); occurrence of a moderate/severe exacerbation; or death. Data in bold are for the composite endpoint.

Abbreviations: IND/GLY, indacaterol/glycopyrronium; SGRQ, St George's Respiratory Questionnaire; BDP, beclometasone dipropionate; CID, clinically important deterioration; FF, formoterol fumarate; G, glycopyrronium; TDI, Transition Dyspnea Index.

Extrafine triple therapy in patients with symptomatic COPD and history of one moderate exacerbation



Eur Respir J 2019; 53: 1900235

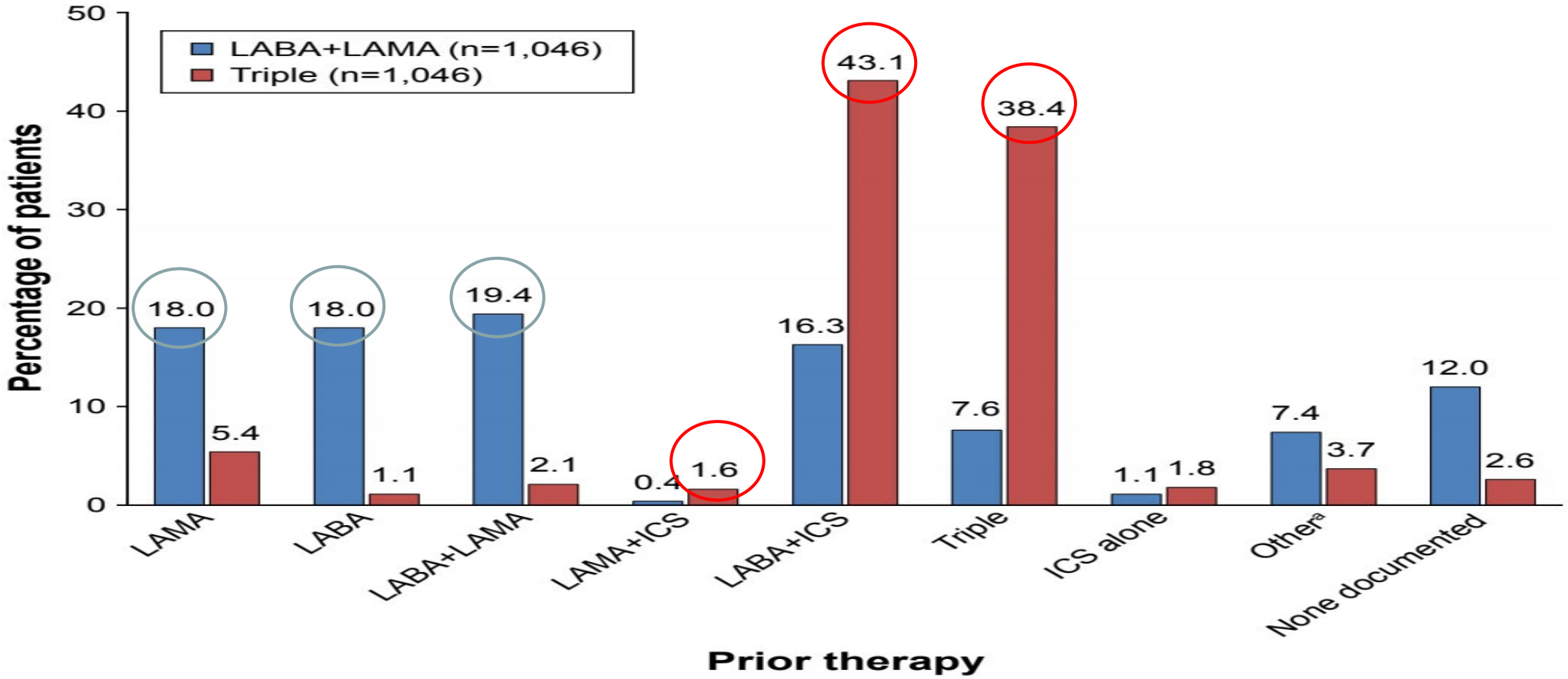
Study	Study Site	No of Participants	Study Period	Inclusion Criteria					Inhalation Therapy		Primary Outcome
				FEV1	Exacerbation history in previous year	Symptom scores	Excluded asthma	Others	Fixed triple	Comparator	
Lipson et al., 2018 (IMPACT) [20]	37 countries	10,355	2014–2017	FEV_1 of 50-80%	≥1 moderate/severe exacerbation if FEV_1 < 50% or ≥2 moderate exacerbations or one severe exacerbation if FEV1 of 50-80%	CAT score ≥ 10	No	≥40 years; MCID: 2 point; use LAMA, a LABA, or an ICS alone or in combination	FF/UME/VIL	FF/VIL or UME/VIL	Annual rate of moderate or severe COPD exacerbations
Papi et al., 2018 (TRIBUTE) [21]	187 sites in 17 countries	1532	2015–2017	FEV1 < 50%	≥1 moderate or severe exacerbation	CAT score ≥ 10	Yes	≥40 years; current or ex-smoker; used ICS/LABA, ICS/LAMA or LABA/LAMA for ≥2 months	BDP/FOR/GB	IND/GB	Moderate to severe COPD exacerbation rate for 52 weeks
Singh et al., 2016 (TRIOLOGY) [22]	159 sites in 14 countries	1368	2014–2016	FEV_1 < 50%	≥1 moderate/severe exacerbation	CAT score ≥ 10	Yes	≥40 years; current or ex-smoker; used ICS/LABA, ICS/LAMA or LABA/LAMA for ≥2 months	BDP/FOR/GB	BDP/FOR	Moderate to severe COPD exacerbation rate for 52 weeks
Rabe et al., 2020 (ETHOS) [24]	740 sites in 26 countries	8509	2015–2019	FEV1 of 25-65%;	≥1 moderate/severe exacerbation if FEV1 < 50% or ≥2 moderate exacerbations or one severe exacerbation if FEV1 ≥ 50%	CAT score ≥ 10	Yes	40 to 80 years; MICD: 2 point; receiving at least two inhaled maintenance therapies at the time of screening; a smoking history of at least 10 pack-years	BUD/FOR/GB	GB/FOR or BUD/FOR	Annual rate of moderate or severe COPD exacerbations
Lipson et al., 2017 (FULFIL)—extension population [33]	160 sites in 15 countries	430	2015–2016	FEV_1 < 50% or 50%-80%	≥2 moderate exacerbations or ≥1 severe exacerbation if FEV1 ≥ 50%	CAT score ≥ 10	Yes	≥40 years; receiving daily maintenance therapy for COPD for at least 3 months	FF/UME/VIL	BUD/FOR	Lung functionand health-related quality of life
NCT02536508 [34]	64 cites in US	627	2015–2017	NA	NA	NA	No	40 to 80 years, moderate to very severe COPD	BUD/FOR/GB	GB/FOR or BUD/FOR	Percent change from baseline in BMD of the lumbar spine

Life 2022, 12, 173. https://doi.org/10.3390/life12020173

Major SITT Triple Therapy Trials

	Primary Endpoint: FEV_1 and/or SGRQ				Primary Endpoint: Exacerbation Rate		
	TRILOGY[25]	KRONOS[20]	FULFIL[21,87]		TRIBUTE[23]	ETHOS[24,88]	IMPACT[22,89]
	52 Weeks	24 Weeks	24 Weeks	52 Weeks	52 Weeks	52 Weeks	52 Weeks
Study arms	BDP/FM/GLY BID (N=687) BDP/FM BID (N=680)	1. BUD/GLY/FM BID (N=639) 2. FM/GLY BID (N=625) 3. BUD/FM BID (N=314) 4. BUD/FM DPI open-label BID (N=318)	FF/UMEC/VI QD (N=911) BUD/FM BID (N=899)	FF/UMEC/VI QD (N=210) BUD/FM BID (N=220)	BDP/FM/GLY BID (N=764) IND/GLY QD (N=768)	1. BUD (320)/GLY/FM BID (N=2137) 2. BUD (160)/GLY/FM BID (N=2121) 3. FM/GLY BID (N=2120) 4. BUD/FM BID (N=2131)	1. FF/UMEC/VI QD (N=4151) 2. FF/VI QD (N=4134) 3. UMEC/VI QD (N=2070)
Run-in period	BDP/FM BID	Ipratropium bromide QID ICS use allowed if patient on a stable dose 4 weeks prior to screening	Current COPD medications		IND/GLY QD	Ipratropium bromide QID ICS use allowed if used prior to screening	Current COPD medications
Recruitment criteria (FEV_1% predicted, exacerbations, and CAT score)	• FEV_1 <50% • ≥1 moderate/severe exacerbation in the preceding year • CAT ≥10	• FEV_1 ≥25–<80% • No history of exacerbations required • CAT ≥10	• FEV_1 <50%; or • FEV_1 ≥50–<80% plus ≥2 moderate or ≥1 severe exacerbation in the preceding year • CAT ≥10		• FEV_1 <50% • ≥1 moderate/severe exacerbation in the preceding year • CAT ≥10	• FEV_1 ≥25–≤65% • ≥1 moderate/severe (if FEV_1 <50%), or ≥2 moderate or ≥1 severe (if FEV_1 ≥50%) exacerbation in the preceding year • CAT ≥10	• FEV_1 <50% plus ≥1 moderate or severe exacerbation in the preceding year; or • FEV_1 ≥50–<80% plus ≥2 moderate or ≥1 severe exacerbation in the preceding year • CAT ≥10

Substantial imbalance of prior therapy ; DACCORD study



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