Are the Current COPD Guidelines Adequate for Managing COPD?

한림대학교 강동성심병원
박용범


COPD
진료지
Chronic obstructive
pulmonary disease
제작: 대한결핵 및 호흡기학회
COPD 진료지침 개정위원회
후원: 근거창출 임상연구
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COPD 진료지침 2018 개정
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NHLBI/WHO Workshop Summary

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Global Initiative for Chron
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REVISED 2011

Global Initiative for Chronic
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Disease

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2018 REPORT

The Goal of GOLD and Korean COPD guideline

- **Produce recommendations for management of COPD based on best scientific information available.**

- **COPD 환자를 진료하는 일선진료 의사가 COPD 환자 또는 유소견자 진료시 진단 및 치료, 그리고 추적 평가하는데 도움을 주고자 하였다.**

Contents

- **COPD Assessment and Prognostic Outcomes**
  - COPD severity and Disease Progression
  - Mortality

- **COPD Treatment**
  - Early COPD
  - ICS in COPD
  - Triple therapy
  - Roflumilast

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- **COPD Assessment and Prognostic Outcomes**
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  - **Early COPD**
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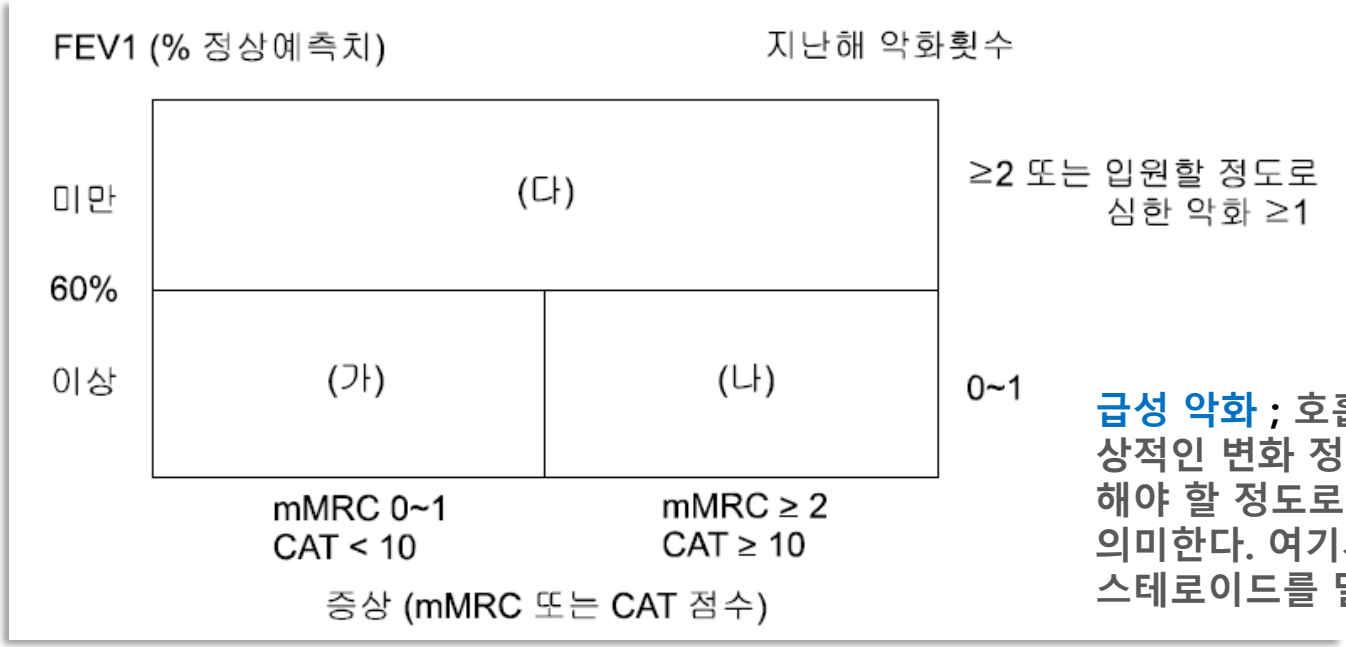
  - **Triple therapy**
  - **Roflumilast**

COPD 종합적 평가 2018

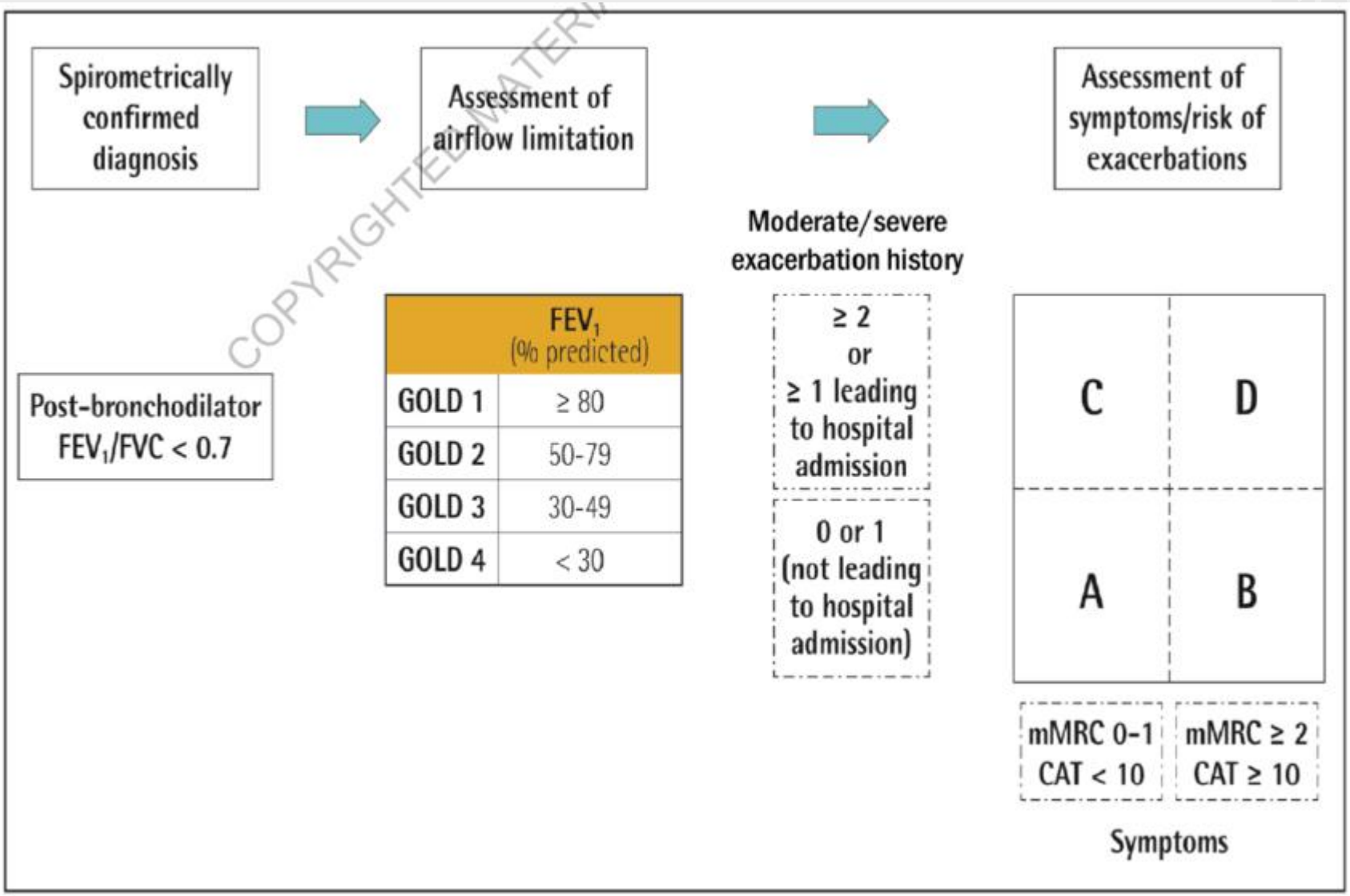


급성 악화 ; 호흡기증상이 매일매일의 일상적인 변화 정도를 벗어나서 약제를 추가해야 할 정도로 증상이 나빠진 급성상태를 의미한다. 여기서 약제는 항생제 또는 스테로이드를 말한다.

가군: 위험 낮음, 증상 경함. 나군: 위험 낮음, 증상 심함.
다군: 위험 높음.

mMRC 혹은 CAT 점수와 상관없이 FEV1 60%미만에 해당하거나 또는 지난 해에 2회 이상 급성 악화가 있었거나 입원할 정도로 심한 악화가 있었던 경우이다.

The refined ABCD Assessment tool
(GOLD 2018)

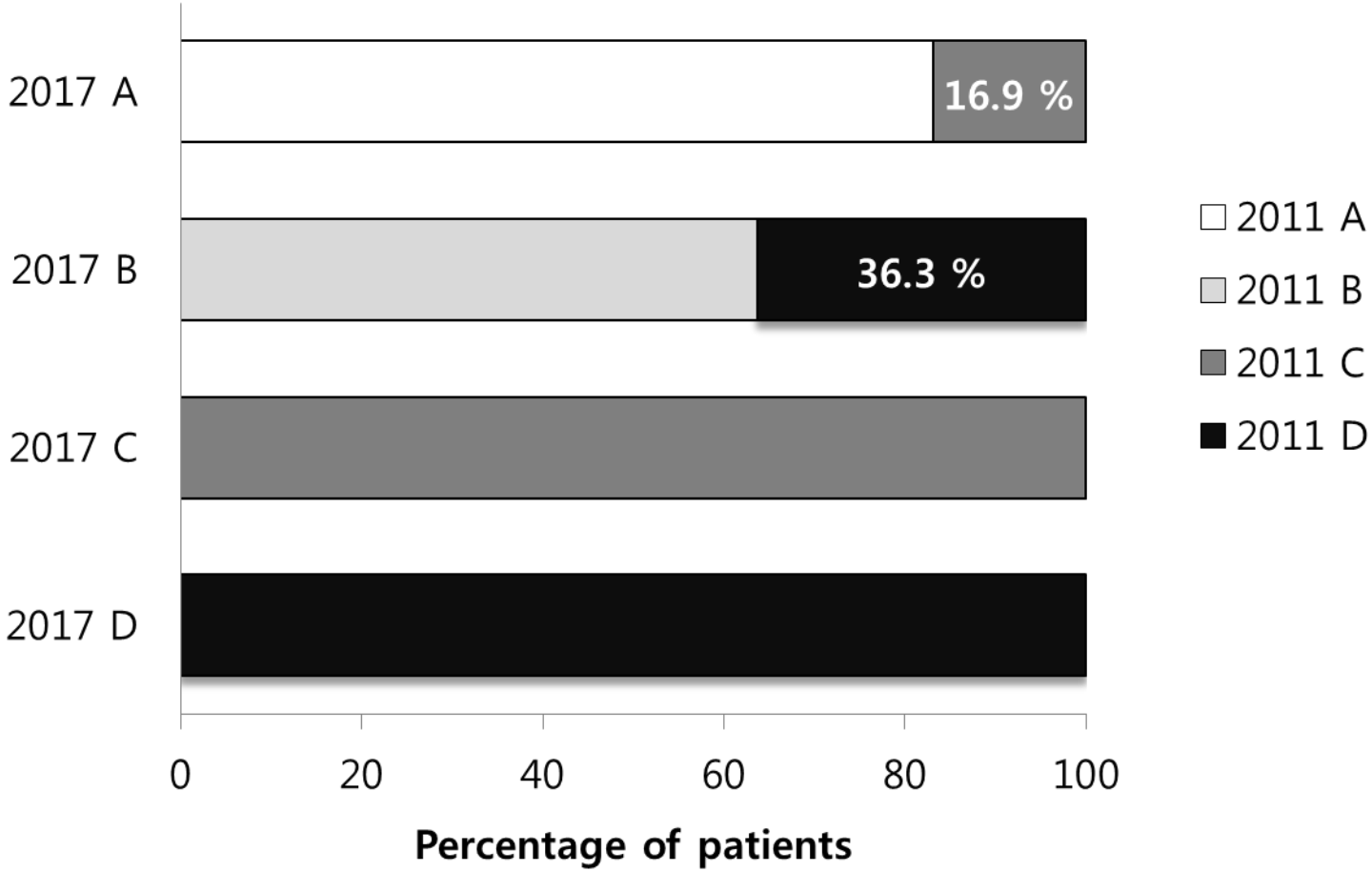


폐활량측정법에 의한 평가

- **FEV_1 : 정상예측치의 60% 기준 유지**

- 아래 이유로 유지하기로
  - FEV1 50% (또는 60%)로 향후 악화 위험 또는 예후를 평가하는 것은 의미 있음
  - 환자 증상/기억만으로 평가하는 것은 신뢰하기 약함
  - 폐활량검사의 중요성을 놓치지 않기 위함.

Which GOLD B patients change to GOLD D using the new classification (2017 GOLD)? KOCOSS cohort



In Submission

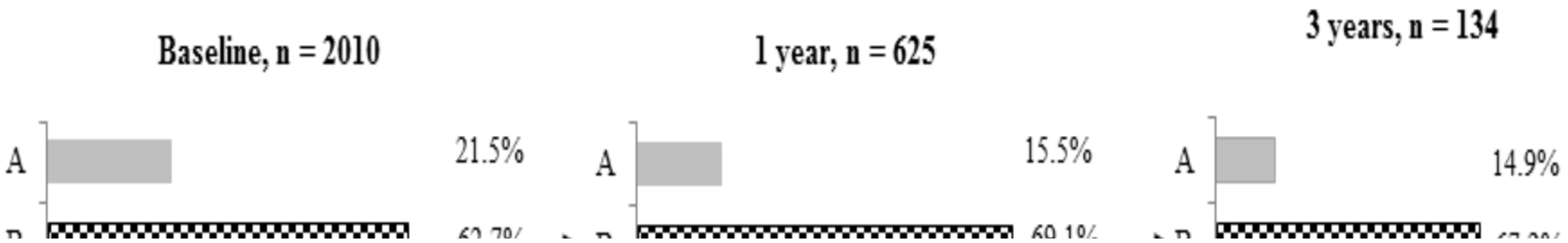
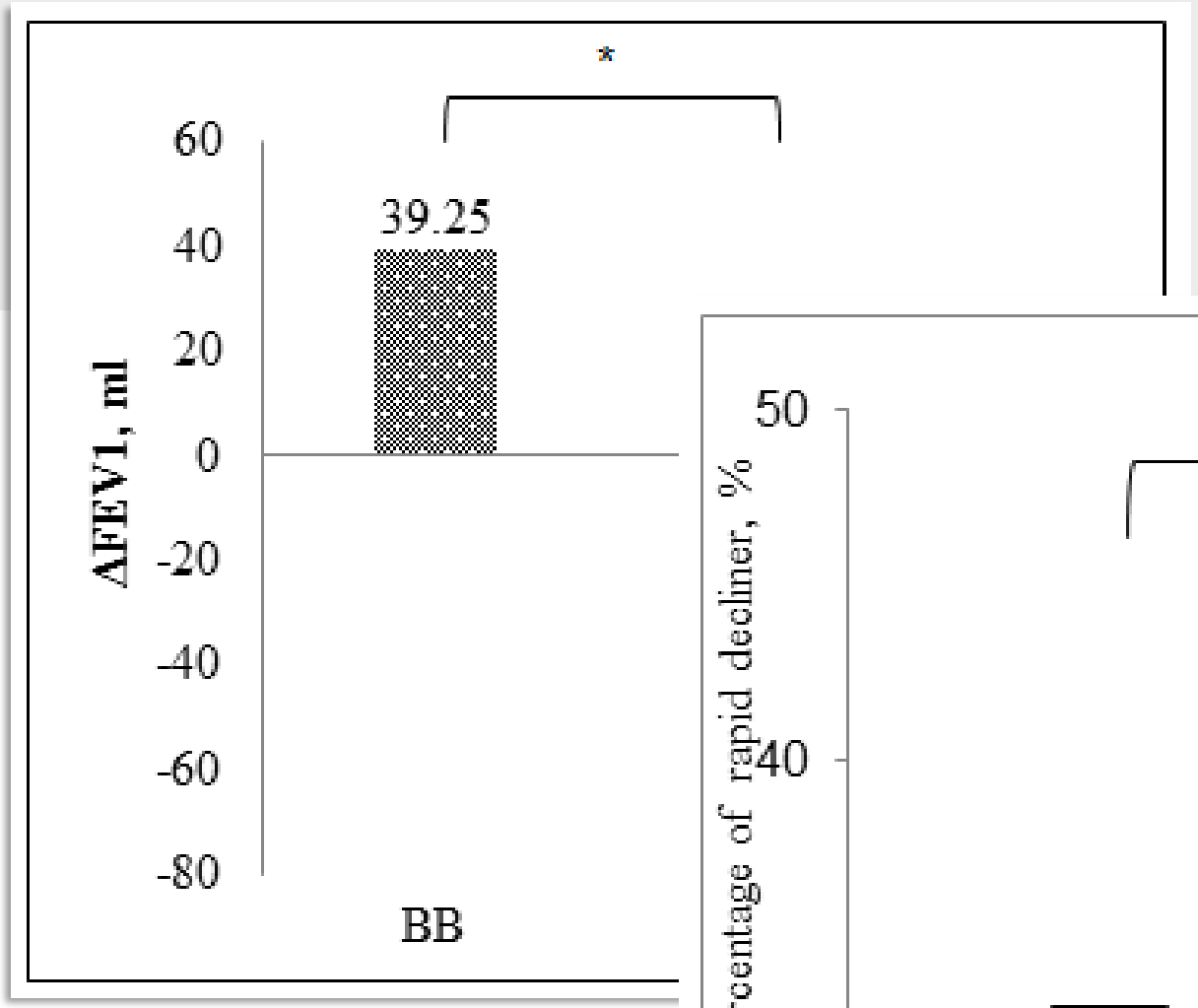
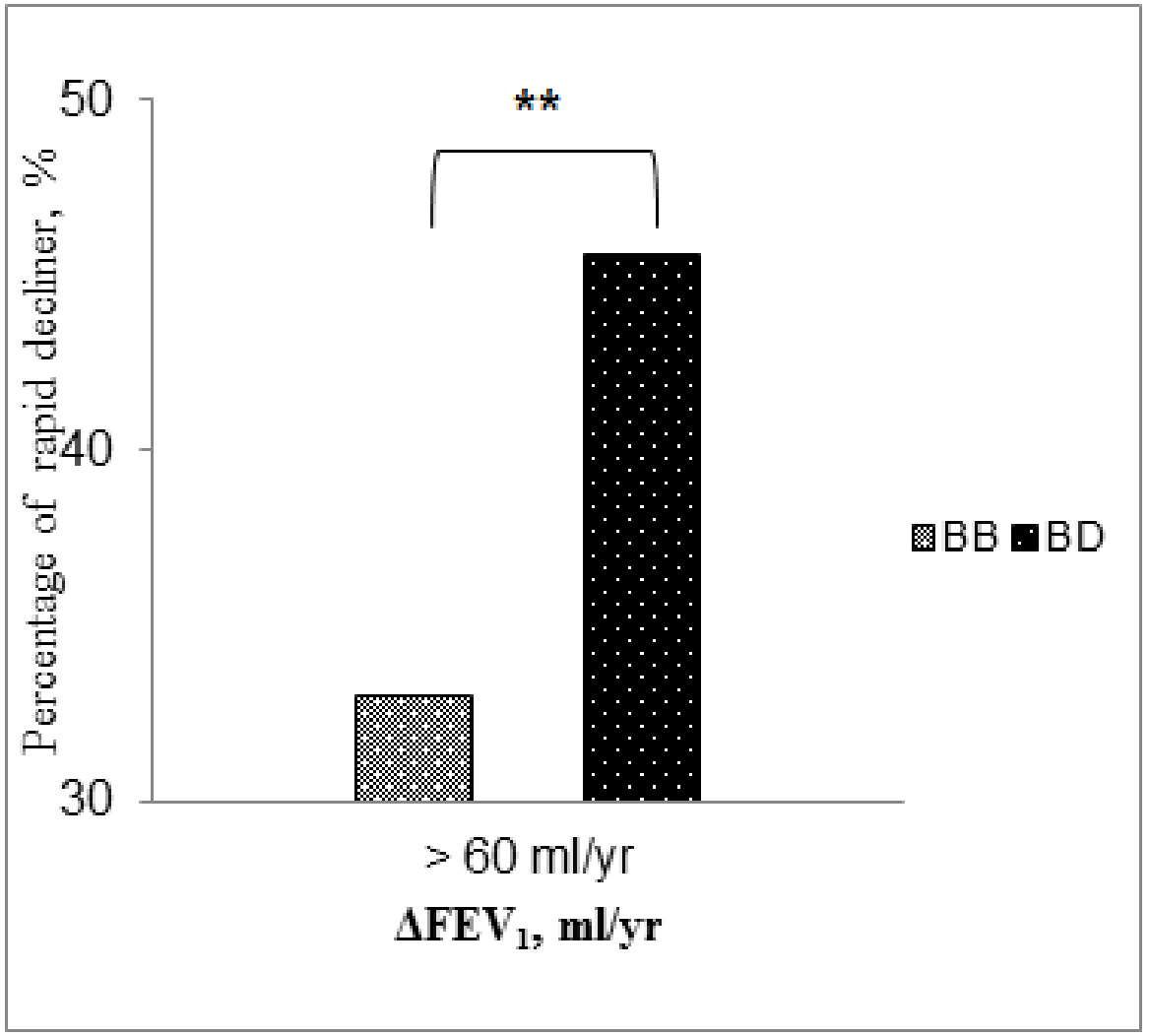


TABLE 3. Multivariate analysis of baseline factors associated with progression from GOLD B to GOLD D over 1 year.

Variable	*p*-value	Exp (B)	95% CI	
Age	0.014	1.049	1.010	1.089
mMRC score	0.005	1.617	1.157	2.259
SGRQ –S score	0.001	1.024	1.010	1.039
FEV1; % predicted	0.013	0.979	0.962	0.995

Adjusted for age, gender, BMI, chronic bronchitis status, SGRQ-A score, SGRQ total score, CAT score, GERD status, and exacerbation frequency at baseline. mMRC score: modified Medical Research Council score; SGRQ-S score: St. George's Respiratory Questionnaire symptom score; FEV1: post-bronchodilator forced expiratory volume in 1 s.


*
60
40
20
0
-20
-40
-60
-80
39.25
ΔFEV1, ml
BB


**
50
40
30
Percentage of rapid decliner, %
BB
BD
> 60 ml/yr
ΔFEV1, ml/yr

Comparison of Korean COPD Guideline and GOLD Initiative Report in Term of Acute Exacerbation: A Validation Study for Korean COPD Guideline (KOCOSS cohort)

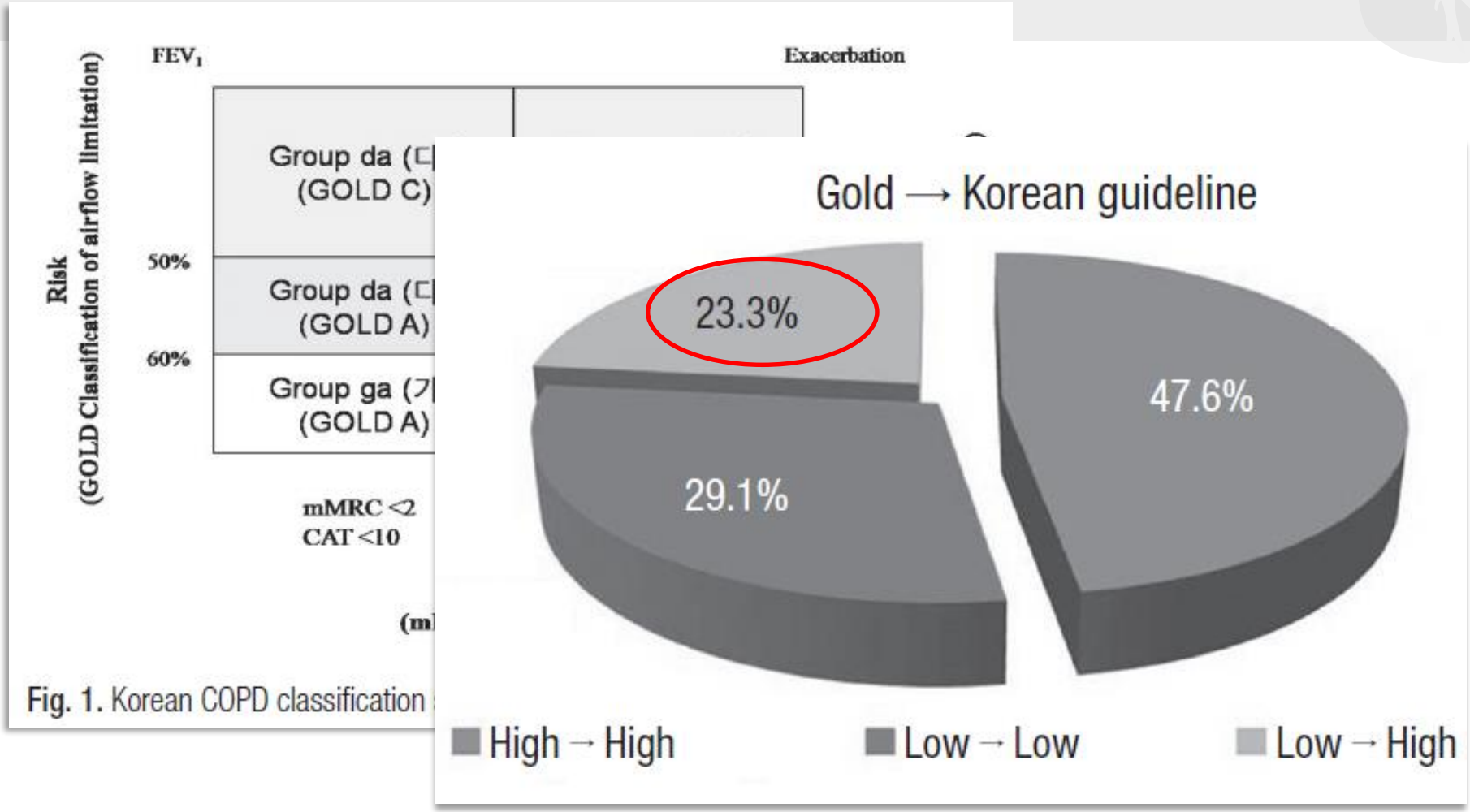
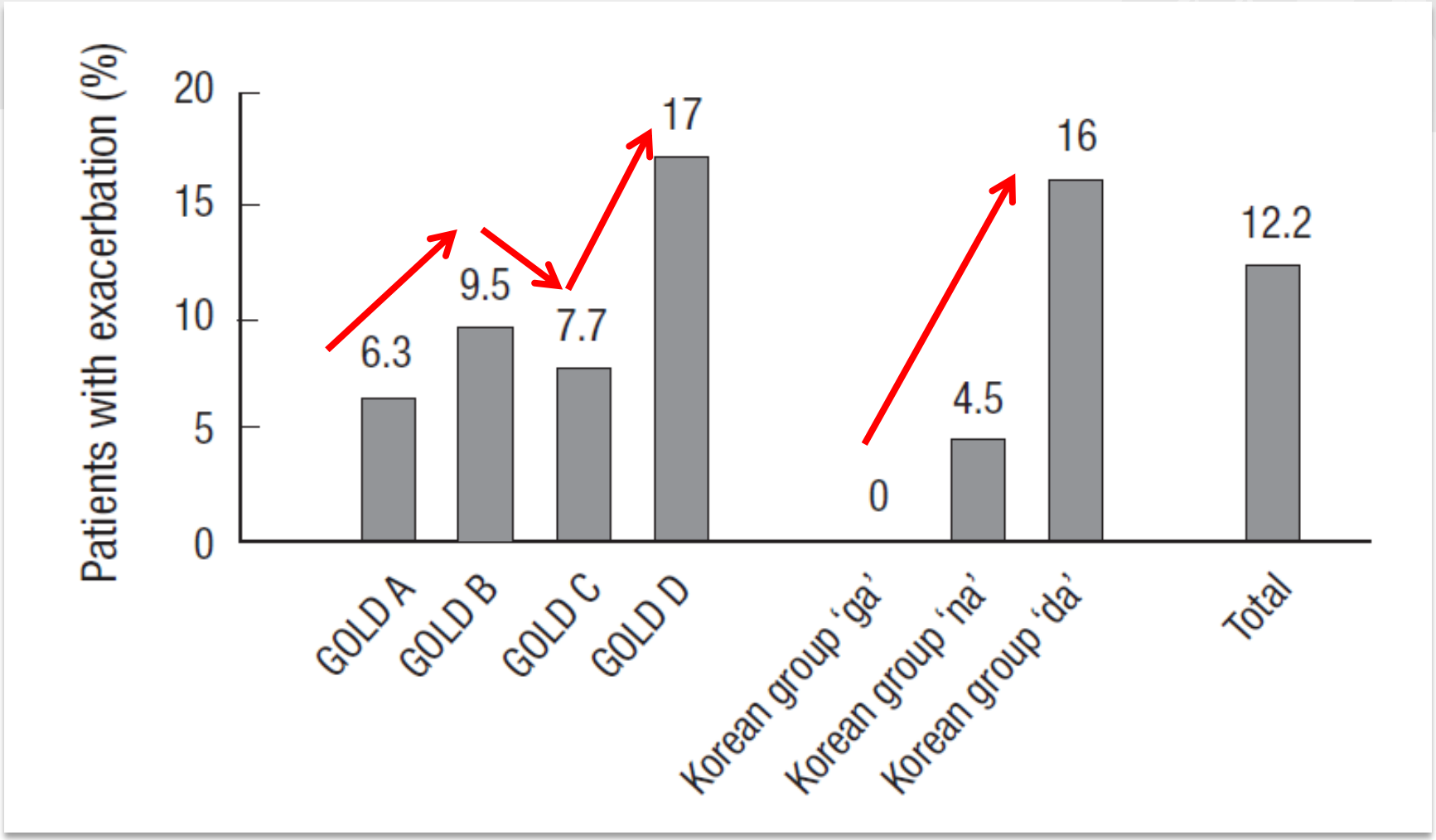


Fig. 1. Korean COPD classification

J Korean Med Sci 2014; 29: 1108-1112



J Korean Med Sci 2014; 29: 1108-1112

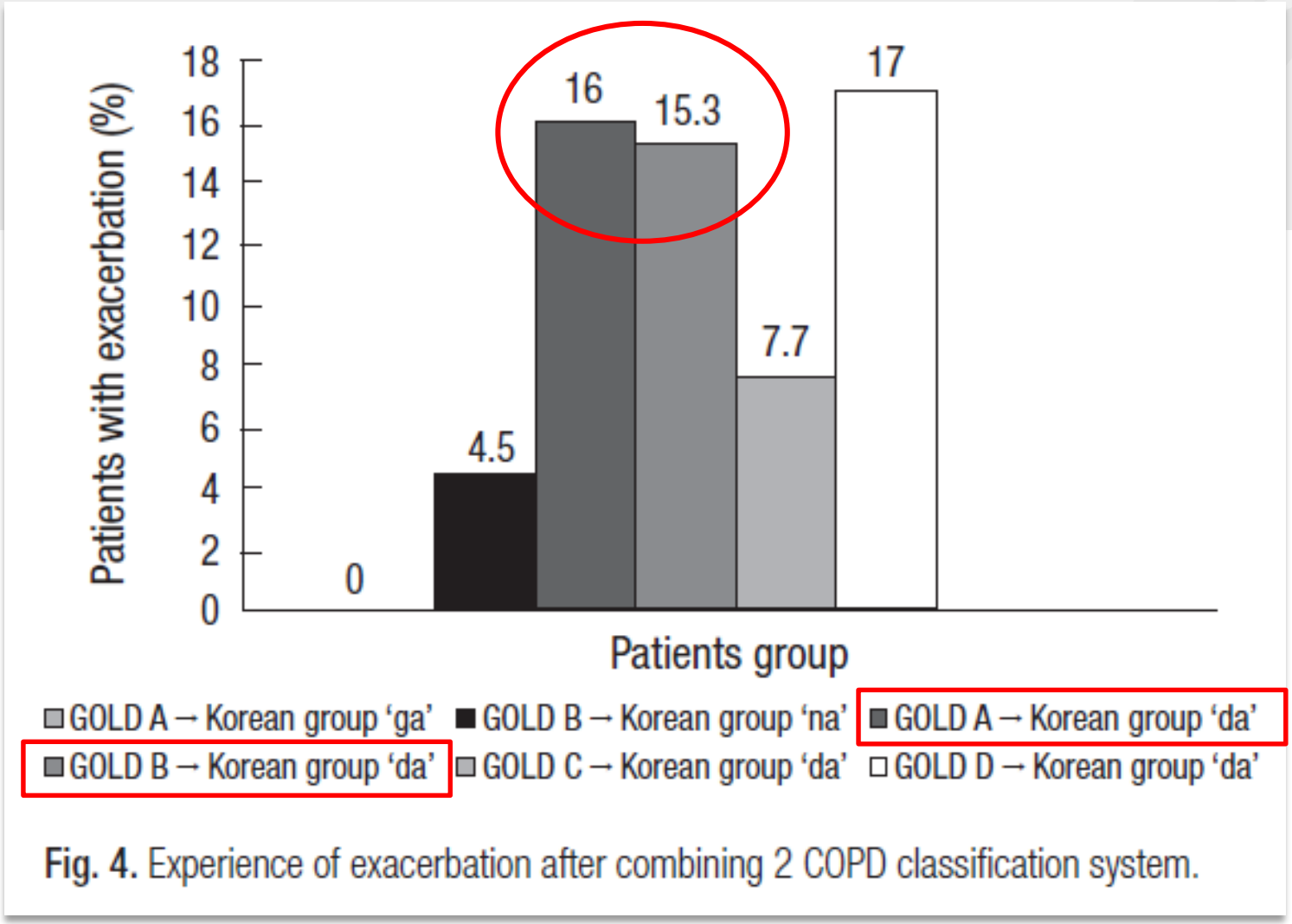
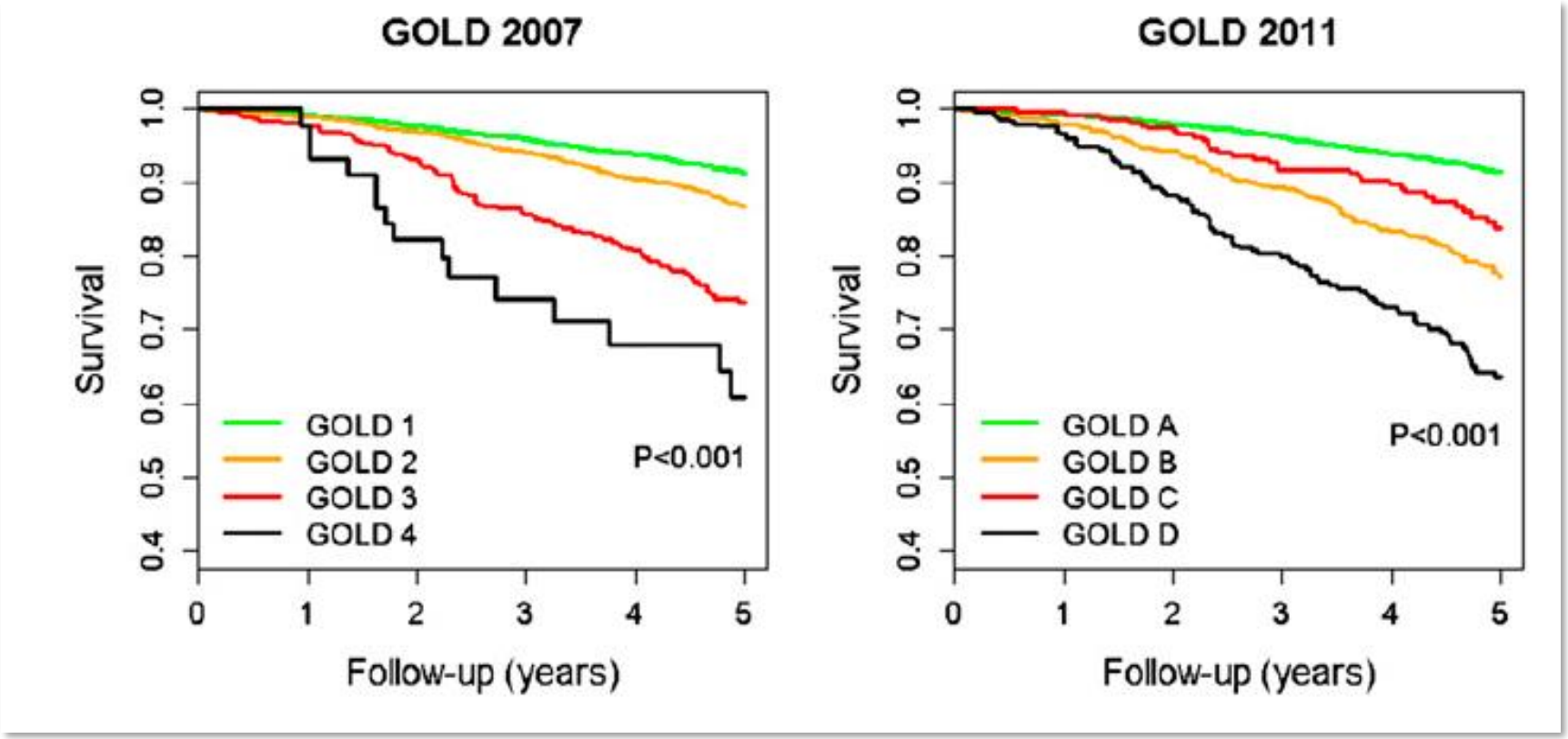


Fig. 4. Experience of exacerbation after combining 2 COPD classification system.

The Korean COPD guideline is useful to differentiate the high risk from low risk for exacerbation in terms of spirometry. This indicates that application of Korean COPD guideline is appropriate to treat Korean COPD patients.

Prediction of the Clinical Course of Chronic Obstructive Pulmonary Disease, Using the New GOLD Classification

A Study of the General Population

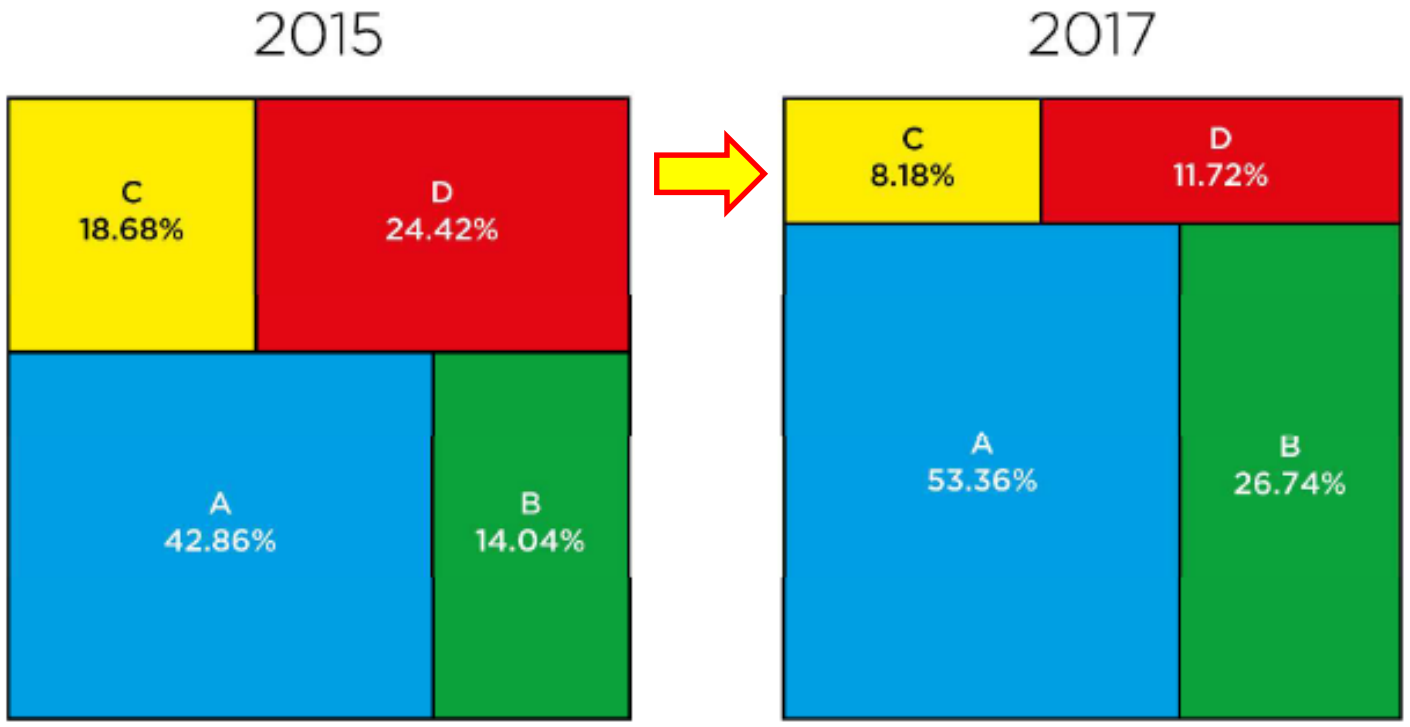


Am J Respir Crit Care Med Vol 186, Iss. 10, pp 975–981, Nov 15, 2012

Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

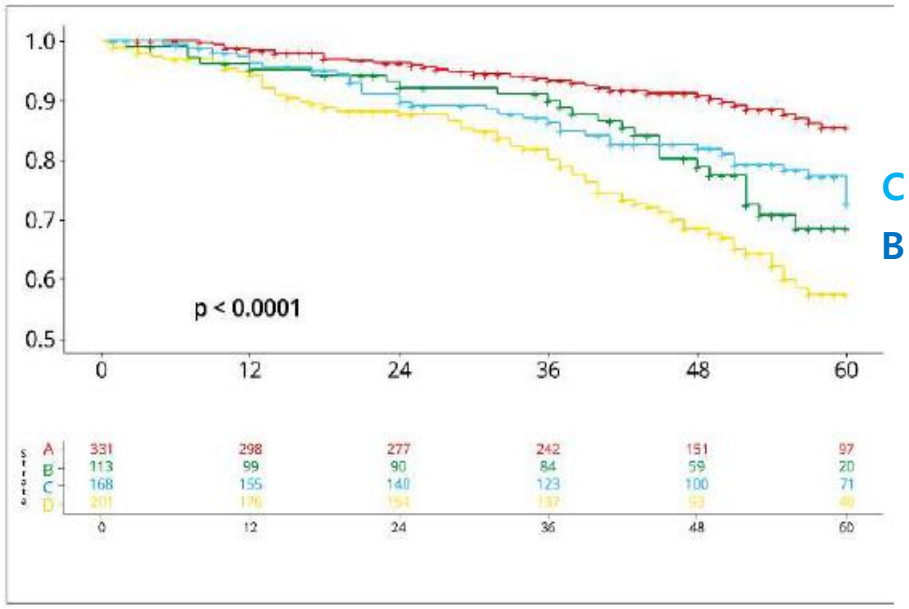
Distribution of the same COPD patients in the different ABCD GOLD grading groups using the 2015 vs. the new 2017 versions (Spain and USA).



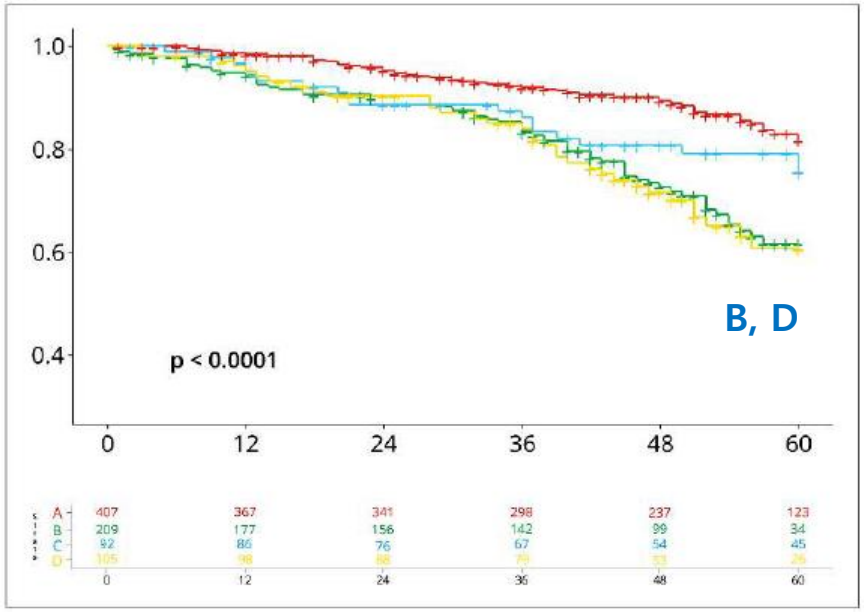
Am J Respir Crit Care Med. 2018;197:463-69

Kaplan Meier curves for survival

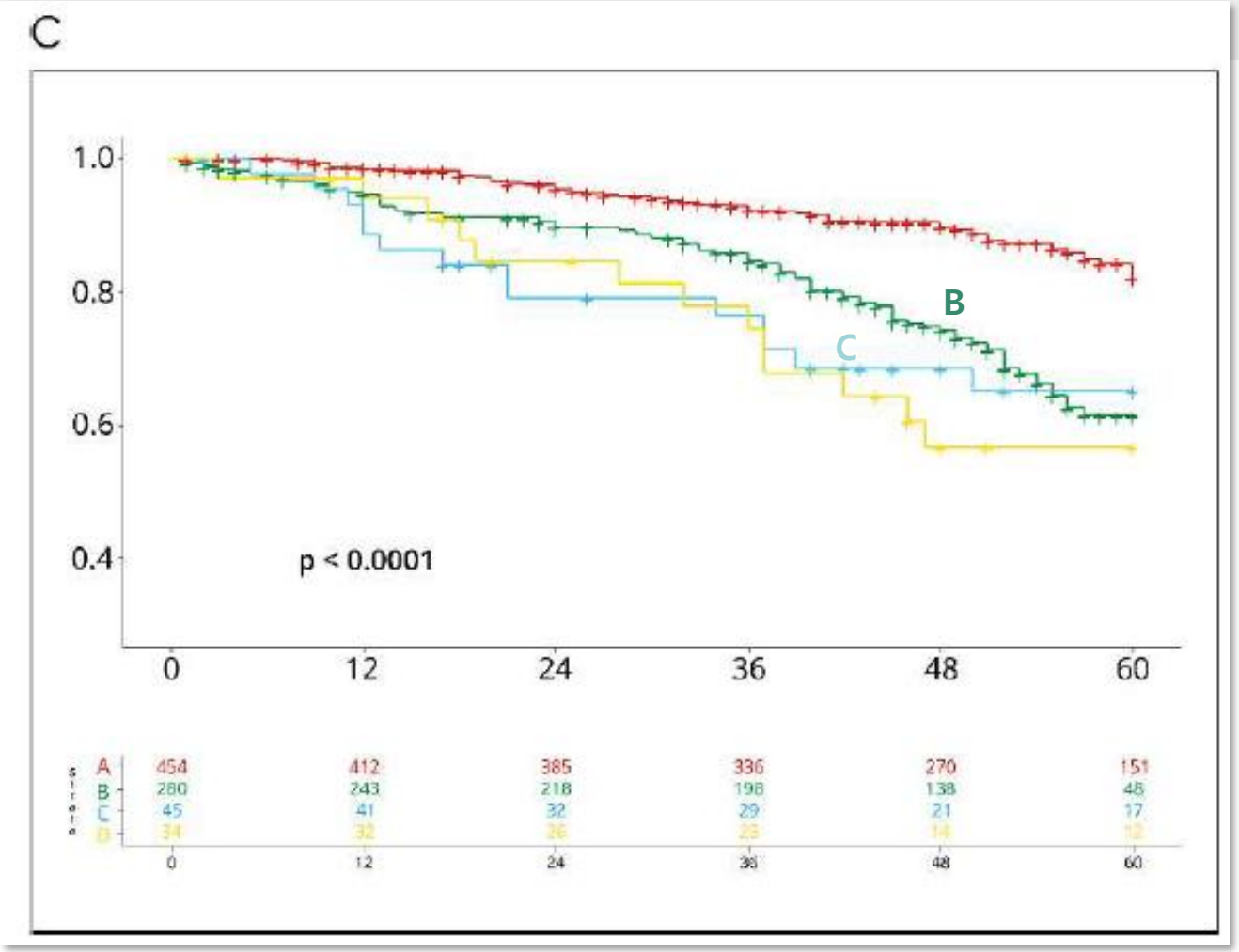
a **GOLD 2015 ABCD grading**



b **New GOLD 2017 ABCD grading**



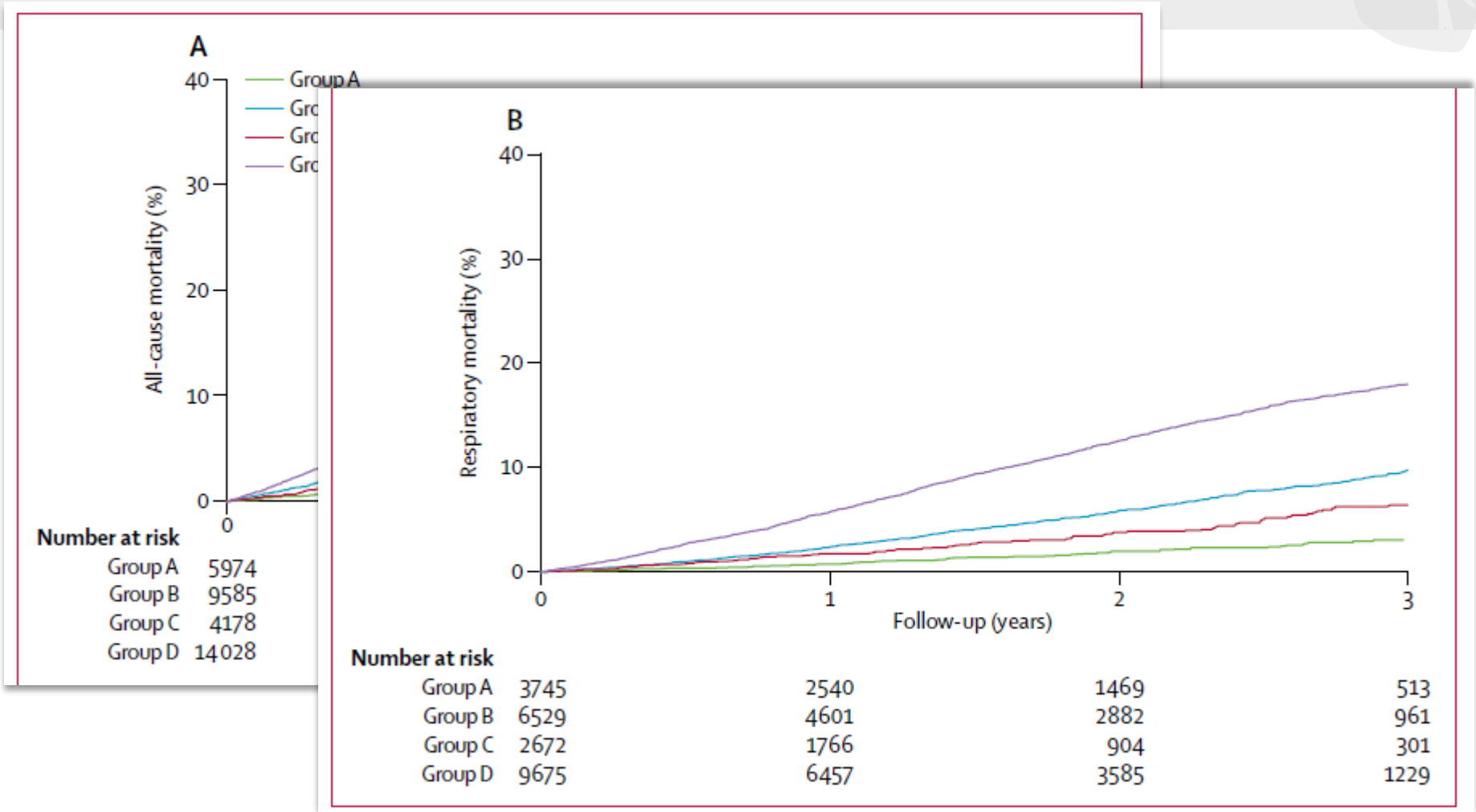
The 2017 ABCD grading, where only hospitalized and not ambulatory exacerbations were used to grade the patient



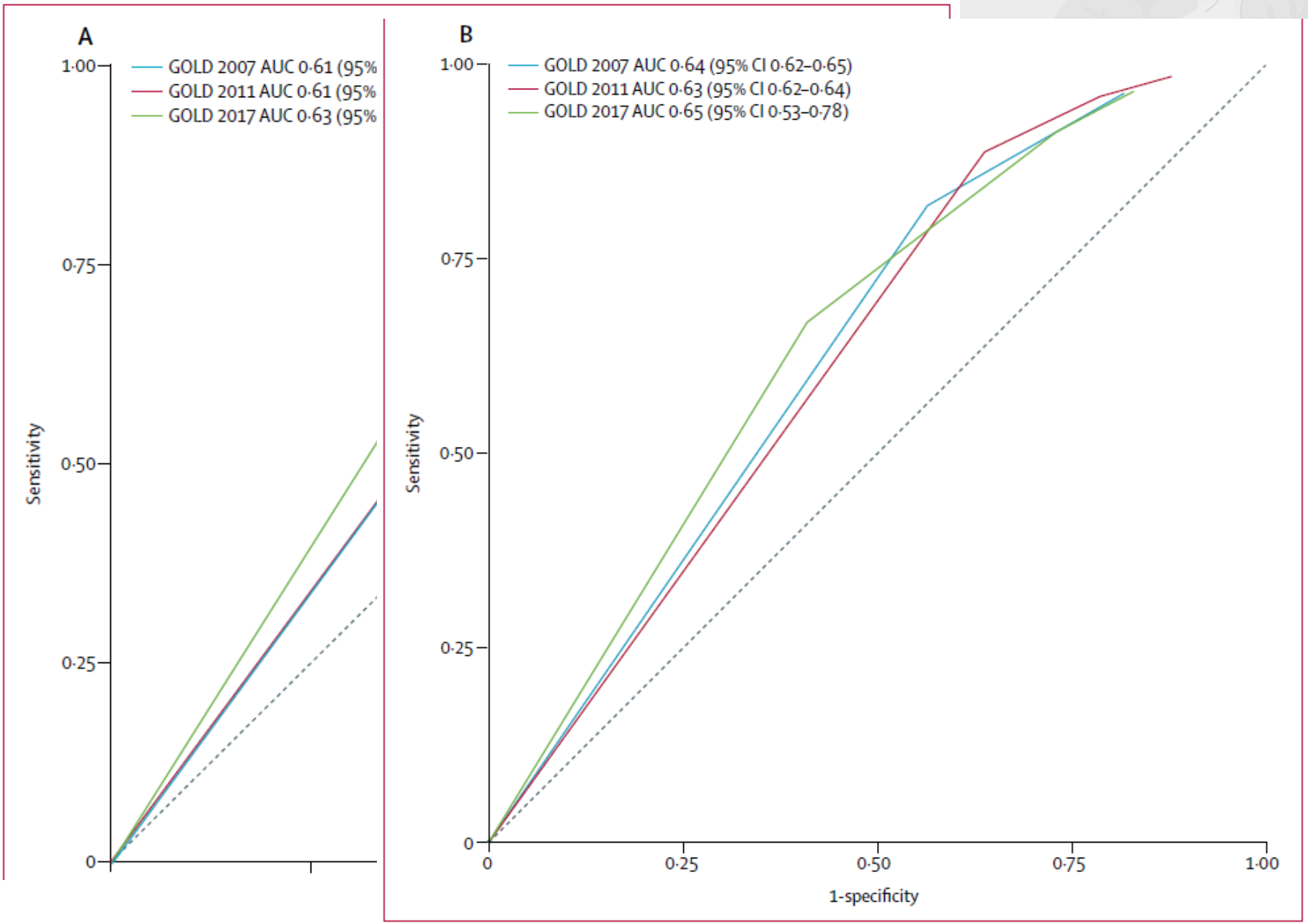
The risk of death were higher in B and D than in A and C.

The mortality risk was better predicted by the 2015 than the 2017 system.

Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study



Lancet Resp Med. 2018;6:204-12



ROC for all-cause (A) and respiratory (B) mortality at 3 year follow-up

Cumulative mortality risk among 33765 patients according to severity of COPD based on the GOLD 2017 classification

	All-cause cumulative mortality		Respiratory cumulative mortality*	
	1 year	3 year	1 year	3 year
Group A	2·3%	10·0%	0·7%	3·0%
Subgroup 1A	0·8%	5·4%	0·5%	1·9%
Subgroup 2A	2·1%	8·8%	0·6%	2·0%
Subgroup 3A	3·1%	14·0%	1·1%	4·9%
Subgroup 4A	5·0%	17·8%	1·7%	8·7%
Group B	6·6%	23·8%	2·3%	9·7%
Subgroup 1B	5·0%	17·1%	1·9%	5·2%
Subgroup 2B	5·0%	17·2%	0·9%	3·7%
Subgroup 3B	7·4%	24·9%	2·5%	9·3%
Subgroup 4B	7·6%	29·8%	3·6%	16·1%
Group C	5·2%	17·4%	1·7%	6·4%
Subgroup 1C	3·8%	11·4%	1·4%	3·0%
Subgroup 2C	4·3%	14·8%	0·9%	4·7%
Subgroup 3C	6·3%	21·5%	2·2%	8·1%
Subgroup 4C	10·7%	29·5%	7·3%	15·4%
Group D	11·6%	36·9%	5·7%	18·0%
Subgroup 1D	11·6%	35·4%	4·1%	10·1%
Subgroup 2D	10·0%	30·9%	3·8%	10·2%
Subgroup 3D	11·4%	35·0%	5·4%	15·9%
Subgroup 4D	12·8%	42·5%	7·1%	23·6%

The GOLD 2017 classification based on ABCD groups only did not predict mortality better than the earlier 2007 and 2011 GOLD classifications.

However, when 16 subgroups (1A to 4D) were defined, the new classification predicted mortality more accurately than the previous systems ($p<0·0001$).

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흡입기관지확장제 및 흡입스테로이드

Bronchodilators

Short- acting

ß-agonists (SABA)

- salbutamol

LAMA

- Tiotropium
- Glycopyrronium
- Acclidinium
- Umeclidinium

Long- acting

LABA

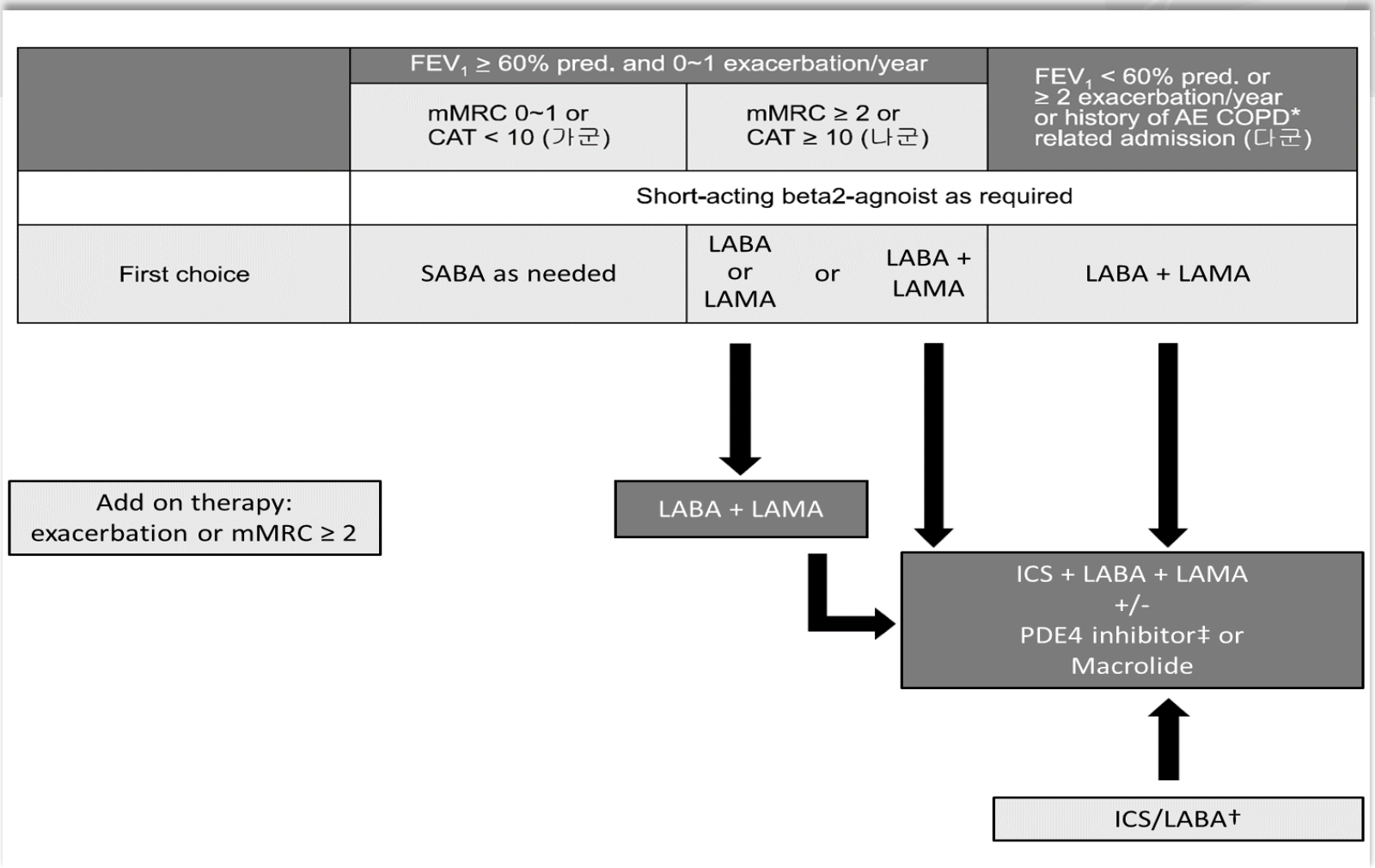
- Indacaterol

LABA+LAMA

Fixed combination

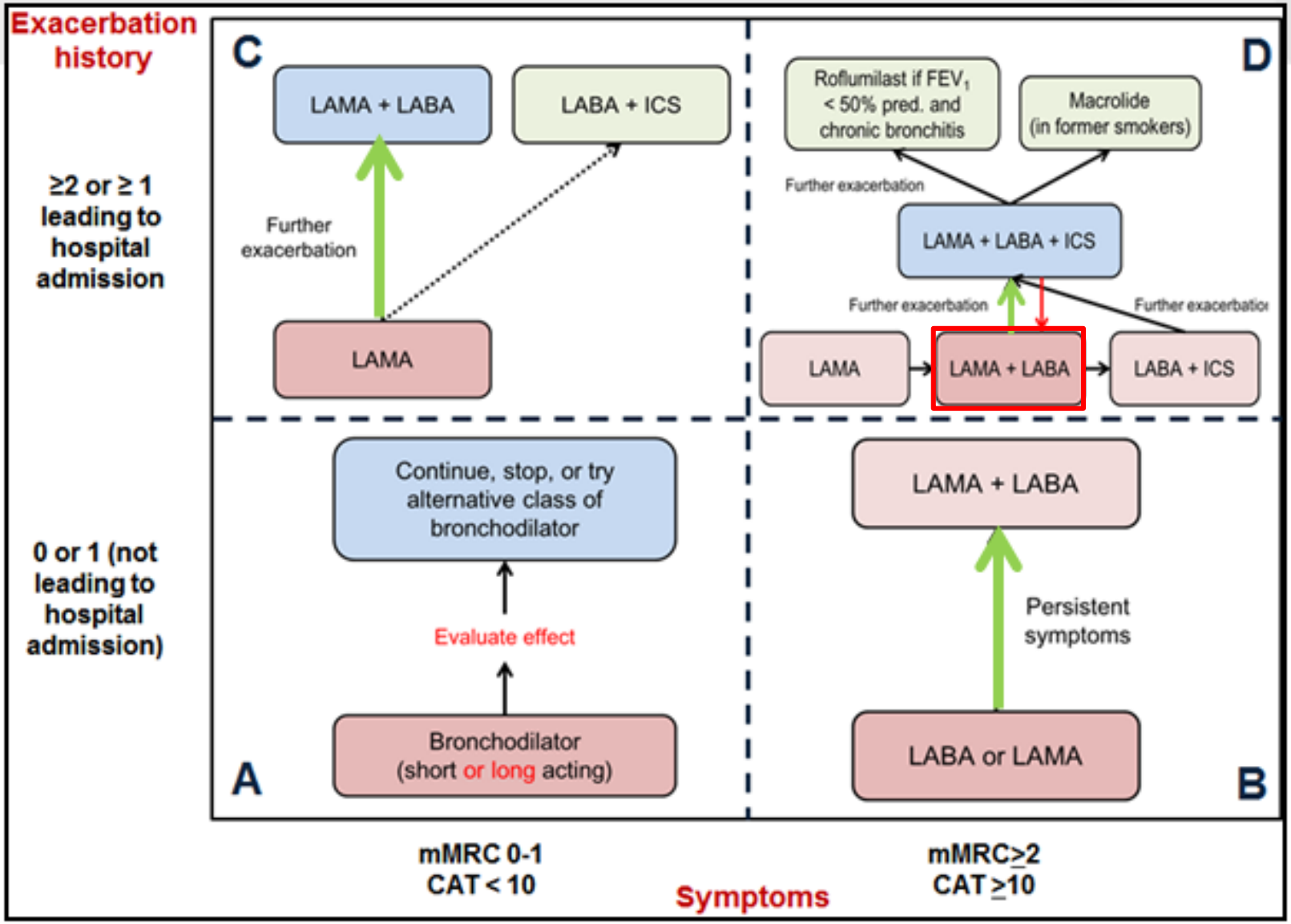
- budesonide+ formoterol
- fluticasone + salmeterol
- fluticasone + vilanterol
- beclomethasone + formoterol

안정 시 COPD의 약물 단계치료 (2018)

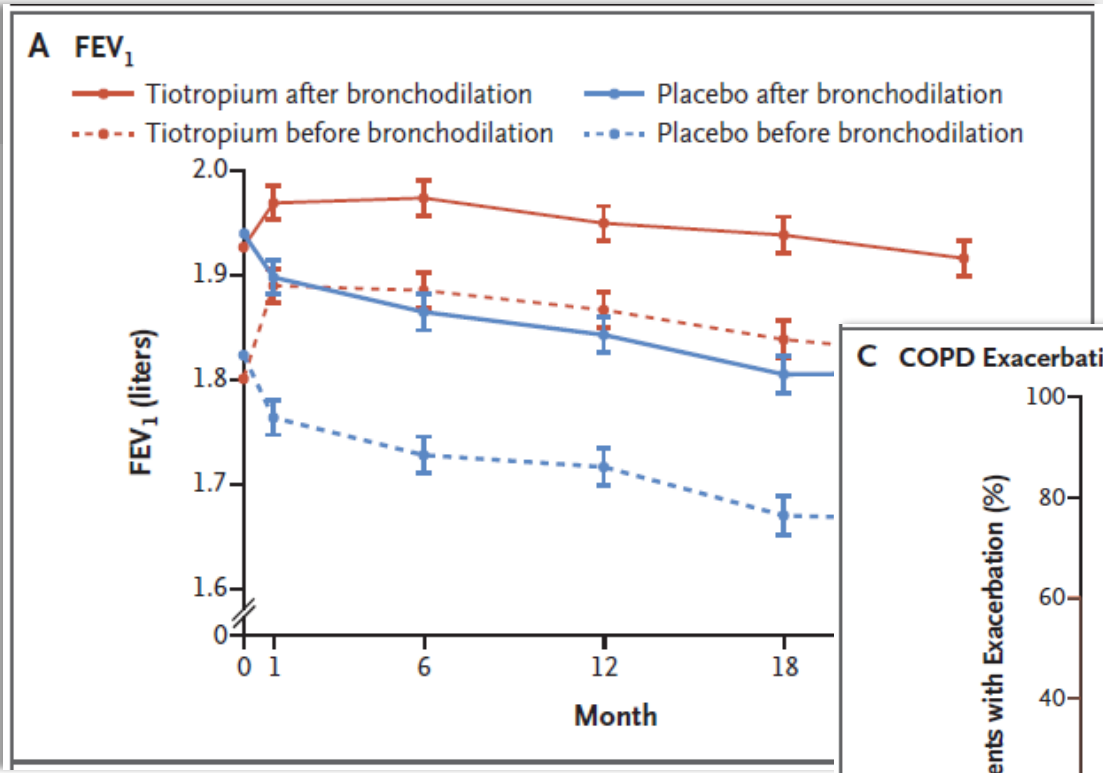


*AE COPD: Acute exacerbation of COPD.
†Asthma overlap or high blood eosinophil
‡급성악화 병력이 있고 만성기관지염을 수반한 COPD: 1) FEV1 < 50% 정상예측치 또는 흡입지속성베타-2작용제나 흡입지속성항콜린제 등의 지속 투여에도 연 2회 이상 급성악화가 발생한 경우

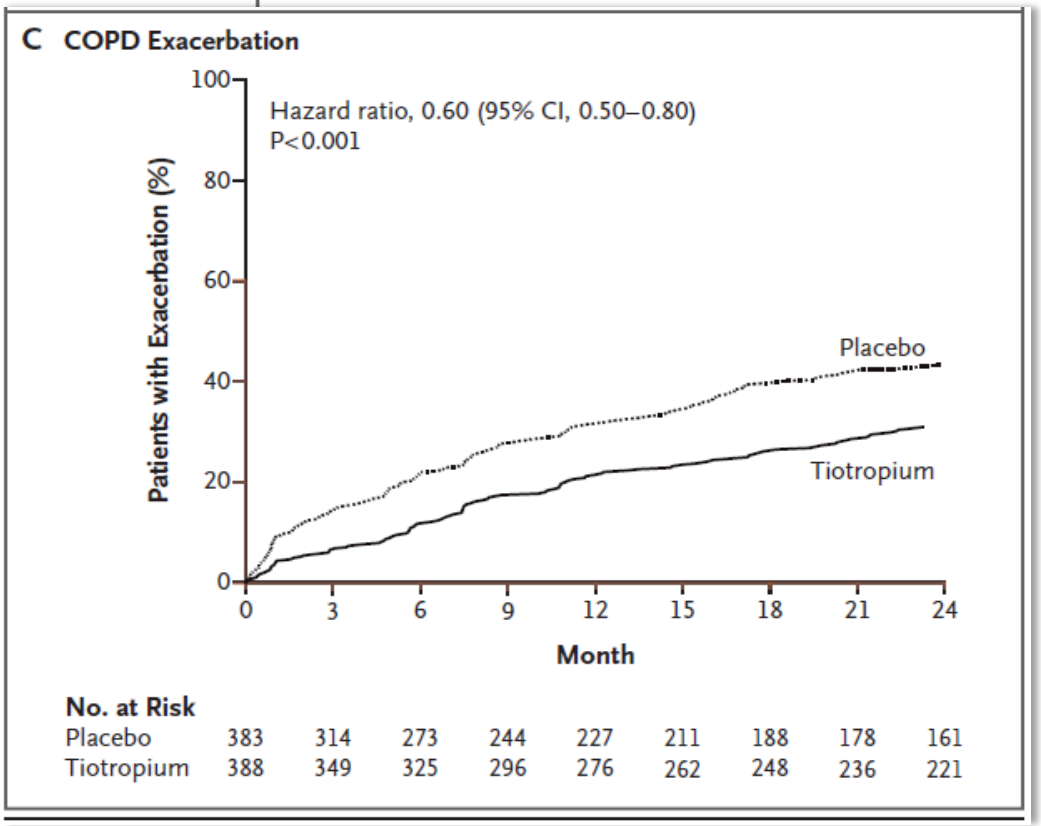
Pharmacologic treatment algorithms by GOLD grade 2018



Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease



GOLD stage 1(44%) or 2(56%)
CAT < 10 ; 73% of patients



Ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 to 133 ml after bronchodilator use; P<0.001 for all comparisons

N Engl J Med Volume 377(10):923-935. September 7, 2017

Annual Declines in the FEV_1, Percent of Predicted FEV_1, before and after Bronchodilator Use.

Variable	Decline per Year			P Value	
	Placebo Group (N=383)	Tiotropium Group (N=388)	Difference (95% CI)†	Unadjusted	Adjusted‡
Total					
FEV_1 (ml)					
Before bronchodilator use	53±6	38±6	15 (−1 to 31)	0.06	0.06
After bronchodilator use	51±6	29±5	22 (6 to 37)	0.006	0.006
FEV_1 (% of predicted value)					
Before bronchodilator use	2.1±0.2	1.6±0.2	0.5 (−0.1 to 1.2)	0.10	0.10
After bronchodilator use	2.1±0.2	1.2±0.2	0.9 (0.2 to 1.5)	0.008	0.007
CAT score <10					
FEV_1 (ml)					
Before bronchodilator use	54±7	37±7	17 (−1 to 35)	0.07	0.07
After bronchodilator use	47±6	28±6	20 (2 to 37)	0.03	0.03
CAT score ≥10					
FEV_1 (ml)					
Before bronchodilator use	48±13	39±11	9 (−24 to 41)	0.60	0.60
After bronchodilator use	63±13	32±11	31 (−2 to 64)	0.07	0.06

International Journal of COPD

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ORIGINAL RESEARCH

Combination therapy of inhaled steroids and long-acting beta2-agonists in asthma–COPD overlap syndrome

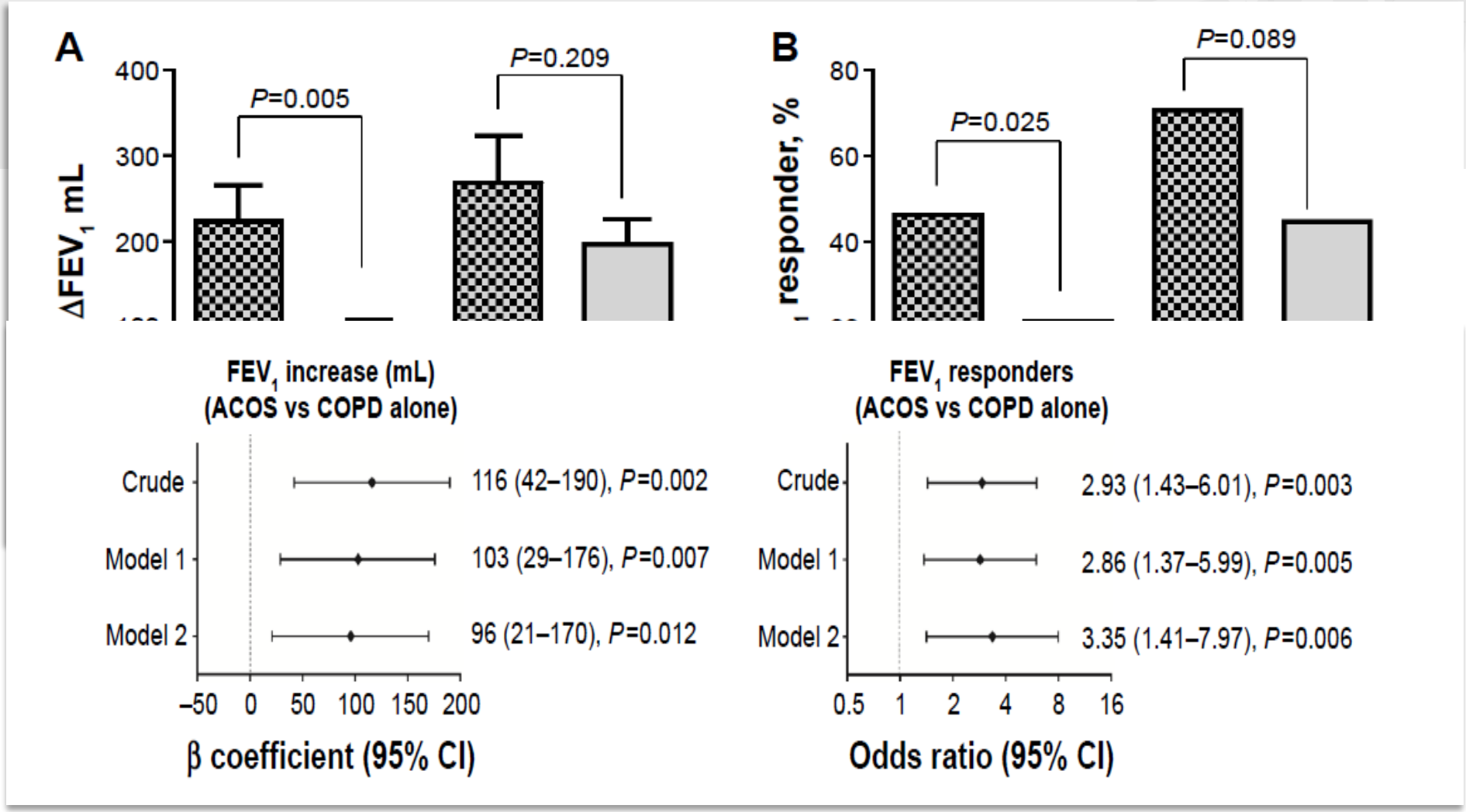
Suh-Young Lee,[1,*] Hye Yun Park,[2,*] Eun Kyung Kim,[3] Seong Yong Lim,[4] Chin Kook Rhee,[5] Yong Il Hwang,[6] Yeon-Mok Oh,[7] Sang Do Lee,[7] Yong Bum Park[1]

On behalf of the KOLD Study Group

Definition of ACOS (KOLD cohort)

1) a personal history of asthma, irrespective of age, and wheezing in the last 12 months in a self-reported survey and 2) a positive bronchodilator response

International Journal of COPD 2016:11 2797–2803



After adjustment for age, BMI, smoking history, initial mMRC dyspnea score, initial FEV1, emphysema index, and high eosinophil count

Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials

Mona Bafadhel, Stefan Peterson, Miguel A De Blas, Peter M Calverley, Stephen I Rennard, Kai Richter, Malin Fagerås

We modelled eosinophil count as a continuous variable to determine the characteristics that determine both exacerbation risk and clinical response to ICS in patients with COPD.

Lancet Respir Med 2018;6: 117–26

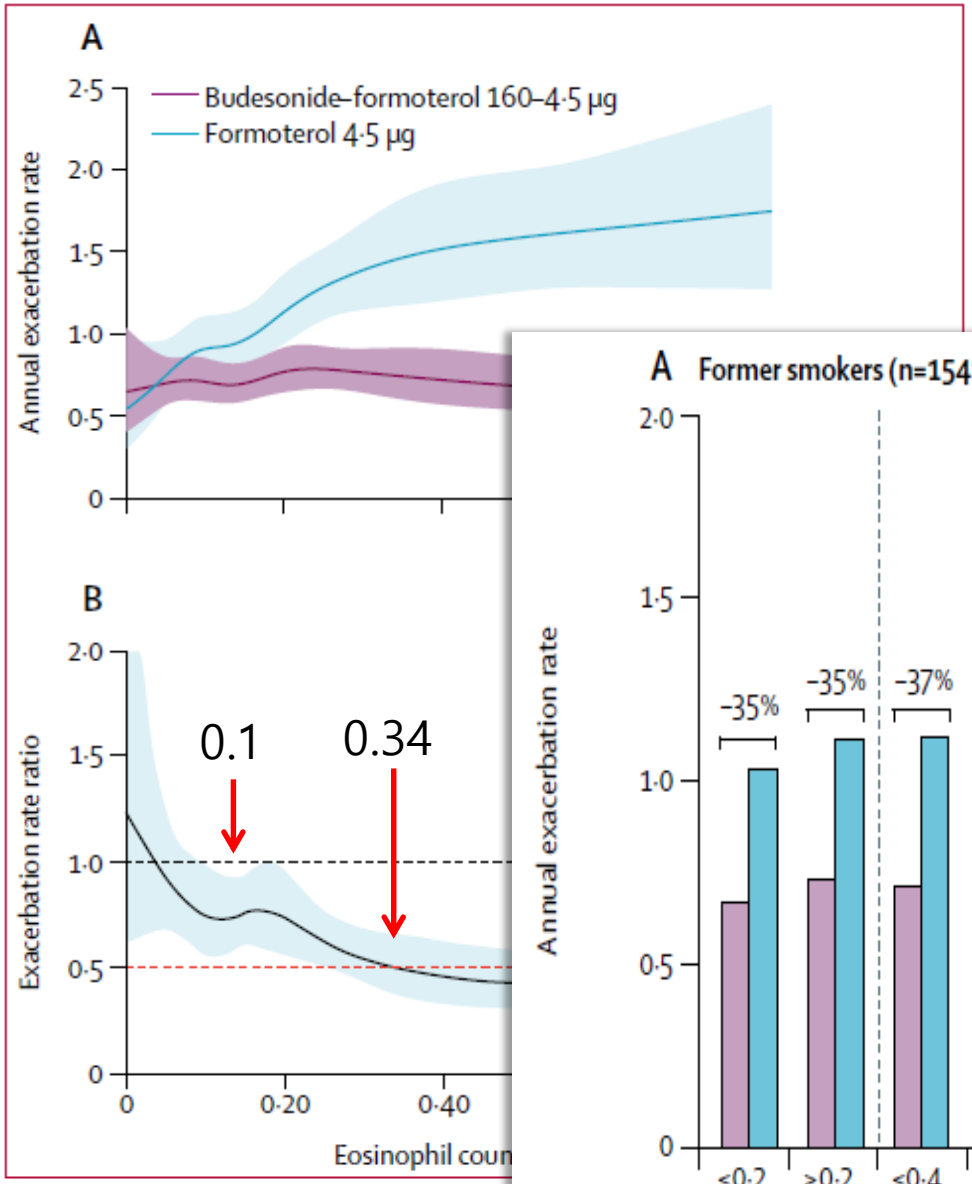
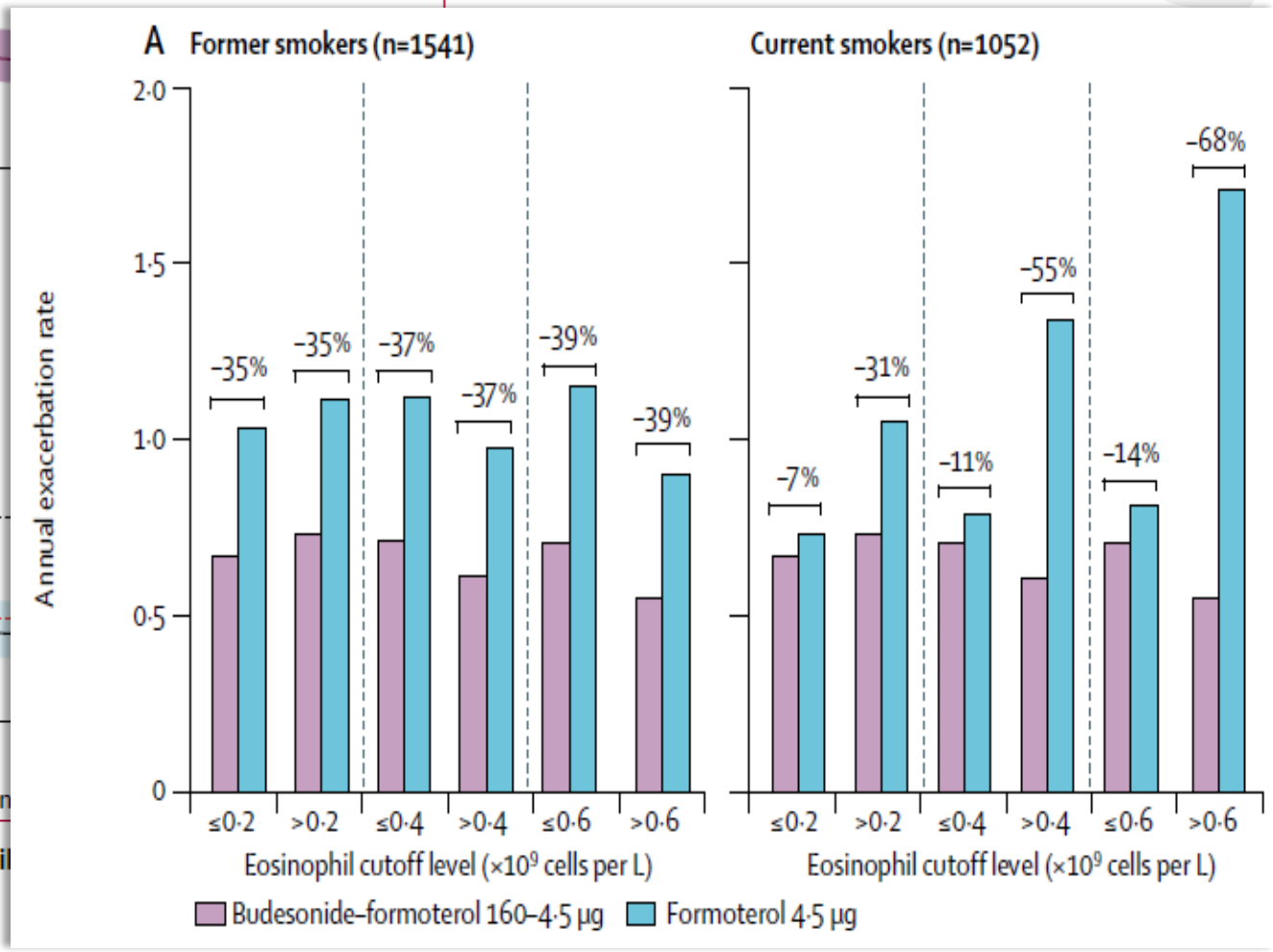


Figure 1: Exacerbation rate by eosinophil



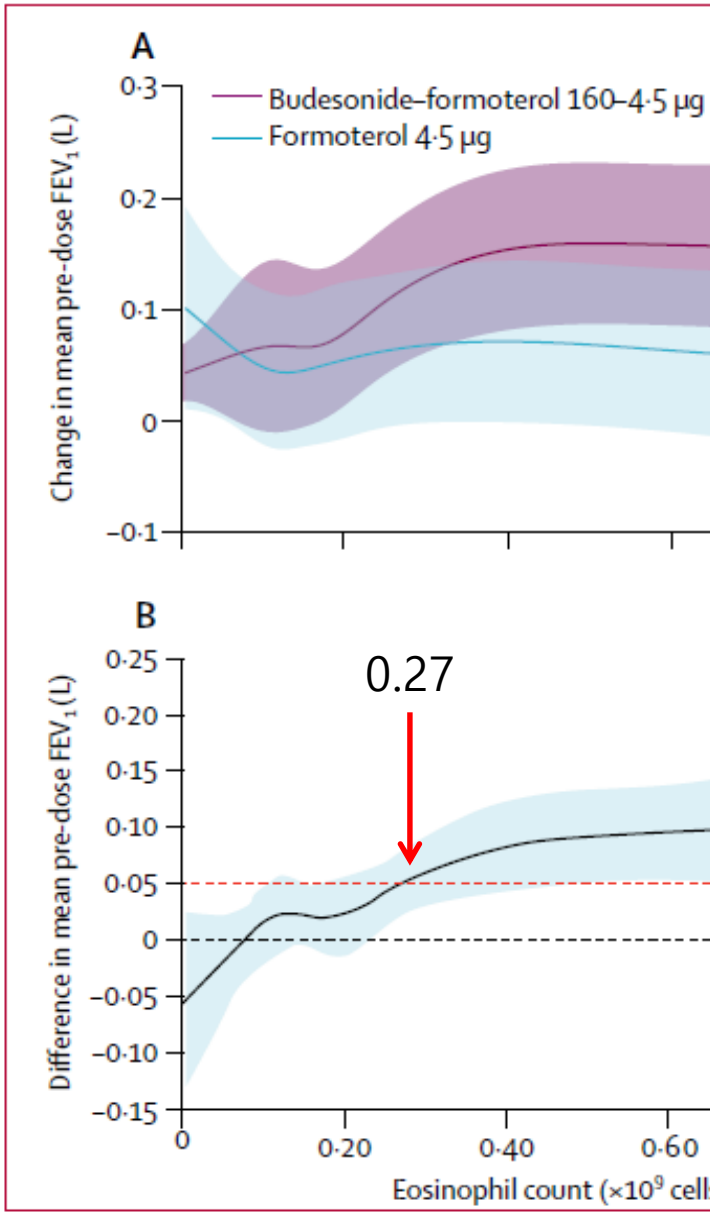


Figure 3: Mean pre-bronchodilator FEV_1 by eosinophil

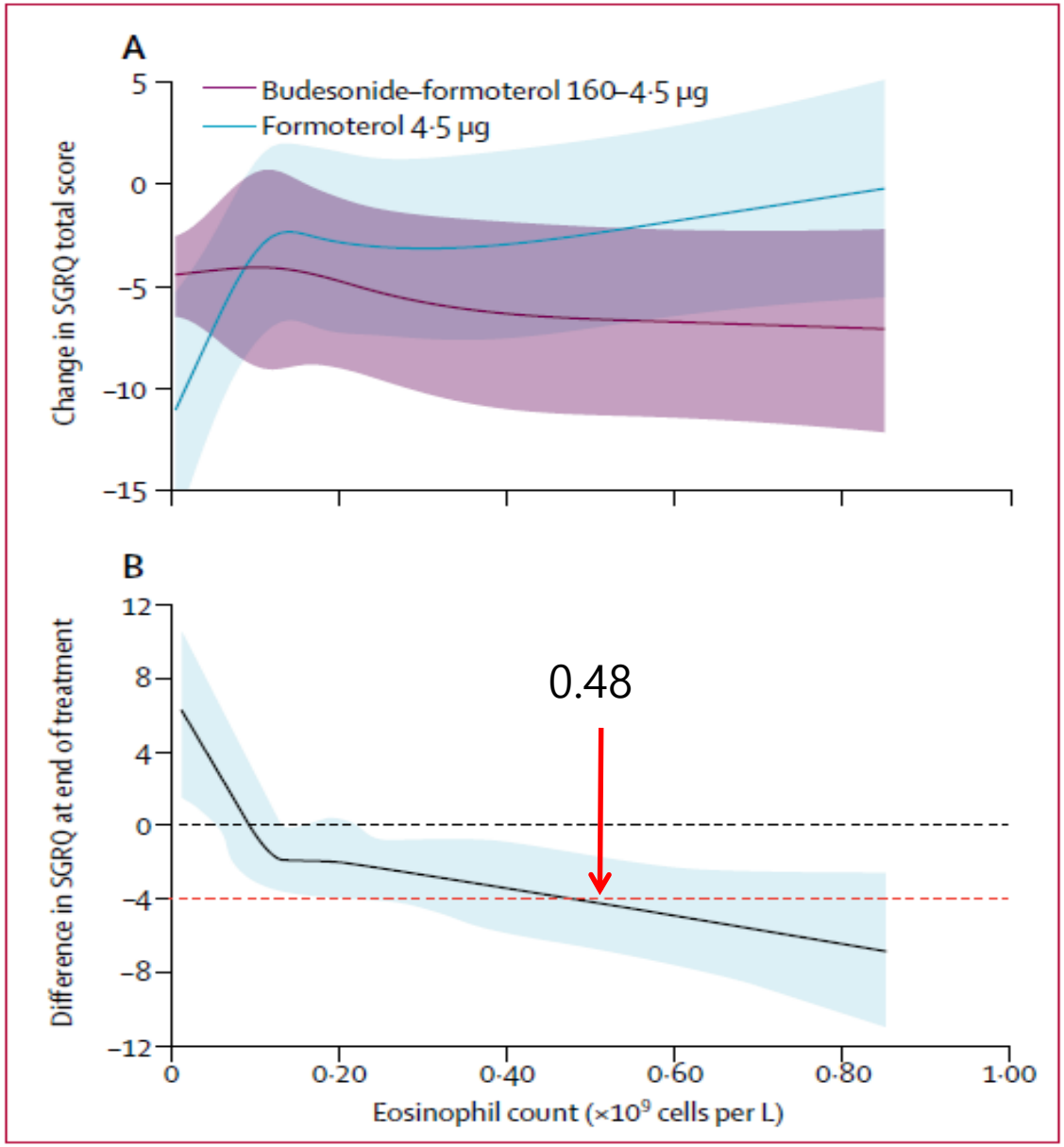


Figure 4: Mean SGRQ total score by eosinophil count*

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

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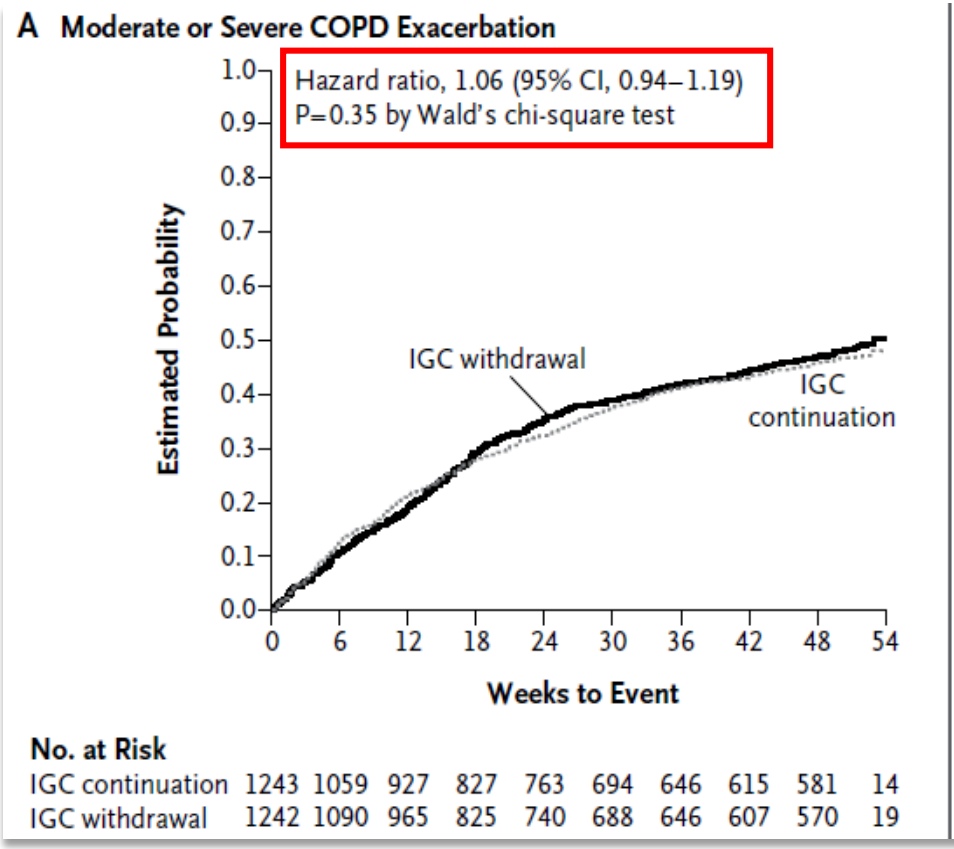
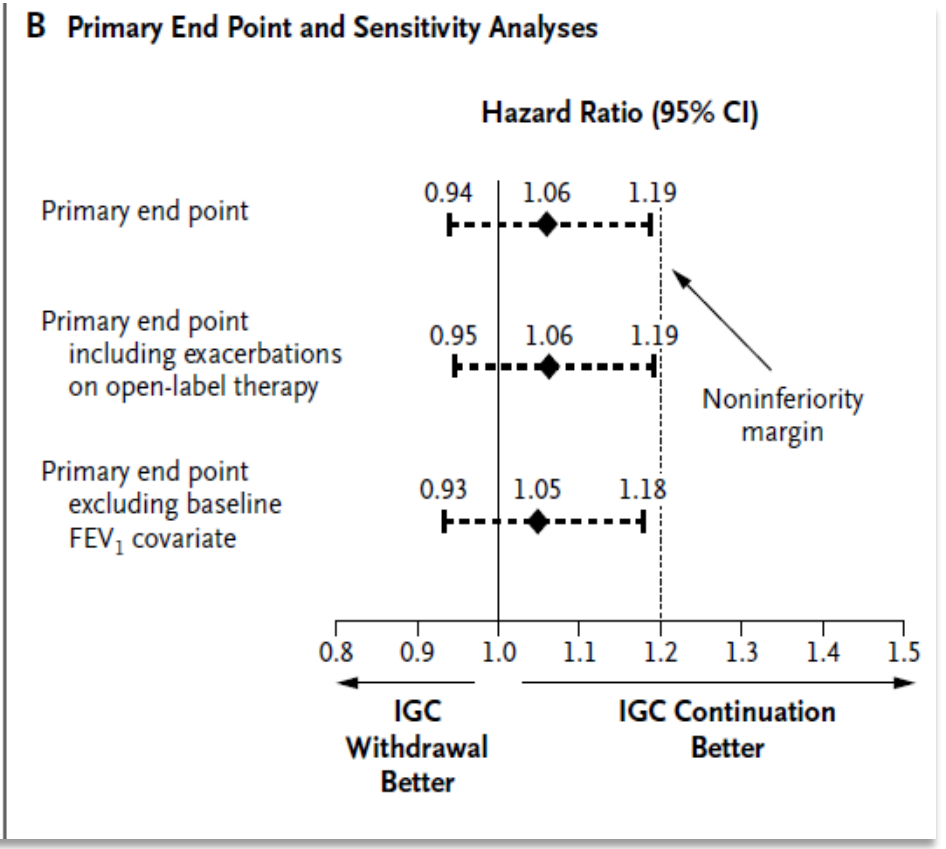
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Glucocorticoid Continuation (N=1243)	Glucocorticoid Withdrawal (N=1242)	All Patients (N=2485)
Male sex — no. (%)	1013 (81.5)	1036 (83.4)	2049 (82.5)
Age — yr	63.6±8.6	64.0±8.4	63.8±8.5
Percentage of predicted FEV_1 after bronchodilation — no. (%)			
30–49%: GOLD 3	760 (61.1)	761 (61.3)	1521 (61.2)
<30%: GOLD 4	473 (38.1)	474 (38.2)	947 (38.1)
Other category‡	10 (0.8)	7 (0.6)	17 (0.7)
Baseline lung function§			
Patients with available data — no.	1223	1218	2441
FEV_1			
Value — liters	0.97±0.36	0.98±0.36	0.98±0.36
Percentage of predicted value	34.2±11.2	34.3±10.8	34.2±11.0
Score on mMRC scale¶			
Patients with available data — no.	1238	1237	2475
Mean score	1.8±0.9	1.9±0.9	1.8±0.9
Medication use — no. (%)			
LAMA	588 (47.3)	578 (46.5)	1166 (46.9)
LABA	807 (64.9)	798 (64.3)	1605 (64.6)
Inhaled glucocorticoid	876 (70.5)	862 (69.4)	1738 (69.9)
Triple therapy with LAMA, LABA, and inhaled glucocorticoid, with or without other pulmonary medication — no. (%)**	479 (38.5)	491 (39.5)	970 (39.0)

N Engl J Med 2014;371:1285-94.

The primary end point :
Time to the first moderate or severe COPD exacerbation





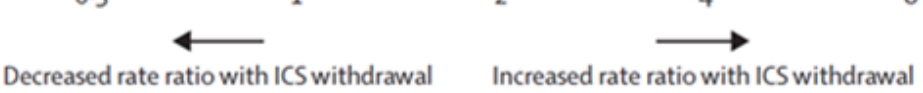
N Engl J Med 2014;371:1285-94.

Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial

Total	2296	1·10 (0·96–1·26)	0·17
Baseline eosinophils (<2% *vs* ≥2%)			
<2%	1039	1·02 (0·83–1·25)	0·84
≥2%	1200	1·22 (1·02–1·48)	0·033
Baseline eosinophils (<3% *vs* ≥3%)			
<3%	1520	1·07 (0·90–1·26)	0·46

B

	n	Rate ratio (95% CI)	p value
Total	2296	1·10 (0·96–1·26)	0·17
Baseline eosinophils (<150 cells per μL *vs* ≥150 cells per μL)			
<150 cells per μL	1067	1·08 (0·88–1·32)	0·44
≥150 cells per μL	1172	1·17 (0·97–1·41)	0·094
Baseline eosinophils (<300 cells per μL *vs* ≥300 cells per μL)			
<300 cells per μL	1791	1·04 (0·89–1·21)	0·59
≥300 cells per μL	448	1·56 (1·14–2·13)	0·0055
Baseline eosinophils (<400 cells per μL *vs* ≥400 cells per μL)			
<400 cells per μL	1992	1·07 (0·92–1·23)	0·39
≥400 cells per μL	247	1·73 (1·15–2·62)	0·0090

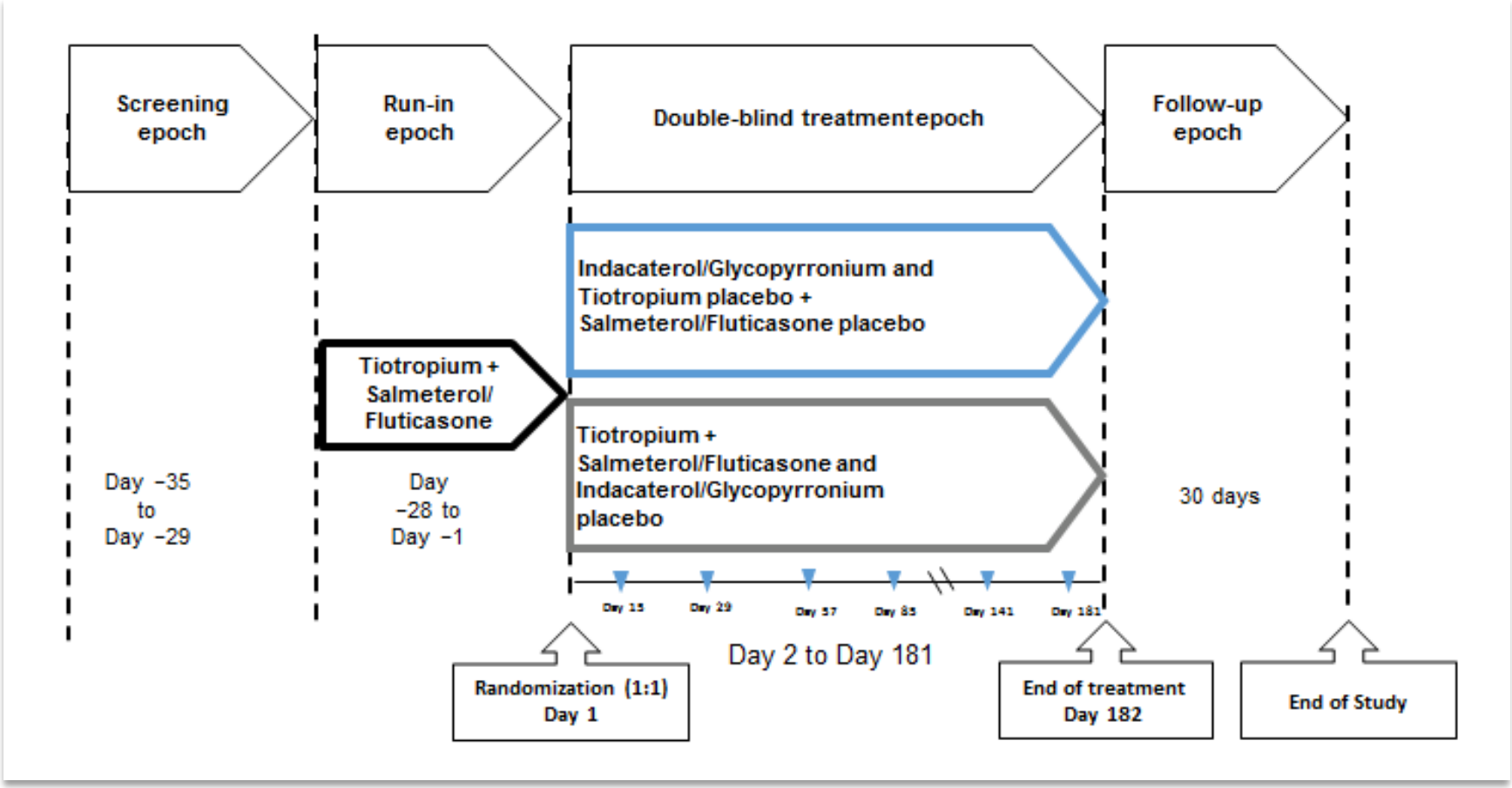


Lancet Respir Med 2016

Long-term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in COPD Patients (SUNSET): a Randomized, Double-Blind, Triple-Dummy Clinical Trial

1053 patients were randomized. 527 patients were assigned to IND/GLY group and 526 patients to TIO+SFC group

26-week, multicenter, randomized, double-blind, triple-dummy, parallel-group, active-controlled Phase IV study (Non-inferiority study)



Chapman KR, et al. Am J Respir Crit Care Med. 2018. Epub ahead of print

Key inclusion and exclusion criteria

Key inclusion criteria

- Aged ≥40 years with stable COPD
- Post-bronchodilator FEV_1 of ≥40% to <80% predicted
- Post-bronchodilator FEV_1/FVC <0.70
- Smoking history of ≥10 pack-years
- Patients with history of ≤1 moderate or severe exacerbation in the previous year
- Patients on long-term triple therapy (LAMA+LABA/ICS) for ≥6 months before enrollment into the study

Key exclusion criteria

- Patients with COPD exacerbation of any severity either 6 weeks before screening or between screening and randomization
- Patients with >1 COPD exacerbation that required treatment with antibiotics and/or OCS and/or hospitalization in the previous year to screening
- Resting QTc (Fridericia method) ≥450 ms for men and women at run-in period
- Blood eosinophil count >600/mm^3 during screening
- Patients with any history of asthma

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Primary objective and key secondary objectives

Primary objective

- To demonstrate the **non-inferiority** of IND/GLY (110/50 µg q.d.) on **change from baseline in** post-dose **trough FEV_1** versus TIO (18 µg q.d.) + SFC (50/500 µg b.i.d.) **after 26 weeks** of treatment in moderate-to-severe COPD patients

Secondary objectives

- To evaluate the **effect** of IND/GLY (110/50 µg q.d.) compared with TIO (18 µg q.d.) + SFC (50/500 µg b.i.d.) over 26 weeks of treatment in terms of:
  - Rate of moderate or severe COPD exacerbations
  - Trough FEV_1 and FVC over 26 weeks
  - TDI and SGRQ-C scores after 12 and 26 weeks
  - Mean rescue medication use
- To assess **safety** and **tolerability**
- The effect of baseline blood eosinophil levels (based on percentage, <2% versus ≥2%; and absolute blood eosinophil counts, <150, 150–<300, ≥300 cells/µL) on trough FEV_1 and exacerbation rate were also evaluated as pre-specified analyses

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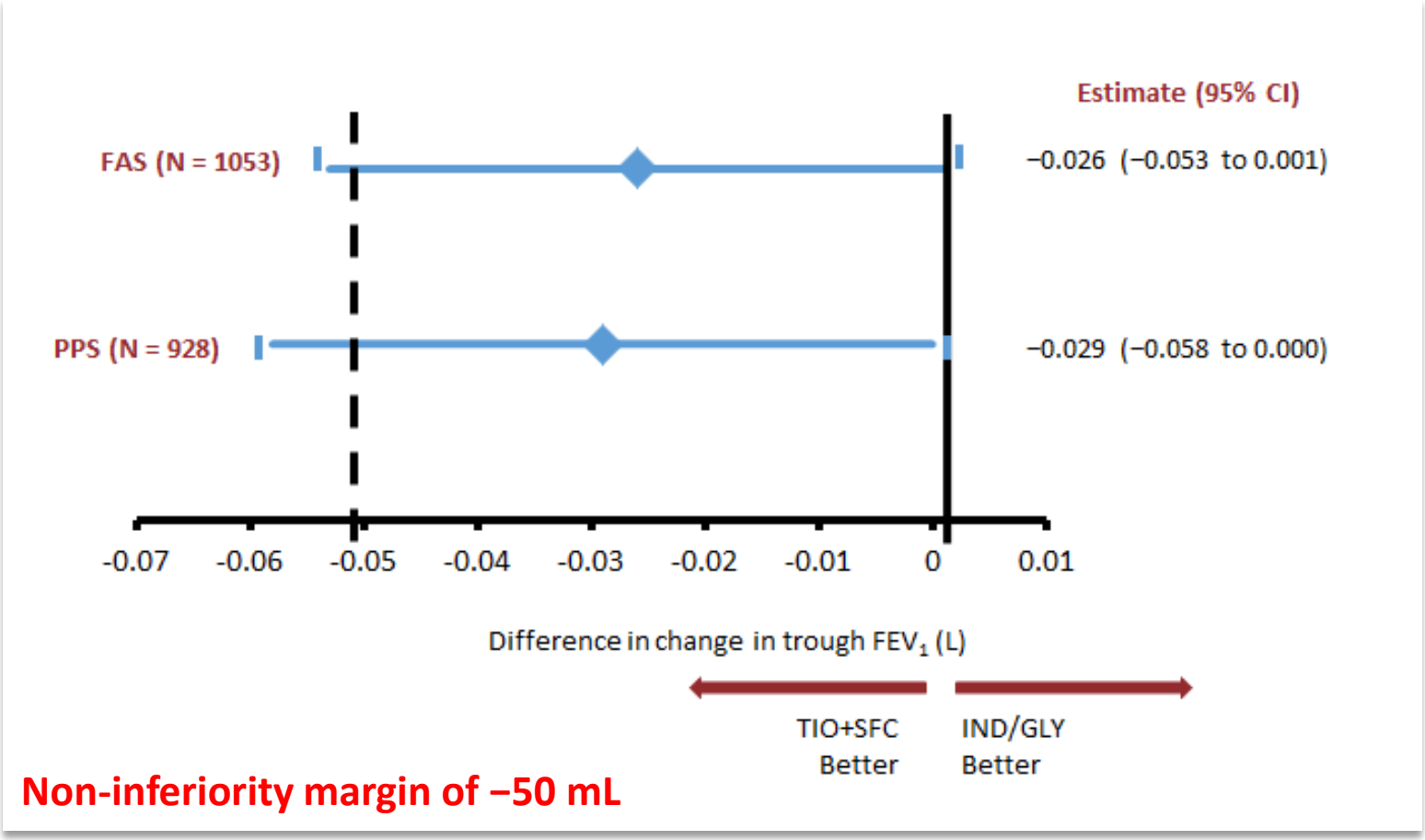
Baseline Characteristics of the Patients

Characteristic	Indacaterol/ glycopyrronium (N = 527)	Tiotropium plus salmeterol/fluticasone (N = 526)	All patients (N= 1053)
Age (years), Mean ± SD	65.4 ± 7.99	65.2 ± 7.62	65.3 ± 7.80
BMI (kg/m^2), Mean ± SD	27.8 ± 5.35	28.2 ± 5.38	27.98 ± 5.37
Sex: Male, n (%)	378 (71.7)	365 (69.4)	743 (70.6)
Airflow limitation (GOLD), n (%)[†]			
Moderate	363 (68.9)	372 (70.7)	735 (69.8)
Severe	161 (30.6)	154 (29.3)	315 (29.9)
Post-bronchodilator FEV_1 (L), Mean ± SD	1.6 ± 0.44	1.6 ± 0.46	1.6 ± 0.45
Post-bronchodilator FEV_1 (% predicted), Mean ± SD	56.2 ± 9.66	57.0 ± 10.30	56.6 ± 9.97
mMRC dyspnea scale, n (%)			
0-1	134 (25.4)	170 (32.3)	304 (28.9)
≥2	393 (74.6)	354 (67.3)	747 (70.9)

Baseline Characteristics of the Patients

Number of COPD exacerbations in the previous year, n (%)			
0 exacerbation	334 (63.4)	360 (68.4)	694 (65.9)
1 exacerbation	193 (36.6)	166 (31.6)	359 (34.1)
Patients with baseline blood eosinophil counts, n (%)[#]			
<300 cells/µL	401 (76.2)	406 (77.3)	807 (76.8)
≥300 cells/µL	125 23.8)	119 (22.7)	244 (23.2)
Patients with consistent and inconsistent blood eosinophil counts at screening and baseline, n(%)[#]			
Consistently <300 cells/µL	359 (68.2)	357 (68.0)	716 (68.1)
Inconsistent: both above and below 300 cells/µL	86 (16.4)	83 (15.8)	169 (16.1)
Consistently ≥300 cells/µL	81 (15.4)	85 (16.2)	166 (15.8)

Primary endpoint: change from baseline in post-dose trough FEV_1 (non-inferiority analysis)



Non-inferiority margin of −50 mL

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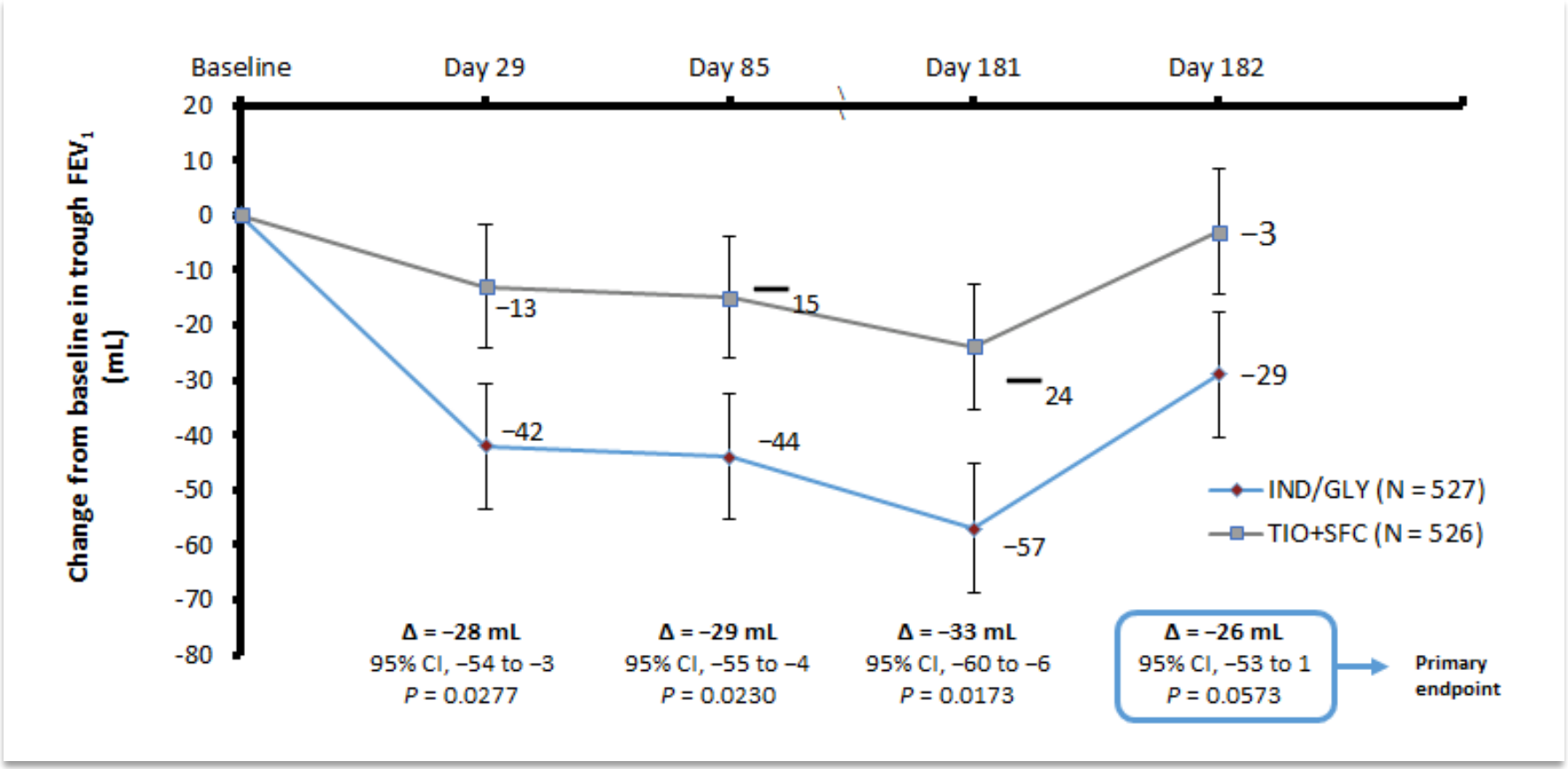
Change from baseline in trough FEV_1 (mL) over 26 weeks of treatment (FAS)



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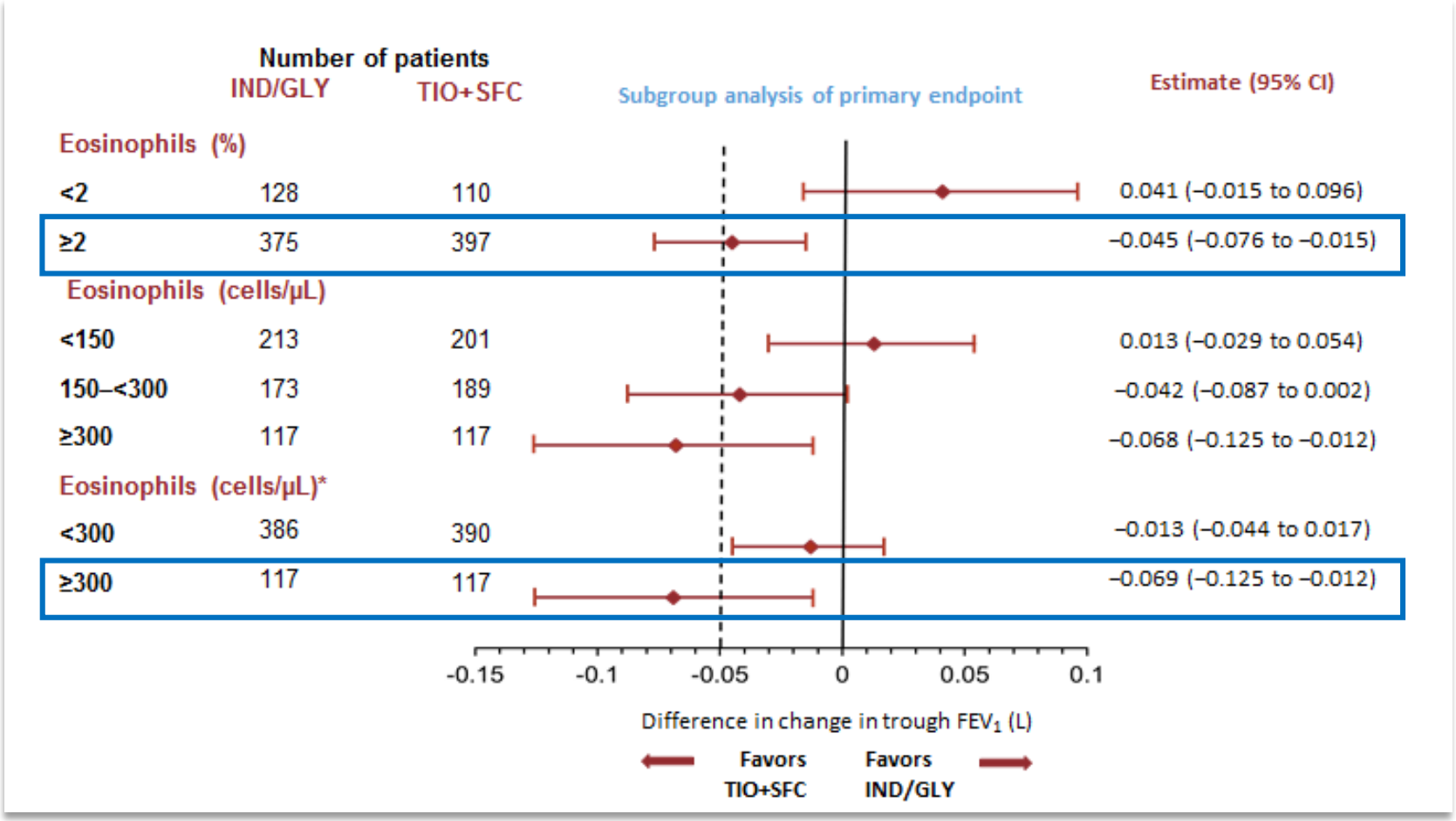
Difference in change from baseline in trough FEV_1 (L) by baseline blood eosinophils (FAS)



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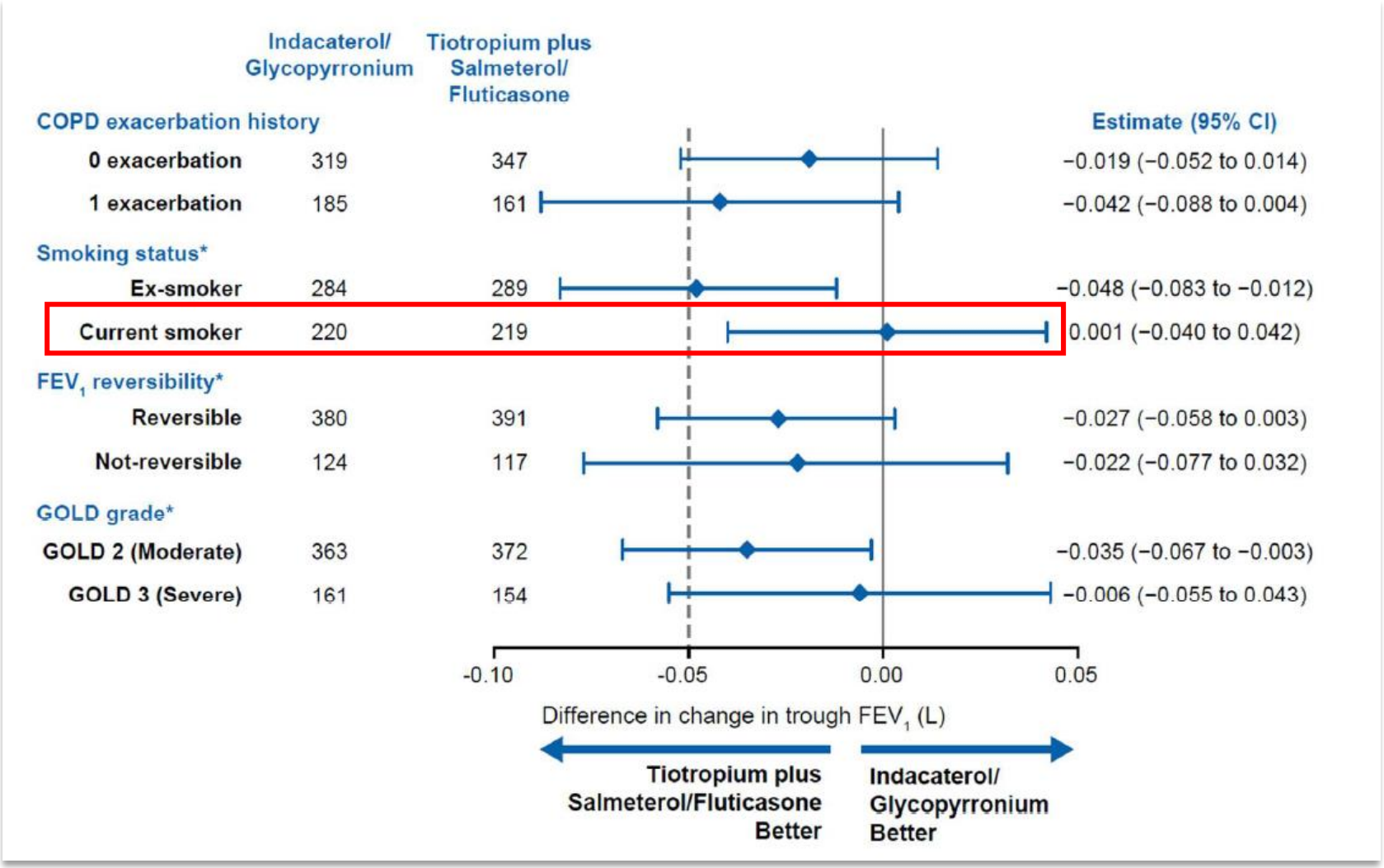
Difference (Indacaterol–glycopyrronium versus Tiotropium plus salmeterol–fluticasone) in mean change from baseline in post-dose trough FEV1 (L) by baseline characteristics



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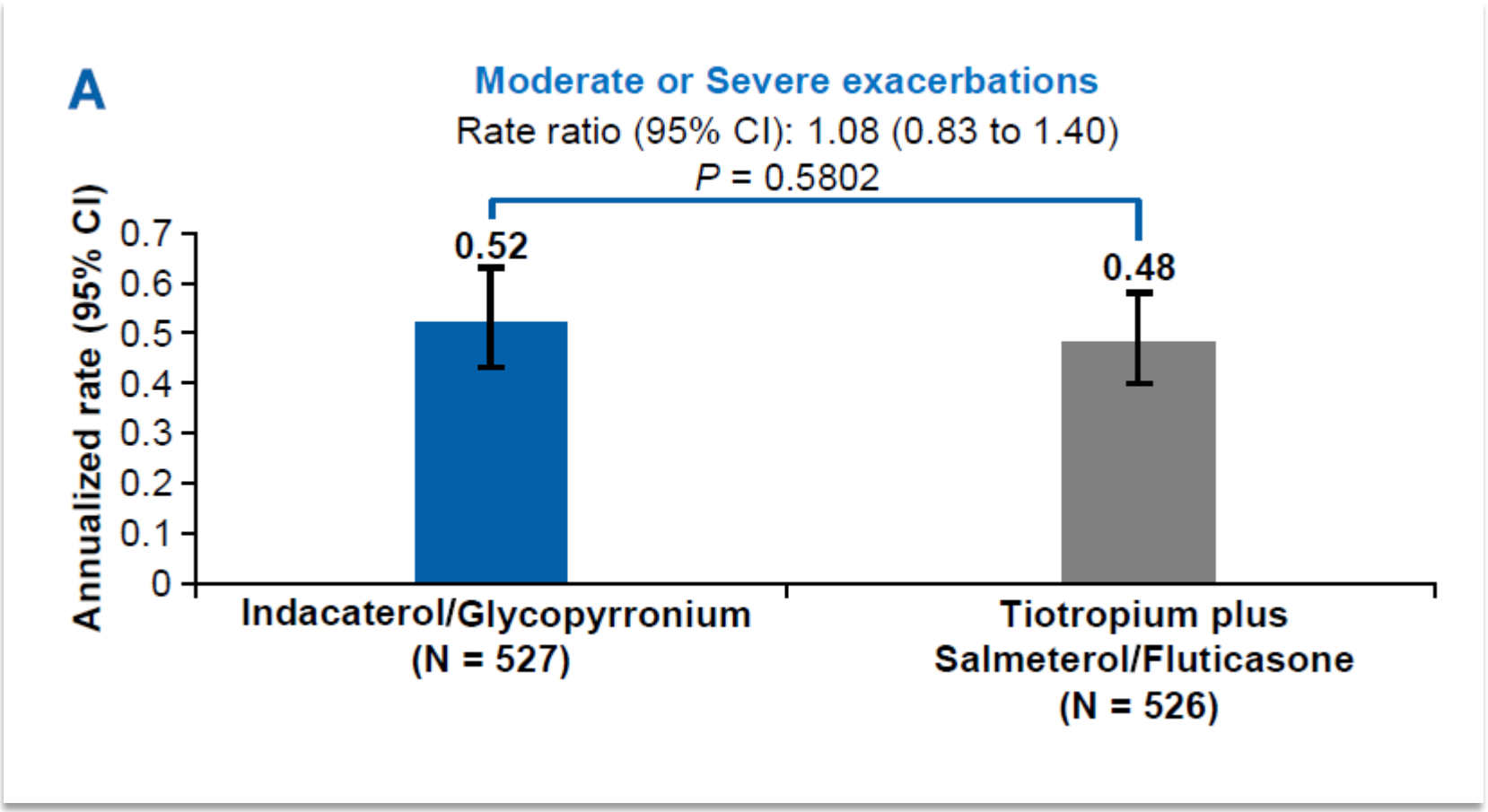
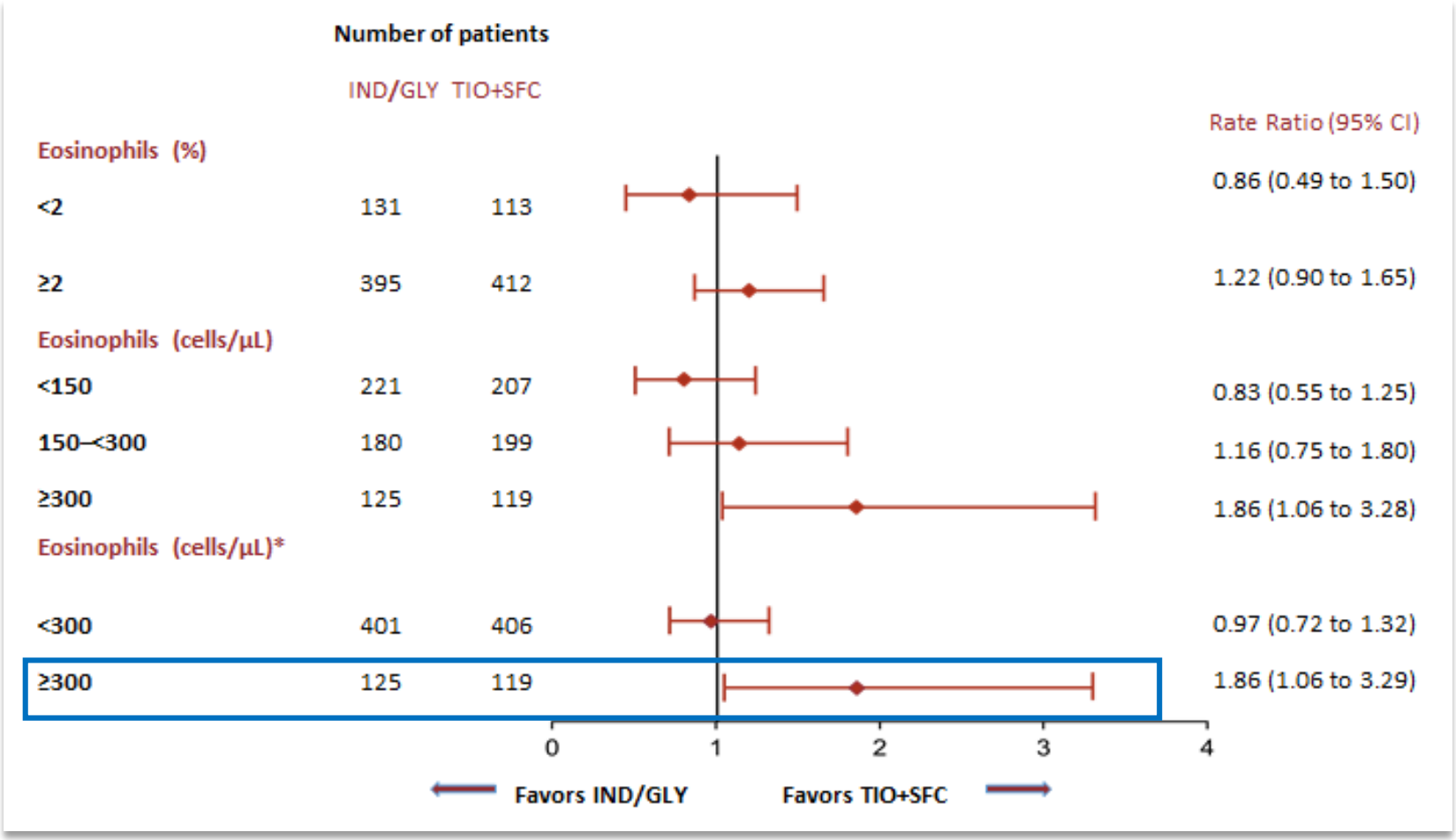
Rate of moderate or severe COPD exacerbations



Rate of moderate or severe COPD exacerbations by baseline blood eosinophils (FAS)



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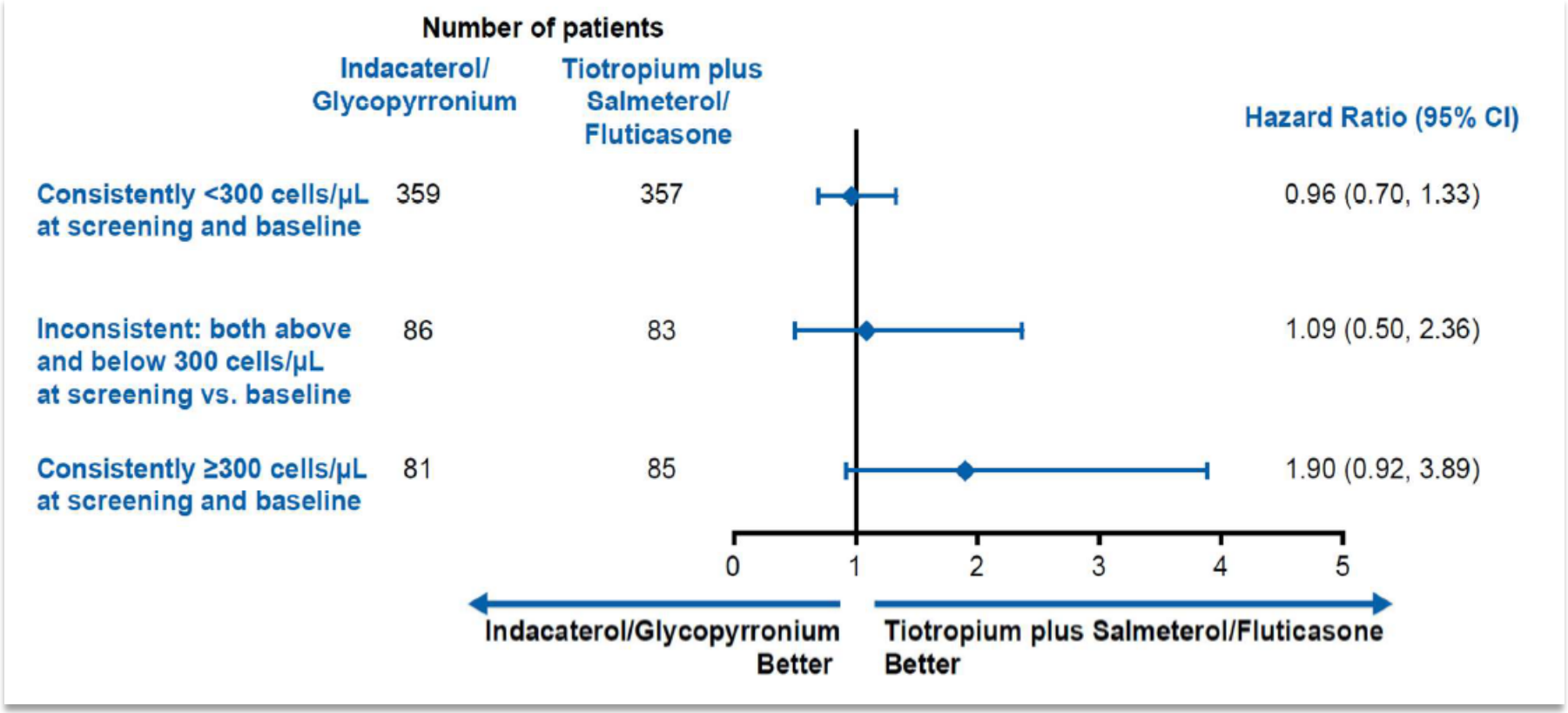
Time to first moderate/severe COPD exacerbation by blood eosinophils category at screening and baseline



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Conclusions

- In **moderate to severe COPD patients without frequent exacerbations** while receiving long-term triple therapy, the direct change to the dual bronchodilator IND/GLY led to a small decrease in lung function, with no difference in COPD exacerbations.
- In patients with **≥300 blood eosinophils/µL** there was a greater decline in lung function and increased exacerbation risk, and these patients are more likely to benefit from continuing triple therapy.
- However, for the **majority of patients** the switch did not have any impact on lung function or exacerbations. The results of the SUNSET study provide evidence for the personalized management of COPD patients.

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

1532 symptomatic COPD, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication

Exclusion from the study of patients already on triple therapy

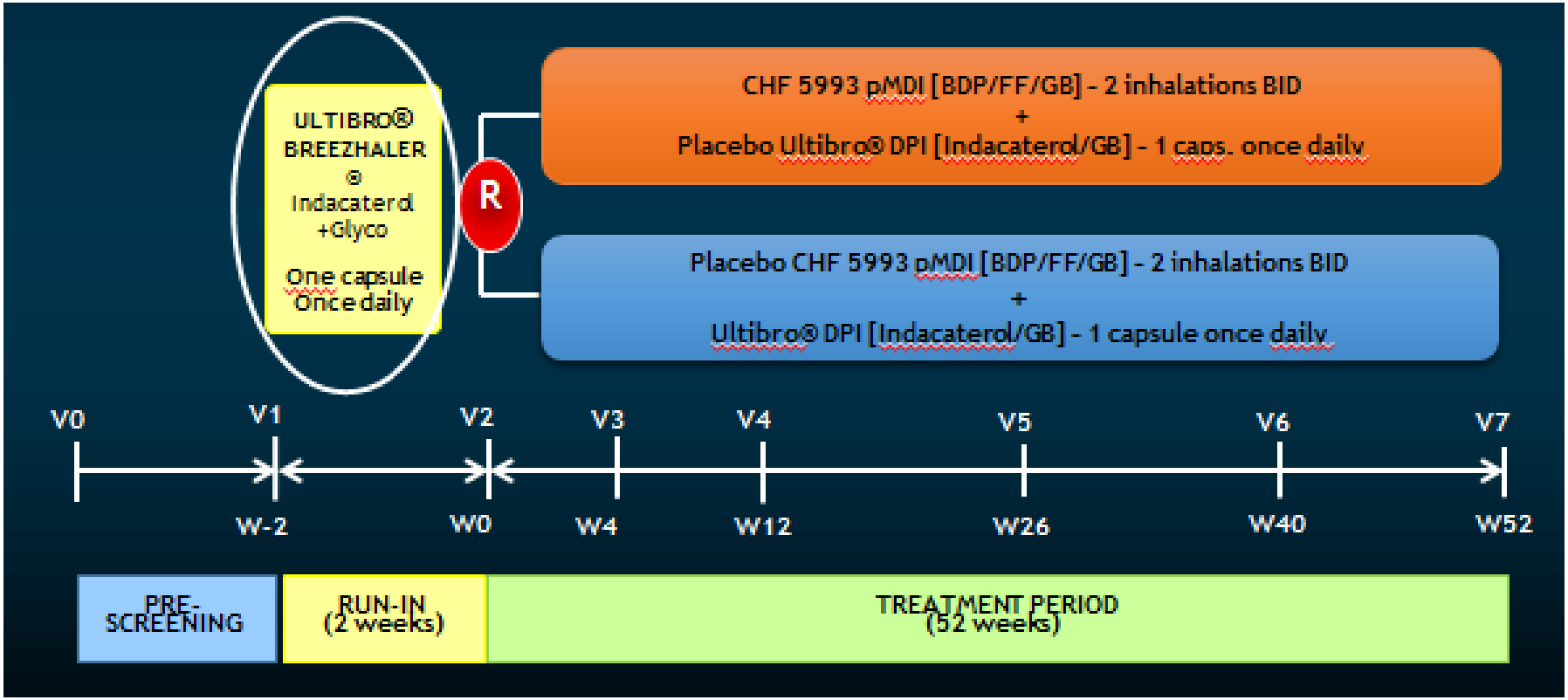
The primary endpoint : the rate of moderate-to-severe COPD exacerbations

Lancet. 2018 Mar 17;391(10125):1076-1084

Triple study 8 (TRIBUTE) - Study Design/ Treatments

Double-blind, Double-dummy, Randomized, Multinational & multicentre

2-arm parallel group, Active-controlled, 52-week treatment



	BDP/FF/G (n=764)	IND/GLY (n=768)
Sex		
Male	548 (72%)	552 (72%)
Female	216 (28%)	216 (28%)
Race*		
White	705 (92%)	708 (92%)
Other	51 (7%)	52 (7%)
Age (years)	64·4 (7·7)	64·5 (7·7)
Body-mass index (kg/m^2)†	25·7 (5·1)	26·6 (5·4)
Blood leukocyte count (10^9 cells per L)	8·05 (2·38)	8·00 (2·04)
Blood eosinophil count (10^9 cells per L)	0·24 (0·20)	0·23 (0·20)
Blood eosinophil	3·14% (2·47)	2·97% (2·30)
Smoking status		
Ex-smoker	413 (54%)	436 (57%)
Current smoker	351 (46%)	332 (43%)
Time since first COPD diagnosis (years)	8·16 (5·76)	7·99 (5·64)
FEV_1 (L)‡	1·07 (0·31)	1·07 (0·31)
Proportion of predicted normal FEV_1 value‡,§	36·4 (8·0)	36·4 (8·1)
<30%	154 (20%)	160 (21%)
≥30% to <50%	609 (80%)	608 (79%)
FVC (L)‡	2·70 (0·78)	2·64 (0·77)
FEV_1:FVC ratio‡	0·41 (0·10)	0·42 (0·10)
Reversibility (%)	8·4% (13·5)	8·8% (13·5)
Clinical COPD phenotype¶		
Chronic bronchitis	434 (57%)	421 (55%)
Emphysema	227 (30%)	235 (31%)
Mixed chronic bronchitis and emphysema	103 (13%)	112 (15%)
Moderate or severe exacerbations in the previous year (range)	1·2 (1–6)	1·2 (1–4)
1	612 (80%)	626 (82%)
≥2	152 (20%)	142 (18%)
COPD medication taken for at least 2 months before study entry		
ICS/LABA	467 (61%)	465 (61%)
ICS/LAMA	36 (5%)	24 (3%)
LABA/LAMA	183 (24%)	199 (26%)
LAMA	77 (10%)	80 (10%)

(Table 1 continues in next column)

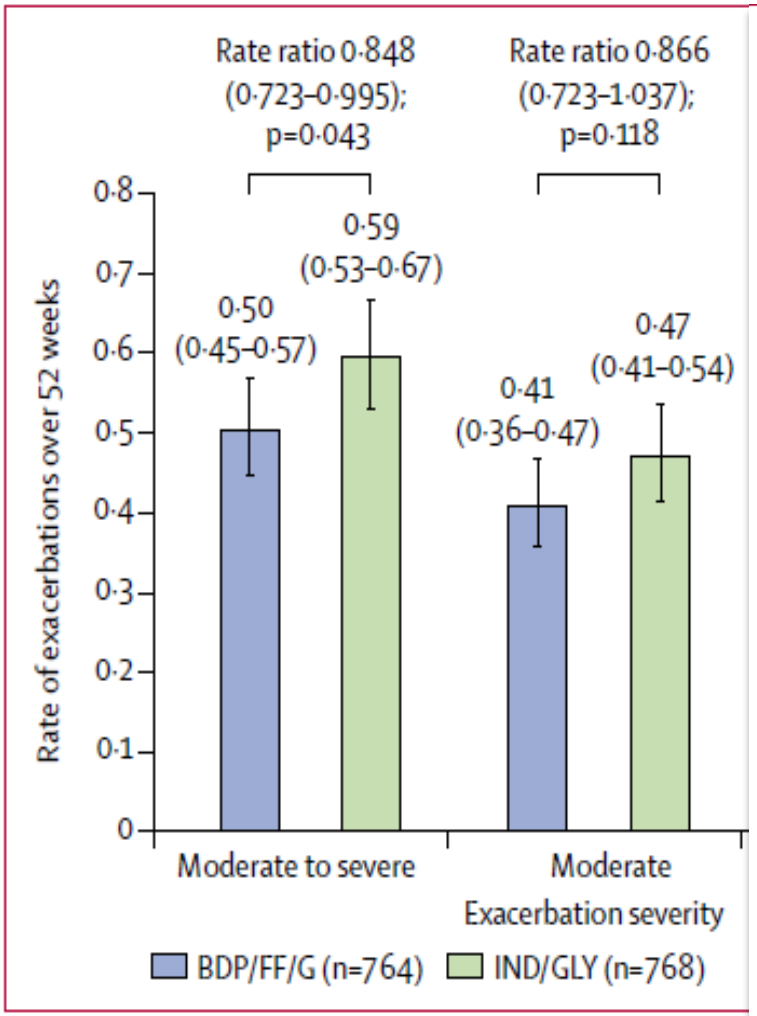
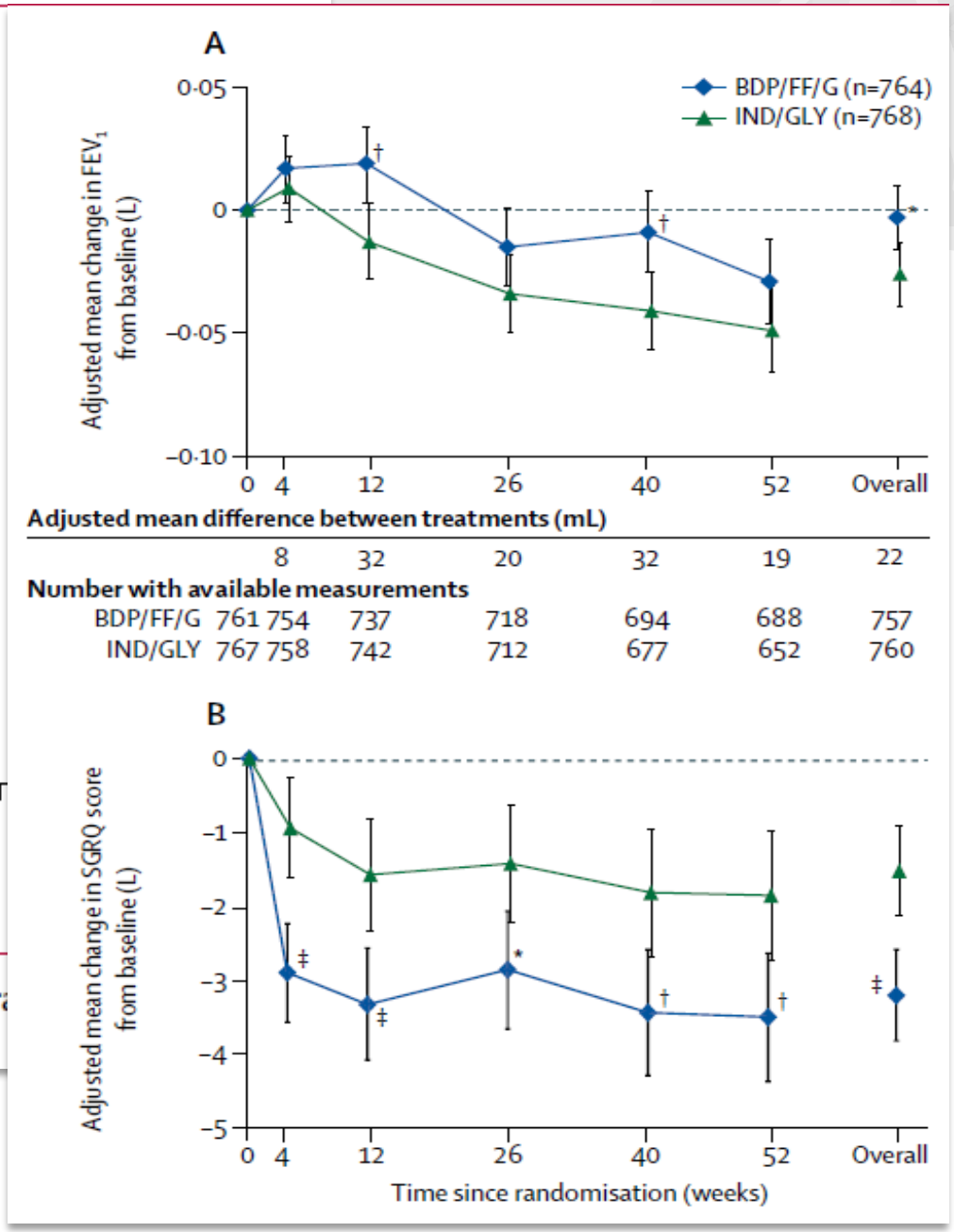


Figure 2: Adjusted rate of moderate-to-severe, moder
exacerbations



Triple study (TRIBUTE) – Conclusion

In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia (4% vs 4%).

↑ in patients with a clinical diagnosis of **chronic bronchitis** and in patients with **eosinophils greater than 2%**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

N Engl J Med. 2018 Apr 18. doi: 10.1056/NEJMoa1713901. [Epub ahead of print]

FEV1 < 50% and a history of at least one moderate or severe exacerbation
FEV1 of 50 to 80% and at least two moderate exacerbations or one severe exacerbation in the previous year.

On trial entry, **38% of the patients : Triple therapy**
29% of the patients : ICS/LABA
8% of the patients : LABA and LAMA

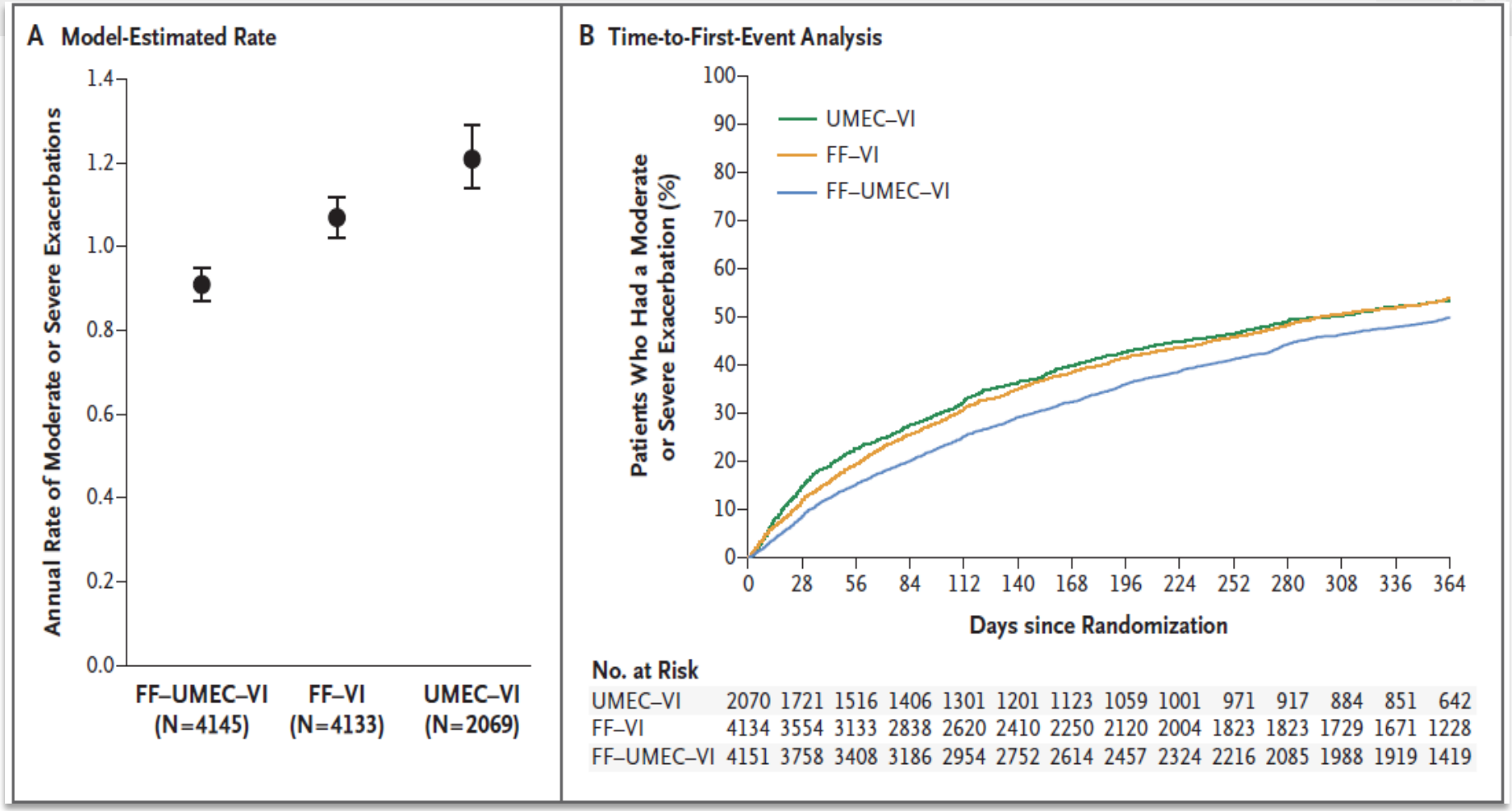
The primary outcome : annual rate of moderate or severe COPD exacerbations during treatment

All the patients underwent baseline chest radiography at trial entry
All the patients with a suspected pneumonia, or moderate or severe exacerbation, have a chest radiograph obtained to help confirm the presence of a new infiltrate and better capture and understand these adverse events.

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

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

Moderate or Severe COPD exacerbations (ITT)



Trough FEV_1 and SGRQ score (ITT)

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)†
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 (95% CI)	—	1.41 (1.29 to 1.55)†	1.41 (1.26 to 1.57)†

* The means presented are least-squares means.
† P<0.001.
‡ Total scores on the SGRQ range from 0 to 100, with lower scores indicating better health-related quality of life.
§ A response was defined as a decrease in the SGRQ total score of at least 4 units, as compared with the baseline value.

Adverse Events of Special interest in the ITT

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)

All-cause mortality

The hazard ratio for triple therapy versus umeclidinium–vilanterol : 0.58 (95% CI, 0.38 to 0.88; 42% difference; unadjusted P = 0.01)
The hazard ratio for fluticasone furoate–vilanterol versus umeclidinium–vilanterol : 0.61 (95% CI, 0.40 to 0.93; 39% difference; unadjusted P = 0.02)

Eosinophil

The annual rate of moderate or severe exacerbations was lower with triple therapy than with either dual-therapy combination, regardless of eosinophil level, although a greater reduction in the exacerbation rate was observed in patients with eosinophil levels of **at least 150 cells per microliter**.

Triple study (IMPACT Trial) – Conclusion

once-daily combination of Triple therapy

lower rate of moderate or severe COPD exacerbations
better lung function and health-related quality of life

than dual therapy with fluticasone furoate–vilanterol or umeclidinium–vilanterol.

Triple therapy also resulted in a **lower rate of hospitalization** due to COPD than umeclidinium–vilanterol in this symptomatic patient population.

International Journal of COPD

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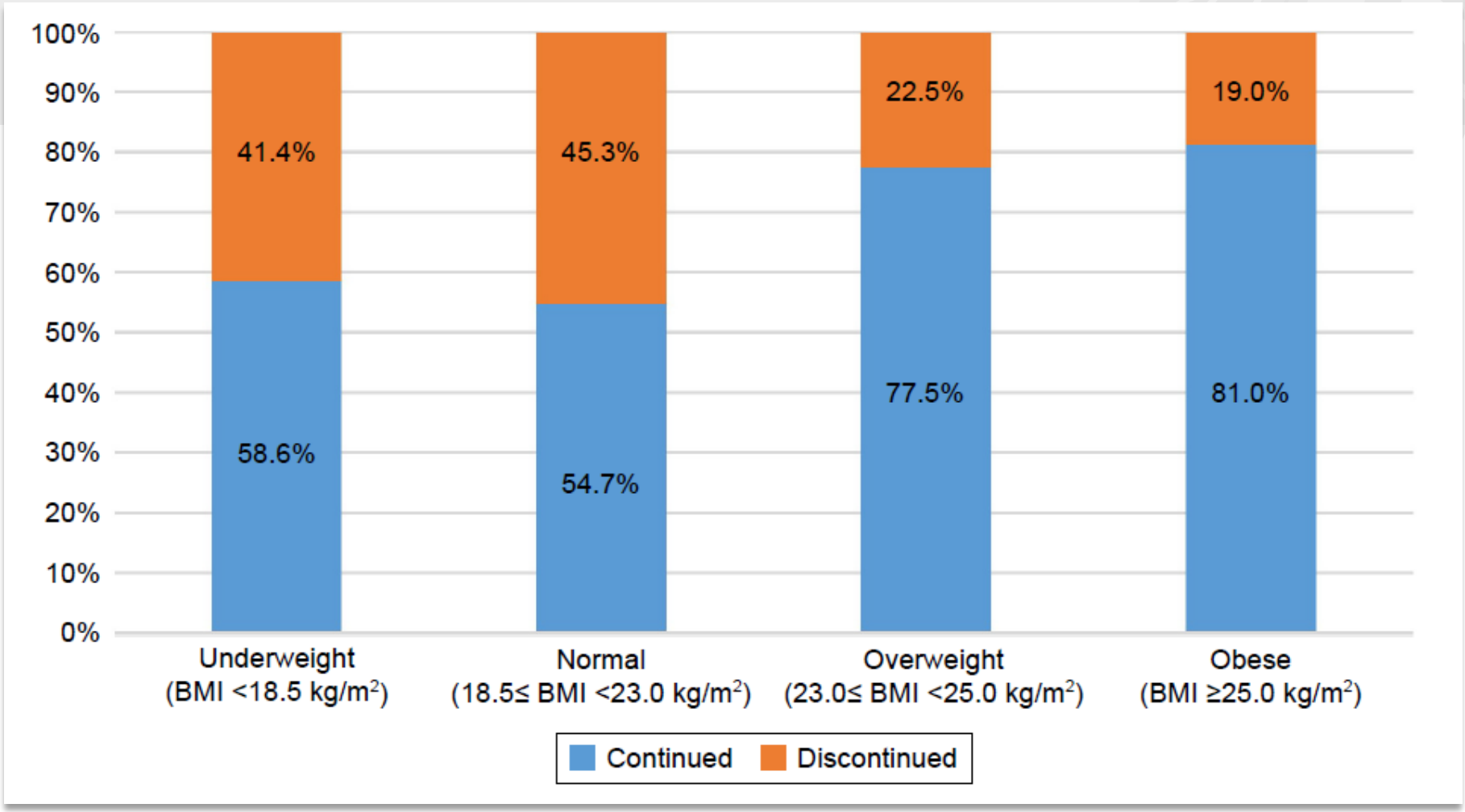
ORIGINAL RESEARCH

Risk factors for the discontinuation of roflumilast in patients with chronic obstructive pulmonary disease

Kyung Hoon Kim,[1] Hye Seon Kang,[2] Ju Sang Kim,[3] Hyoung Kyu Yoon,[4] Sung Kyoung Kim,[5] Chin Kook Rhee[1]

International Journal of COPD 2017:12 3449–3456


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
41.4%
58.6%
45.3%
54.7%
22.5%
77.5%
19.0%
81.0%
Underweight
(BMI <18.5 kg/m²)
Normal
(18.5≤ BMI <23.0 kg/m²)
Overweight
(23.0≤ BMI <25.0 kg/m²)
Obese
(BMI ≥25.0 kg/m²)
Continued
Discontinued

Factors associated with roflumilast discontinuation (Multivaiate analysis)

Risk factor	OR	95% CI	*p*-value
Model A			
Age	1.006	0.966–1.047	0.778
BMI (per 1-unit decrease)	1.165	1.046–1.298	0.006
Sex (female)	0.659	0.191–2.277	0.510
% of predicted post-bronchodilator FEV_1	0.993	0.970–1.016	0.540
Model B			
Age	1.006	0.966–1.047	0.789
BMI <23 kg/m^2	2.960	1.410–6.215	0.004
Sex (female)	0.566	0.163–1.964	0.370
% of predicted post-bronchodilator FEV_1	0.996	0.973–1.020	0.755

Notes: Model A is the result of analyzing BMI as a continuous variable. Model B is the result of analyzing BMI as a nominal variable.

International Journal of COPD

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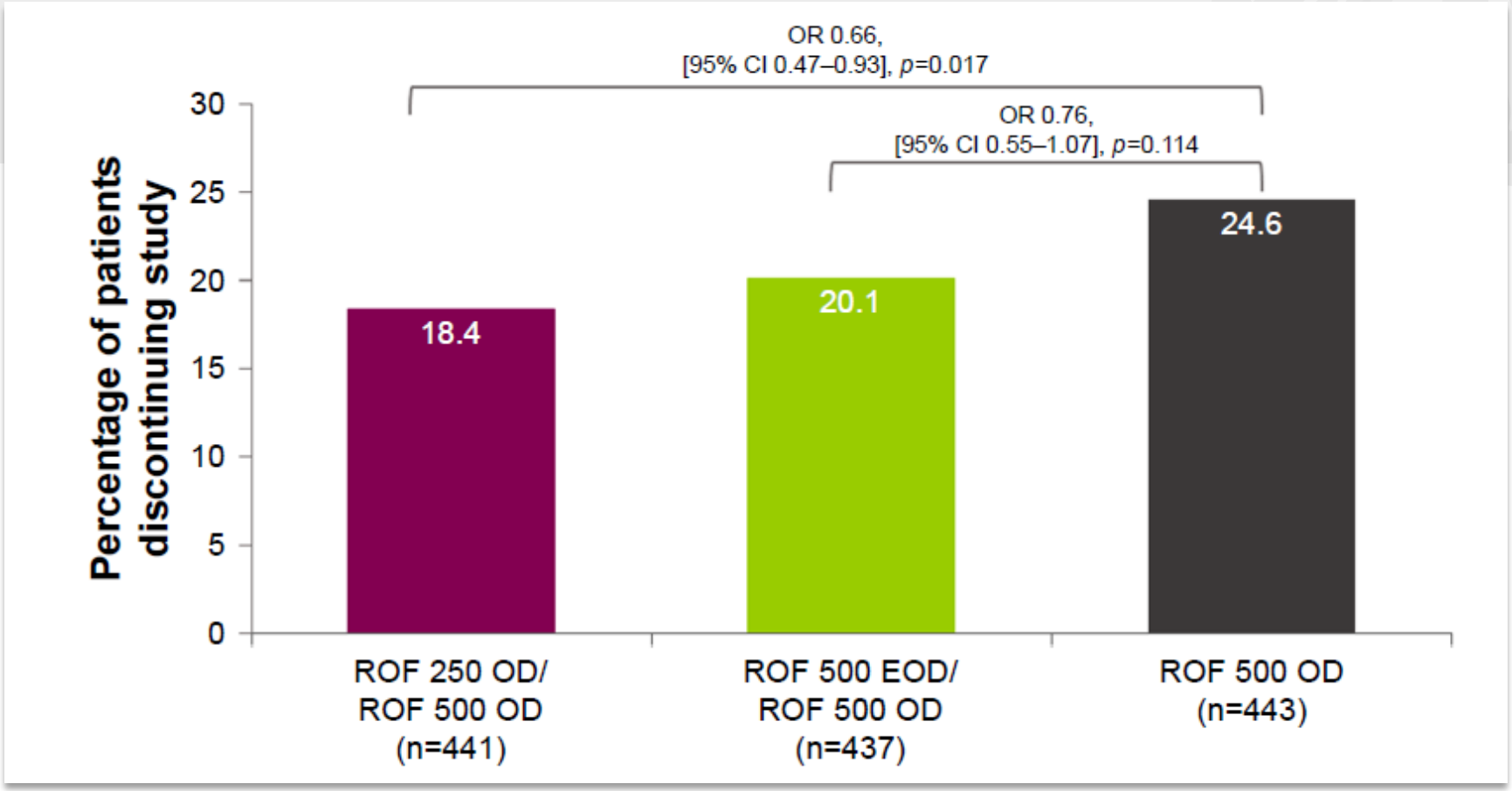
ORIGINAL RESEARCH

Use of a 4-week up-titration regimen of roflumilast in patients with severe COPD

International Journal of COPD 2018:13 813–822



A dose of ROF 250µg OD for 4 weeks before escalation to the approved maintenance dose of 500µg OD resulted in reduced treatment discontinuation and improved tolerability.

Biologics in COPD

Completed and reported phase 2 and 3 trials of biologics in COPD

Drug, Dose & Duration	Population	Primary outcome	Secondary outcome
Anti- Pro-inflammatory, neutrophilic, non-T2 inflammation			
Anti-IL8	Mod-severe COPD (n = 109)	↓ Severity of dyspnoea as measured by TDI	↔ Health status, lung function, 6-min walk test, rescue use of albuterol
800 mg loading dose, 400 mg/month for 2 months, 5 month follow-up (47)	>50 years, MRC ≥1		
	>20 pack year smoking history		
Anti-TNFα (Etanercept)	≥35 years old (n = 81)	↔ FEV_1 over 14 days from exacerbation onset	↔ 90-day treatment failure, dyspnoea, health status
50 mg, 90 days (42)	Enrolled at exacerbation onset		
Anti-TNFα (Infliximab)	Mild-mod COPD (n = 22)	↔ Sputum inflammatory cells	↔ FEV_1, SGRQ
5mg/kg, 8 weeks (50)	Current smokers		
Anti-TNFα (Infliximab)	Mod-severe COPD (n = 234)	↔ CRQ	↔ FEV_1, 6-min walk test, TDI
3 mg/kg or 5 mg/kg, 44 weeks (43)	>40 years, CRQ<120		↑ Malignancy, pneumonia
Anti-IL1 (MEDI 8968)	Mod-very severe COPD (n = 324)	↔ Moderate-to-severe exacerbations	↔ SGRQ-C
300 mg every 4 weeks, 52 weeks (53)	45–75 years, ≥2 exacerbations in past year		

Biologics in COPD

Anti- eosinophilic, T2 inflammation			
Benralizumab/ IL-5	Mod-severe COPD (n = 101)	↔ Moderate-to-severe exacerbations	↑ FEV_1 in intervention group
100 mg every 4 weeks (3 doses) then every 8 weeks (5 doses), 56 week (45)	40–85 years, ≥1 exacerbation in past year		↔ health status
	Sputum eosinophils ≥3%		↓ Blood and sputum eosinophils
Mepolizumab/ IL5	Mod-severe COPD (n = 18)	↓ Sputum eosinophils	↓ Blood eosinophil
750 mg/month, 6 months (62)	Sputum eosinophils >3% ≥1 exacerbation in previous year		↔ FEV_1, CAT, CRQ, exacerbations
Mepolizumab/ IL-5	Mod-very severe COPD, (n = 836)	↓ Exacerbations in pre-specified eosinophilic group	↓ Time to first exacerbation
100 mg or 300 mg every 4 weeks, 52 weeks (46)	>40 years, ≥2 moderate or ≥1 severe exacerbation in previous year		↔ FEV_1, SGRQ, CAT
Mepolizumab/ IL-5	Mod-very severe COPD, (n = 674), >40 years, ≥2 moderate or ≥1 severe exacerbation in previous year, blood eosinophils >150/µL	↓ Exacerbations	↓ Time to first exacerbation
100 mg or 300 mg every 4 weeks, 52 weeks (55)			↔ FEV_1, SGRQ, CAT

Conclusion

- The treatment of COPD has become increasingly effective.
- The pharmacological treatment of COPD is one of the cornerstones of COPD management, and there have been many advances in this area in recent years.

- Future developments of precision medicine in COPD require identification of relevant endotypes combined with proper identification of phenotypes involved in the complex and heterogeneous manifestations of COPD

Conclusion

Precsion Medicine

Treatment according to Guideline

Risk reduction
Early diagnosis and proper intervention