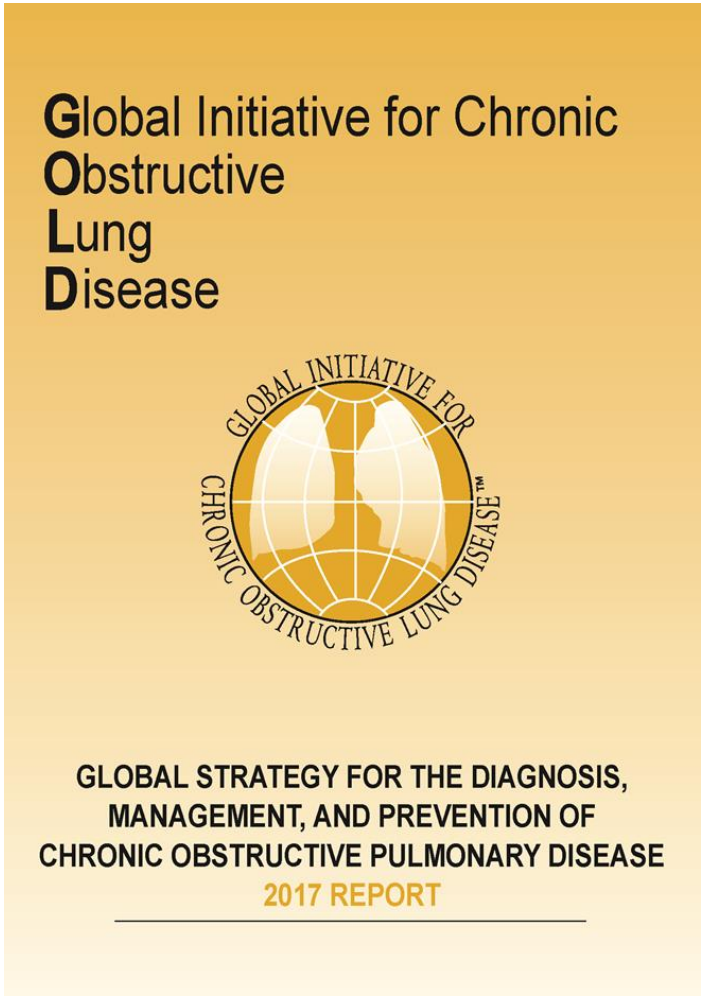
Is eosinophil important in use of ICS in patients with COPD ?

순천향의대 호흡기내과
나주옥

GOLD 2017 Report



ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool

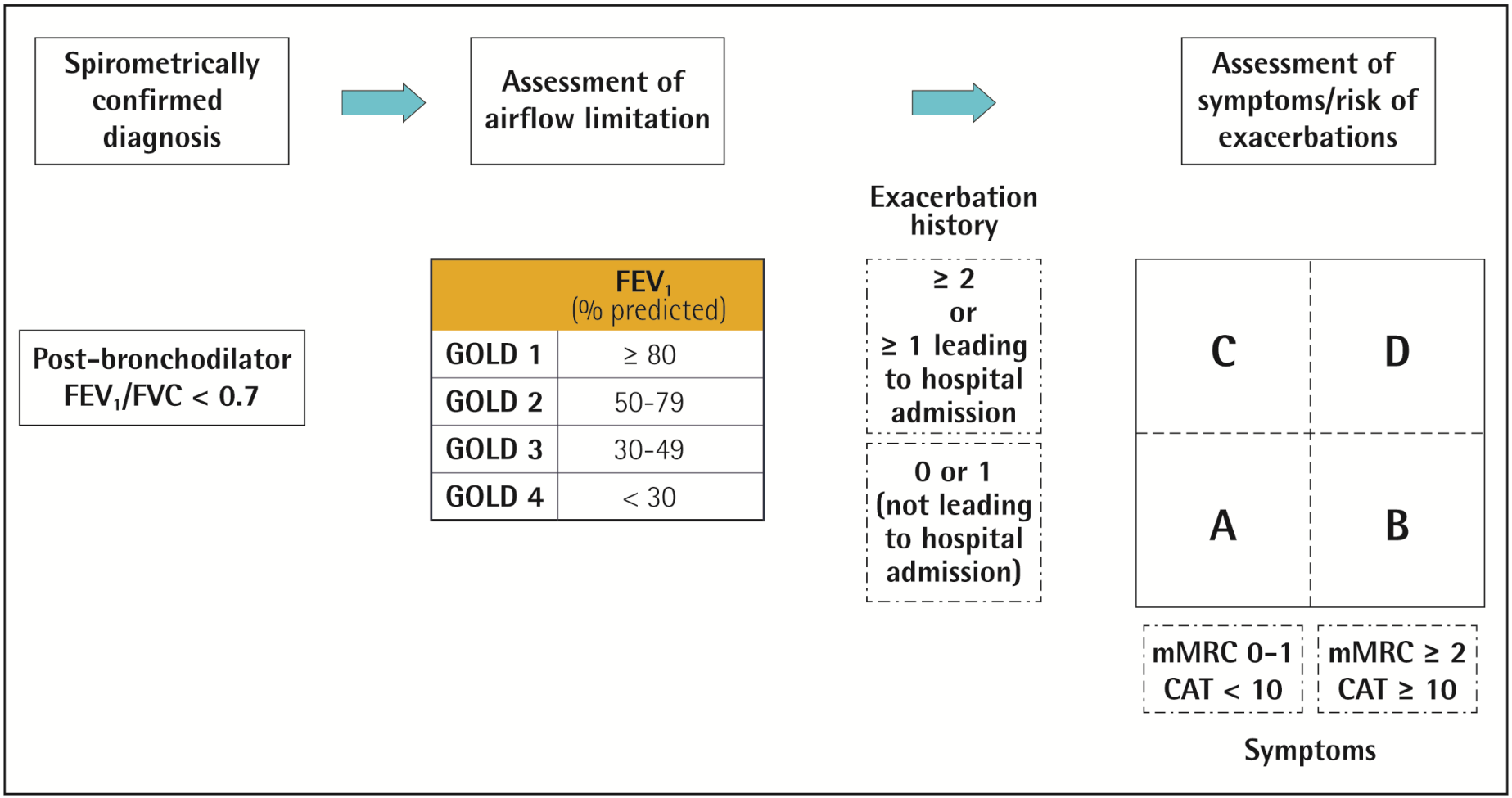
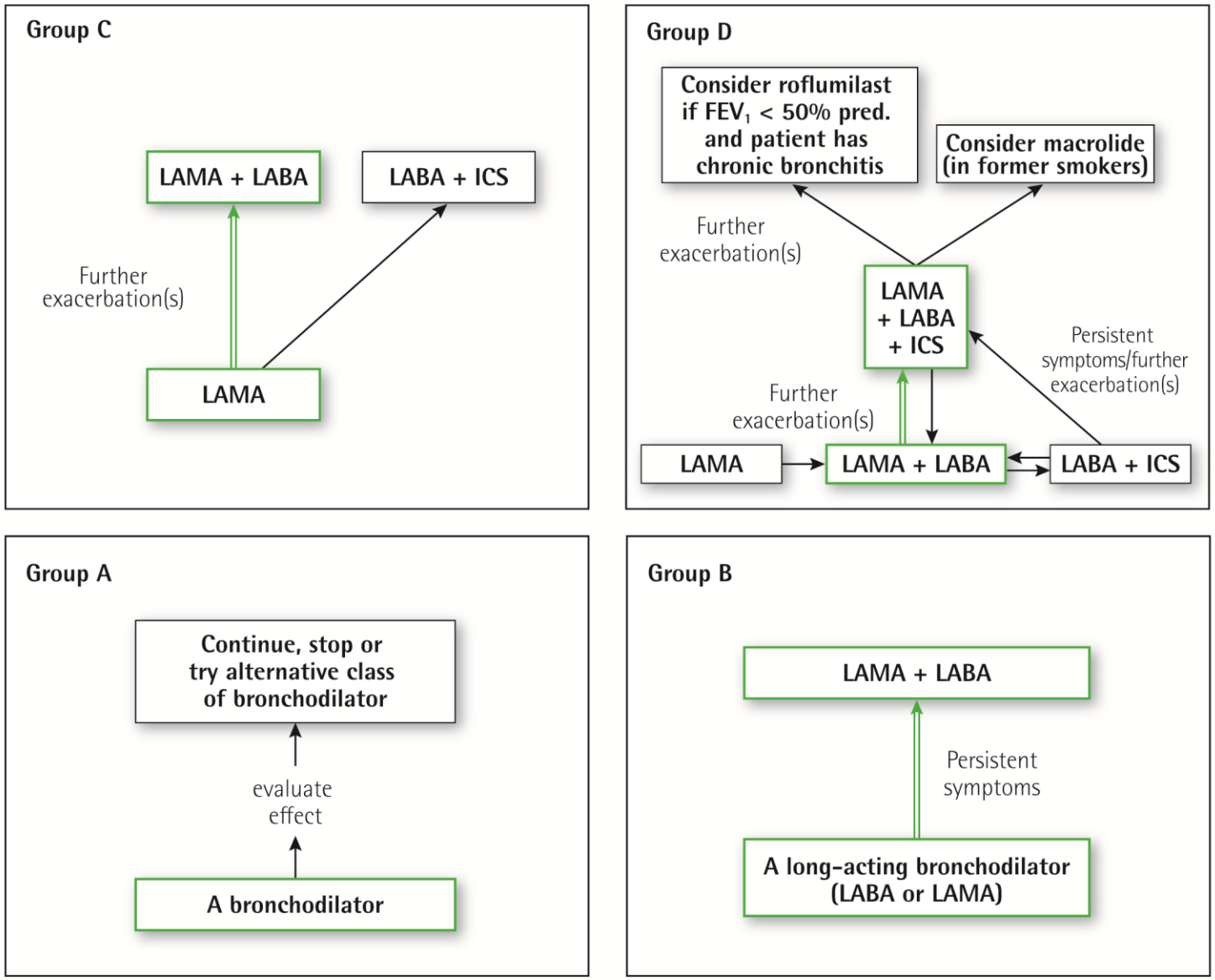


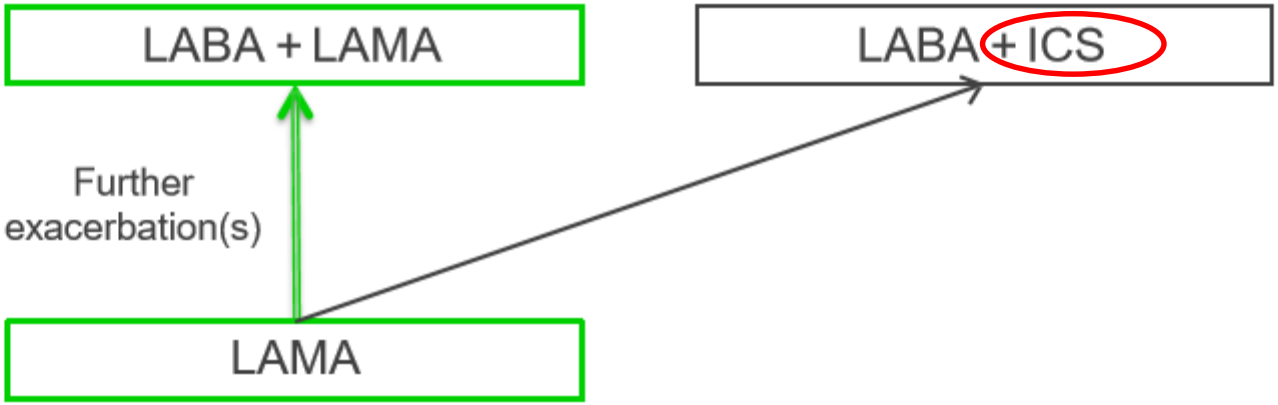
Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

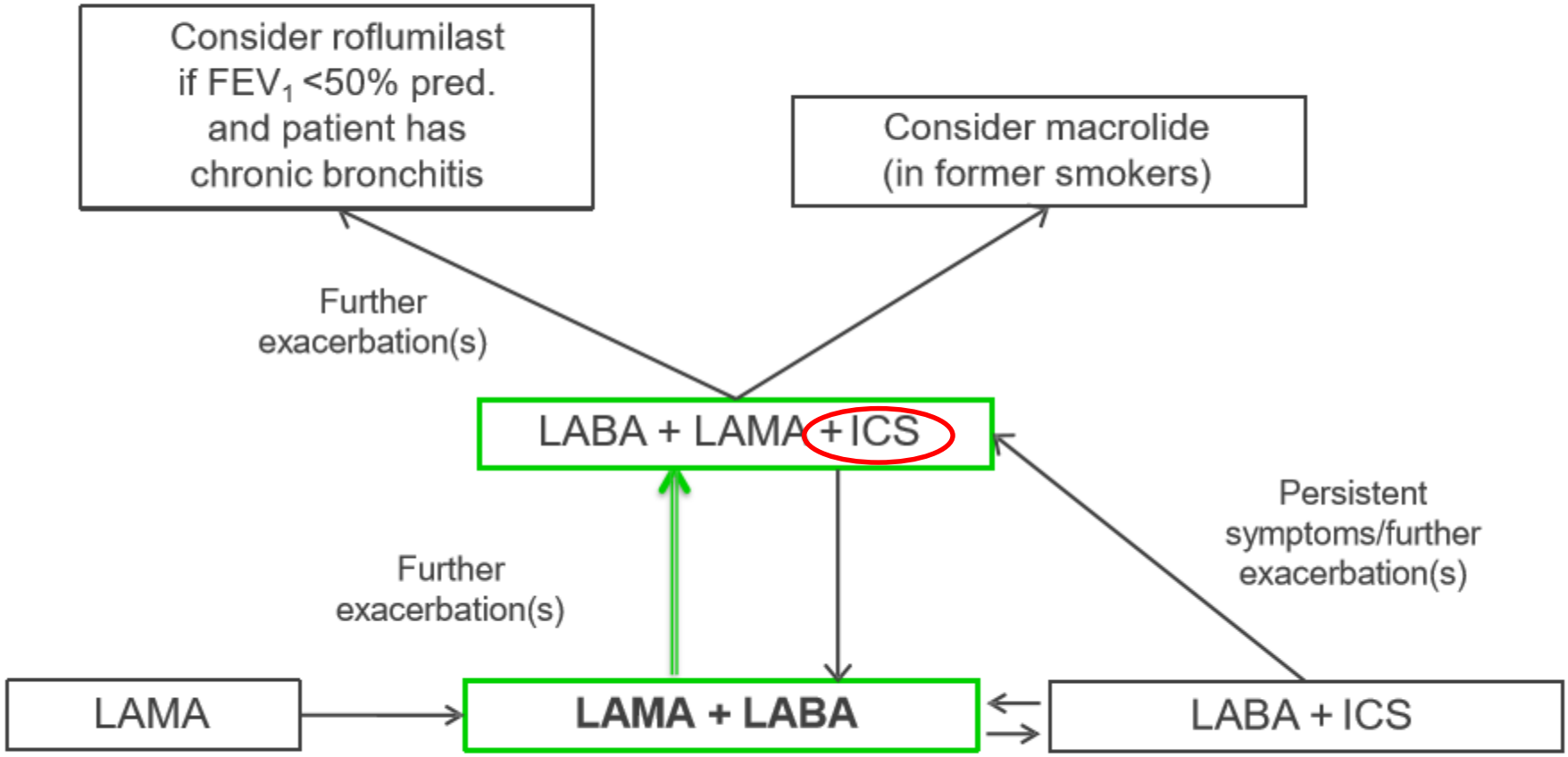
A new approach to treatment recommendations: Group C



- Patients with persistent exacerbations may benefit from addition of LABA or a combination of ICS/LABA[1]
  - LAMA/LABA is the preferred choice due to the pneumonia risk associated with ICS[1]
  - There is also no evidence to suggest superiority of ICS/LABA over LABA/LAMA[2]
- Triple therapy is not recommended in GOLD C[1]

1. GOLD 2017 (© 2016 Global Strategy for Diagnosis, Management and Prevention of COPD all rights reserved. Use is by express license from the owner)
2. Wedzicha JA, et al. N Engl J Med 2016

A new approach to treatment recommendations: Group D



Pharmacologic treatment algorithms

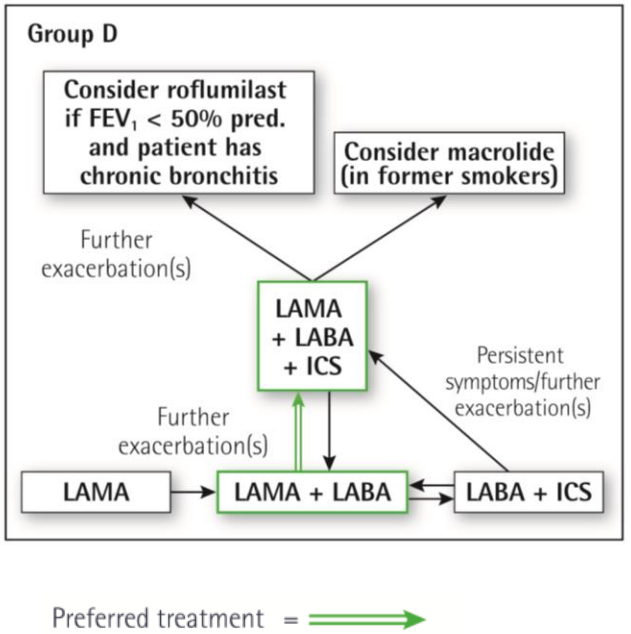
Group D

- recommend starting therapy with a LABA/LAMA

1) LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs

2) A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients

3) Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.



Pharmacologic treatment algorithms

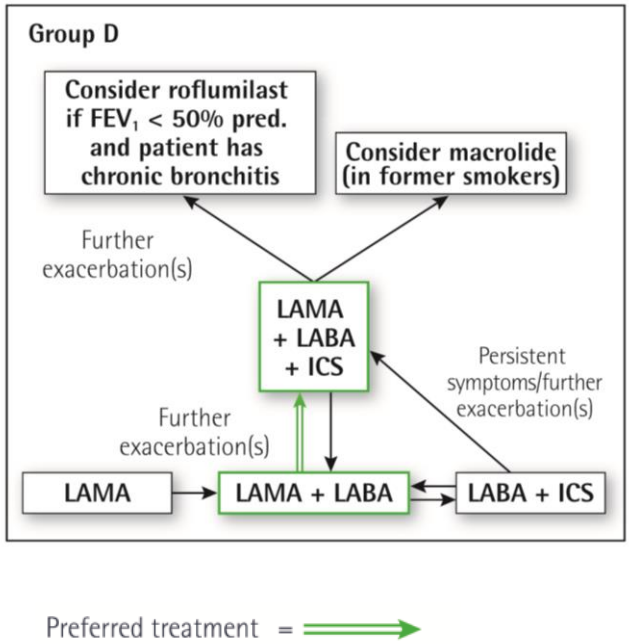
Group D (continued)

- In some patients initial therapy with LABA/ICS may be the first choice.

  - Asthma-COPD overlap.
  - High blood eosinophil counts

- In patients who develop further exacerbations on LABA/LAMA therapy we suggest two alternative pathways:

  - Escalation to LABA/LAMA/ICS.
  - Switch to LABA/ICS.



GOLD 2017 recommend ICS use only in a specific patient population

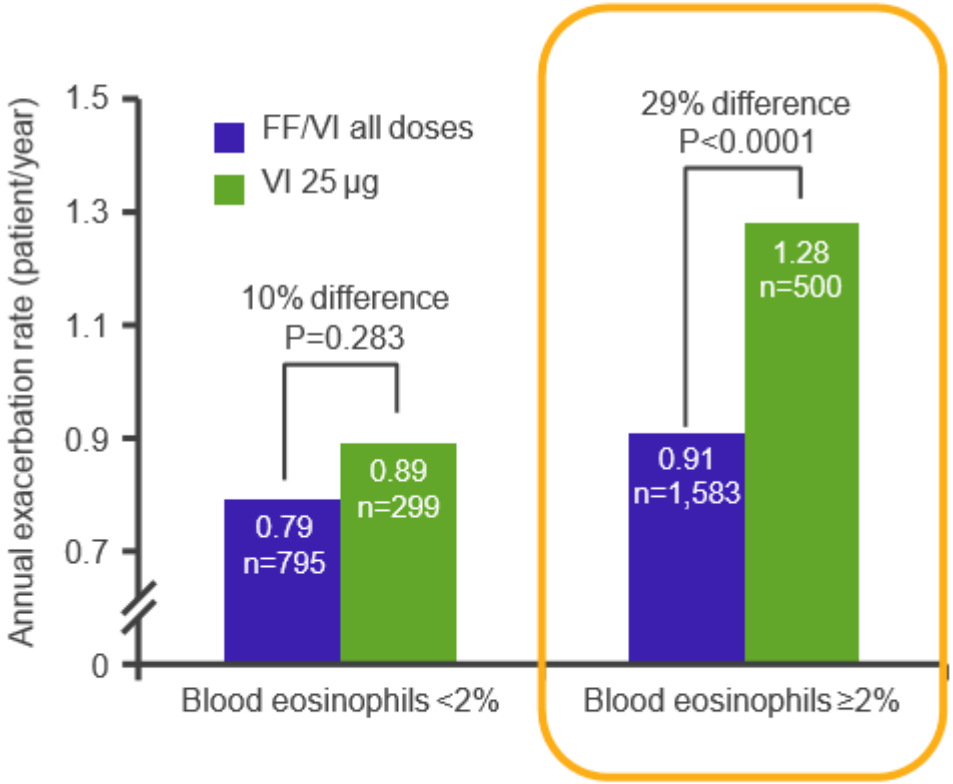
- ICS therapy is only recommended in a minority of patients in GOLD C & D
- Patients with a history and/or findings of asthma-COPD overlap
- Patients who develop further exacerbations following initial dual bronchodilator treatment
- High blood eosinophils may be considered as a parameter to support the use of ICS, although this is still under debate

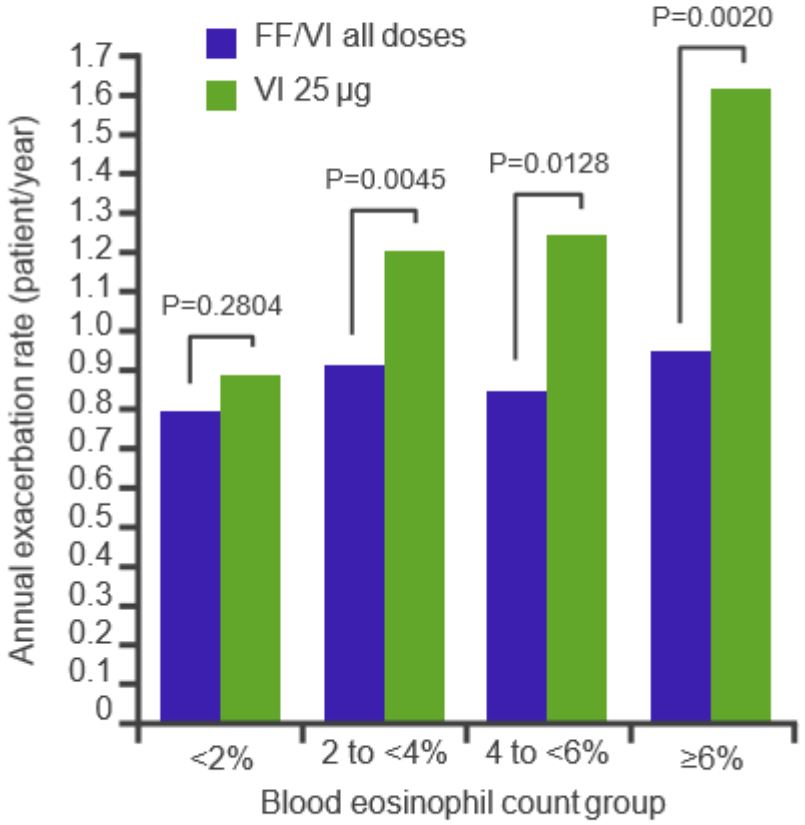
1. GOLD 2017; 2. Wedzicha JA, et al. N Engl J Med 2016

High blood eosinophils

- A biomarker of exacerbation risk in patients with a history of exacerbations
- Predict the effect of ICS on exacerbation prevention

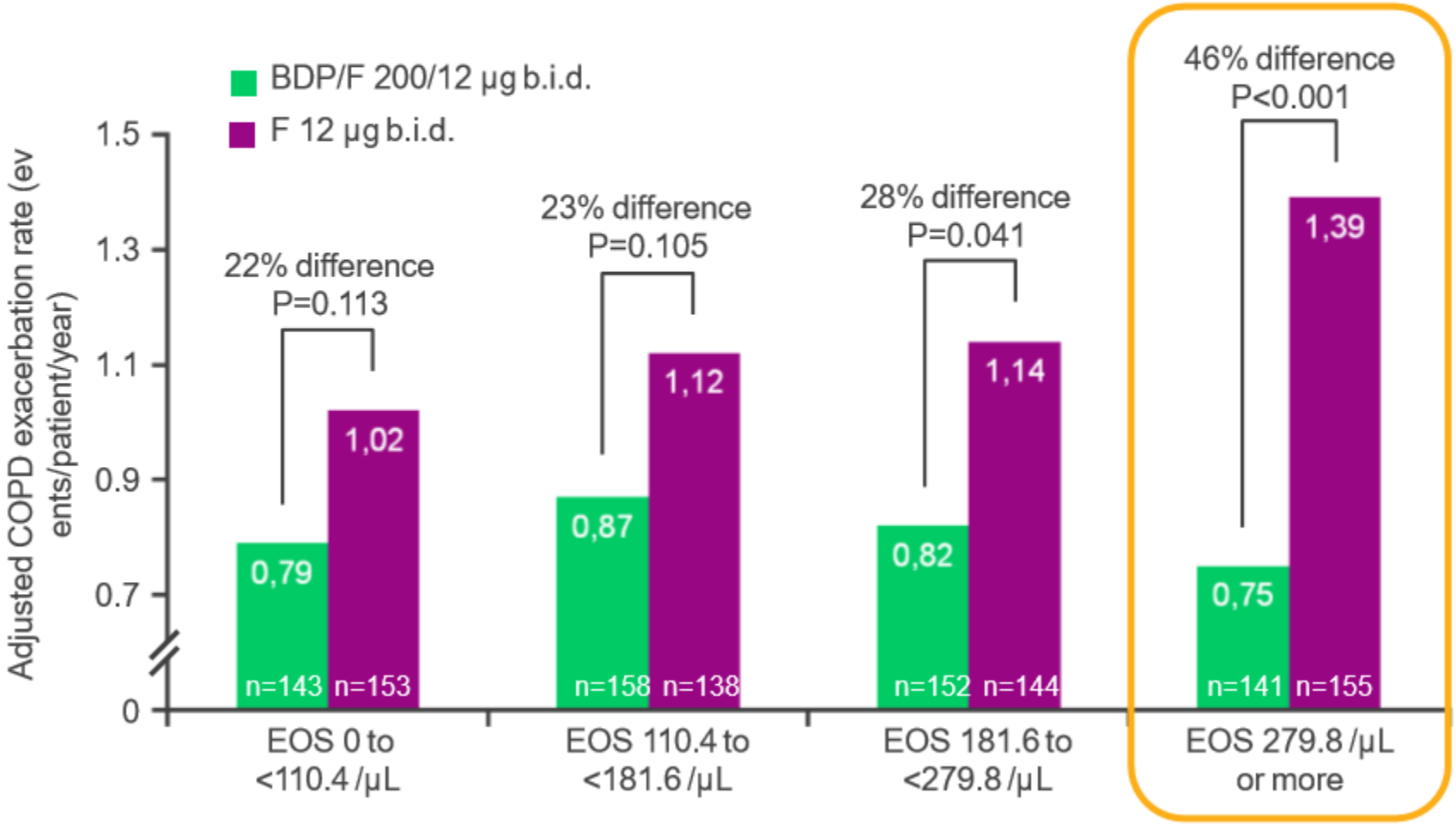
FF/VI showed the greatest benefit over VI in exacerbation prevention in patients with ≥2% blood eosinophils (post-hoc analysis)





Pascoe S, et al. Lancet Respir Med 2015

FORWARD: BDP/F showed the greatest benefit over F in exacerbation prevention in patients with ≥279.8 cells/µL absolute blood eosinophils (post-hoc analysis)



EOS = eosinophils; F = formoterol fumarate

Siddiqui S, et al. Am J Respir Crit Care Med 2015

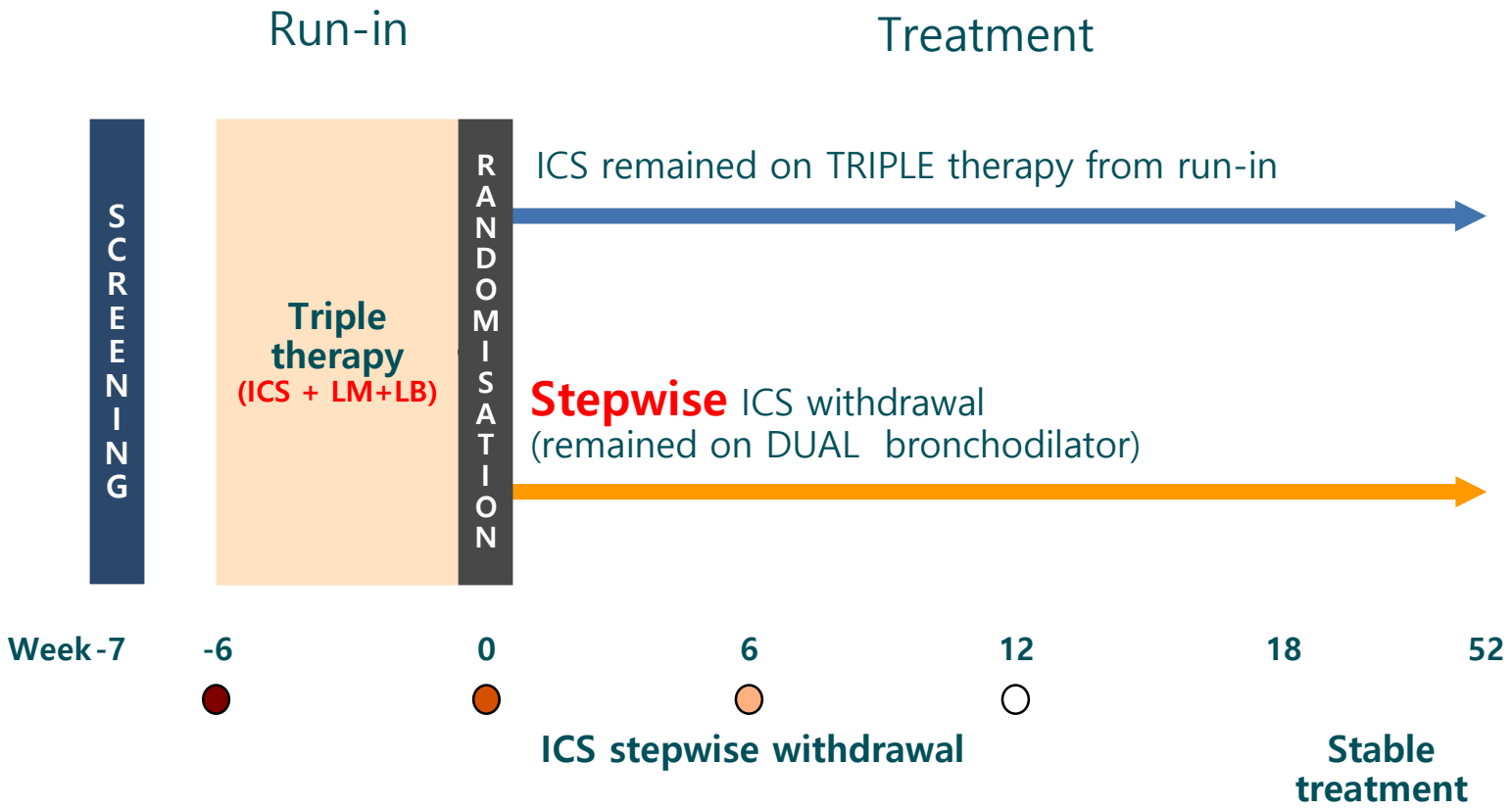
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 2, 2014 VOL. 371 NO. 14

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial : severe to very severe COPD

Study design



Triple therapy regimen

- Tiotropium 18 µg QD
- Salmeterol 50 µg BID
- Fluticasone propionate 500 µg BID

Fluticasone propionate 12-week withdrawal schedule

- 500 µg BID
- Reduced to 250 µg BID
- Reduced to 100 µg BID
- Reduced to 0 µg (placebo)

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

Patient characteristics

	ICS (n=1243)	ICS withdrawal (n=1242)
Male, %	81.5	83.4
Mean (SD) age, years	63.6 (8.6)	64.0 (8.4)
Mean (SD) body mass index, kg/m^2	25.3 (5.1)	25.2 (5.1)
Current smoker, %	34.8	32.1
Lung function		
Mean (SD) post-dose screening FEV_1, L	0.93 (0.29)	0.94 (0.30)
GOLD 3, %	61.1	61.3
GOLD 4, %	38.1	38.2
Mean (SD) baseline FEV_1, L*	0.97 (0.36)	0.98 (0.36)

*After 6-week run-in on triple therapy

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

Pre-study medication

	ICS (n=1243)	ICS withdrawal (n=1242)
≥1 respiratory medication	88.4	88.2
LAMA	47.3	46.5
LABA	64.9	64.3
Corticosteroids		
Inhaled	70.5	69.4
Oral	1.2	1.4
LAMA + LABA + ICS	38.5	39.5

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

Endpoints

Primary endpoint

Time to 1st moderate or severe on-treatment exacerbation during 12 -month randomised period

Secondary endpoints

Included lung function, health status (SGRQ) and dyspnea (mMRC)

Definition of exacerbations

Moderate

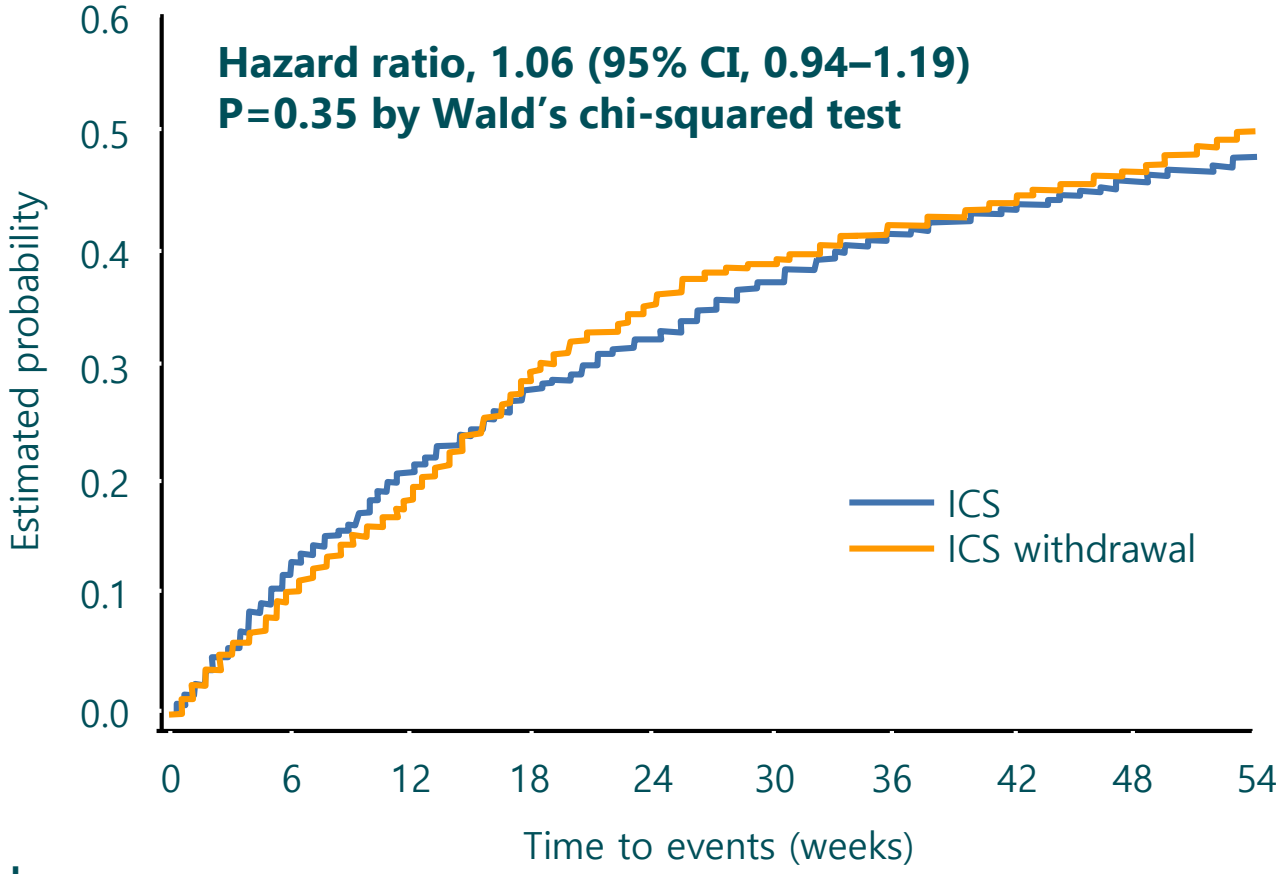
Increase or new onset of ≥2 lower respiratory symptoms related to COPD with ≥1 symptom lasting ≥3 days and requiring treatment with antibiotics and / or systemic steroids

Severe

Requires hospitalisation in an urgent care unit

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

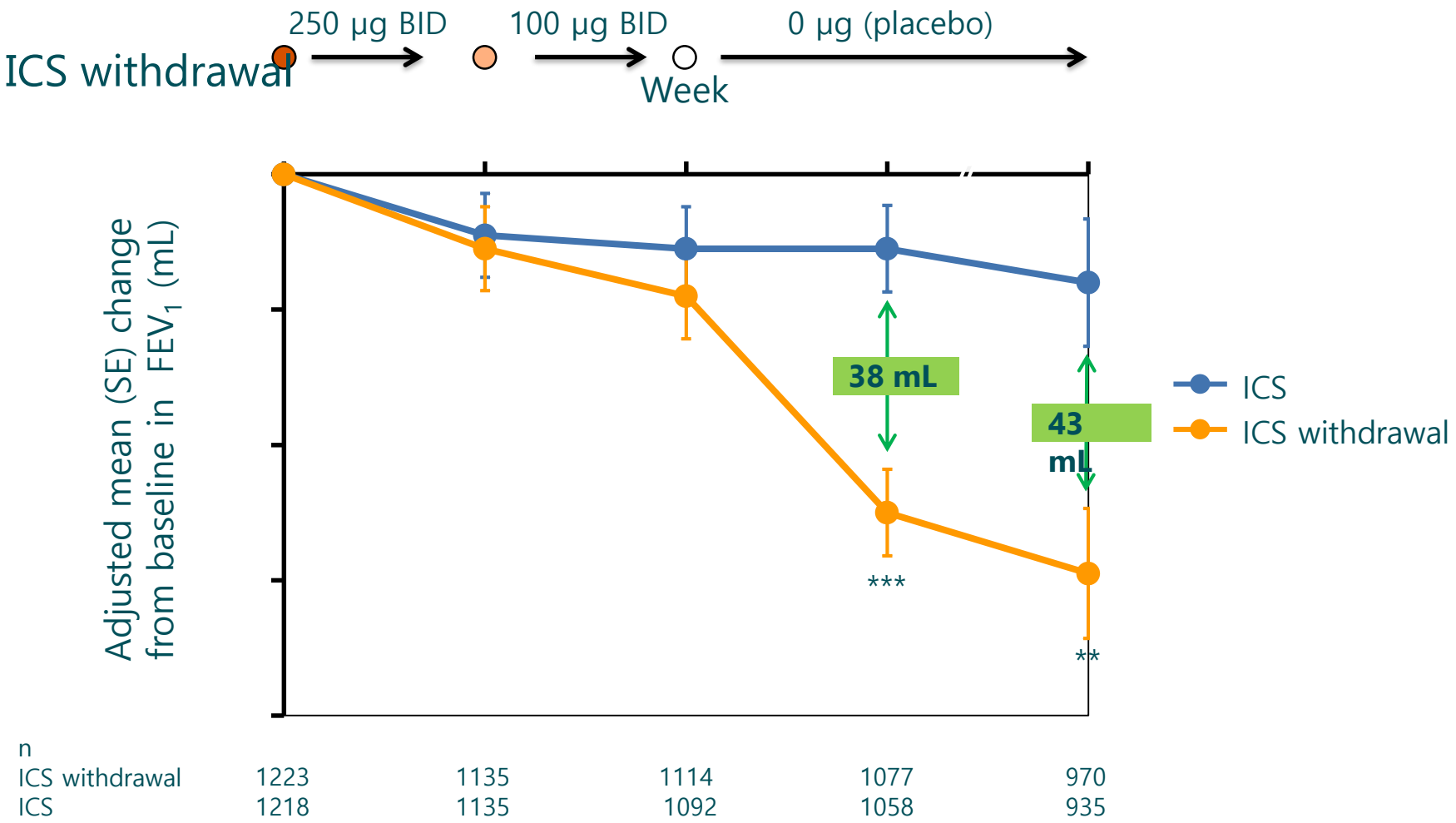
Moderate or severe COPD exacerbation risk



No. at risk										
ICS	1243	1059	927	827	763	694	646	615	581	14
ICS withdrawal	1242	1090	965	825	740	688	646	607	570	19

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

Mean change from baseline in FEV_1



n					
ICS withdrawal	1223	1135	1114	1077	970
ICS	1218	1135	1092	1058	935

**p<0.01; ***p<0.0001 vs ICS; restricted maximum likelihood repeated measures model; baseline values 970 mL for ICS, 981 mL for ICS withdrawal

Helgo Magnussen, M.D. *N Engl J Med* 2014; 371:1285-1294

Implications

WISDOM study results imply that with respect to **moderate/ severe exacerbations** in patients with **severe/very severe COPD**:

- Many patients with a history of exacerbations may not benefit from the addition of an ICS on top of tiotropium and a LABA.
- WISDOM results have indicated that **not all patients seem to benefit from inclusion of an ICS**.
- The new evidence from WISDOM indicates that the **decision to initiate an ICS should be made on a case-by-case basis**, with the aim of reducing unnecessary ICS-related side effects and considering more alternative treatment choices.

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

Dr Henrik Watz, MD, Prof Kay Tetzlaff, MD, Prof Emiel F M Wouters, MD, Anne Kirsten, MD, Prof Helgo Magnussen, MD, Prof Roberto Rodriguez-Roisin, MD, Prof Claus Vogelmeier, MD, Prof Leonardo M Fabbri, MD, Prof Pascal Chanez, MD, Prof Ronald Dahl, MD, Bernd Disse, MD, Helen Finnigan, MSc, Prof Peter M A Calverley, DSc

The Lancet resp Medicine 2016:4(5): 390-8

WISDOM study (post-hoc analysis): Blood eosinophil stratification

Eosinophil stratification based on %

- Eosinophils <2%: 46% (n=1113)
- Eosinophils ≥2%: 54% (n=1307)
- Eosinophils ≥3%: 32% (n=786)
- Eosinophils ≥4%: 20% (n=476)
- Eosinophils ≥5%: 12% (n=299)

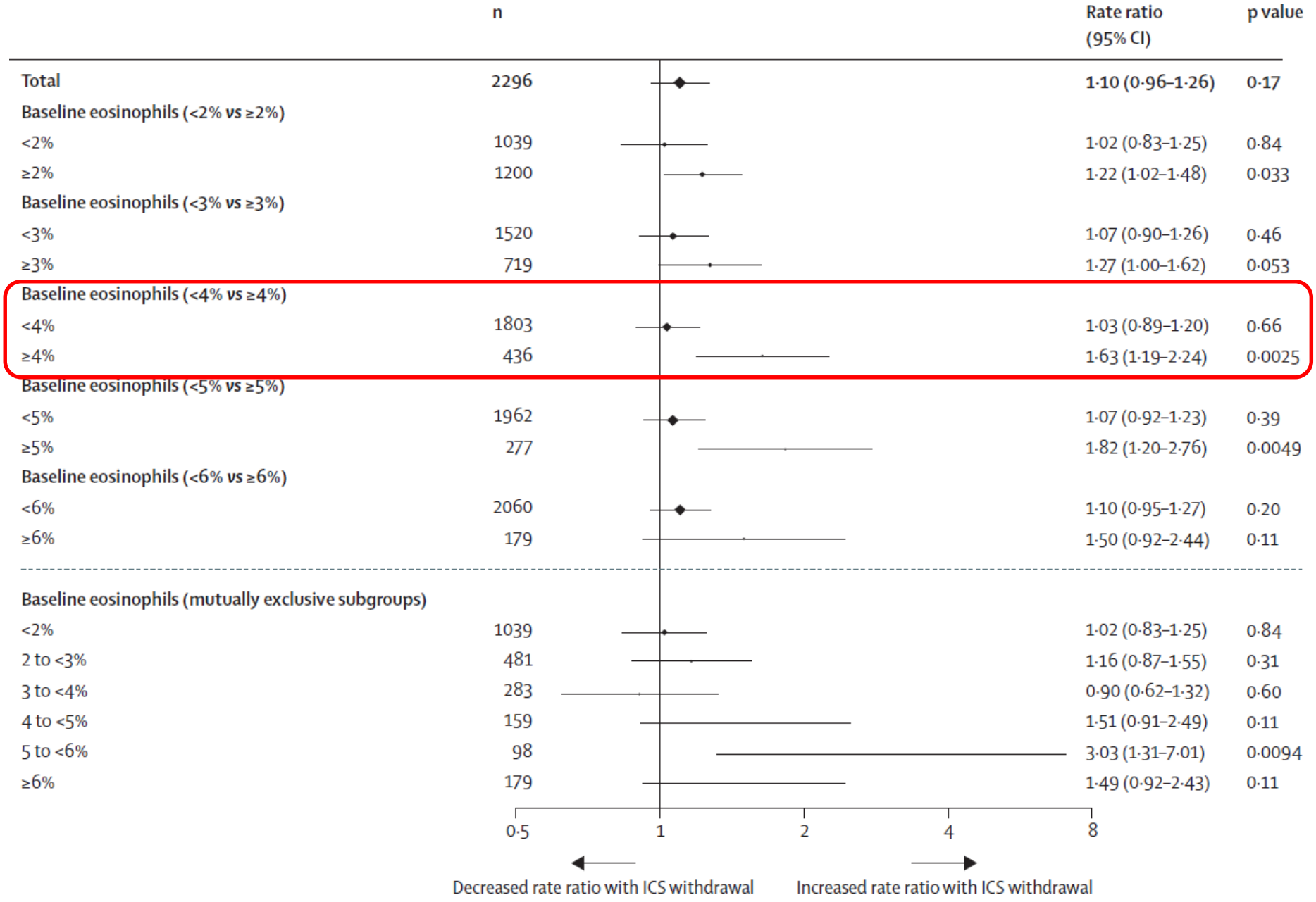
Eosinophil stratification based on cell counts

- Eosinophils ≥150 cells/µl: 53% (n=1275)
- Eosinophils ≥300 cells/µl: 20% (n=490)
- Eosinophils ≥400 cells/µl: 11% (n=270)

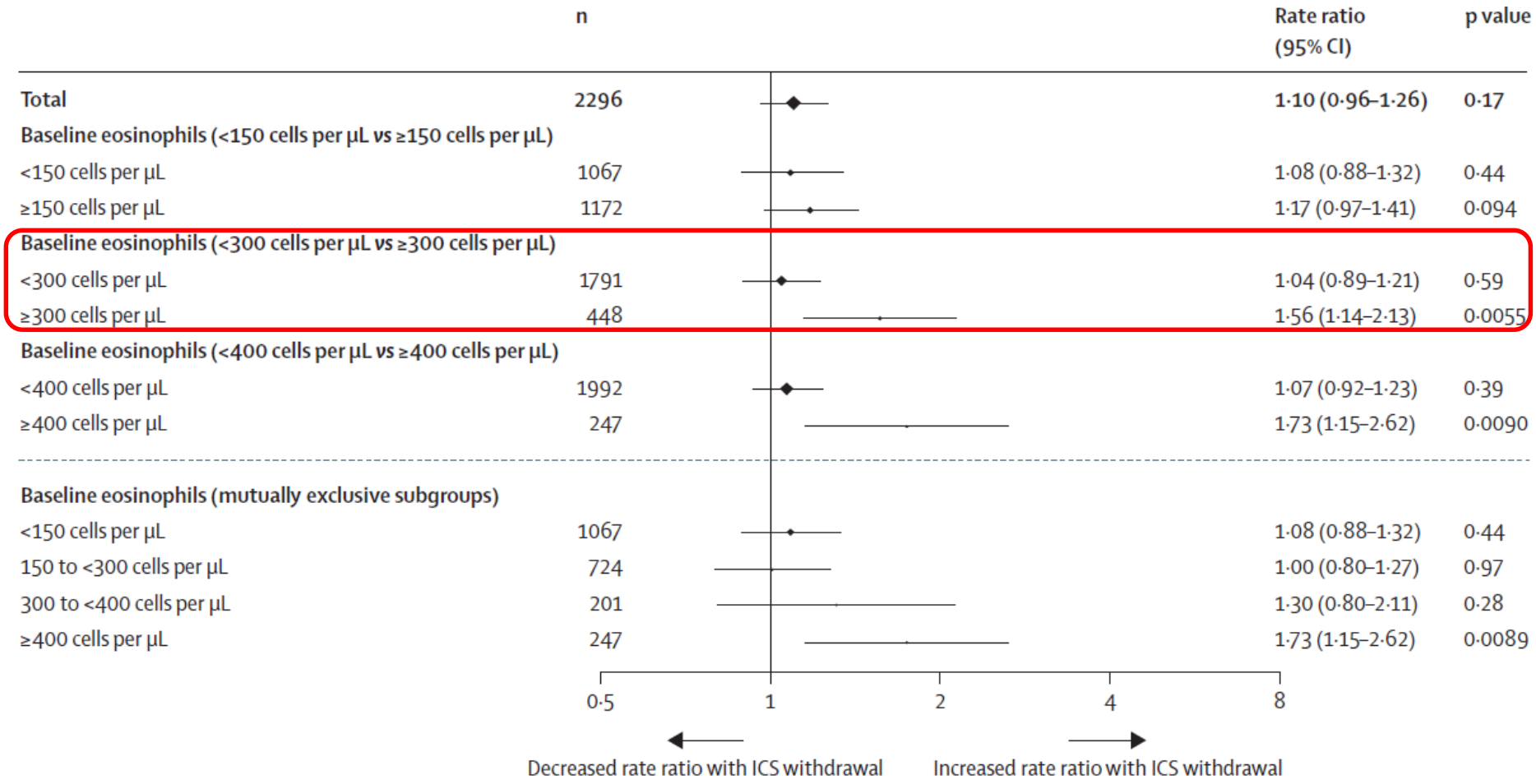
The Lancet resp Medicine 2016:4(5): 390-8

	n	Hazard ratio (95% CI)	p value
All patients	2255	1·126 (0·987–1·285)	0·078
<2% eosinophils	1017	1·112 (0·914–1·354)	0·29
≥2% eosinophils	1182	1·184 (0·987–1·421)	0·069
<3% eosinophils	1490	1·094 (0·932–1·285)	0·27
≥3% eosinophils	709	1·289 (1·013–1·640)	0·039
<4% eosinophils	1766	1·087 (0·938–1·259)	0·27
≥4% eosinophils	433	1·516 (1·099–2·091)	0·011
<5% eosinophils	1924	1·114 (0·967–1·283)	0·13
≥5% eosinophils	275	1·667 (1·085–2·561)	0·020
<6% eosinophils	2022	1·143 (0·995–1·314)	0·059
≥6% eosinophils	177	1·321 (0·806–2·165)	0·27
<150 cells per μL	1043	1·161 (0·955–1·411)	0·14
≥150 cells per μL	1156	1·144 (0·953–1·375)	0·15
<300 cells per μL	1754	1·079 (0·930–1·251)	0·31
≥300 cells per μL	445	1·532 (1·122–2·094)	0·0074
<400 cells per μL	1954	1·106 (0·960–1·274)	0·16
≥400 cells per μL	245	1·664 (1·091–2·538)	0·018

Table 3: Analysis of time to first moderate or severe on-treatment COPD exacerbation over 9 months after complete ICS withdrawal by subgroup in all treated patients with baseline FEV_1 data



The Lancet resp Medicine 2016:4(5): 390-8



The Lancet resp Medicine 2016:4(5): 390-8

Summary

- **Blood eosinophil counts at screening** were related to the exacerbation rate after complete withdrawal in patients with severe to very severe COPD and a history of exacerbations.

- **Eosinophil counts of 4% or greater 300 cells per uL** or more might identify a deleterious effect of ICS withdrawal, an effect not seen in most patients with eosinophil counts below these thresholds

The Lancet resp Medicine 2016:4(5): 390-8

WISDOM retrospective post hoc analysis

	1 exacerbation hx [p value]	≥2 exacerbations hx [p value]
≥300 cells/uL	1.45 [0.0764]	1.75 [0.0205]
≥400 cells/uL	1.25 [0.3962]	2.96 [0.0017]

Am J Respir Crit Care Med. 2017 Mar 17

Summary

- high eosinophil counts (≥300, or ≥400 cells/μl)에서 frequent exacerbations hx (≥2 exacerbations/year)이 있을수록 ICS-withdrawal 후에 악화 위험이 증가

Am J Respir Crit Care Med. 2017 Mar 17

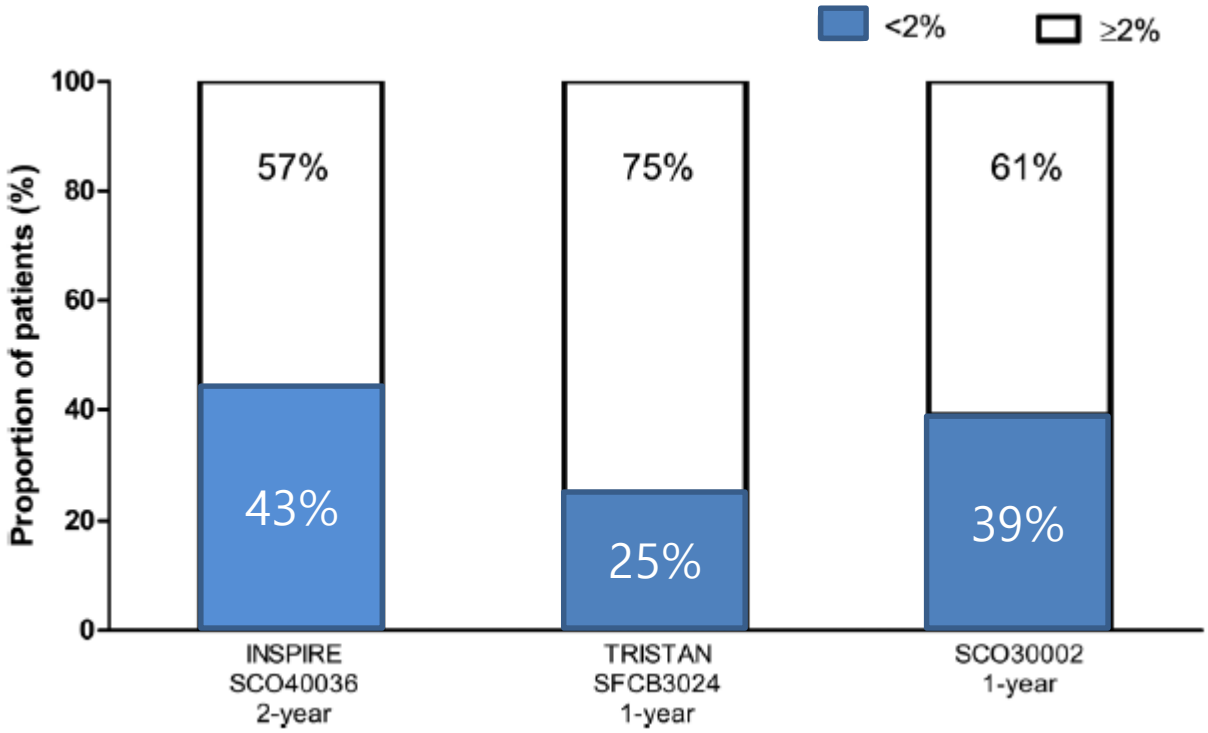
ORIGINAL ARTICLE

Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD

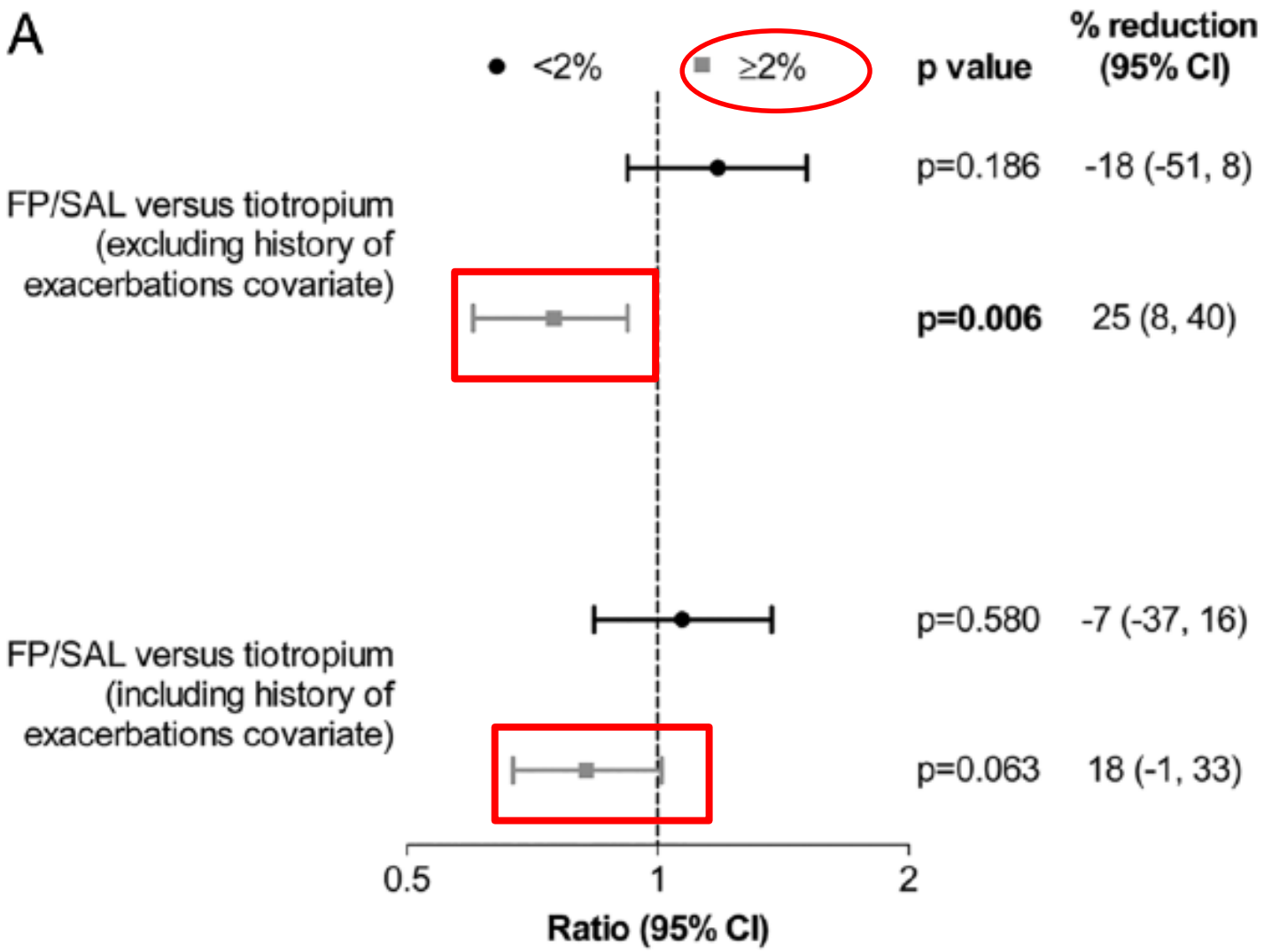
Ian D Pavord,[1] Sally Lettis,[2] Nicholas Locantore,[3] Steve Pascoe,[3] Paul W Jones,[4] Jadwiga A Wedzicha,[5] Neil C Barnes[6,7]

Thorax 2016:7(2);118-125

Proportion of all patients with baseline blood eosinophil level< 2% and ≥ 2% in 1- year studies of FP/SAL in patients with COPD

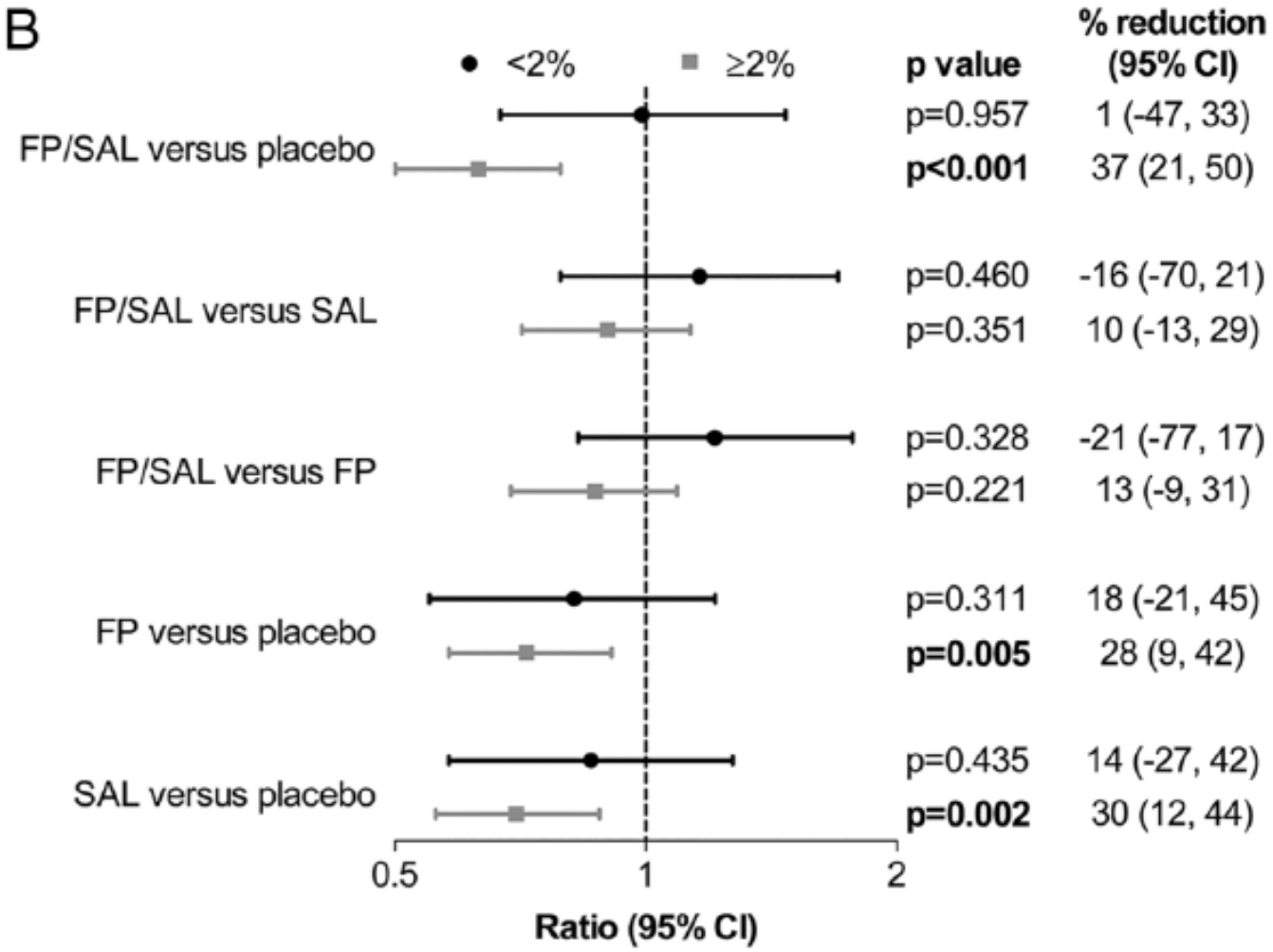


Thorax 2016:7(2);118-125



Inspire study

Thorax 2016:7(2);118-125



Tristan study

Thorax 2016:7(2);118-125

Conclusion

- COPD 환자 중 급성 악화의 병력이 있으면서 baseline blood eosinophil count 증가가 있는 환자는 ICS 의 사용이 급성 악화의 예방에 도움이 될 것으로 보인다.

- Biomarker of COPD acute exacerbations