Recent Advances in the Management and Prevention of COPD Exacerbations

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To begin with…I am not this individual

Disclosures

FJM has been a member of advisory boards and/or consultant for AstraZeneca, Boehringer Ingelheim, Bridge Therapeutics, Chiesi, ConCert, Genentech, GlaxoSmithKline, Nitto, Novartis, Patara, Pearl, Proterrix Bio, Sunovion, Teva, Theravance, and Zambon.

He has been a member of steering committees for studies sponsored by Afferent/Merck, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Promedior, ProMetic, Respivant/Patara, Veracyte.

He has served on speaker's bureaus or in continuing medical education activities sponsored by American College of Chest Physicians, AstraZeneca, Boehringer Ingelheim, Canadian Respiratory Network, Columbia University, Dartmouth University, France Foundation, GlaxoSmithKline, Inova Health System, Methodist Hospital, Miller Communications, National Association for Continuing Education, New York University, Novartis, PeerView, Potomac, Prime, Puerto Rican Respiratory Society, Rockpointe, University of Alabama Birmingham, UpToDate, WebMD/MedScape, Western Connecticut Health Network

He has served on DSMBs for Biogen, Boehringer Ingelheim, Genentech and GSK.

Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?

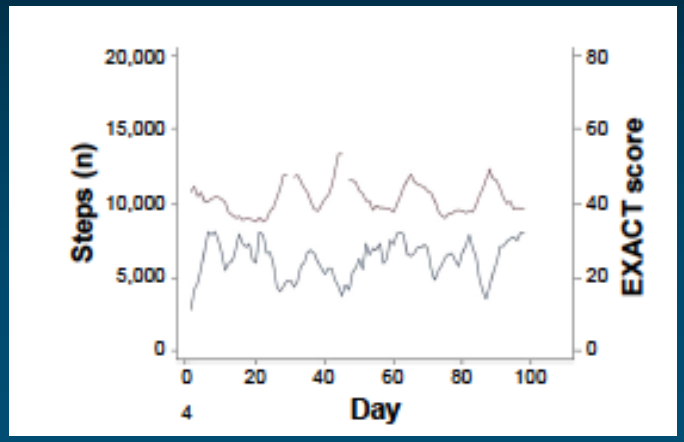
COPD Exacerbations

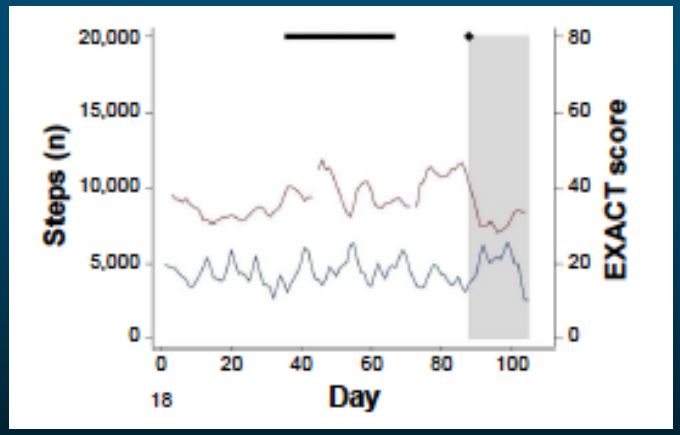
Consequences

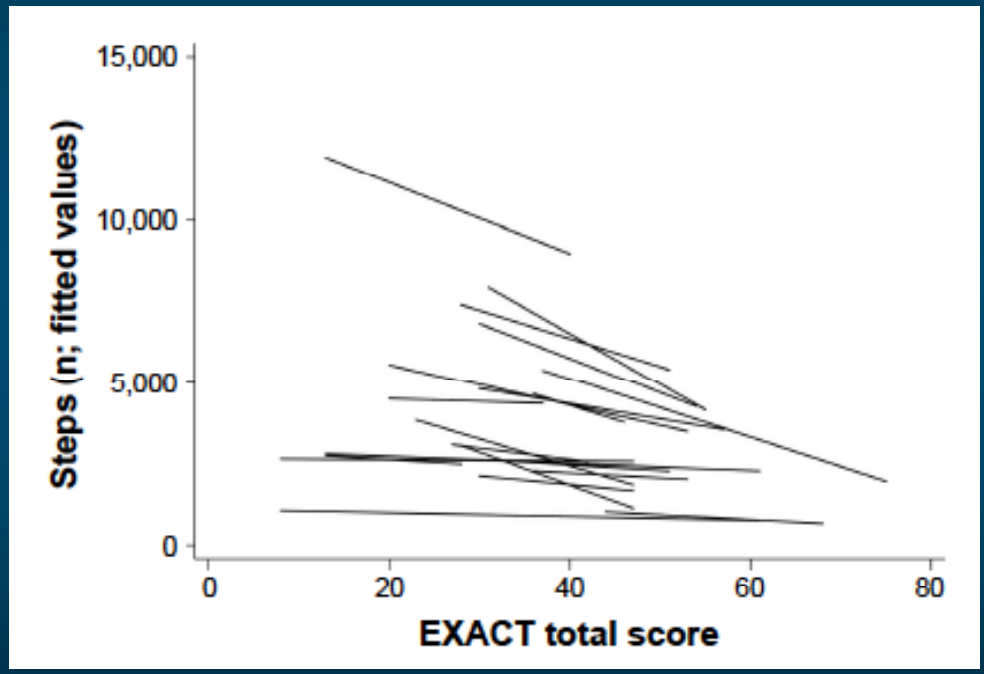
- ↓quality of life[1,2]
- ↑loss of lung function[2]
- ↑hospitalization rate[3]
- ↑use of healthcare resources[4]
- ↑mortality[2]

Donaldson GC, et al *Am J Respir Crit Care Med* 2015; **192**(8): 943-50.
Hurst JR, et al. *N Engl J Med* 2010; **363**(12): 1128-38.
Hurst JR, et al *Am J Respir Crit Care Med* 2009; **179**(5): 369-74.
Donaldson GC, et al *Respir Res* 2013; **14**: 79.

AECOPD are associated with decreased physical activity

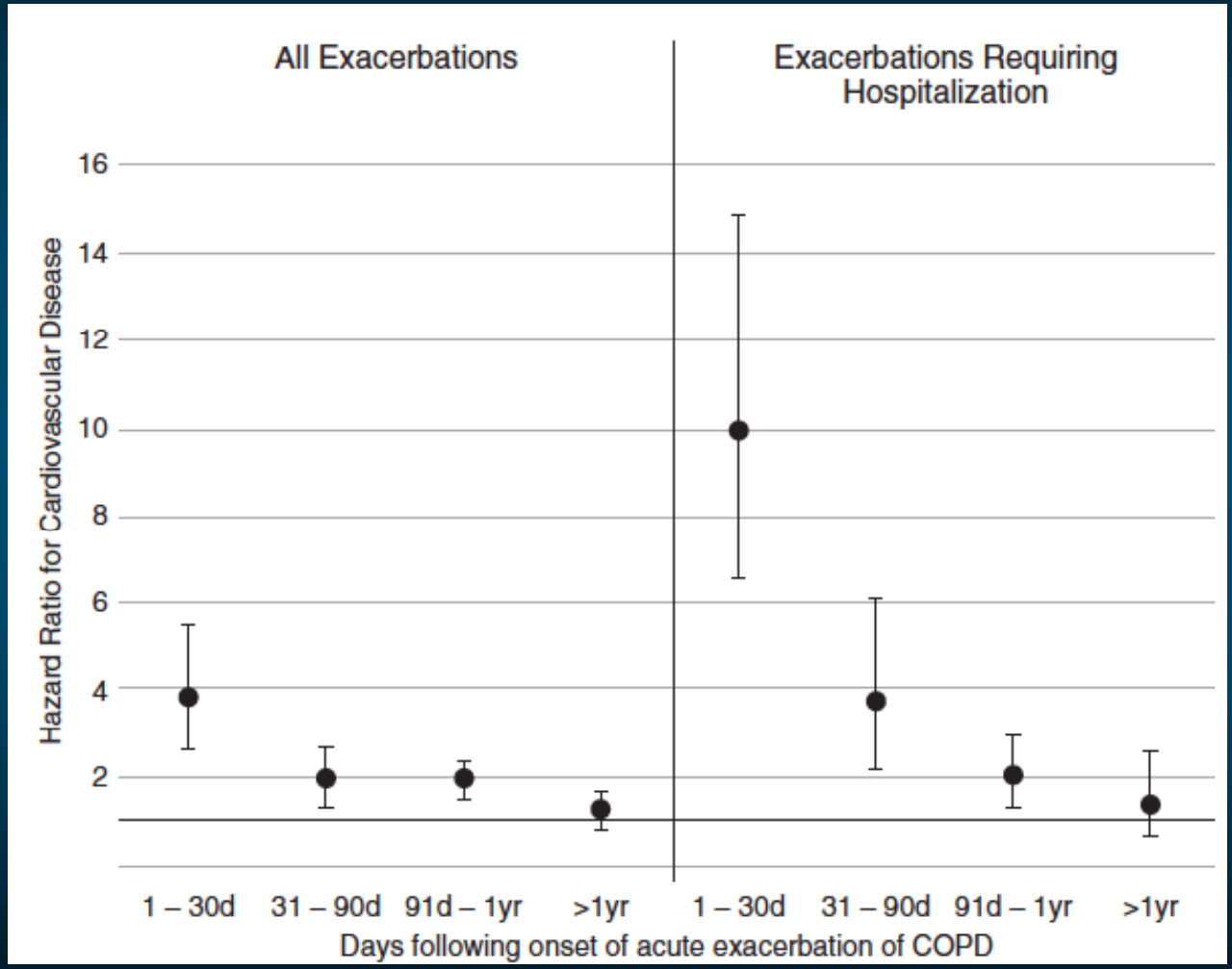






Crook S, et al. *Int J COPD.* 2018; 13: 2199-206.

AECOPD are associated with subsequent increased risk of CV event



Kunisacki KM, et al. *Am J Respir Crit Care Med.* 2018; 198: 51-7.

Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
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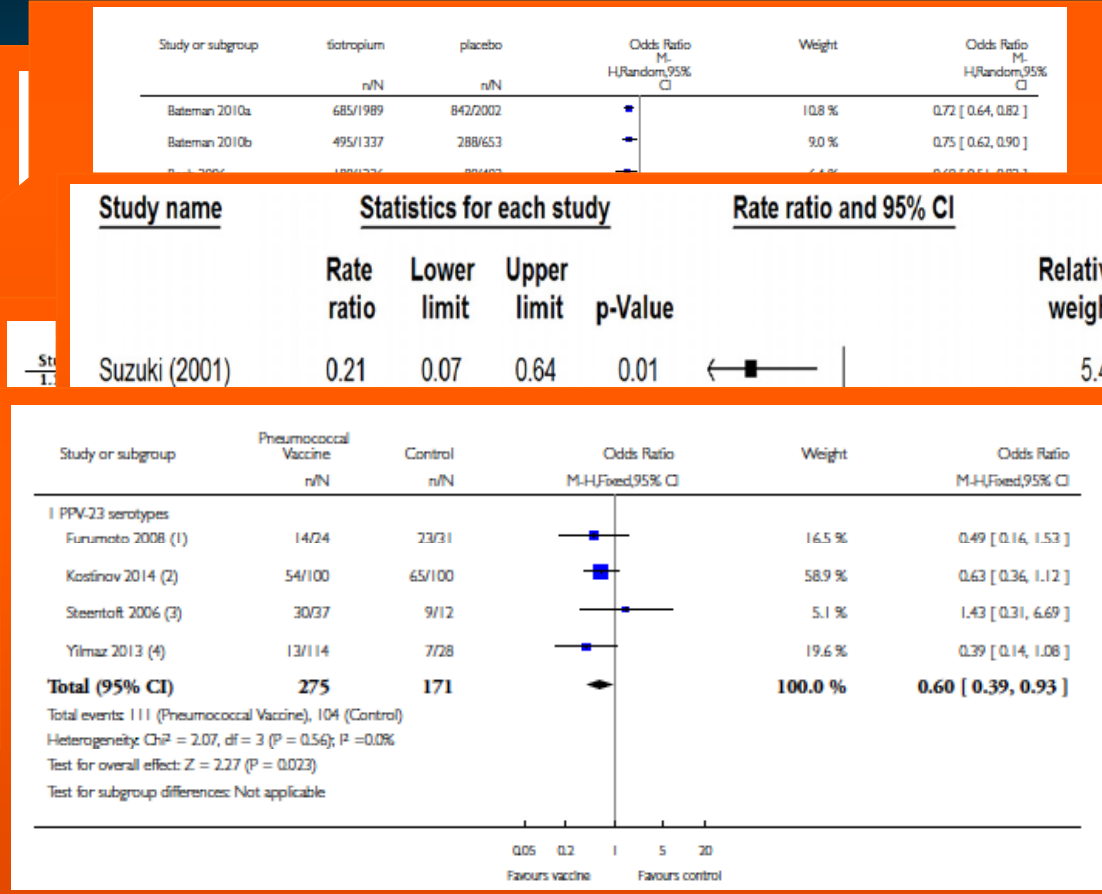
Which of the following has been demonstrated to decrease AECOPD rates

- 1. ICS/LABA
- 2. LAMA
- 3. ICS/LABA/LAMA
- 4. Azithromycin
- 5. All of the above

Multiple agents have been shown to decrease exacerbation rates

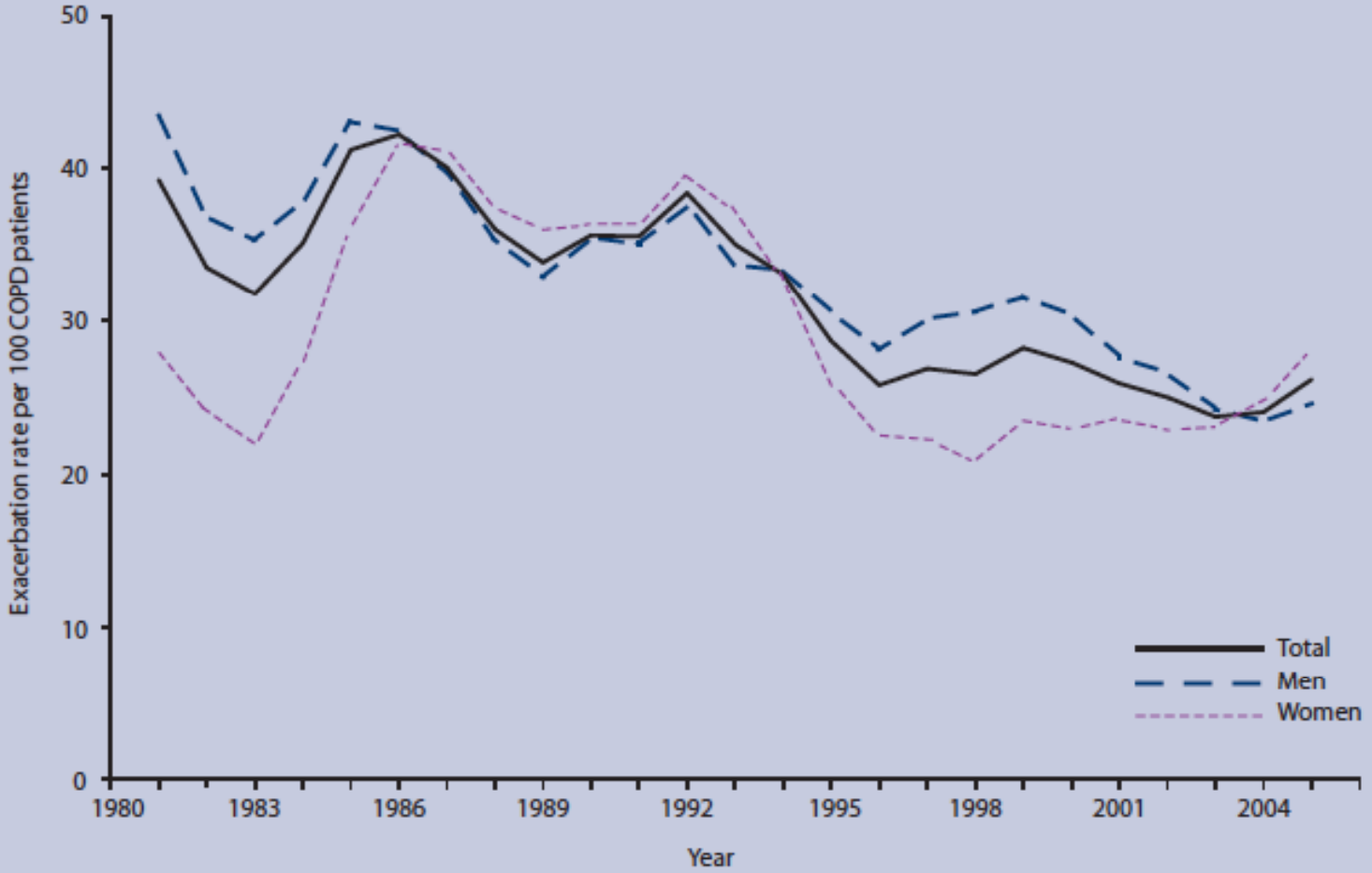
- ICS
- LABA
- ICS/LAB
- LAMA
- LABA/LAMA
- Macrolides
- Vaccines



Walters JAE et al; *Cochrane Database of Systematic Reviews;* Art. No.: CD001390

Horita N et al, *Cochrane Database of Systematic Reviews* 2017; Art. No: CD012066

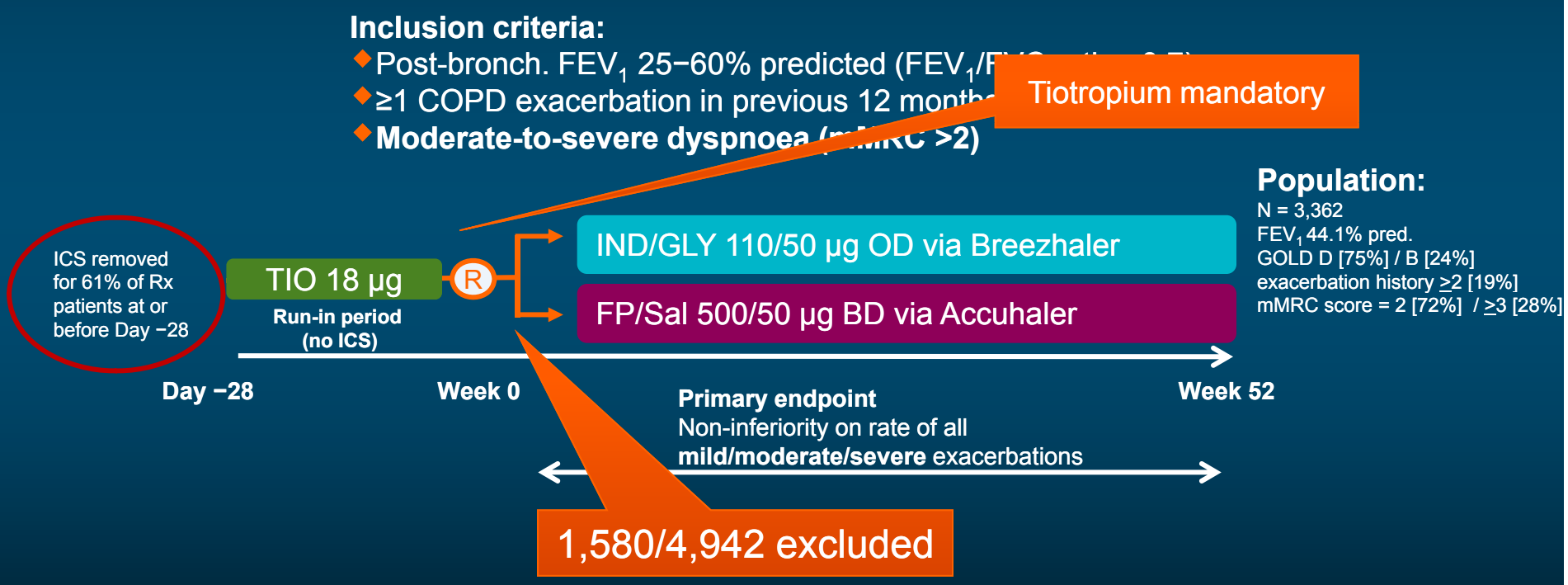
Exacerbation rates in Netherlands have decreased over the past 25 years



Lines start at 1981 (average of 1980, 1981, 1982) and end at 2005 (average of 2004, 2005, 2006).

Bischoff EWMA et al; *Br J Gen Pract* 2009; 59: 927-33

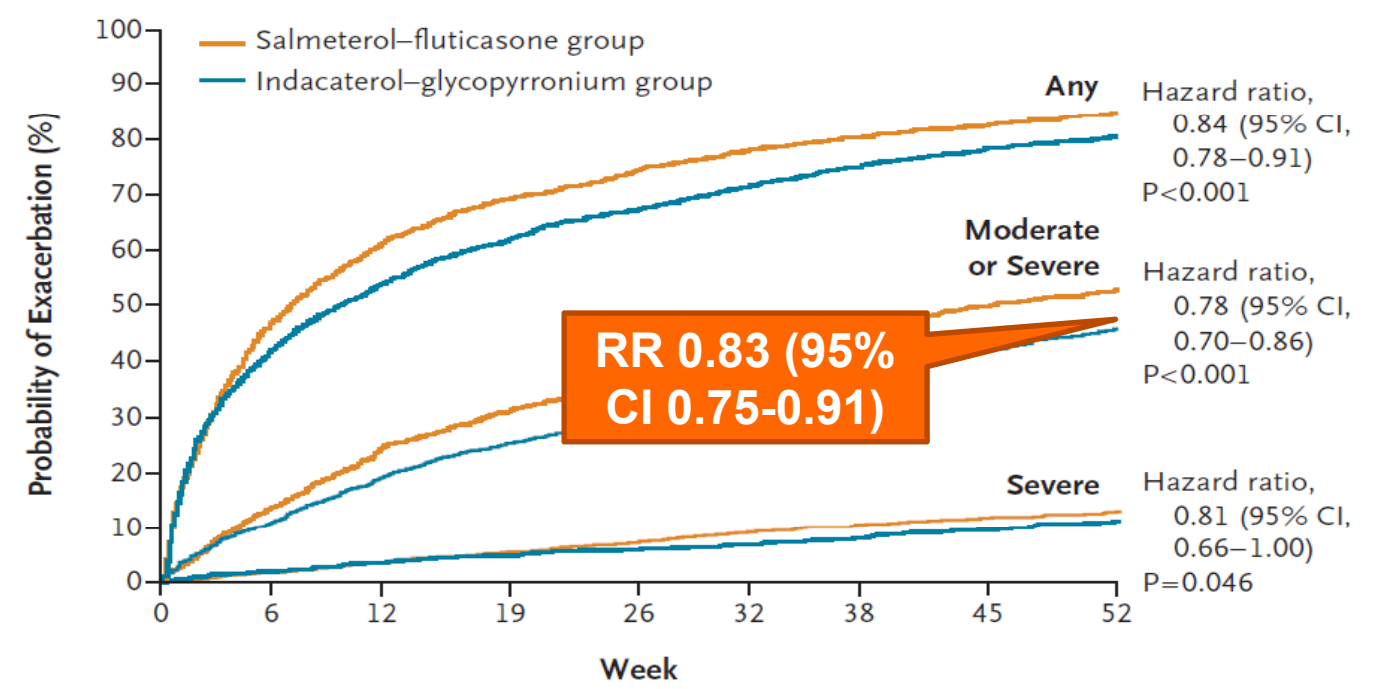
FLAME study design



Wedzicha JA, et al. *N Engl J Med.* 2016;374:2222–2234 (Supplementary Appendix).

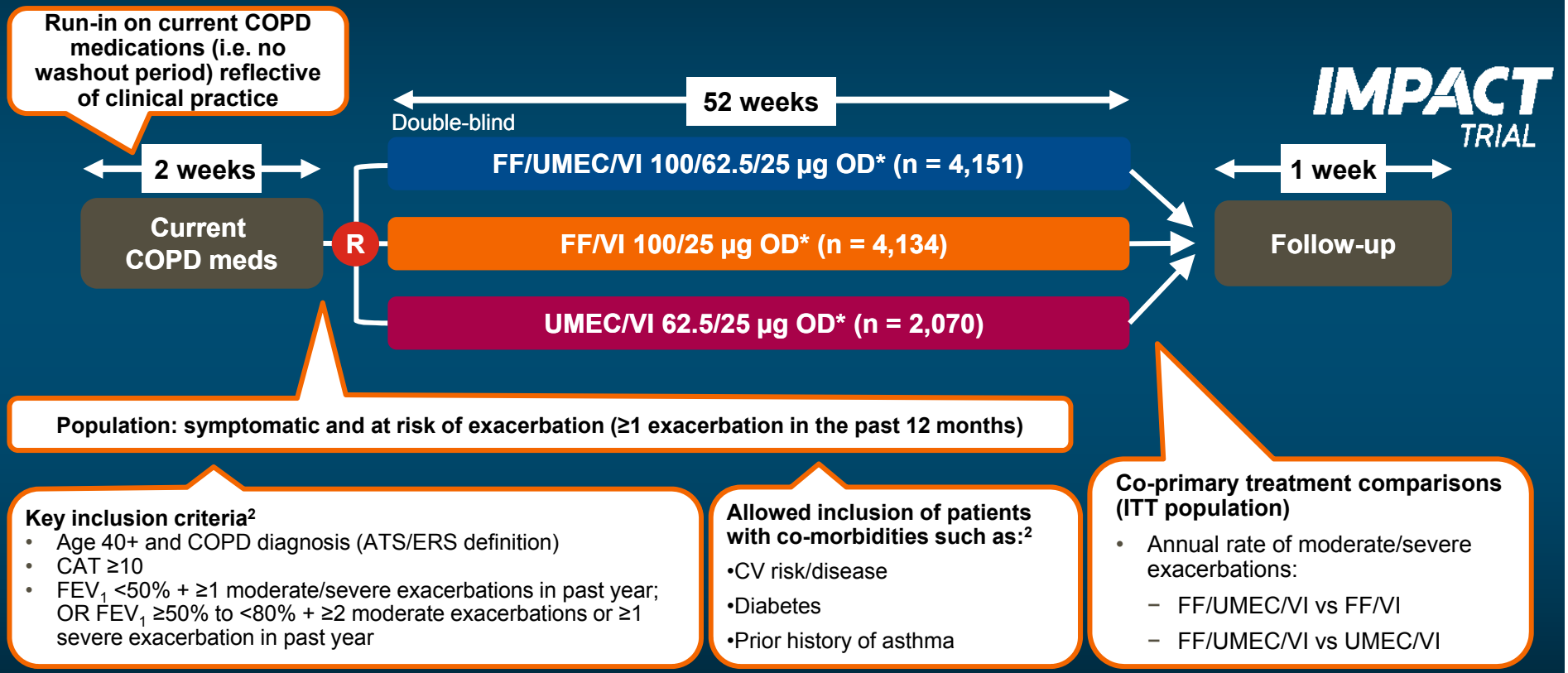
FLAME: Probability of a first mild, moderate or severe exacerbation on treatment

- In a breathless patient population (mMRC≥2) with a prior exacerbation history, dual bronchodilation with QVA149 reduced the risk of all exacerbation types vs. salmeterol-fluticasone proprionate



Wedzicha JA, et al. *N Engl J Med* 2016;374:2222–2234

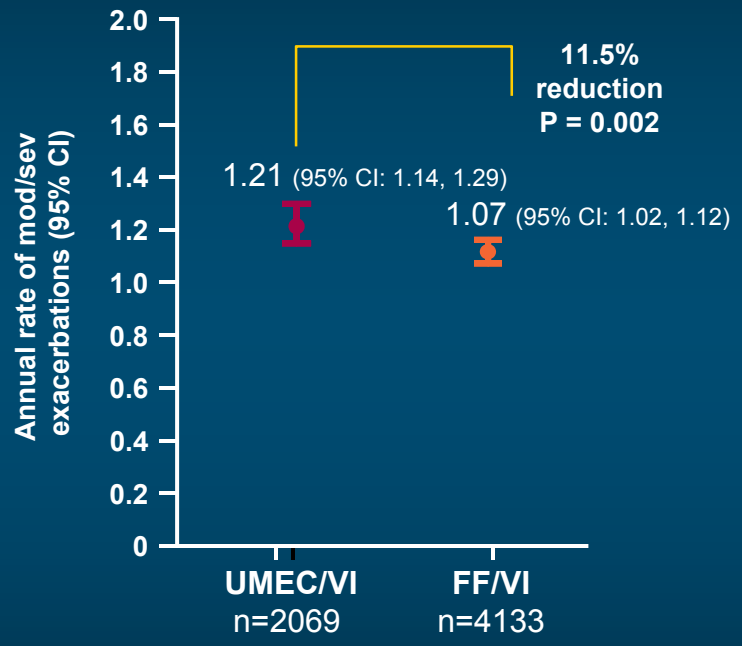
IMPACT: InforMing the PAthway of COPD Treatment study design[1]



* For all combinations, delivered doses were as follows: FF (92 µg), UMEC (55 µg) and VI (22 µg); all treatments were administered via the ELLIPTA inhaler.

1. Lipson DA, et al. *N Engl J Med.* 2018;378:1671–1680; 2. Lipson DA, et al. *N Engl J Med.* 2018;378:1671–1680 (Supplementary Protocol).

ICS/LABA decreased the rate of on-treatment moderate/ severe exacerbations compared with LAMA/LABA



IMPACT TRIAL

Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.

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

How can we attempt to compare FLAME with IMPACT?

IMPACT TRIAL

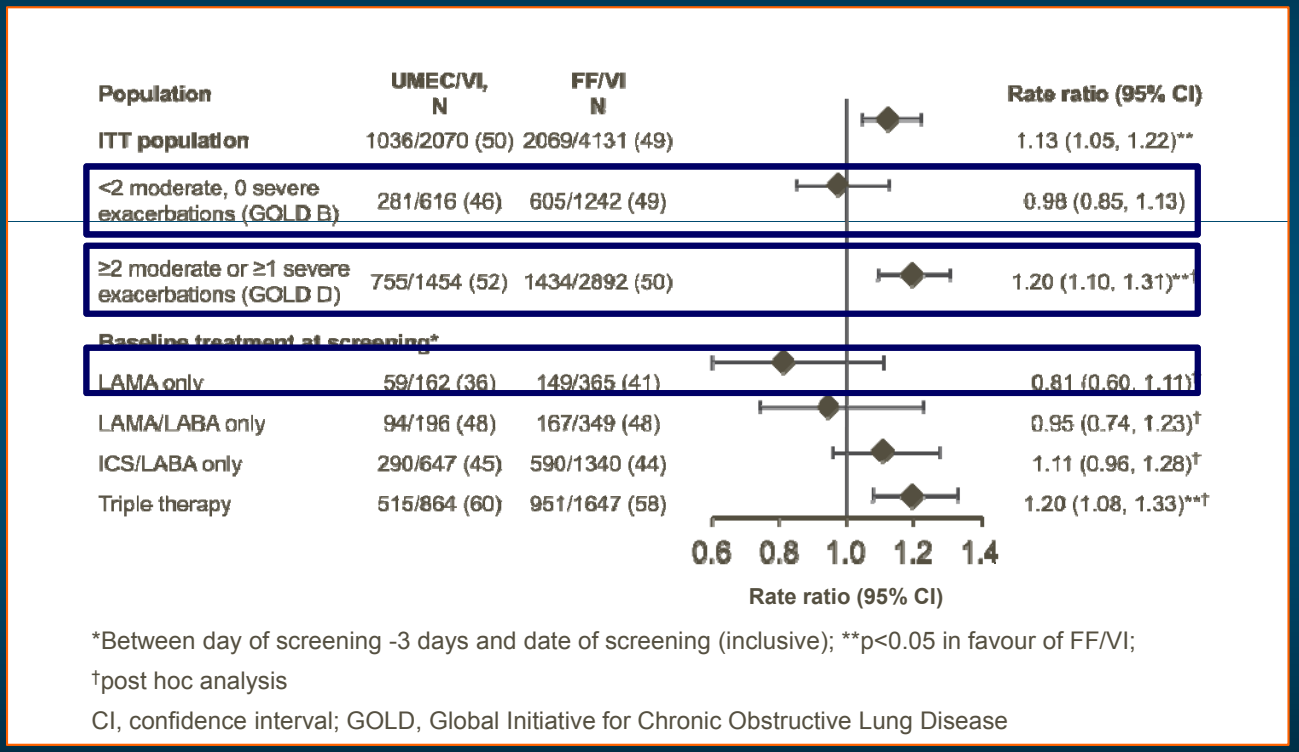
	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)	Overall (N=10355)
Baseline COPD medications,* n (%)				
ICS + LABA + LAMA	1672 (40%)	1647 (40%)	864 (42%)	4183 (40%)
ICS + LABA	1354 (33%)	1340 (32%)	647 (31%)	3341 (32%)
LABA + LAMA	389 (9%)	349 (8%)	196 (9%)	934 (9%)
LAMA	304 (7%)	365 (9%)	162 (8%)	831 (8%)

* These were the most common baseline combinations; treatment combinations may have included phosphodiesterase-4 inhibitor and/or a xanthine

ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist

Lipson DA, ERS Poster PA4384

AECOPD rates in IMPACT by prior exacerbation history or baseline therapy



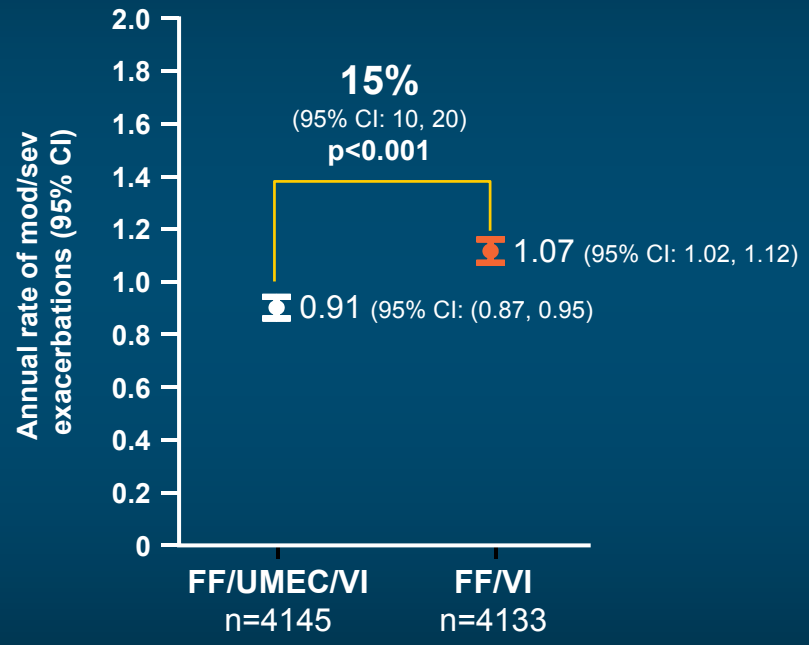
*Between day of screening -3 days and date of screening (inclusive); **p<0.05 in favour of FF/VI;

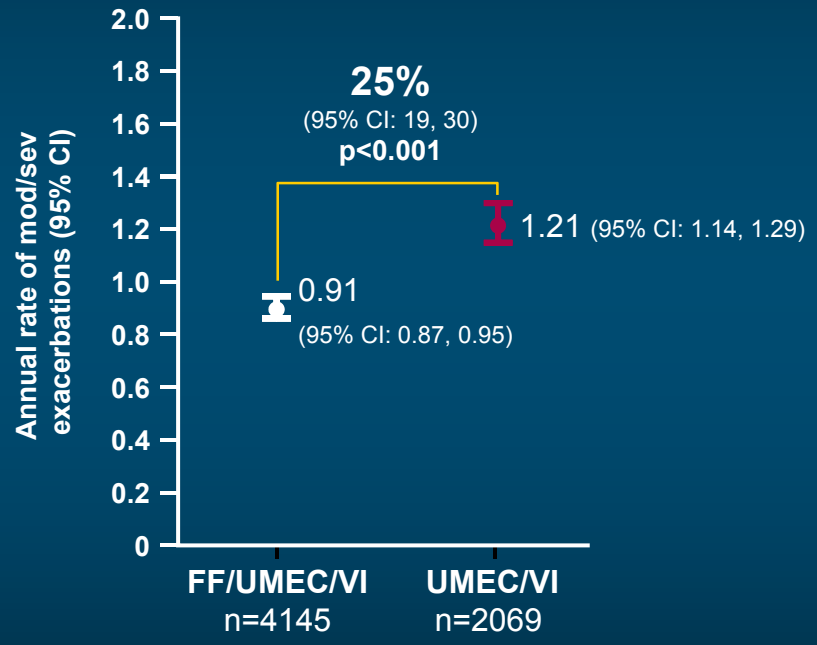
†post hoc analysis

CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Lipson DA, et al. *ERS 2018; Poster PA4384*

LABA/LAMA/ICS reduces moderate/severe exacerbations compared with individual dual combinations in same device





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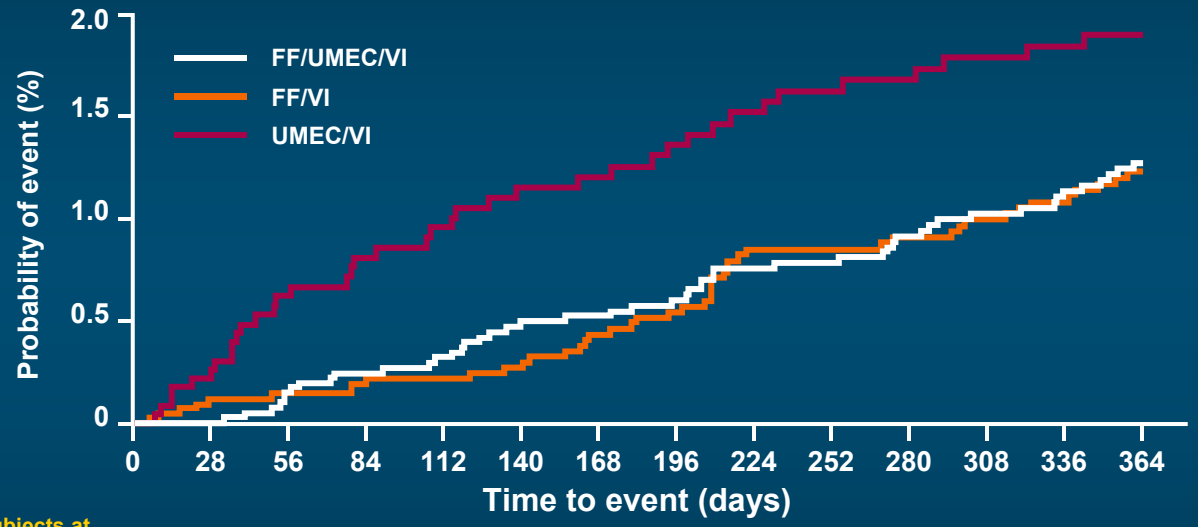
Lipson DA, et al. *N Engl J Med*. 2018; 378: 1671-80

ICS is associated with improved all-cause mortality (on-treatment data) in IMPACT[1,2]



Number of subjects at risk														
FF/UMEC/VI	4151	4082	3968	3898	3838	3752	3714	3690	3613	3581	3545	3486	3454	3346
FF/VI	4134	3984	3798	3694	3619	3496	3443	3391	3291	3258	3230	3182	3152	3044
UMEC/VI	2070	1993	1880	1820	1769	1713	1685	1656	1612	1595	1578	1548	1531	1485

Relative risk reduction:

FF/UMEC/VI vs UMEC/VI

42.1%

HR 0.58
(95% CI: 0.38, 0.88)
p=0.011

FF/VI vs UMEC/VI

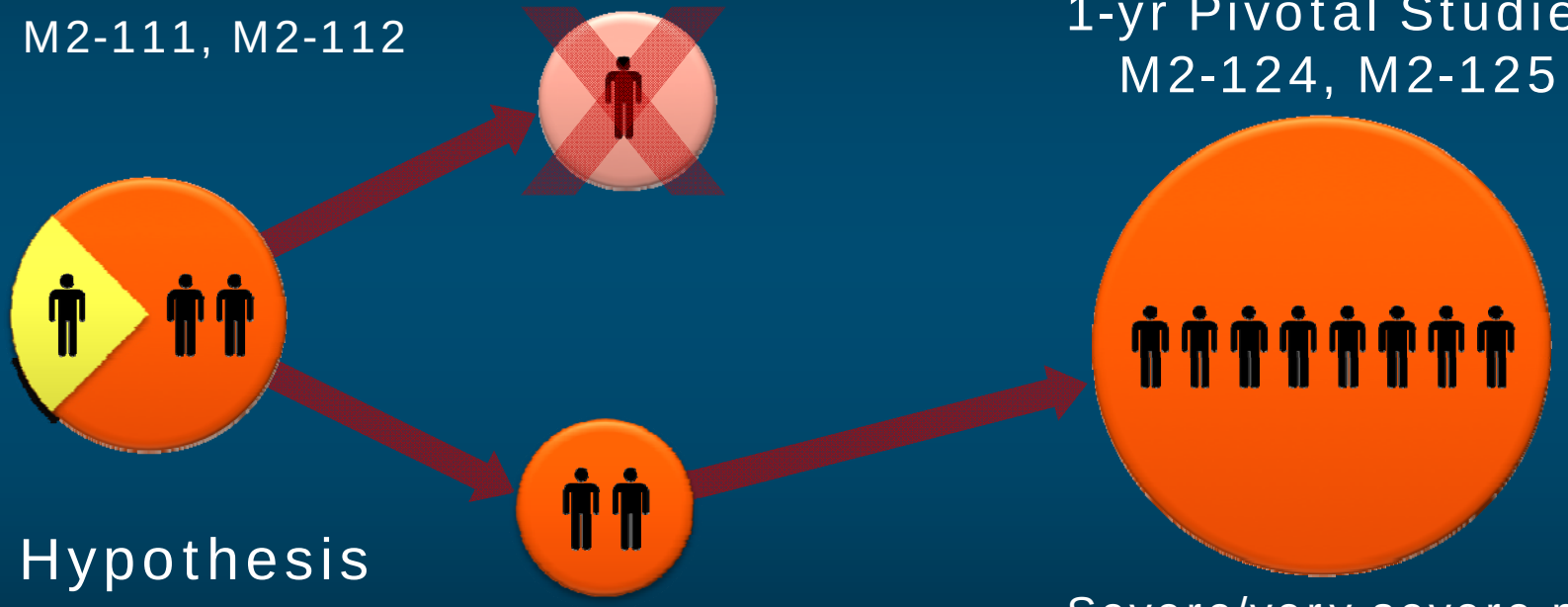
38.7%

HR 0.61
(95% CI: 0.40, 0.93)
p=0.022

1. Lipson DA, et al. ATS 2018; 2. Lipson DA, et al. *N Engl J Med*. 2018; 378: 1671-80

EVOLUTION OF ROFLUMILAST PROGRAM
IDENTIFICATION OF TARGET PATIENT POPULATION

Subgroup analyses of early Phase III Studies M2-111, M2-112

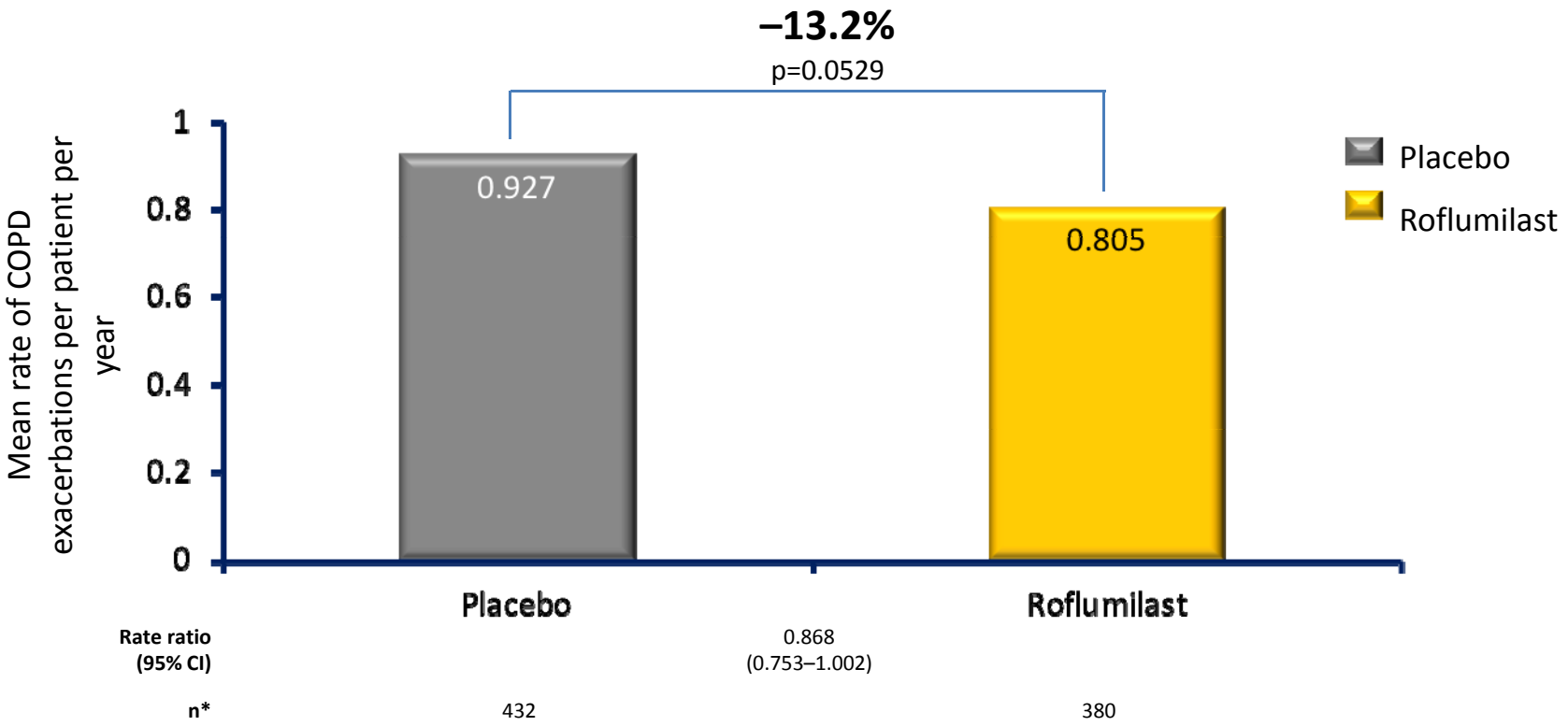


Hypothesis Generation

Confirmatory 1-yr Pivotal Studies M2-124, M2-125

- Severe/very severe patients
- History of chronic cough and sputum
- History of exacerbations

In the primary analysis (Poisson regression, ITT), roflumilast reduced the rate of moderate or severe exacerbations by 13.2% (p=0.0529)

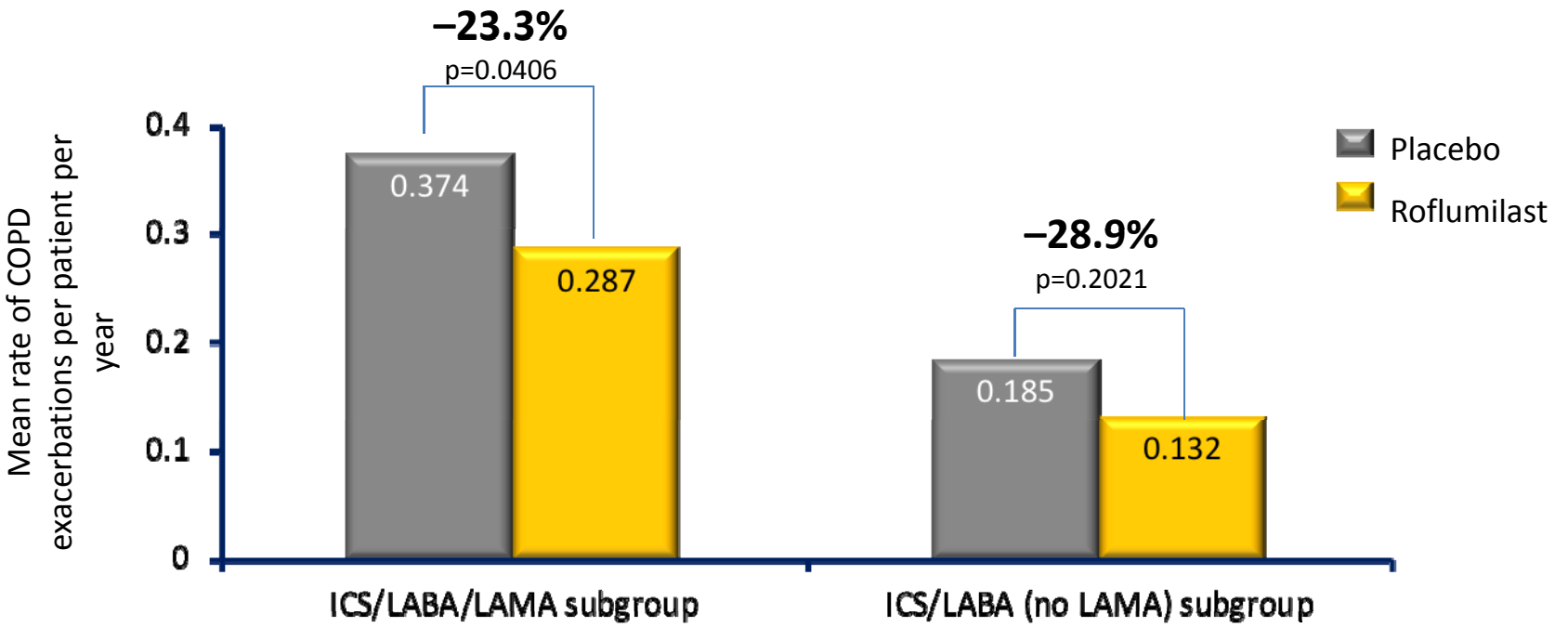


	Placebo		Roflumilast
Rate ratio (95% CI)		0.868 (0.753–1.002)	
n*	432		380

CI: confidence interval; ITT: intention to treat
*Patients experiencing at least one exacerbation
Rate ratios, 95% CI and p-values are based on a Poisson regression analysis in the ITT population

MARTINEZ FJ ET AL . *LANCET* 2015; 385: 857-66

In patients receiving ICS/LABA/LAMA, roflumilast significantly reduced the rate of severe exacerbations



Rate ratio (95% CI)	0.767 (0.595–0.989)	0.711 (0.421–1.201)
n*	152 125	40 26

*Patients experiencing at least one exacerbation; rate ratios, 95% CI and p-values are based on a negative binomial regression analysis in the ITT population

MARTINEZ FJ ET AL . *LANCET* 2015; 385: 857-66

Objectives

- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?

Benefit–risk balance should be tailored to individual patient characteristics

Individual presentation and underlying mechanisms

- Mortality
- Disease progression
- Lung function
- Symptoms: cough, sputum production, and dyspnea
- Exercise tolerance
- Exacerbations
- Disability
- Health status and quality of life

Individualization of treatment choices in COPD

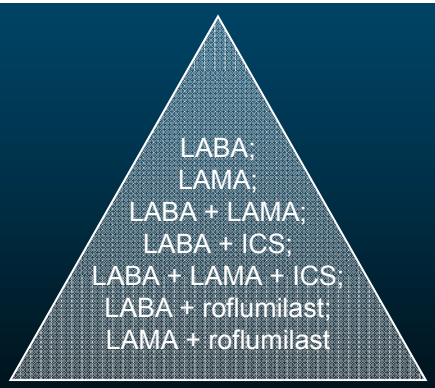
Individual risk factors and comorbidities

- Pneumonia
- Tuberculosis
- Skin bruising
- Osteoporosis or fractures
- Muscle dysfunction
- Nutritional impairment
- Cataract
- Diabetes
- Tremor
- Cardiovascular events
- Neuropsychological events
- Gastrointestinal symptoms

Expected benefits

Present COPD pharmacological treatments

Expected risks



Woodruff PG, et al. Lancet 2015;385:1789–98

71-year-old with 4-year history of exertional breathlessness, osteoporosis with past compression fracture, rheumatic fever, syringomyelia, and past pneumonia. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA.

He has experienced a hospitalization since your last visit.

His eosinophil count is 100.

What is would be your therapy?

1.LAMA/LABA

2.ICS/LABA

3.ICS/LABA + LAMA

4.LABA/LAMA + ICS

71-year-old with 4-year history of exertional breathlessness, osteoporosis with past compression fracture, rheumatic fever, syringomyelia, and past pneumonia. He noted no sputum production but notes worse breathlessness.

He has CAT of 20 and mMRC of 2.

He has been taking a LAMA.

He has experienced a hospitalization since your last visit.

His eosinophil count is 300.

What is would be your therapy?

1.LAMA/LABA

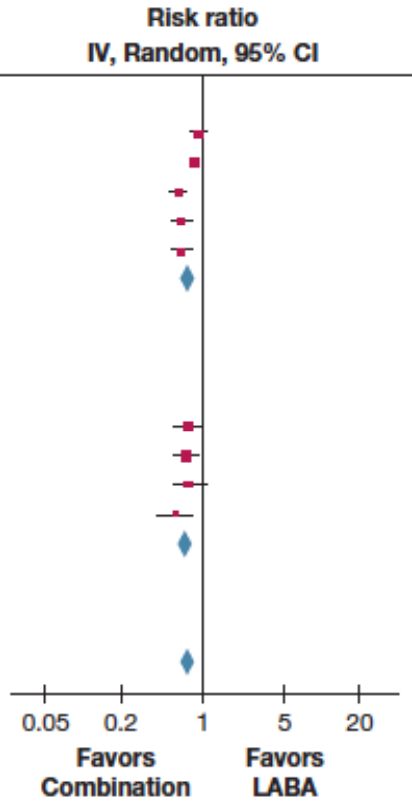
2.ICS/LABA

3.ICS/LABA + LAMA

4.LABA/LAMA + ICS

ICS/LABA decreases AECOPD compared too LABA monotherapy

Study or Subgroup	log[Rate ratio]	SE	Weight	Risk ratio IV, Random, 95% CI	Year
1.1.1 Fluticasone/salmeterol					
TRISTAN	-0.07	0.0734	13.4%	0.93 (0.81-1.03)	2003
TORCH	-0.13	0.044	16.0%	0.88 (0.81-0.93)	2004
Kardos 2007	-0.4308	0.073	13.5%	0.65 (0.56-0.75)	2004
Ferguson 2008	-0.3638	0.091	11.8%	0.70 (0.58-0.83)	2008
Anzueto 2009	-0.3624	0.091	11.8%	0.70 (0.58-0.83)	2009
Subtotal (95% CI)			**66.6%**	**0.77 (0.66-0.89)**	
Heterogeneity: Tau² = 0.02; χ^2 = 21.64, df = 4 (*P* = .0002); I^2 = 82%					
Test for overall effect: *z* = 3.56 (*P* = .00004)					
1.1.2 Budesonide/formoterol					
Szafranski 2003	-0.26	0.125	9.1%	0.77 (0.60-0.99)	2003
Calverley 2003	-0.294	0.12	9.4%	0.75 (0.59-0.94)	2003
Tashkin 2008	-0.2357	0.15	7.5%	0.79 (0.59-1.03)	2008
Rennard 2009	-0.4943	0.15	7.5%	0.61 (0.45-0.82)	2009
Subtotal (95% CI)			**33.4%**	**0.73 (0.64-0.83)**	
Heterogeneity: Tau² = 0.00; χ^2 = 1.03, df = 3 (*P* = .60); I^2 = 0%					
Test for overall effect: *z* = 4.66 (*P* < .00001)					
Total (95% CI)			**100.0%**	**0.76 (0.68-0.81)**	
Heterogeneity: Tau² = 0.02; χ^2 = 25.18, df = 8 (*P* = .001); I^2 = 68%					
Test for overall effect: *z* = 5.22 (*P* < .00001)					
Test for subgroup differences: χ^2 = 0.24, df = 1 (*P* = .63), I^2 = 0%					



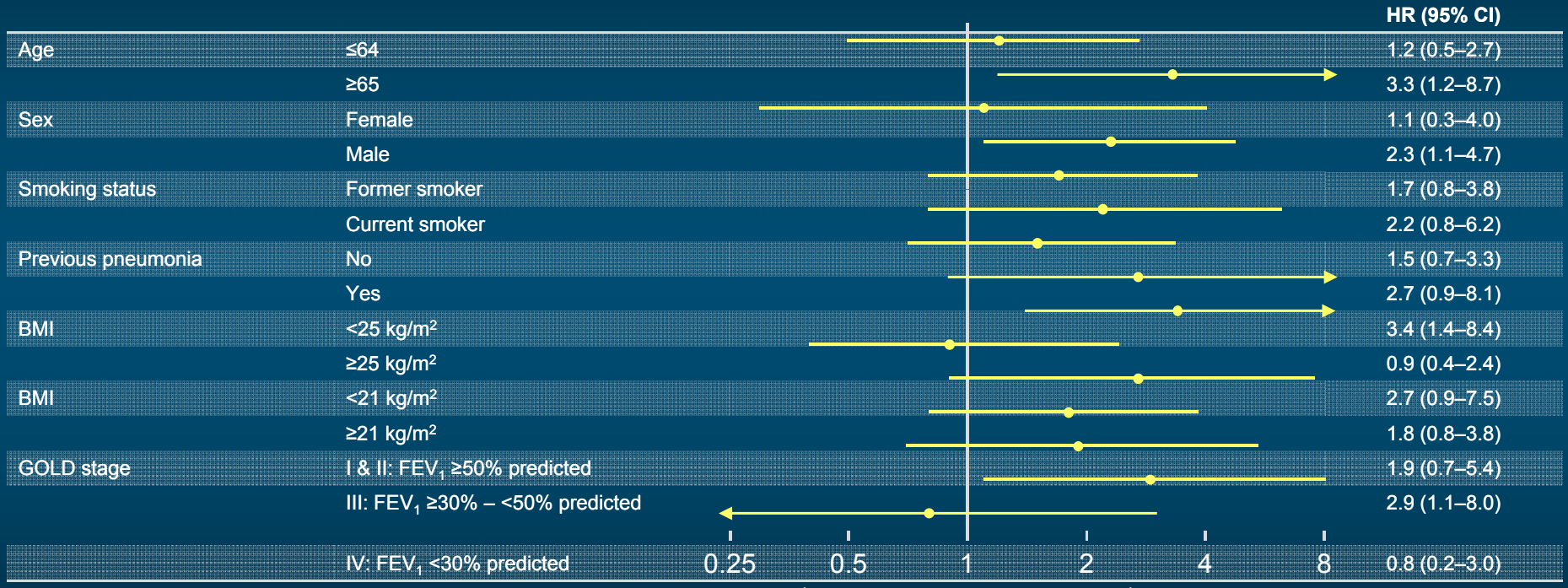
Nannini LJ et al. *Cochrane Database Syst Rev 2012; 9:CD006829*

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risk of pneumonia with inhaled corticosteroid-containing medicines when used to treat COPD.

The PRAC review confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view is that the benefits of inhaled corticosteroids continue to outweigh their risks

14/07/2016 EMA/488280/2016

Risk factors associated with CXR confirmed pneumonia in COPD patients treated with ICS

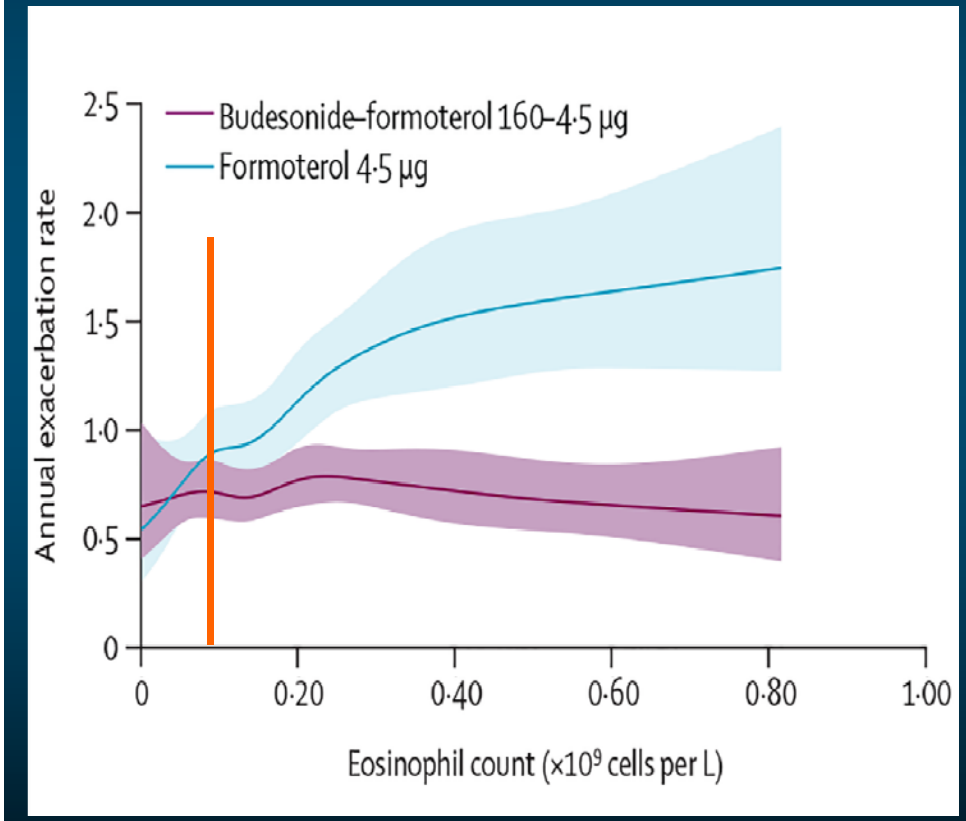


Risk factors associated with pneumonia was a secondary endpoint. The primary endpoint was the annual rate of moderate (requiring treatment with SCS and/or antibiotics) and severe (necessitating hospitalization) exacerbations)

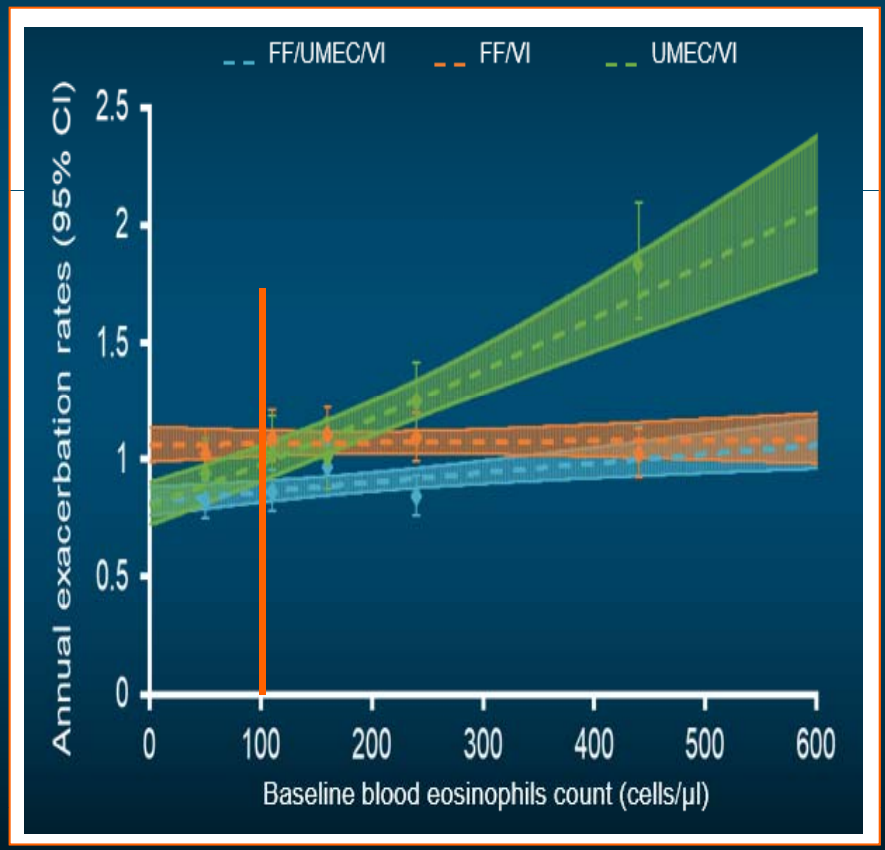
BMI, body mass index; CXR, chest x-ray; VI, vilanterol.

Crim C, et al. Ann Am Thorac Soc 2015;12:27–34

Eosinophil Count Associates in continuous fashion with Response to ICS/LABA compared with LABA Alone

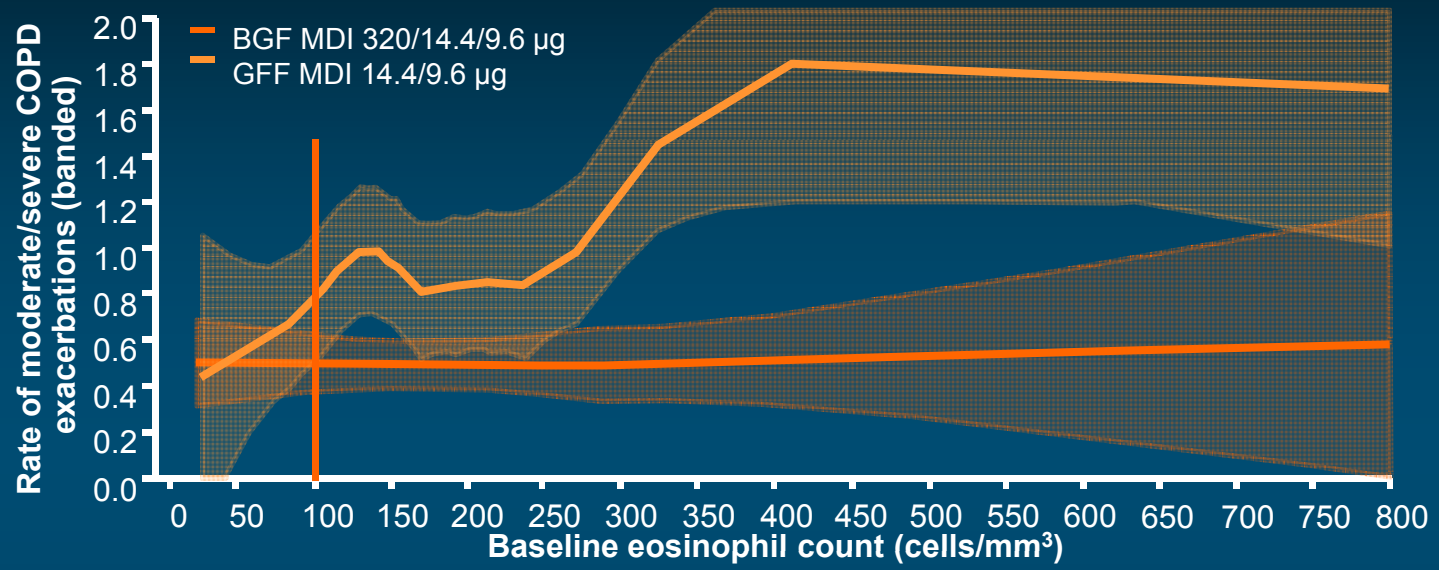


Bafadhel M et al, *Lancet Respir Med* 2018;6:117-126.

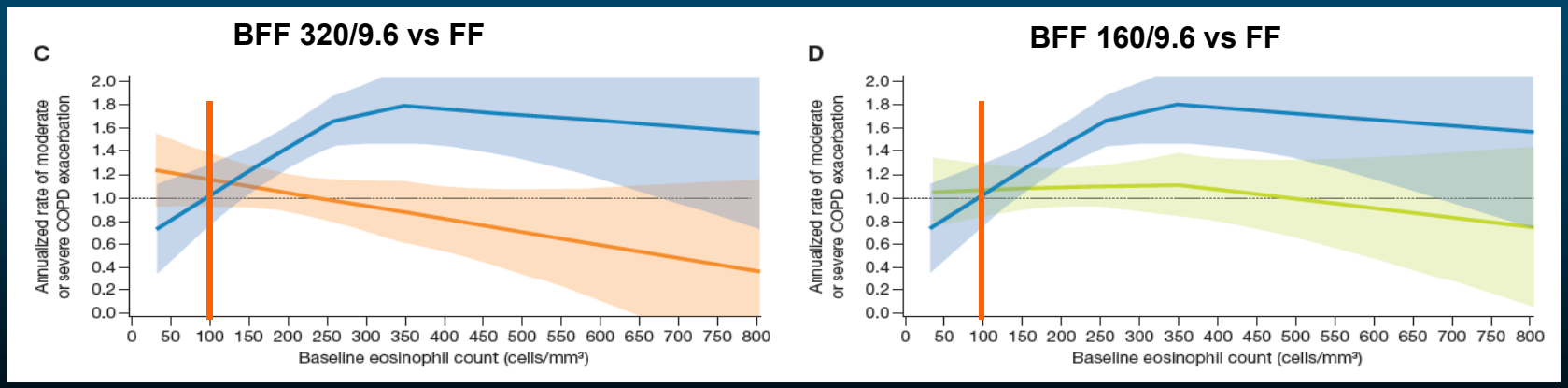


Pascoe S, et al. ERS 2018. Oral Presentation OA2127

Budesonide/formoterol vs LABA/LAMA (KRONOS) or LABA (SOPHOS)



PT010 (BGF) is in development and is not currently licensed for use in COPD
BGF, budesonide, glycopyrronium and formoterol fumarate; FEV_1, forced expiratory volume in 1 second; GFF, glycopyrronium and formoterol fumarate
Ferguson GT, et al. Lancet Respir Med 2018; doi 10.1016/S2213-2600(18)30327-8 [Epub ahead of print]



Hanania N et al (ATS 2019)

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3.ICS/LABA/LAMA

4.Azithromycin

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4.Azithromycin

Treatment of stable COPD

- Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 4.2**).
- Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be needed.

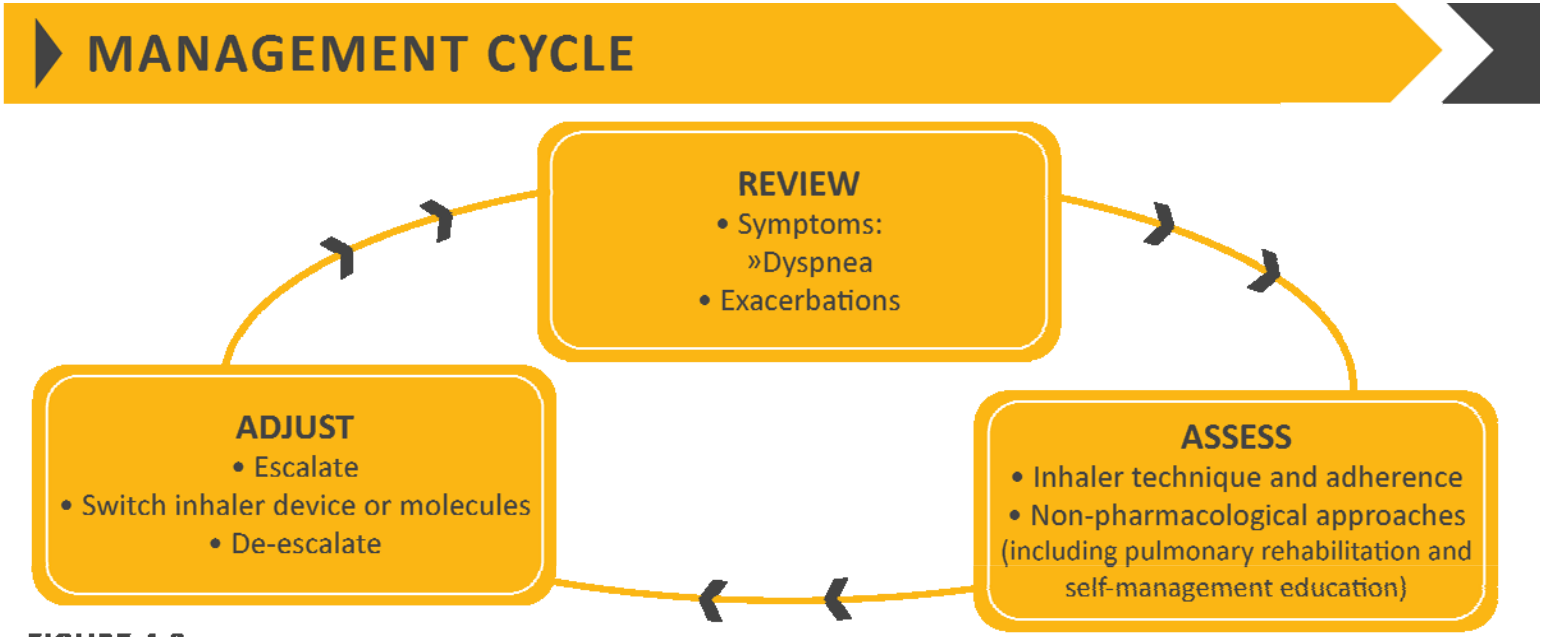


FIGURE 4.2

ABCD assessment tool

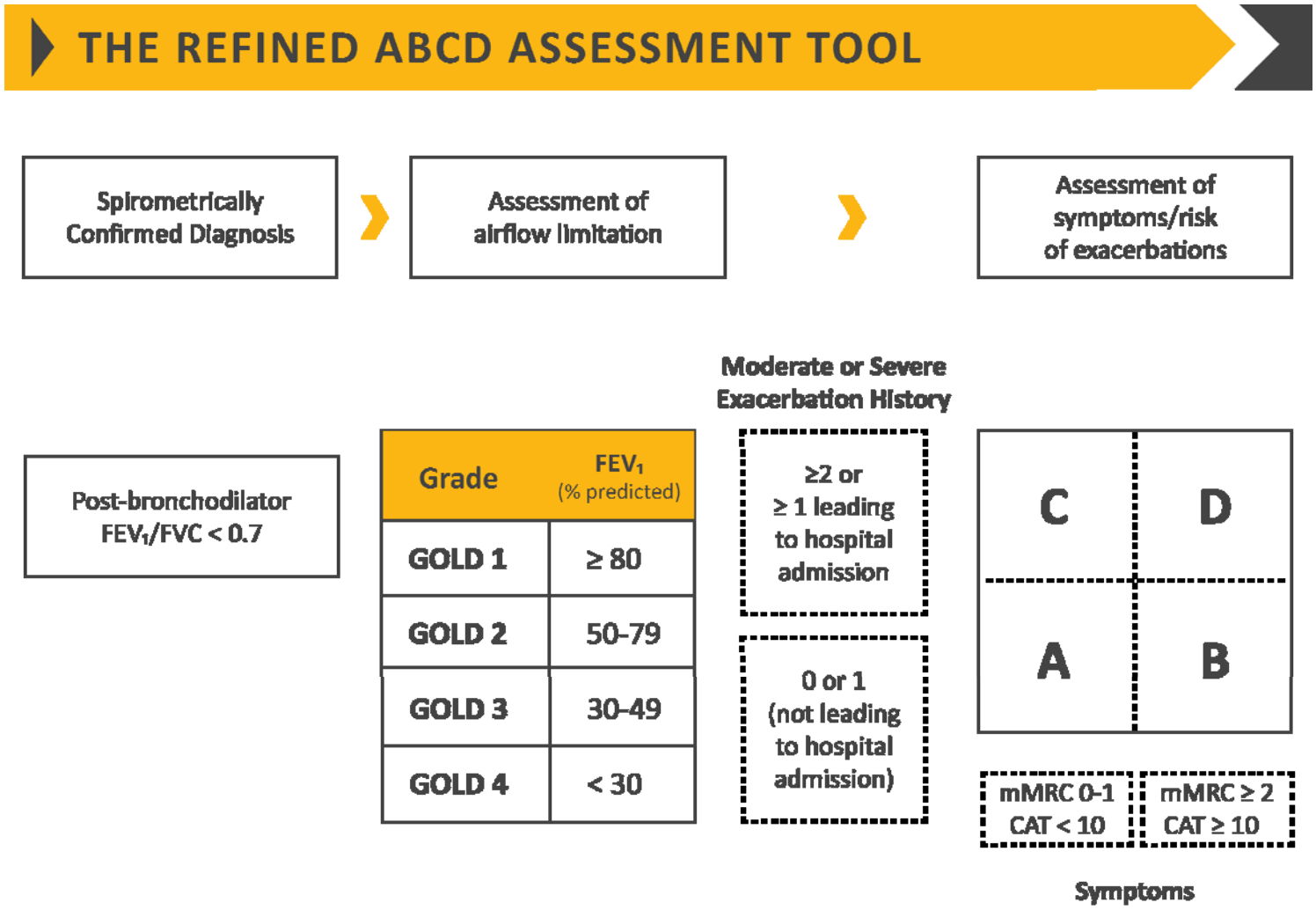


FIGURE 2.4

Treatment of stable COPD

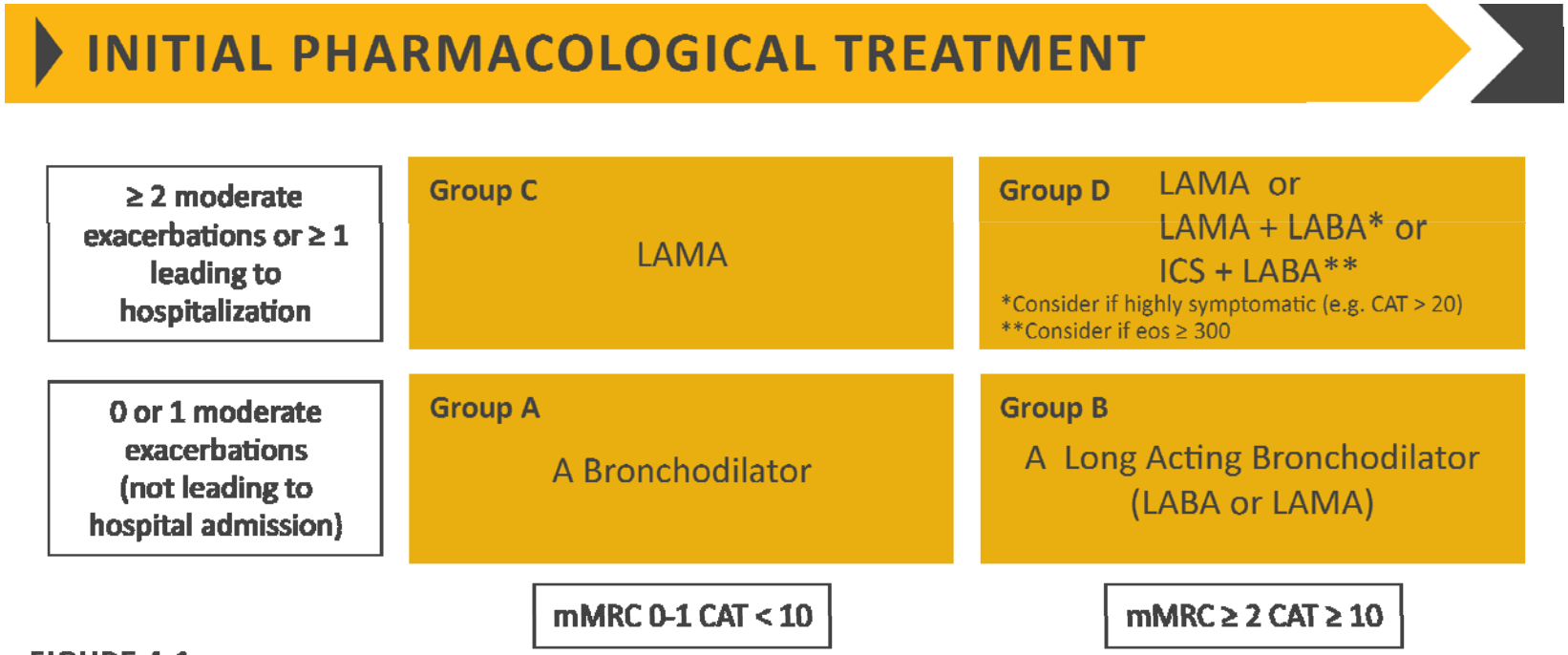
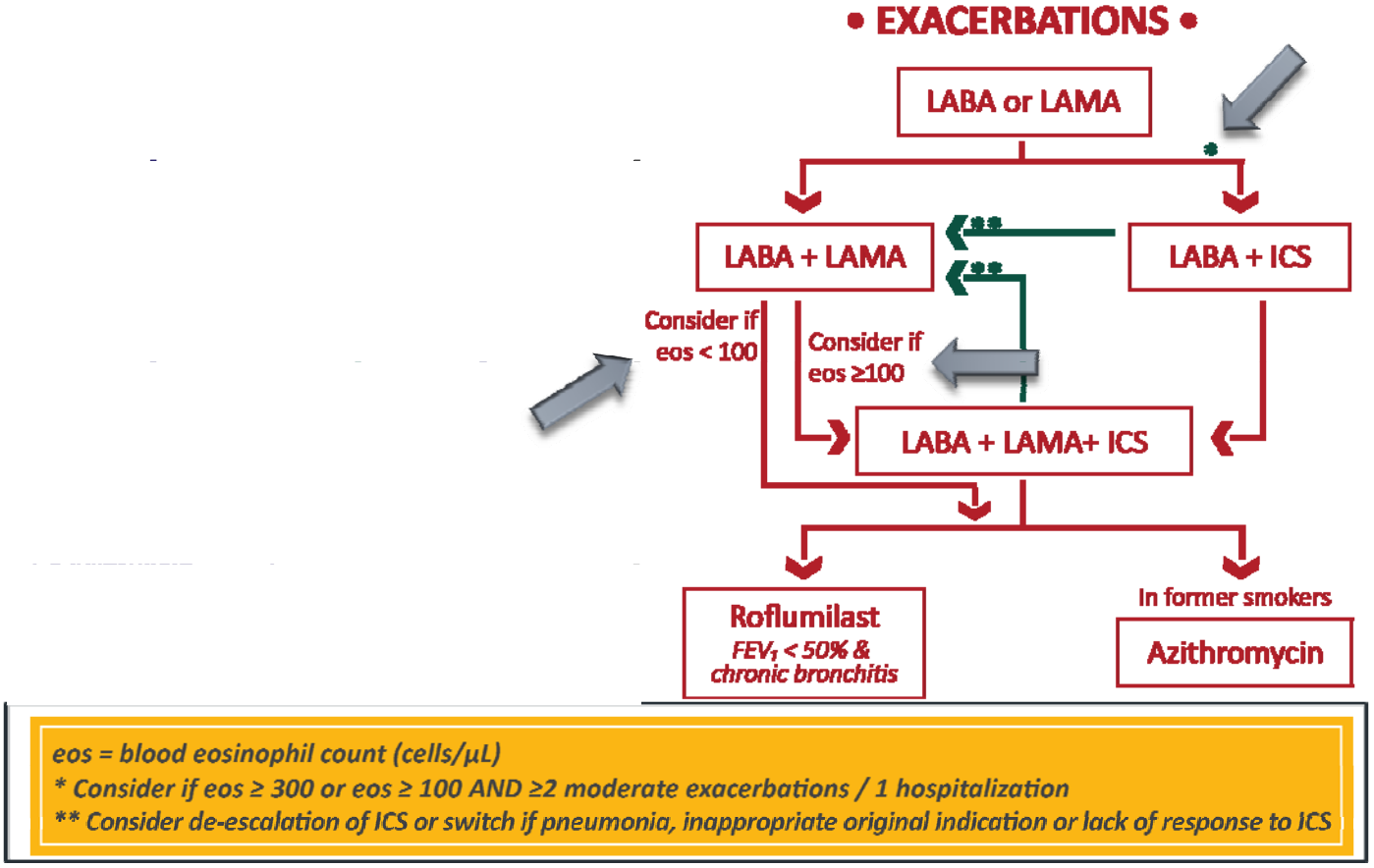


FIGURE 4.1

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

A 63 year old man has known severe COPD (FEV1 40% predicted), no chronic sputum production, CAD (S/P PCI two years ago and 2 acute exacerbations two years ago. Since that time he has been remarkably stable while on inhaled LAMA/LABA/ICS.

He has CAT of 20 and mMRC of 2.

His eosinophil count is 300.

What would you do therapeutically at this point?

1. Prescribe chronic azithromycin (MWF)
2. Add roflumilast
3. No change in therapy
4. Discontinue ICS
5. Discontinue the LAMA

ICS Withdrawal – controversy continues

POINT:

Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 ($30\% \leq FEV_1 < 50\%$ Predicted) COPD? Yes

James D. Chalmers, MD, PhD
Dundee, Scotland

PODCAST

COUNTERPOINT:

Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 ($30\% \leq FEV_1 < 50\%$ Predicted) COPD? No

Ian D. Pavord, FMedSci
Oxford, England

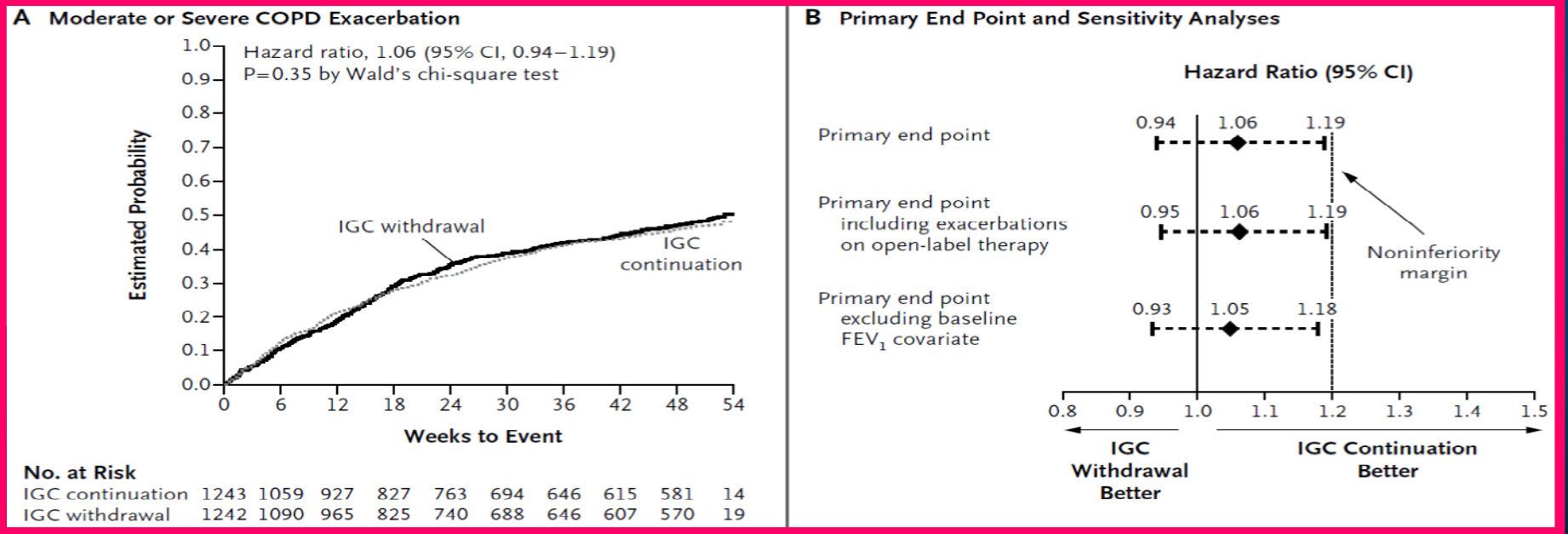
PODCAST

Chalmers JD *Chest* 2018; 153: 778-82
Pavord ID. Chest 2018; 153: 782-4

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Withdrawal of Inhaled Glucocorticoids



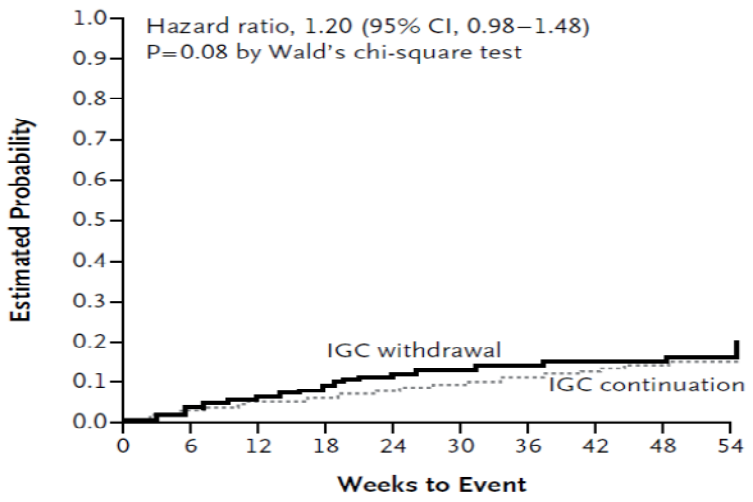
Magnussen et al, *NEJM* 2014; 371: 1285-94

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Withdrawal of Inhaled Glucocorticoids

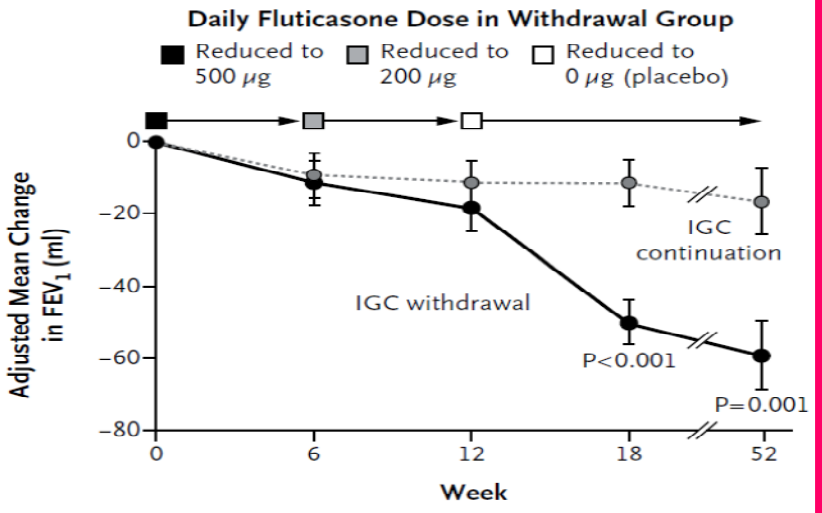
C Severe COPD Exacerbation



No. at Risk

IGC continuation	1243	1180	1117	1066	1026	993	957	928	895	20
IGC withdrawal	1242	1189	1119	1044	986	941	918	889	863	25

D Change from Baseline in Trough FEV_1

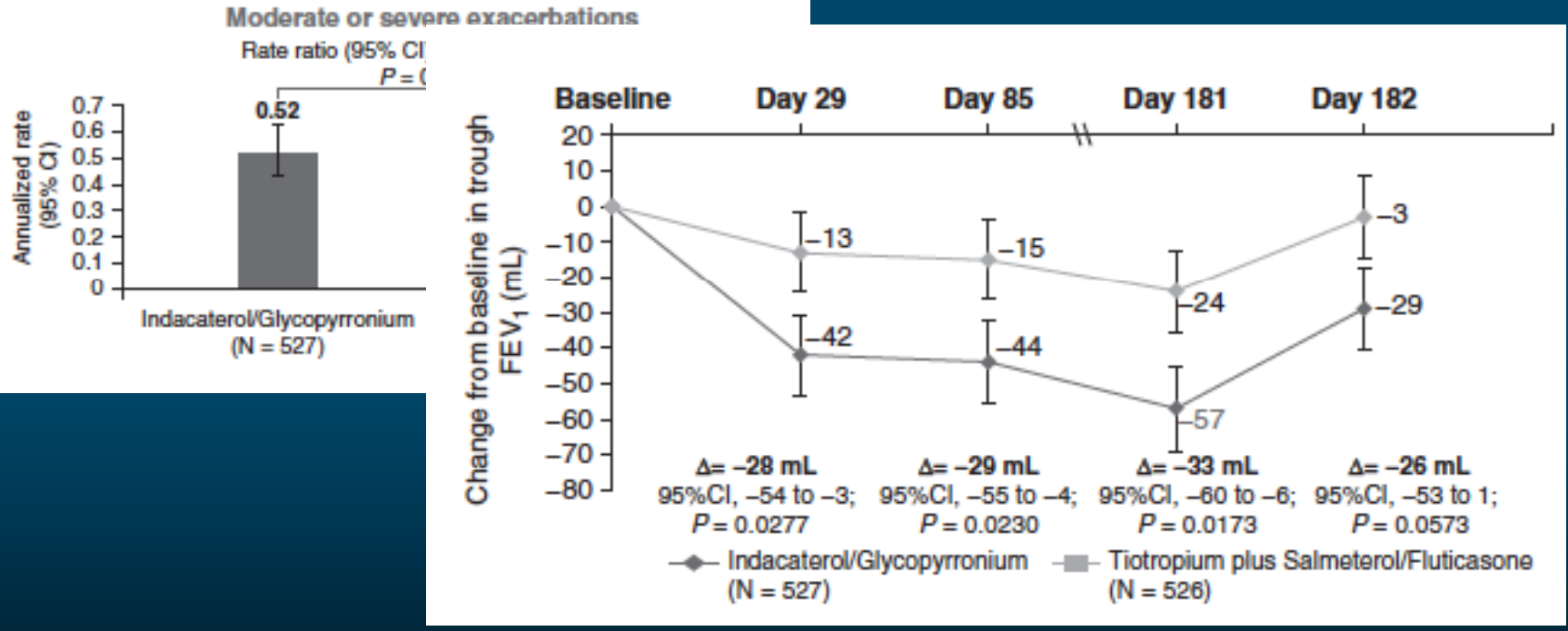


No. at Risk

IGC continuation	1223	1135	1114	1077	970
IGC withdrawal	1218	1135	1092	1058	935

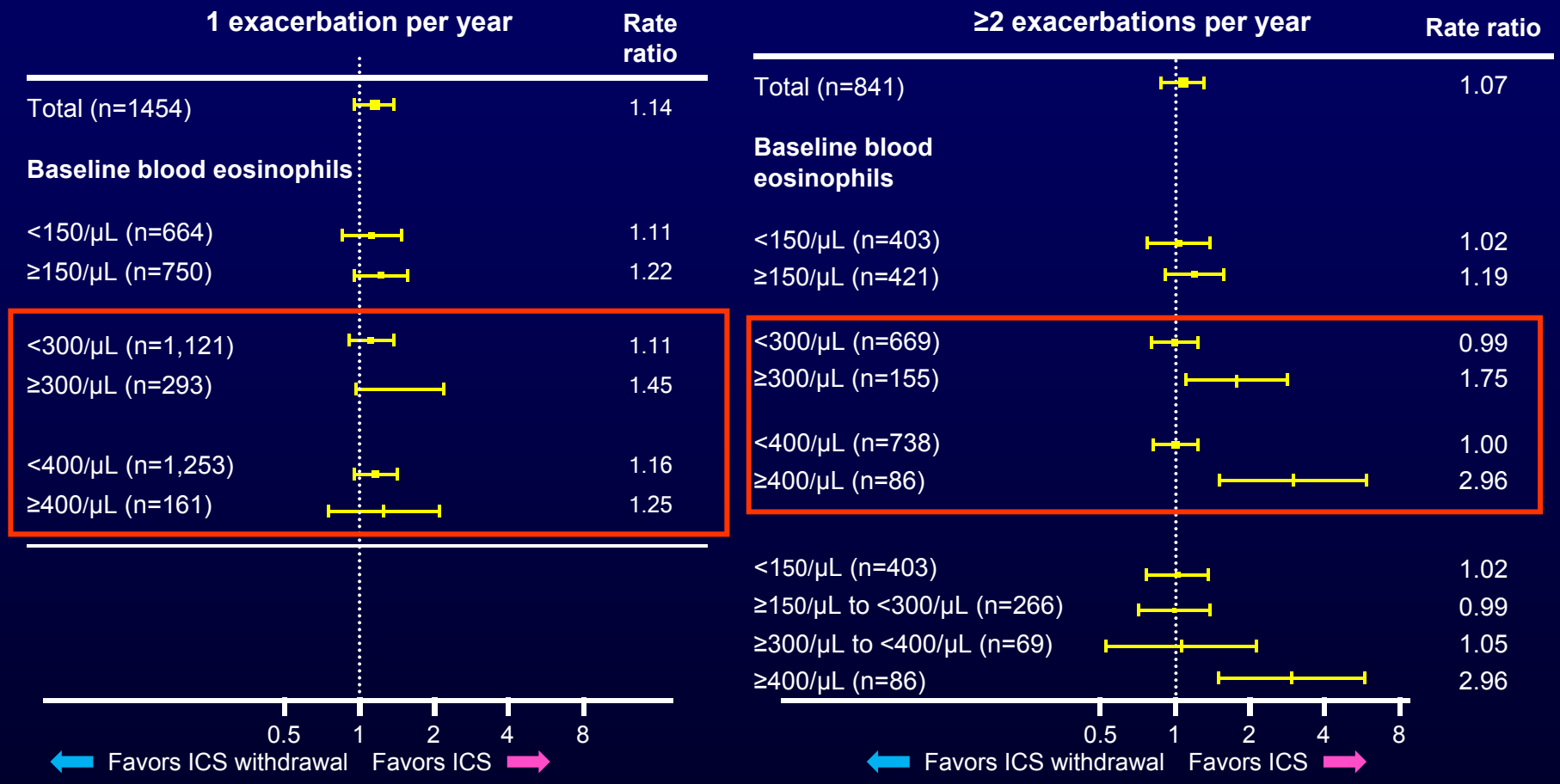
Magnussen et al, *NEJM* 2014; 371: 1285-94

Long-Term Triple Therapy De-escalation to Indacaterol/ Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial



Chapman KR et al, *AJRCCM* 2018; 198: 329-39

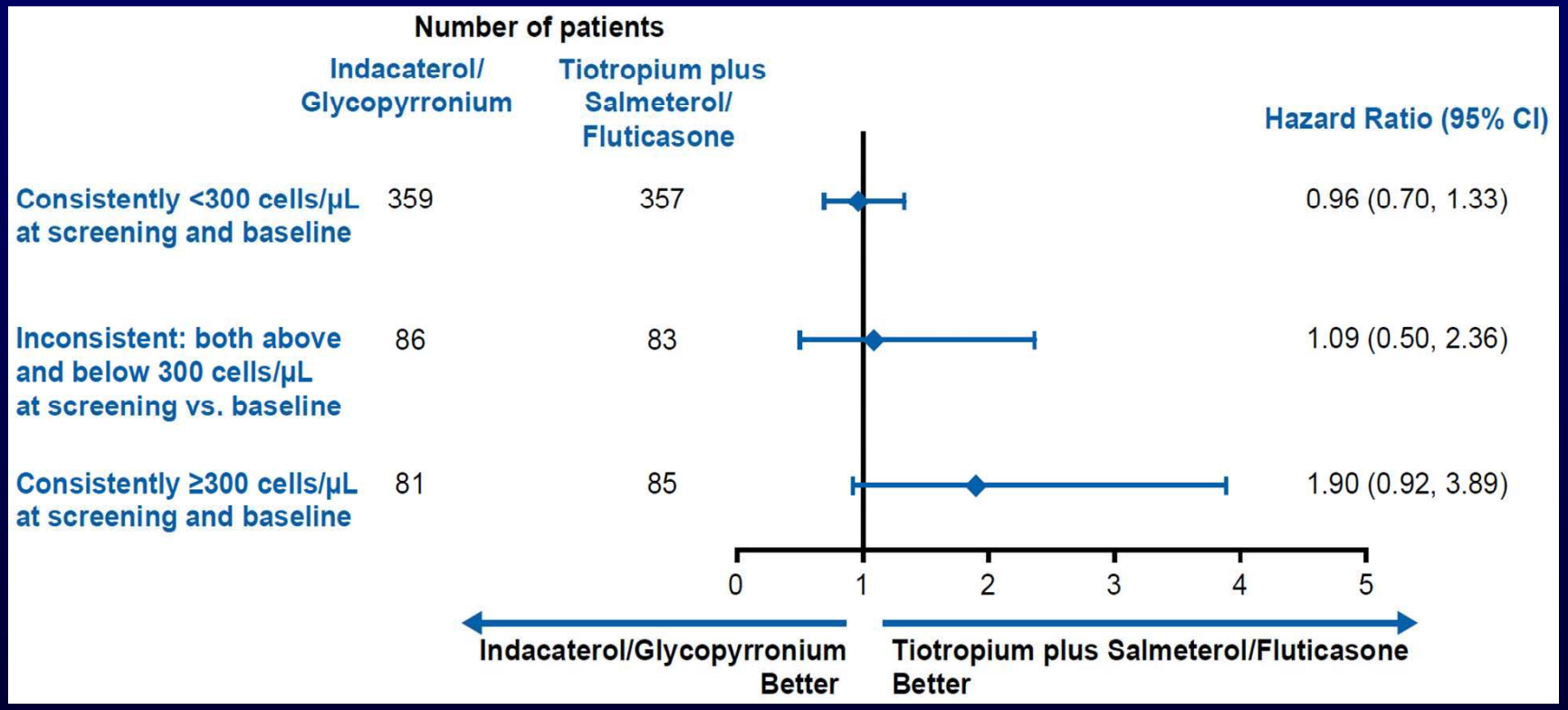
WISDOM post-hoc analysis: ICS withdrawal only increased exacerbation risk in patients with ≥2 prior exacerbations and elevated blood eosinophils



Total study population = 2,485

Calverley PMA, et al. Am J Respir Crit Care Med 2017

SUNSET study – exacerbation rate analysis by blood eosinophil level consistency



The primary objective was to demonstrate non-inferiority of IND/GLY versus TIO+SFC on change from baseline in post-dose trough FEV_1 after 26 weeks of treatment

Chapman K, et al. Am J Respir Crit Care Med 2018. Supplement

FOLLOW-UP PHARMACOLOGICAL TREATMENT

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2. **IF NOT:**
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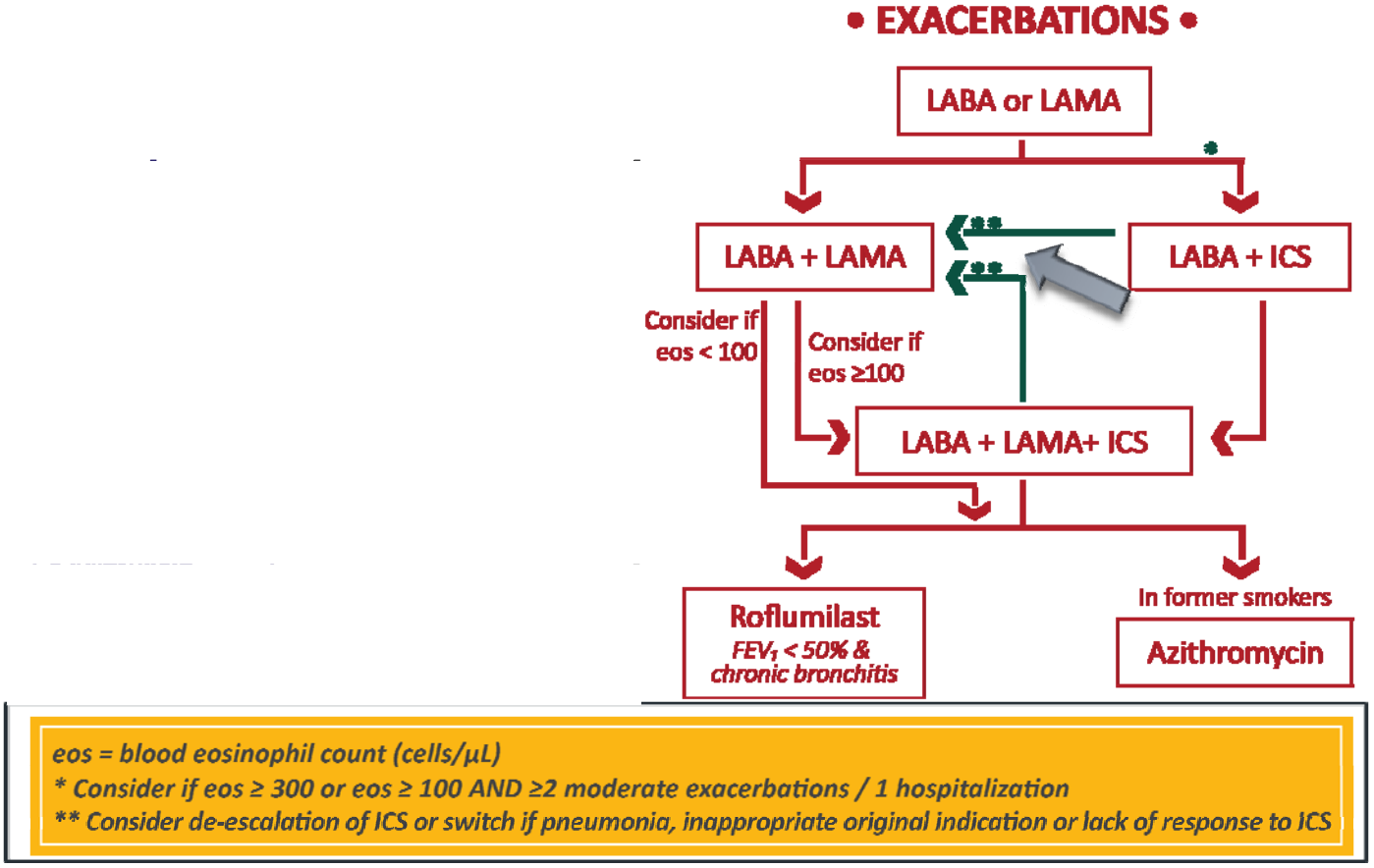

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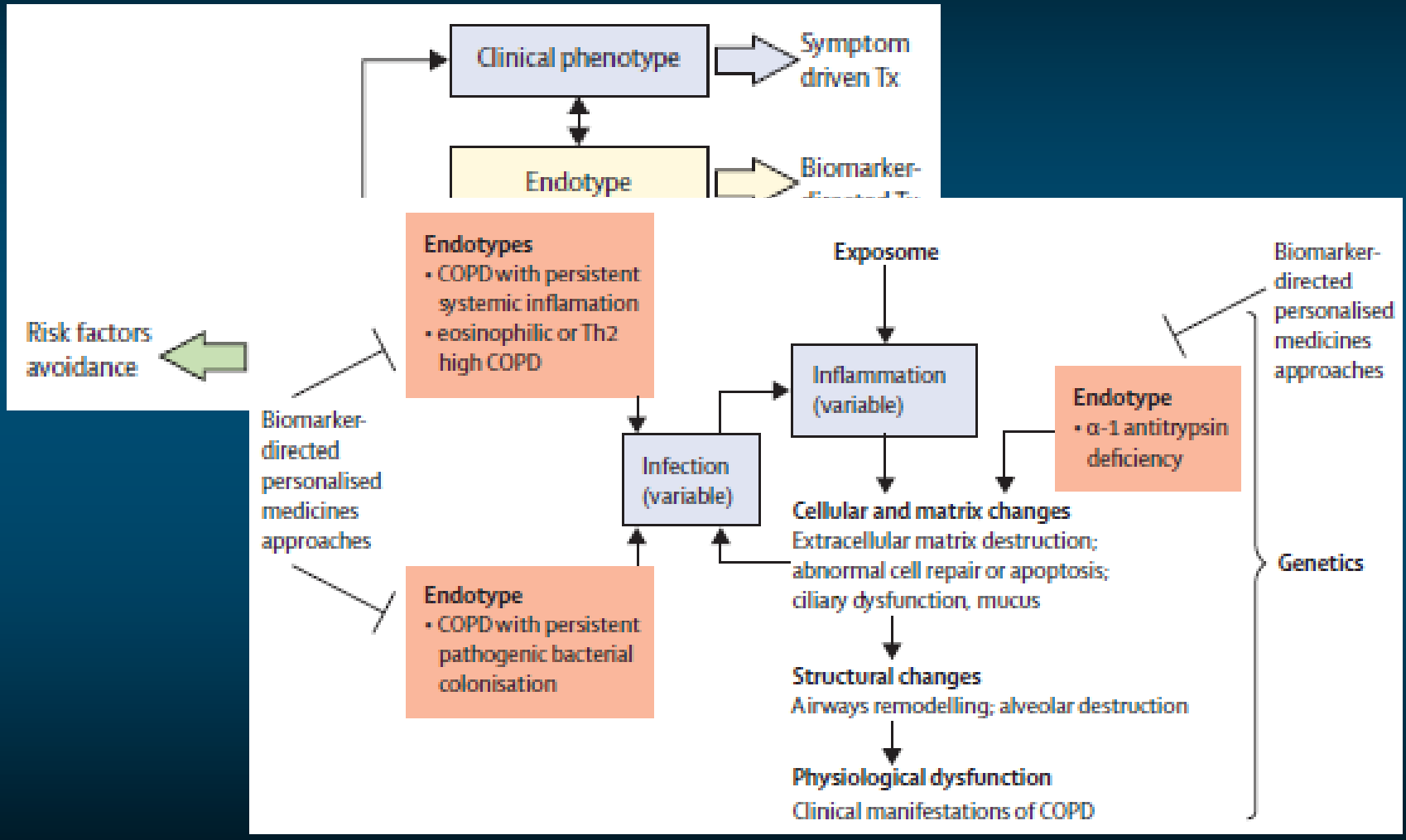
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

Objectives

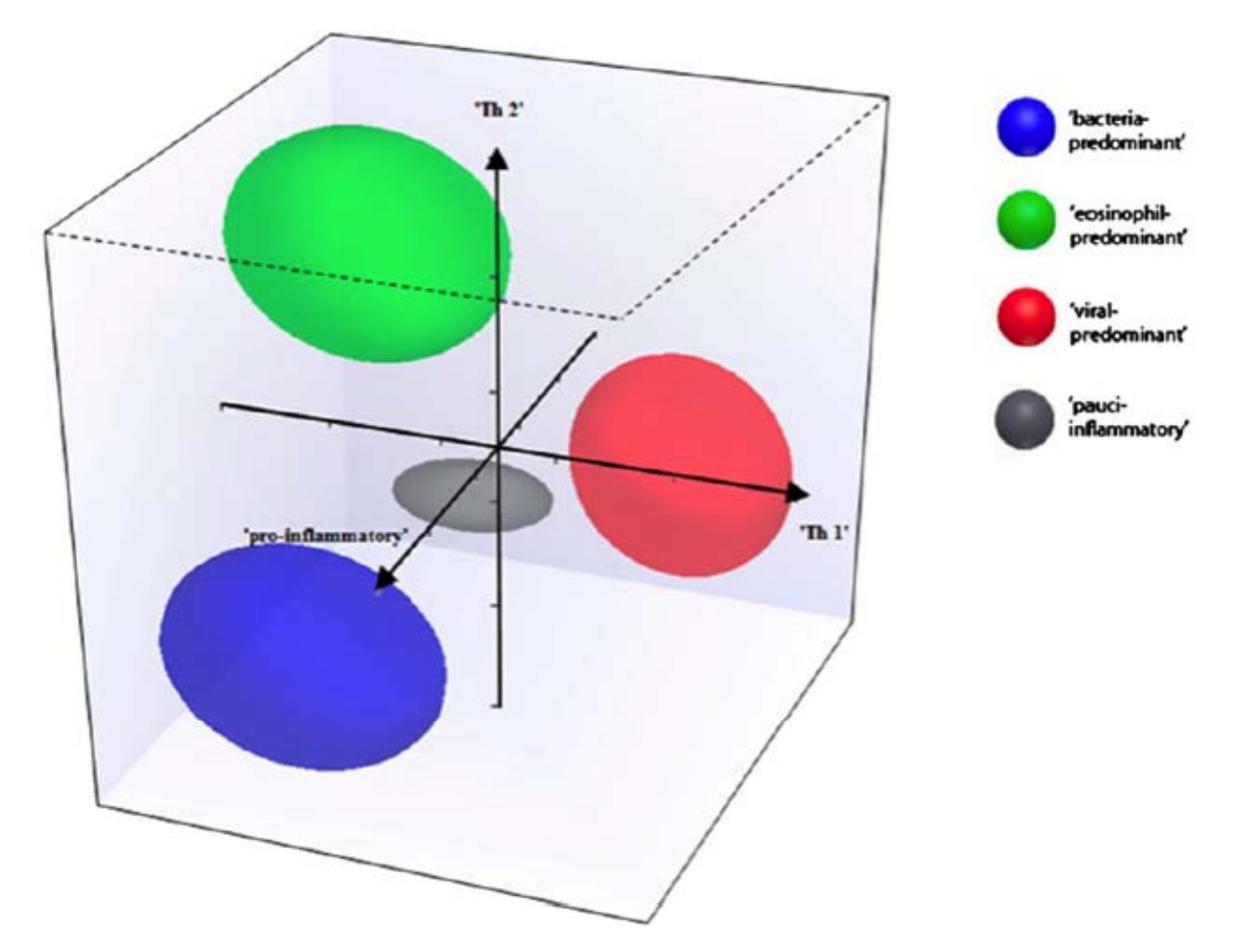
- Why target exacerbations?
- What have we accomplished so far in exacerbation prevention?
- What has GOLD recommended for exacerbation prevention in the latest strategy recommendations?
- What does the future hold?

Progression from clinical phenotypes to biological endotypes



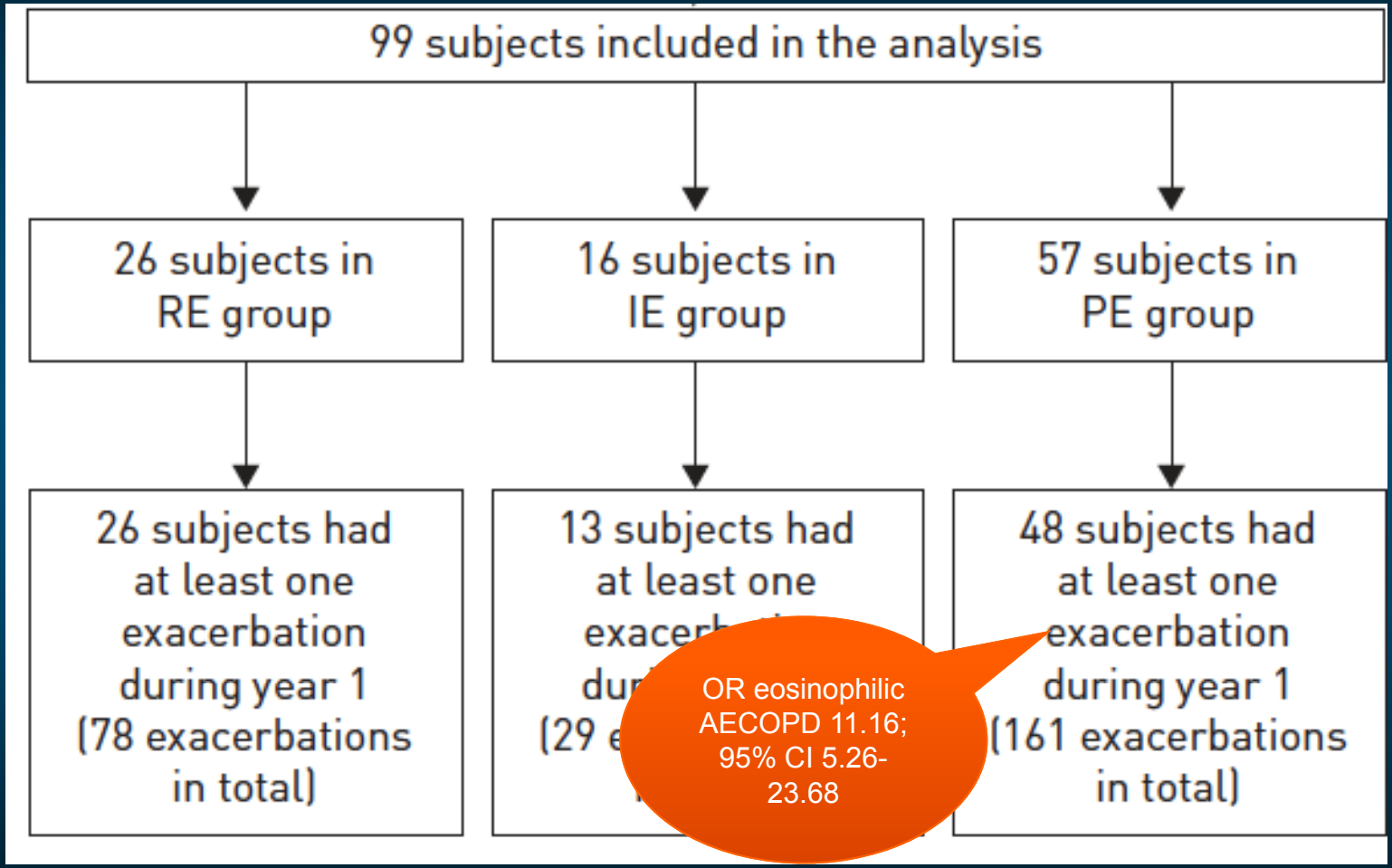
Woodruff PG et al; *Lancet* 2015; 385: 1789-98

AECOPD can be biologically 'clustered'



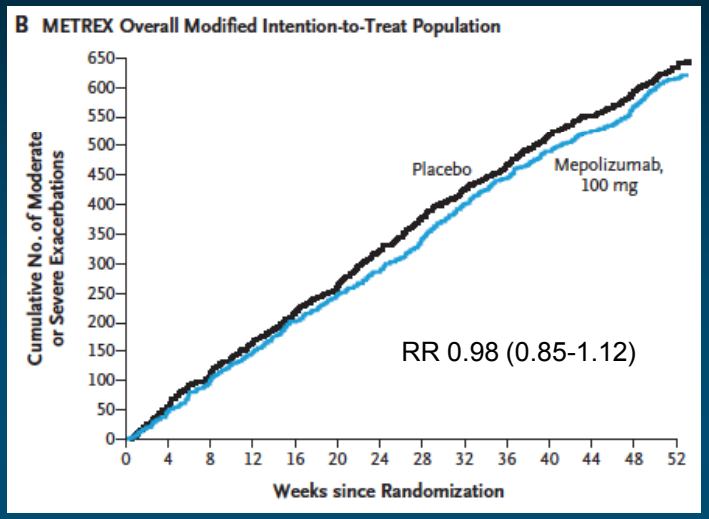
Bafadhel M et al; *AJRCCM* 2011; 184: 662-71

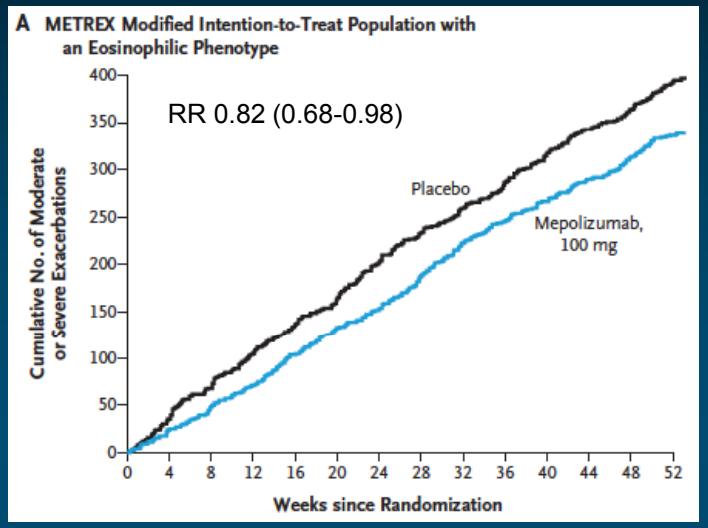
Blood eosinophils at stable state associate with eosinophilic AECOPD

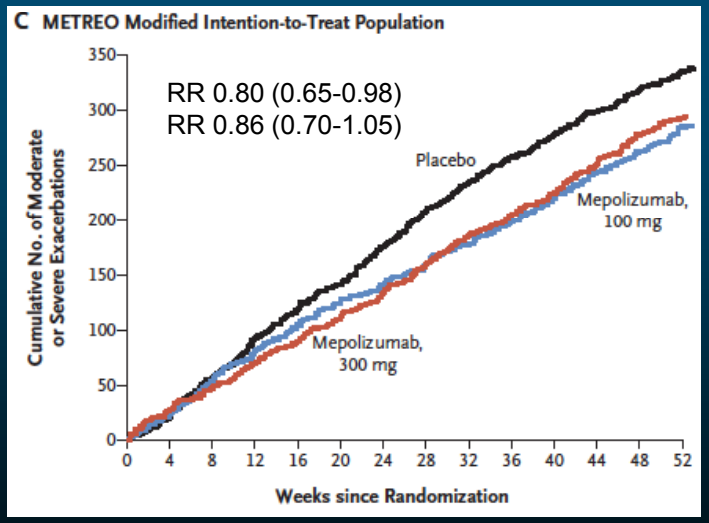


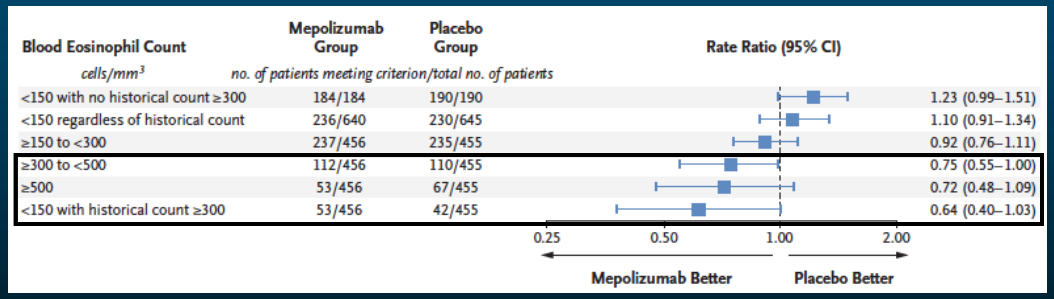
Kim VL et al; *ERJ* 2017; 50: 1700853

Mepolizumab has intriguing effect on AECOPD





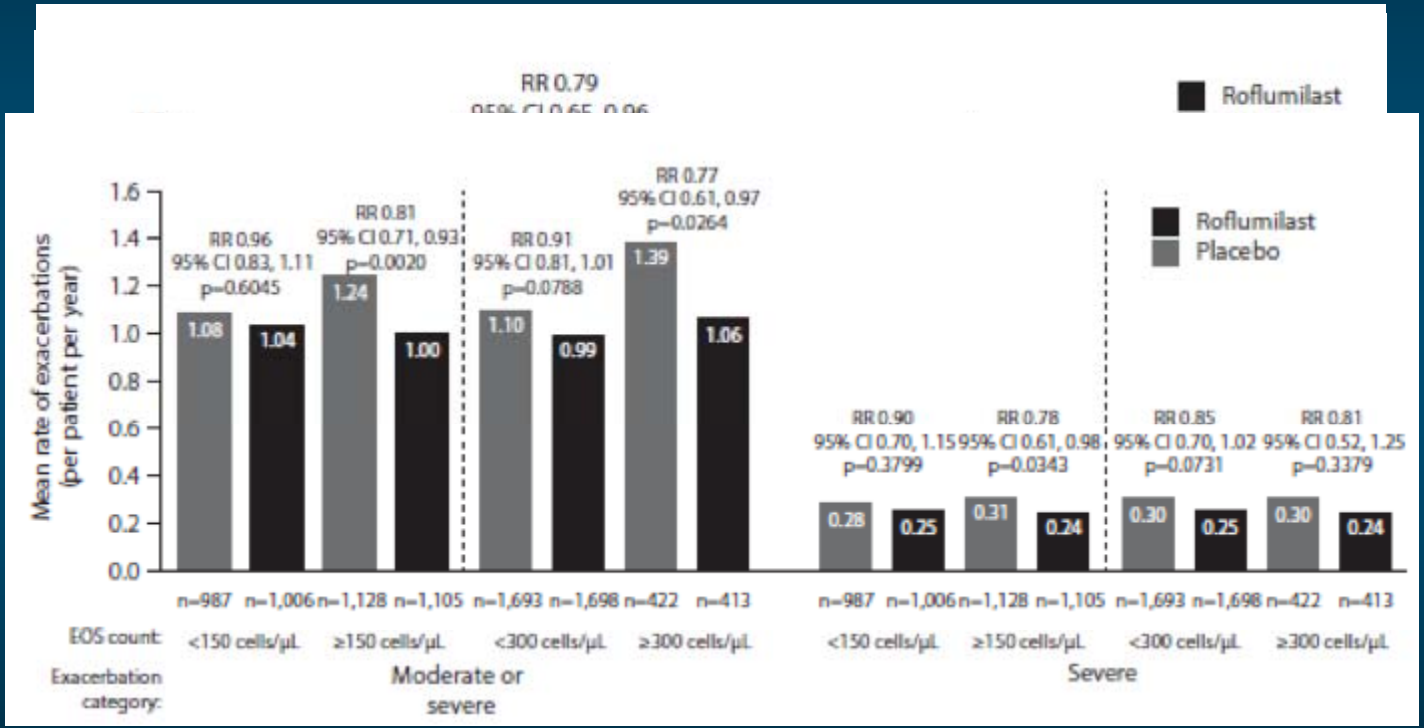




Blood Eosinophil Count	Mepolizumab Group	Placebo Group	Rate Ratio (95% CI)
cells/mm³	*no. of patients meeting criterion/total no. of patients*		
<150 with no historical count ≥300	184/184	190/190	1.23 (0.99–1.51)
<150 regardless of historical count	236/640	230/645	1.10 (0.91–1.34)
≥150 to <300	237/456	235/455	0.92 (0.76–1.11)
≥300 to <500	112/456	110/455	0.75 (0.55–1.00)
≥500	53/456	67/455	0.72 (0.48–1.09)
<150 with historical count ≥300	53/456	42/455	0.64 (0.40–1.03)

Pavord ID et al; *NEJM* 2017 (on line as doi: 10.1056/NEJM0a1708208)

Roflumilast Response is Particularly Evident in COPD Patients with distinct phenotypes



Martinez FJ et al. *Am J Resp Crit Car Med.* 2018; 198: 1268-78

So … in conclusion

- AECOPD remain a major event in the natural history of COPD patients
- Reducing AECOPD risk remains a major component of therapeutic paradigms
- Pharmacotherapy can decrease AECOPD risk
- Pharmacotherapy should be tailored to the patient based on clinical and biomarker characteristics
- The future will utilize a better understanding of AECOPD biology to further improve personalized management strategies