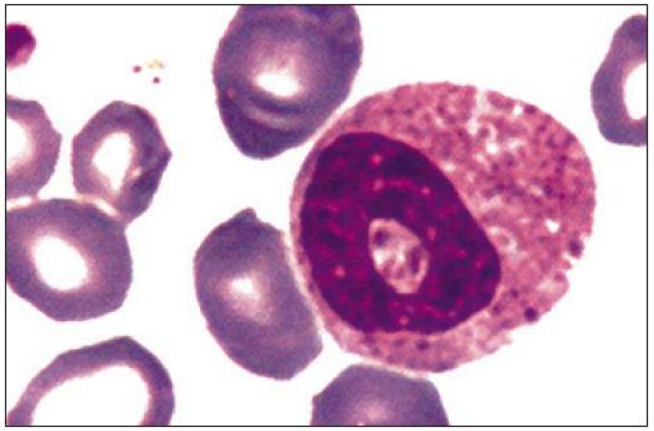

Eosinophils in COPD: myths and reality

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Conflicts of interest

- I was an employee and shareholder of Novartis Pharma AG until 31.10.2018
- I have received honoraria for presentations and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Menarini, Novartis and Sanofi
- My department has received funding and grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Innovis, ELPEN, GSK, Menarini, Novartis and NuvoAir
- I am a member of the GOLD Assembly

Respiratory Ioannina

Konstantinos Kostikas
Just now ·

10 Days to Xmas 2019!
The power ballad of the Swedish duo was originally released as a Christmas song before becoming the mega-hit of the Pretty Woman movie!
R.I.P. Marie Fredriksson...

YOUTUBE.COM
Roxette - It Must Have Been Love (Christmas For The Broken Hearted) 1987

Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
- The early days: exacerbations et al.
- Predicting future risk
- Identifying ICS responders
- Real world evidence: the new must (?)
- An imperfect biomarker
- A more targeted approach?

Eosinophils in COPD: myths and reality

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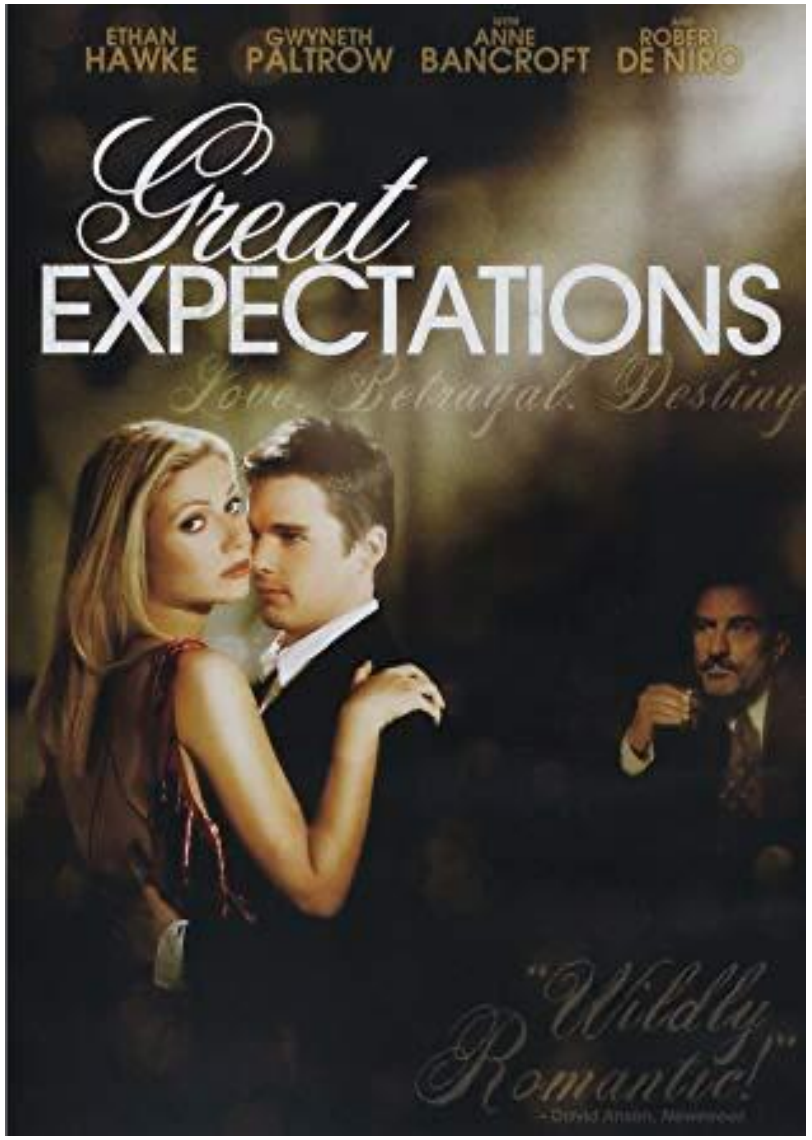
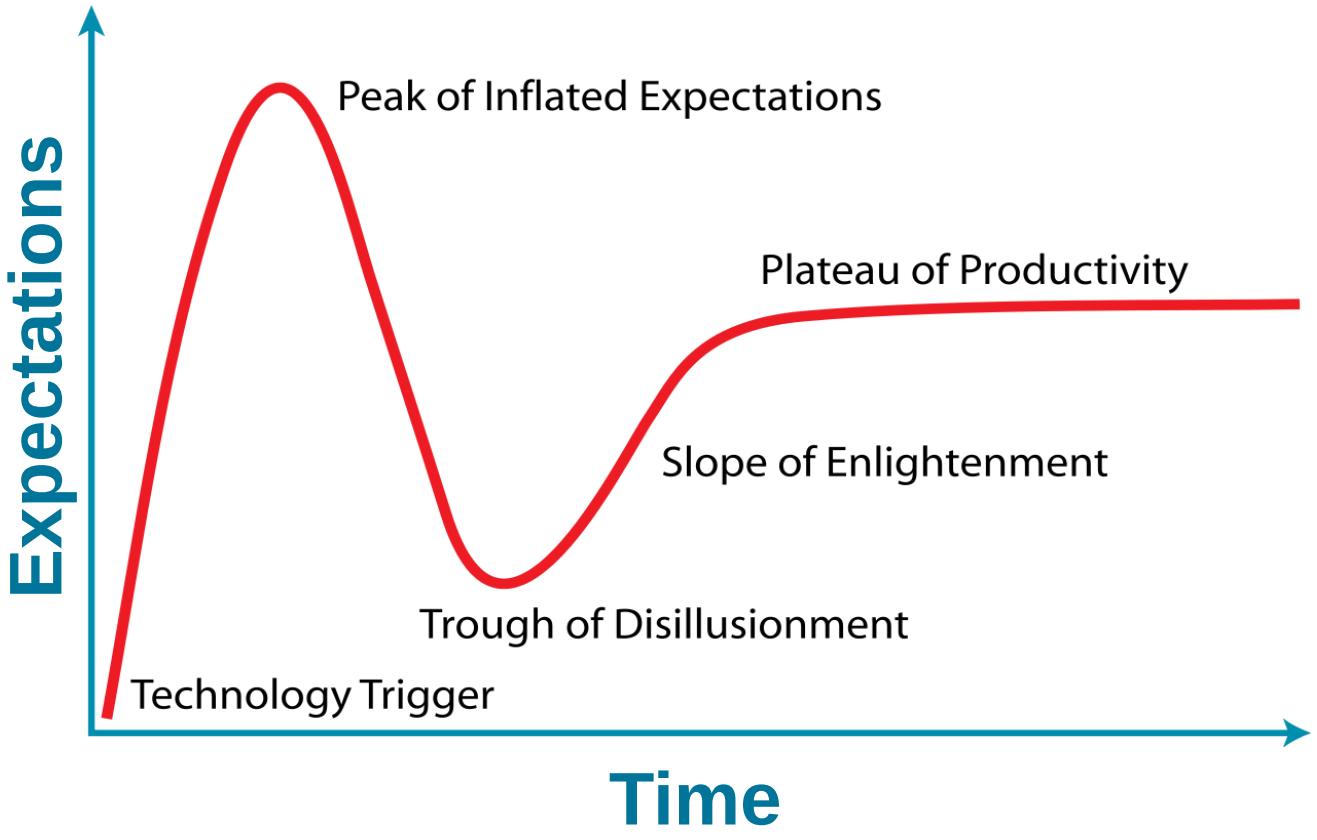
The hype around blood EOS and the need for biomarkers in COPD

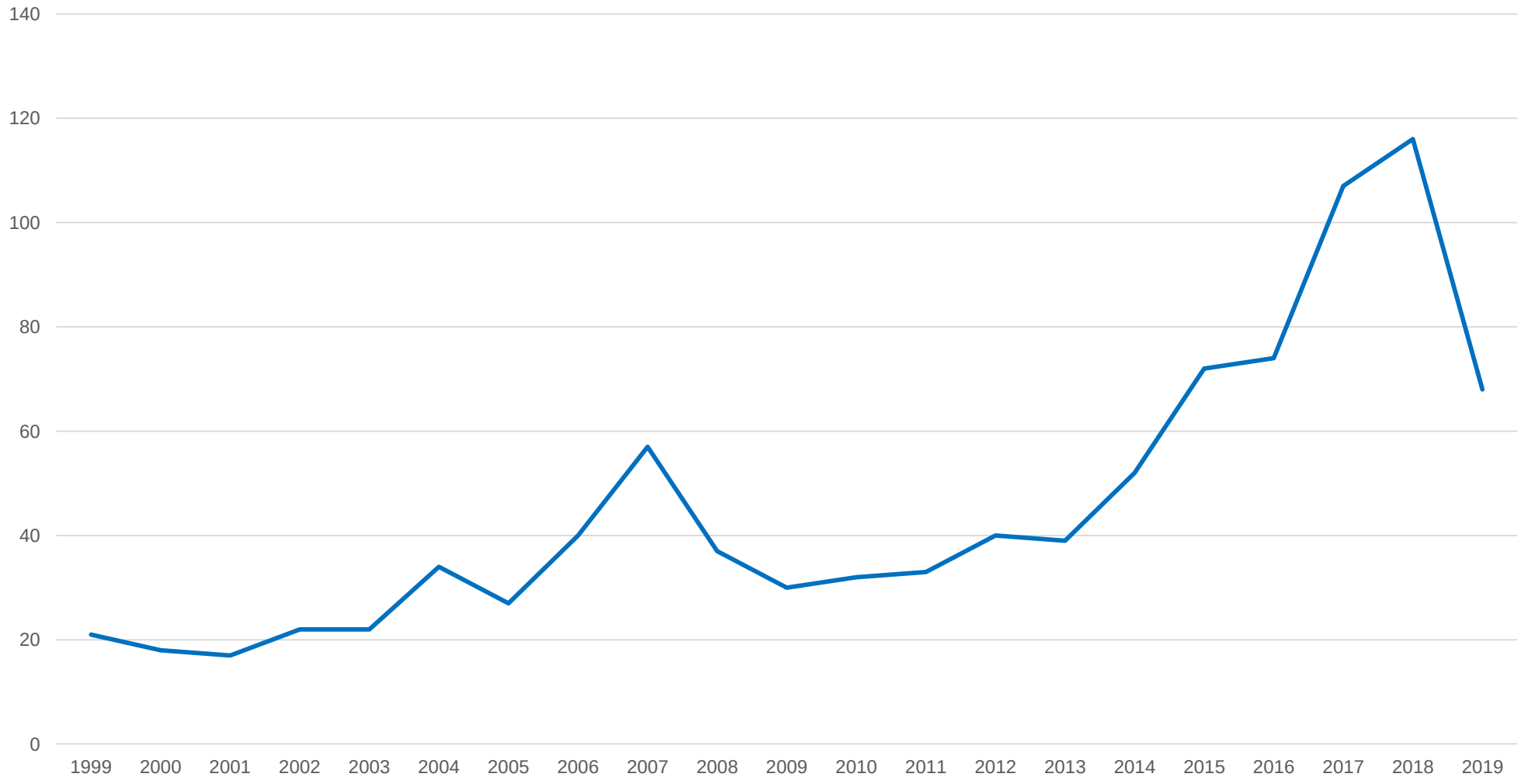


The Gartner Hype Cycle



http://www.gartner.com/technology/research/methodologies/hype-cycle.jsp

Blood EOS in COPD studies in PubMed in the past 20 years



08.12.2019: 784 publications

Systemic Biomarkers in the Evaluation and Management of COPD

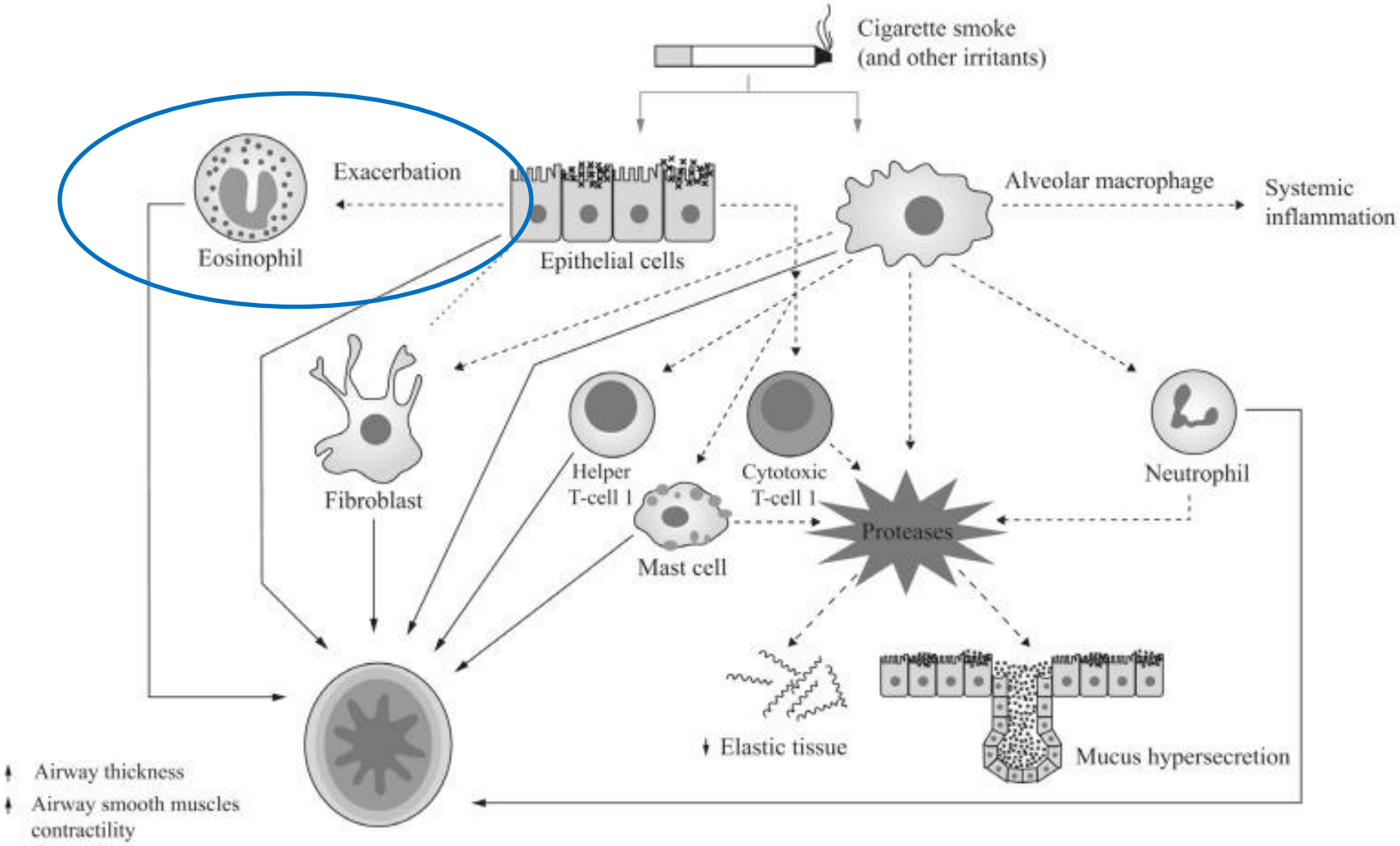
Table 4. Synoptic Presentation of Major Candidate Systemic Biomarkers in COPD Associated with Treatment Response and Guidance

Biomarker	Clinical Implication
CRP	Responsive to oral CS and high-dose ICS in a small trial [115]; may be useful to guide antibiotic treatment [104]
SP-D	Significant reduction after 8 weeks treatment with ICS and ICS/LABA combination [117]; reductions associated with FEV_1 and quality of life improvements [117]; reduced by oral CS [42]
PARC/CCL-18	Reduced by oral CS [78]
Procalcitonin	Reduction in the use of antibiotics in patients with AECOPD without difference in outcomes [126]
Blood eosinophils	Reduction in the use of systemic CS [132]

AECOPD: acute exacerbations of COPD; CRP: C-reactive protein; CCL-18: chemokine ligand 18; CS: corticosteroids; ICS: inhaled corticosteroids; LABA: long-acting β2-agonists; PARC: pulmonary and activation regulated chemokine; SP-D: surfactant protein-D.

Kostikas K et al, Current Drug Targets, 2013, 14, 177-191

Airway inflammation in COPD: the role of eosinophils



Kostikas K, et al., Curr Drug Targets 2018;19(16):1882-96; Barnes PJ, Chest 2008;134(6):1278–1286

Potentially relevant pulmonary treatable traits in patients with COPD

Trait	Biomarker	Treatments	Likely outcome	Comments
Airflow limitation	FEV_1/FVC ratio < 0.7	β_2-Agonists, antimuscarinic agents, theophylline	Improved symptoms, lung function, and exercise capacity	Caused by multiple factors, including airway smooth muscle contraction, mucus plugging, airway wall edema, small-airway fibrosis, and loss of airway support; components not readily distinguishable and likely to respond to treatments differently
Eosinophilic airway inflammation	See Table II	ICSs; oral CSs; anti–IL-5, anti–IL-4, and anti–IL-13; anti-TSLP	Reduced exacerbations and variable and smaller improvement in symptoms and lung function	Well-defined, identifiable, and treatable; likely the results of different pathways (Fig 1)
Neutrophilic airway inflammation	Induced sputum neutrophil count; ? CRP	? Macrolides; CXCR2 antagonists	? Reduced exacerbations; ? Reduced rate of decrease in lung function; ? reduced cough and sputum	Not at all well-defined; might be multiple pathways, including infection-associated pathways, caused by exogenous stimuli (ie, smoking) and autoimmune processes (ie, rheumatoid-associated airway disease)
Cough reflex hypersensitivity	24-h Cough counts, Leicester Cough Questionnaire	Gabapentin; ? P2X3 antagonists	Improved cough	Recent progress with new measurement techniques and treatments
Mucus overproduction	CT-based assessment; sputum production	Carbocysteine; no other well-established treatments in patients with COPD	Improved sputum; ? reduced exacerbations	Unclear whether independent of airway inflammation

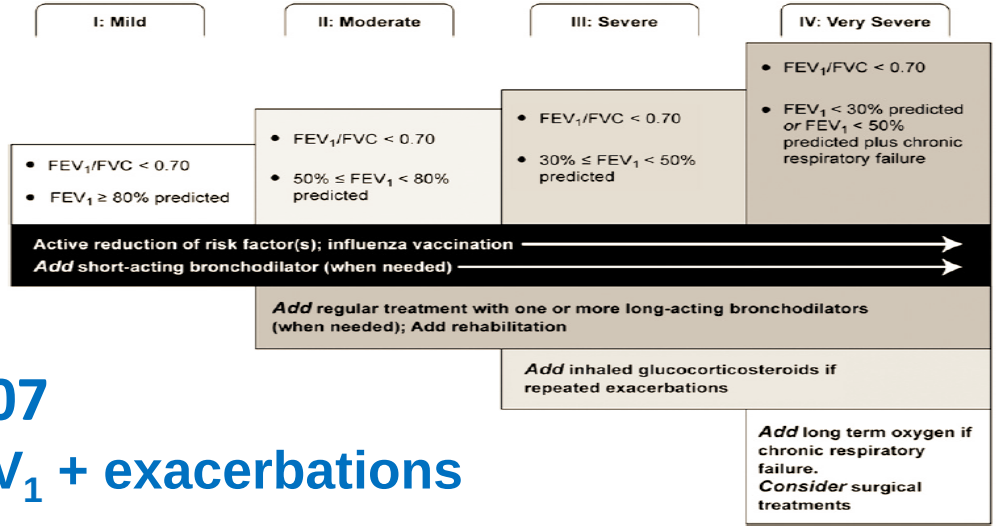
CRP, C-reactive protein; *CS*, corticosteroid; *CT*, computed tomography; *FVC*, forced vital capacity; *TSLP*, thymic stromal lymphopoietin.

Pavord ID, J Allergy Clin Immunol 2018;141:1983-91

The GOLD journey in time

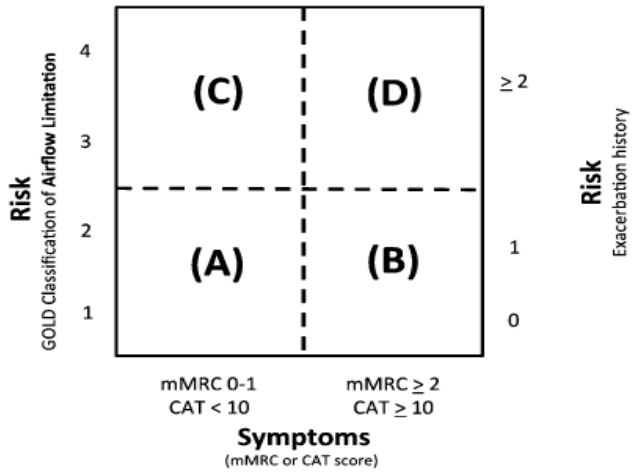
Stage	Characteristics	Recommended Treatment	
All		Avoidance of risk factors Influenza vaccination	
0: At risk	Chronic symptoms (cough, sputum) Exposure to risk factors Normal spirometry		
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without symptoms	Short-acting bronchodilator when needed	
II: Moderate COPD	IIA $FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB $FEV_1/FVC < 70\%$ $30\% \leq FEV_1 > 50\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or presence of respiratory failure or right heart failure	Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments	

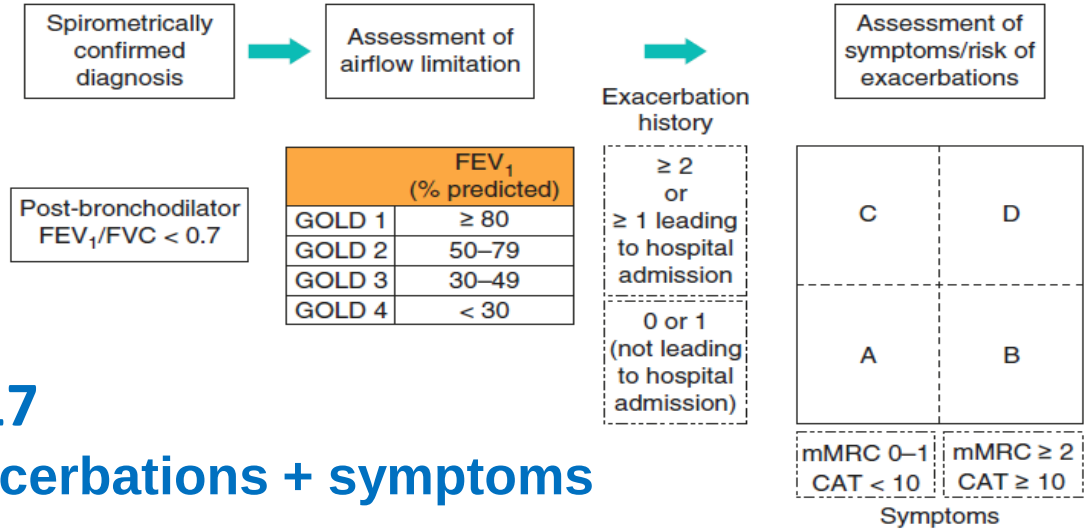
2001
FEV_1



2007
FEV_1 + exacerbations

2011
FEV_1 + exacerbations + symptoms





2017
exacerbations + symptoms

Pauwels RA et al., Respir Care 2001; 46: 798-825; Rabe KF et al., Am J Respir Crit Care Med. 2007;176:532-555
Vestbo J et al., Am J Respir Crit Care Med.2013;187:347-365; Vogelmeier CFet al., Am J Respir Crit Care Med. 2017;195:557-582

GOLD 2020: symptoms + exacerbations + eosinophils

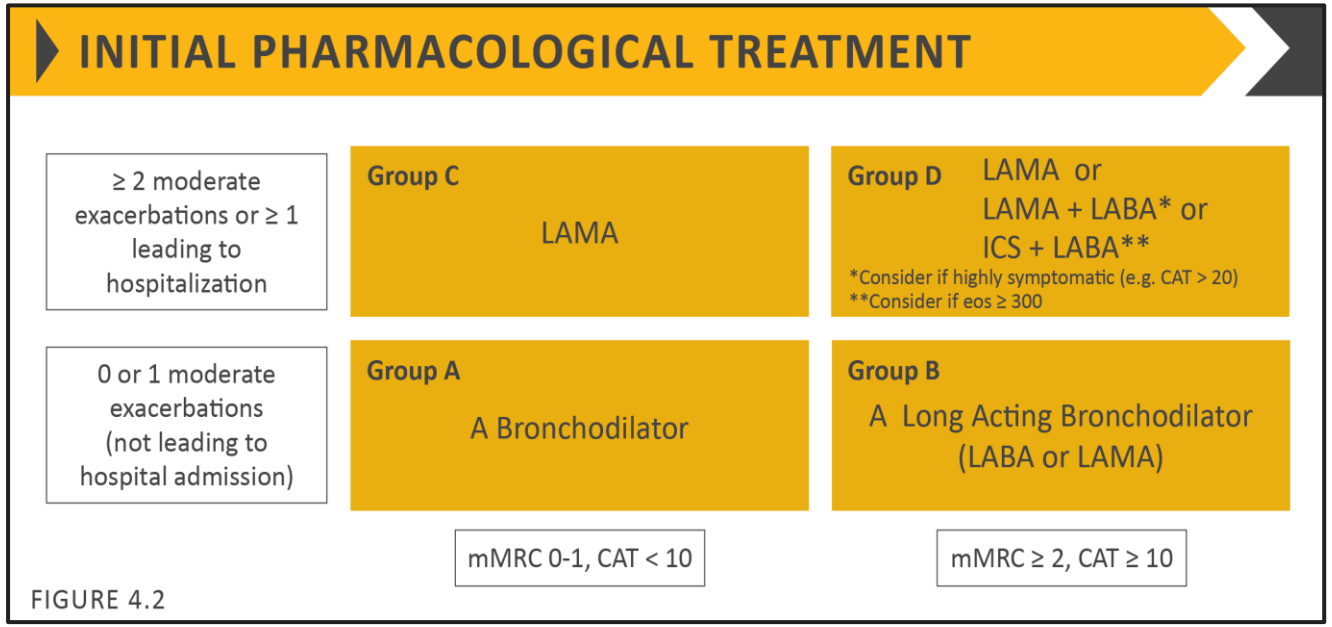


FIGURE 4.2

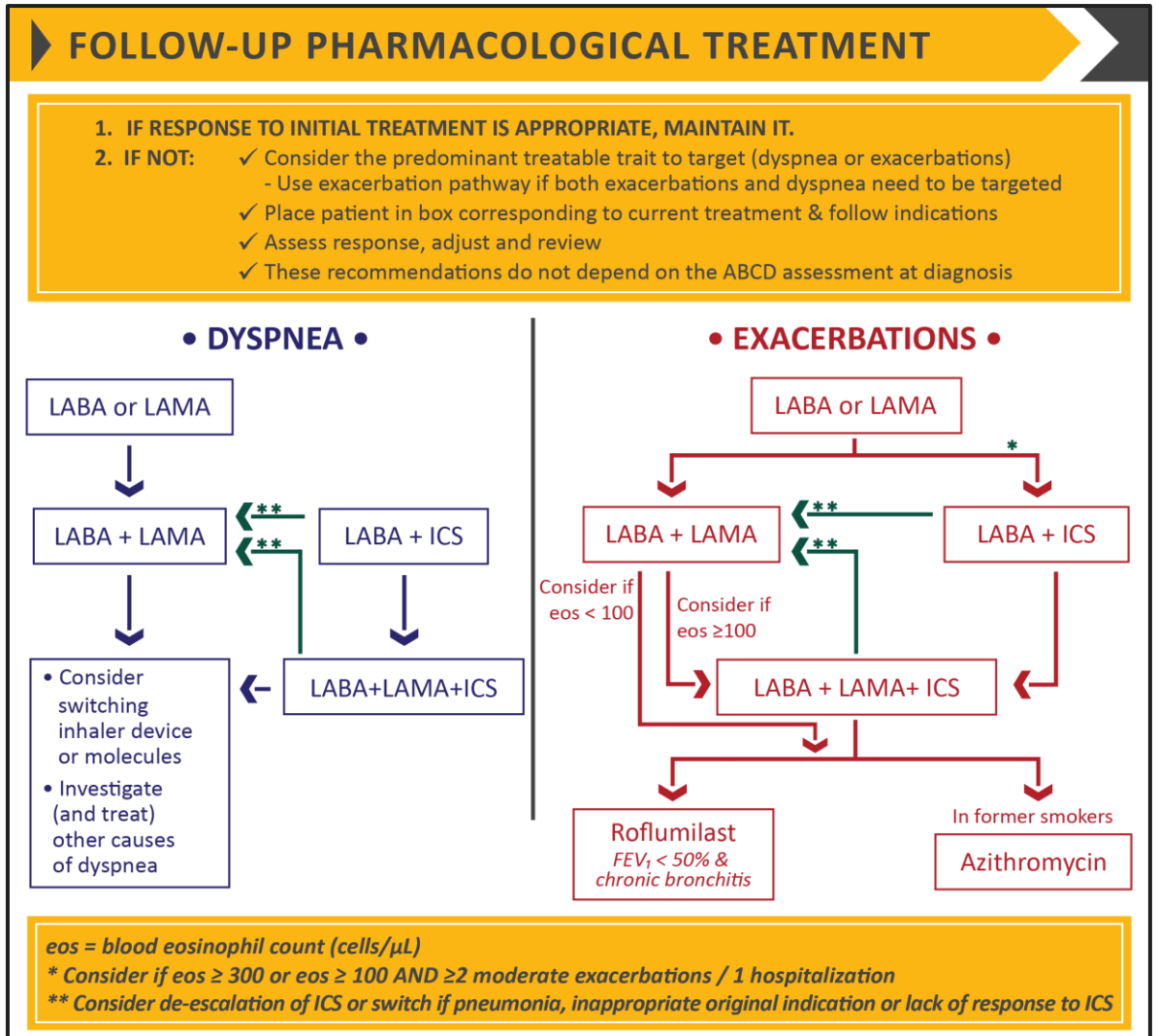
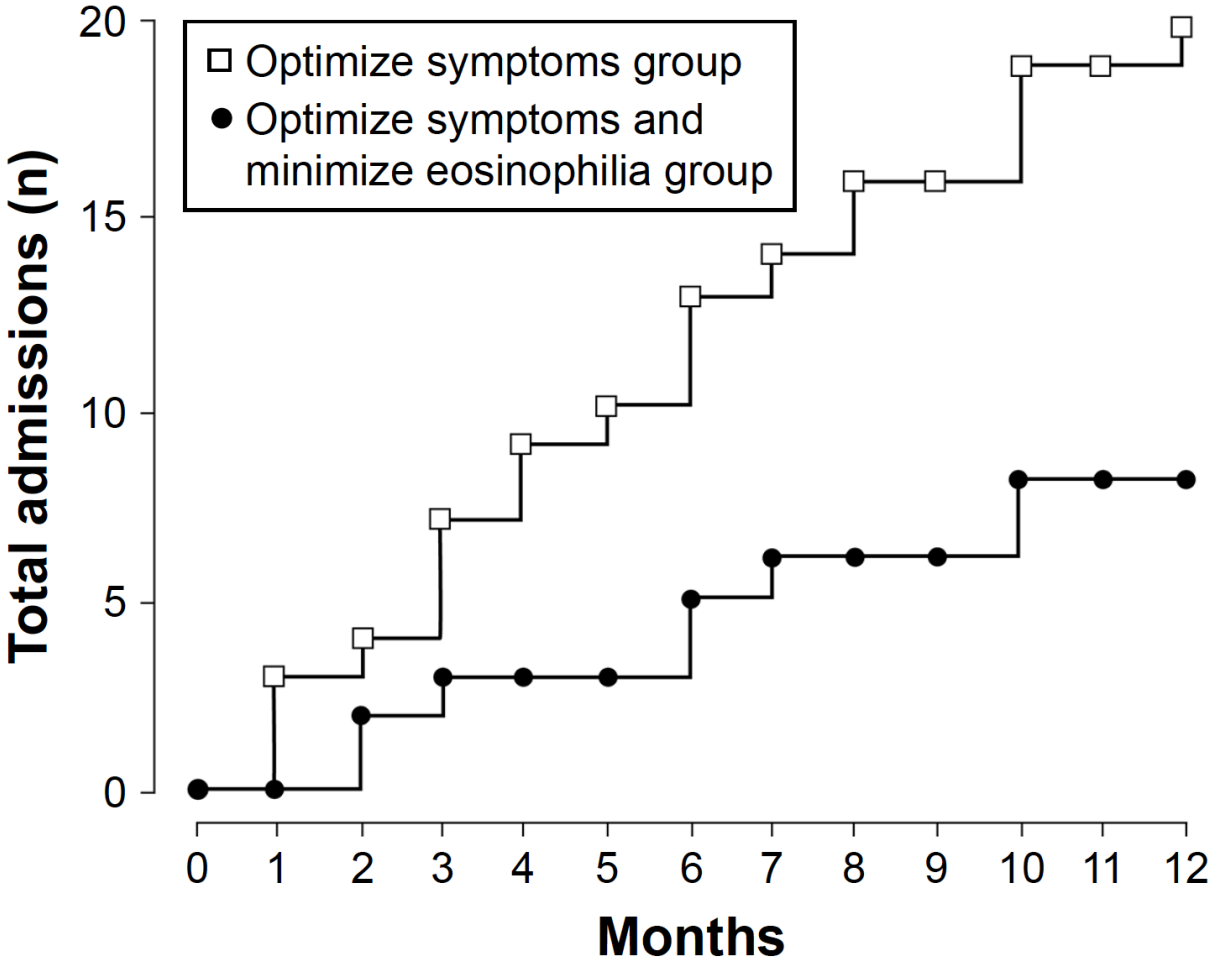


FIGURE 4.4

Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
- **The early days: exacerbations et al.**
- Predicting future risk
- Identifying ICS responders
- Real world evidence: the new must (?)
- An imperfect biomarker
- A more targeted approach?

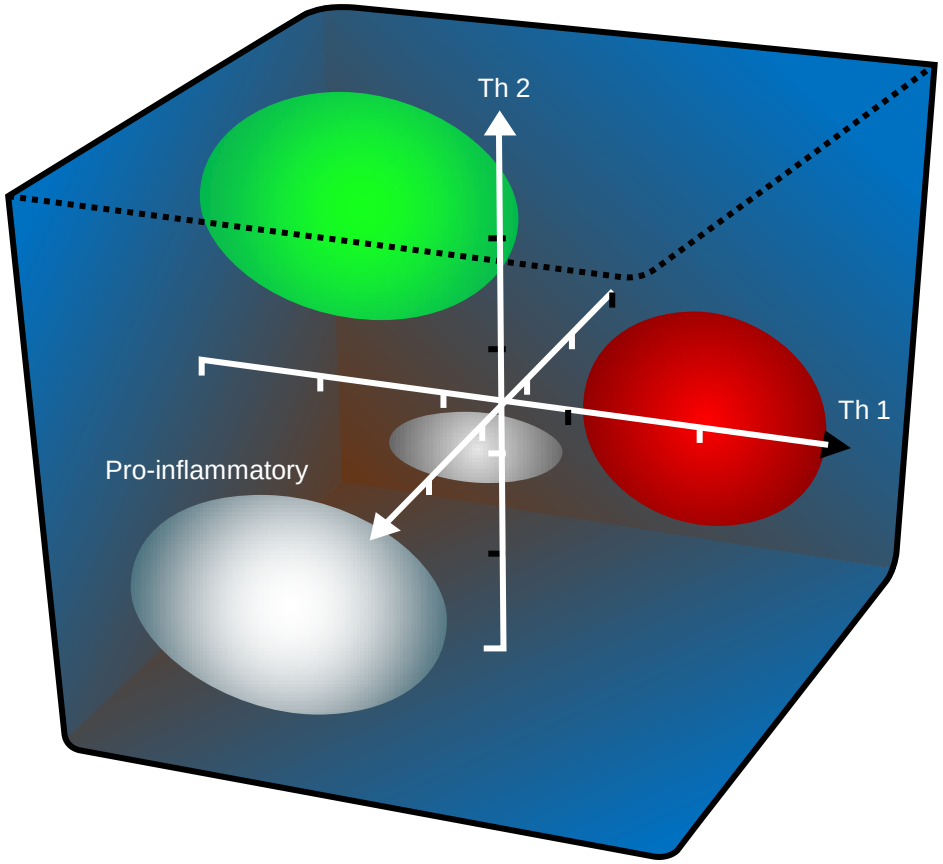
Management by sputum EOS and COPD hospitalizations RCT



Bafadhel M, et al., Eur Respir J. 2007;29(5):906–913

Stratification of COPD exacerbations by biomarkers

- Observational, 1-year study of 182 exacerbations in 86 patients identified four distinct biologic COPD exacerbation phenotypes
- Eosinophil-predominant phenotype was most responsive to corticosteroid treatment



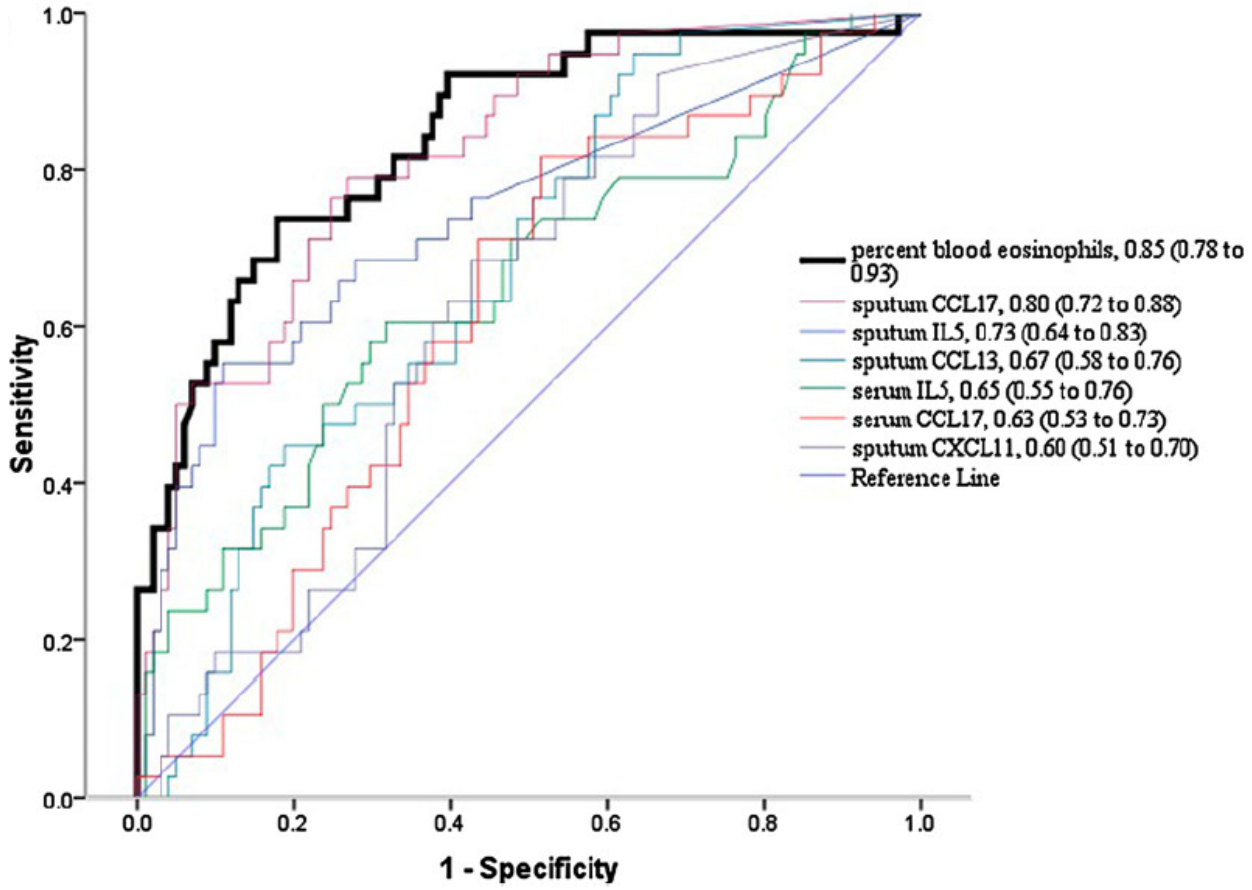
Biologic phenotype (clinical biomarker)

- Bacteria-predominant (sputum IL-1β)
- Eosinophil-predominant (% peripheral EOS)
- Viral-predominant (CXCL10)
- Pauci-inflammatory

Bafadhel M, et al. AJRCCM 2011;184:662–71

Stratification of COPD exacerbations by biomarkers

- Sputum eosinophilia (>3%) was observed in 28% of exacerbations
- Percent peripheral blood EOS count was the best predictor of sputum eosinophilia during exacerbation

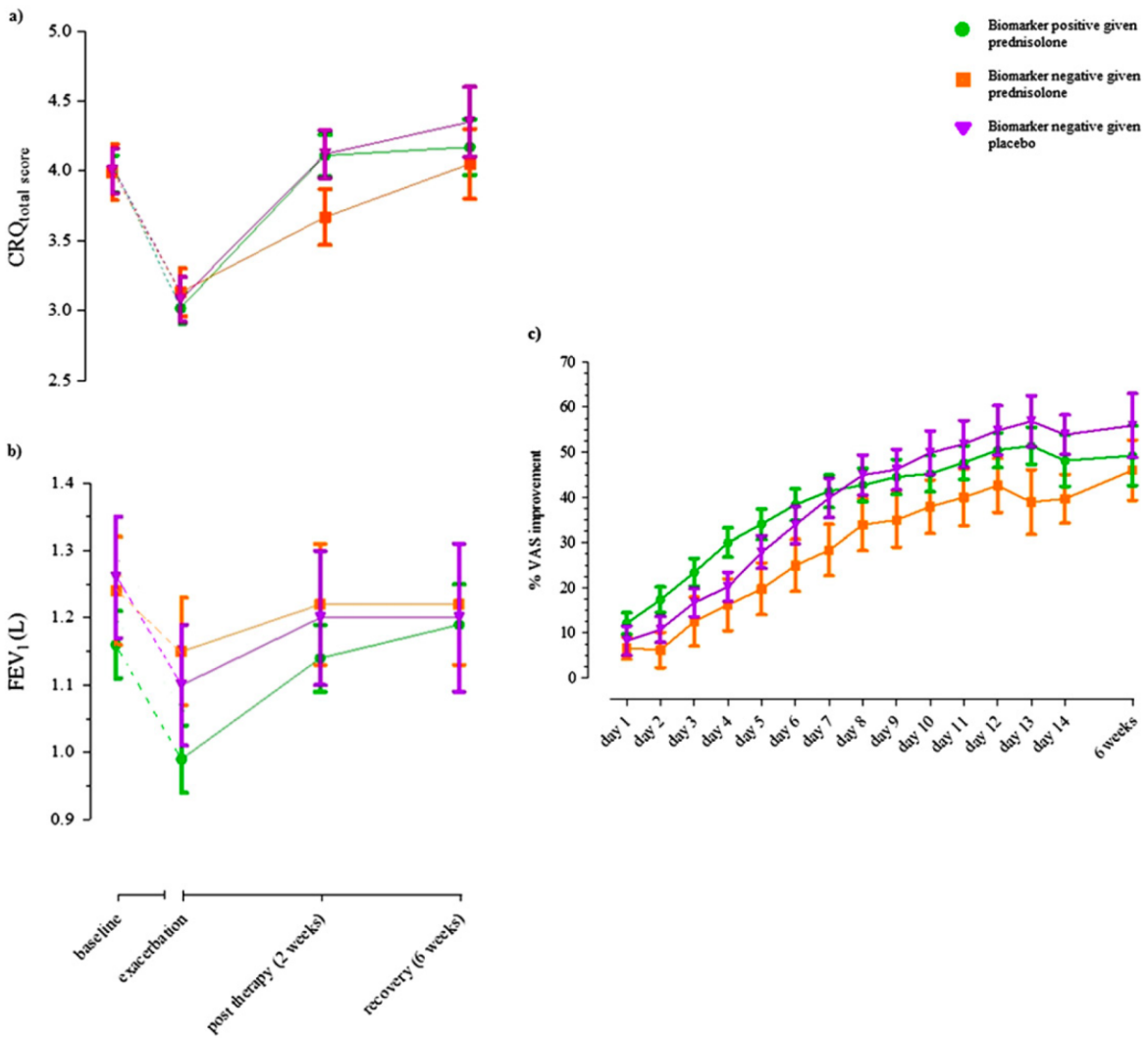


- **% blood eosinophils**
- Serum IL-5
- Serum CCL17
- Serum VCAM1
- Serum TNF-1B
- Serum C reactive protein
- Serum IL-6
- Serum TNF-1B
- Serum amyloid A1
- Reference Line

Prediction of sputum EOS >3%
- % blood eosinophils AUC=0.85
- 2% cut off = 90% sensitivity, 60% specificity

Bafadhel M, et al. AJRCCM 2011;184:662–71

Blood EOS-driven management of outpatient COPD exacerbations



Bafadhel M, et al. AJRCCM 2012;186(1):48–55

Eosinopenia and in-hospital mortality in COPD exacerbations

Table 2 Independent categorical predictors of inhospital mortality

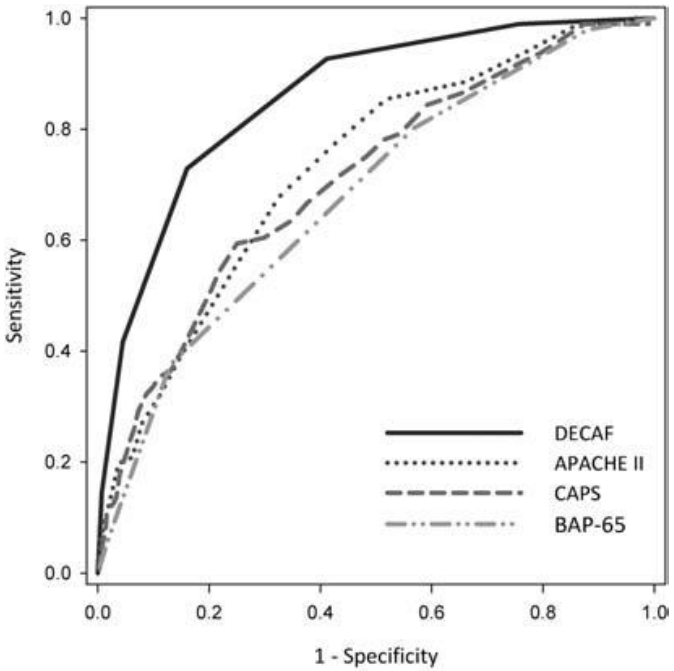
Variable	B	Odds ratio (95% CI)	Significance
eMRCD 1–4		1	
eMRCD 5a	1.63	5.11 (2.62 to 9.97)	<0.001
eMRCD 5b	1.99	7.30 (3.77 to 14.2)	<0.001
Coexistent consolidation	1.06	2.88 (1.69 to 4.90)	<0.001
Eosinophil count $<0.05 \times 10^9$/l	1.02	2.76 (1.58 to 4.83)	0.001
pH <7.3	0.99	2.68 (1.41 to 5.09)	0.003
AF	0.98	2.66 (1.39 to 5.09)	0.003
Ineffective cough	0.94	2.57 (1.37 to 4.84)	0.003
Albumin <36 g/l	0.84	2.32 (1.36 to 3.96)	0.002
Cerebrovascular disease	0.70	2.02 (1.18 to 3.42)	0.037
Age ≥80	0.70	2.01 (1.18 to 3.42)	0.011
BMI <18.5 kg/m^2	0.60	1.83 (1.00 to 3.33)	0.049
Intercept	−4.30		

AF, atrial fibrillation; BMI, body mass index; eMRCD, extended MRC dyspnoea.

Table 3 The DECAF Score

Variable	Score
Dyspnoea	
eMRCD 5a	1
eMRCD 5b	2
Eosinopenia ($<0.05 \times 10^9$/l)	1
Consolidation	1
Acidaemia (pH <7.3)	1
Atrial fibrillation	1
Total DECAF Score	6

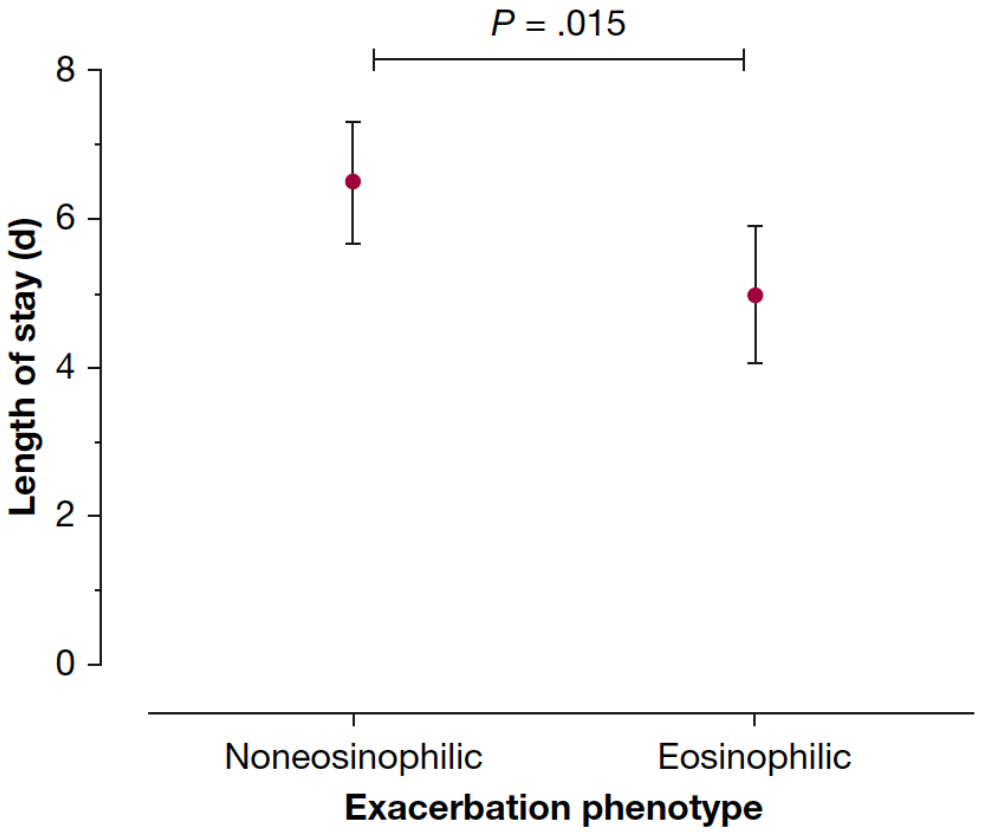
DECAF, Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; eMRCD, extended MRC dyspnoea.

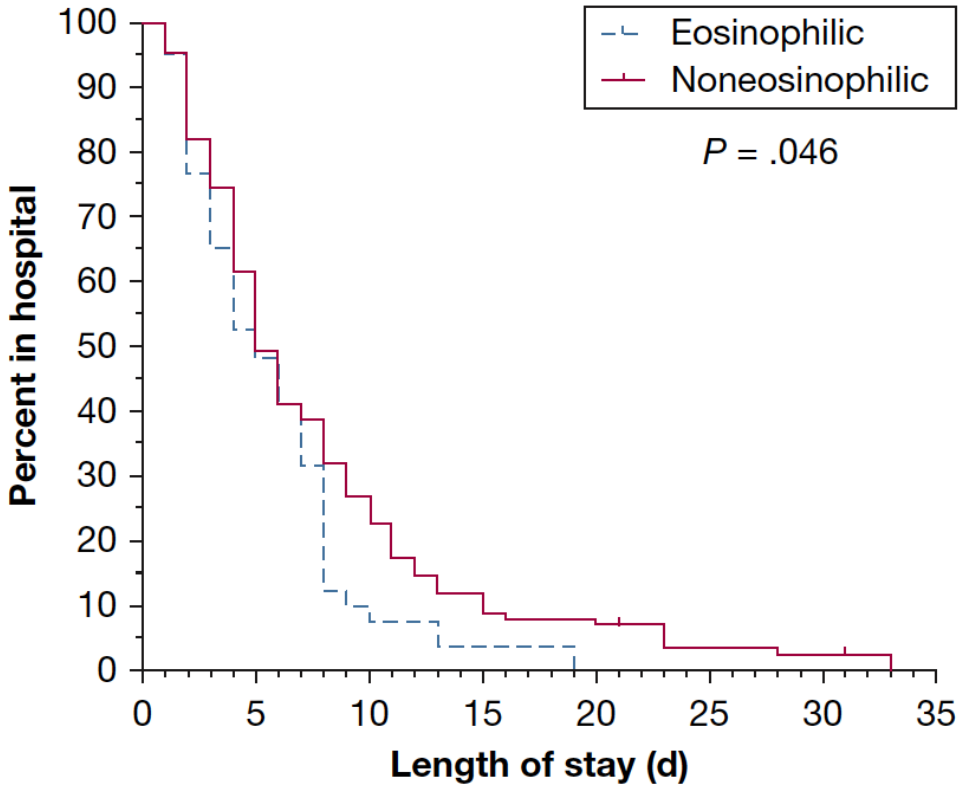


APACHE II, Acute Physiology and Chronic Health Evaluation II; BAP-65, Blood urea nitrogen, Altered mental status, Pulse >109/min, Age >65 years; CAPS, COPD and Asthma Physiology Score; COPD,chronic obstructive pulmonary disease.

Steer J, et al. Thorax 2012;67:970–976

Blood eosinophilia on admission and shorter hospital stay

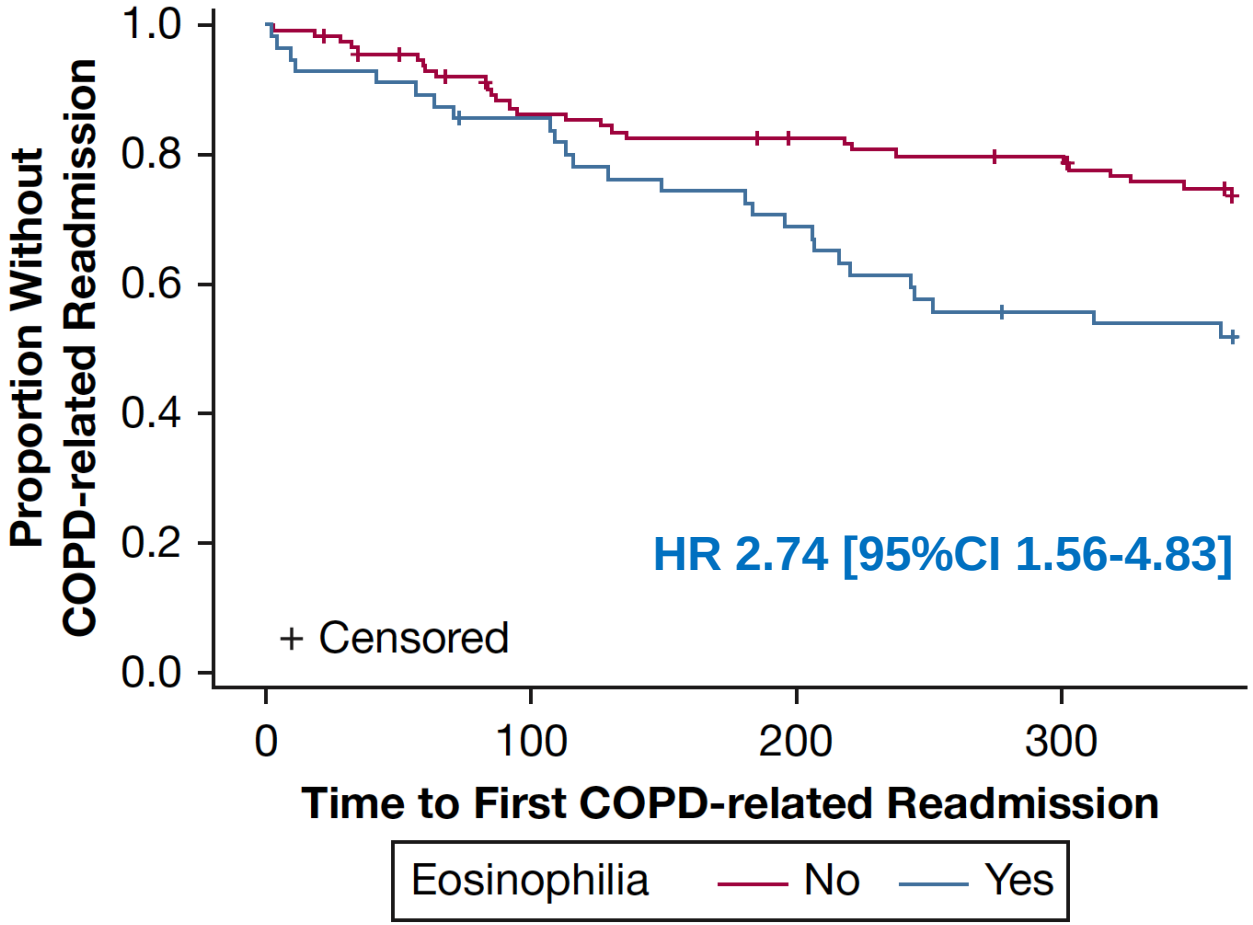




Post-hoc analysis of a two-center acute rehabilitation study in the UK (n=243 patients)
Eosinophilia was defined as blood eosinophil level on admission was **≥200 cells/mL and/or ≥2%**

Bafadhel M, et al. Chest 2016; 150(2):320-328

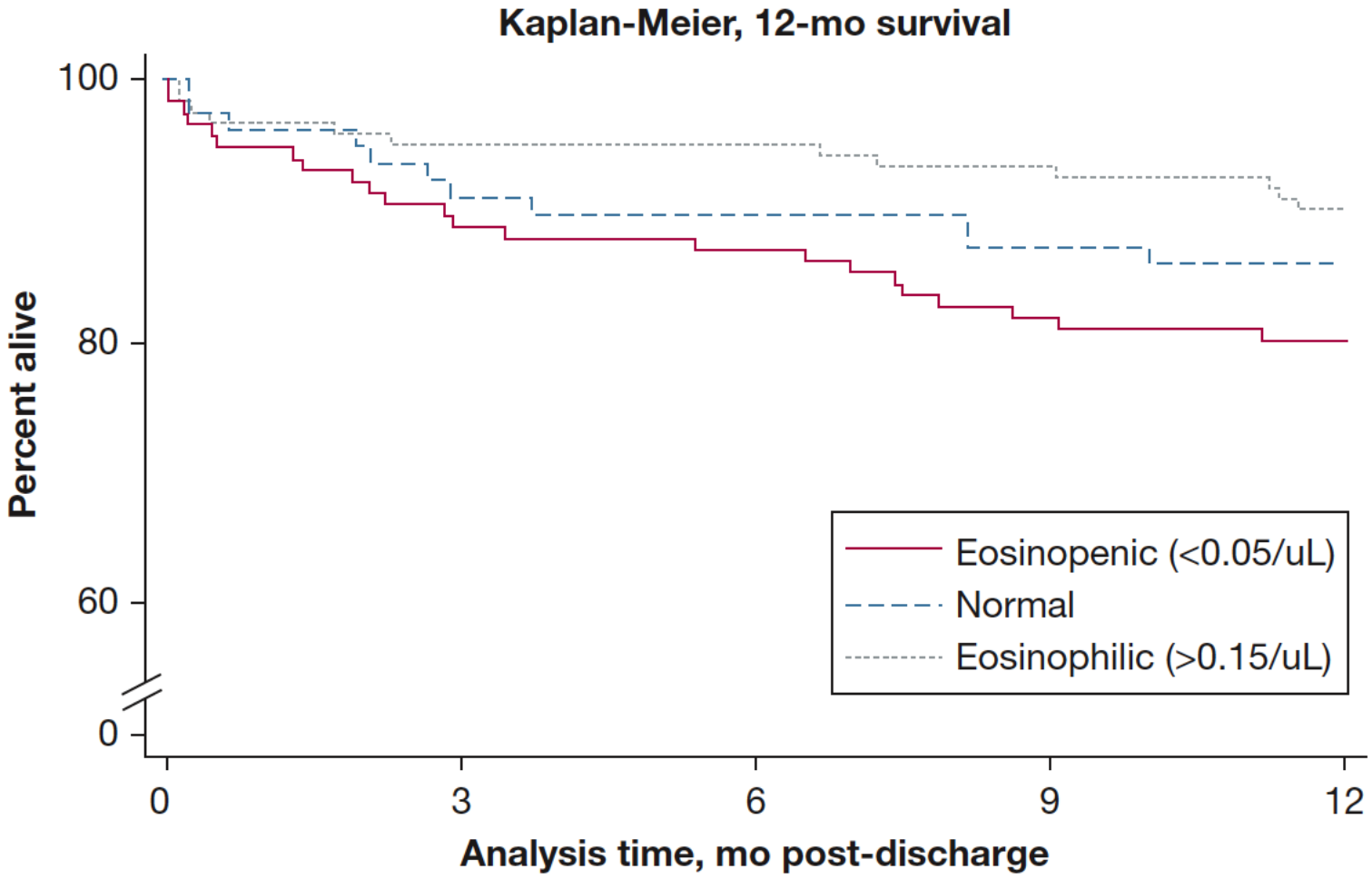
Blood eosinophilia on admission and increased readmission risk



Observational study in Sherbrooke, Quebec, Canada
167 patients with a corticosteroid-free CBC count on admission available
Eosinophilia was defined as blood eosinophil level on admission was **≥200 cells/mL and/or ≥2%**

Couillard S, et al. Chest 2017; 151(2):366-373

Blood eosinophilia on admission and better 1-year survival



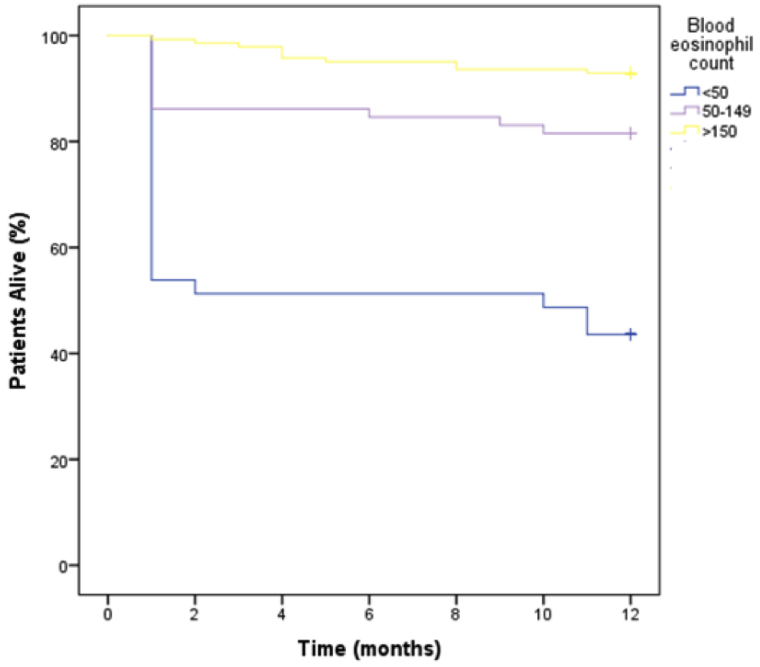
Two derivation (n=242) and validation (n=99) cohort studies of patients hospitalized for AECOPD

MacDonald MI, et al. Chest 2019; 156(1):92-100

Blood Eosinophils as Predictor of Outcomes in hospitalized COPD Exacerbations: Results from a Prospective Study

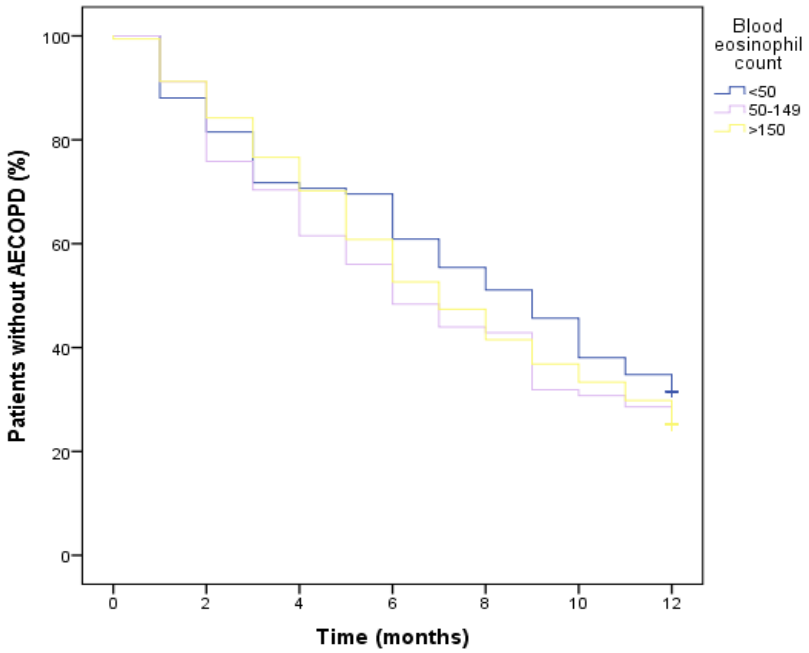
Respiratory Ioannina

↓ Mortality



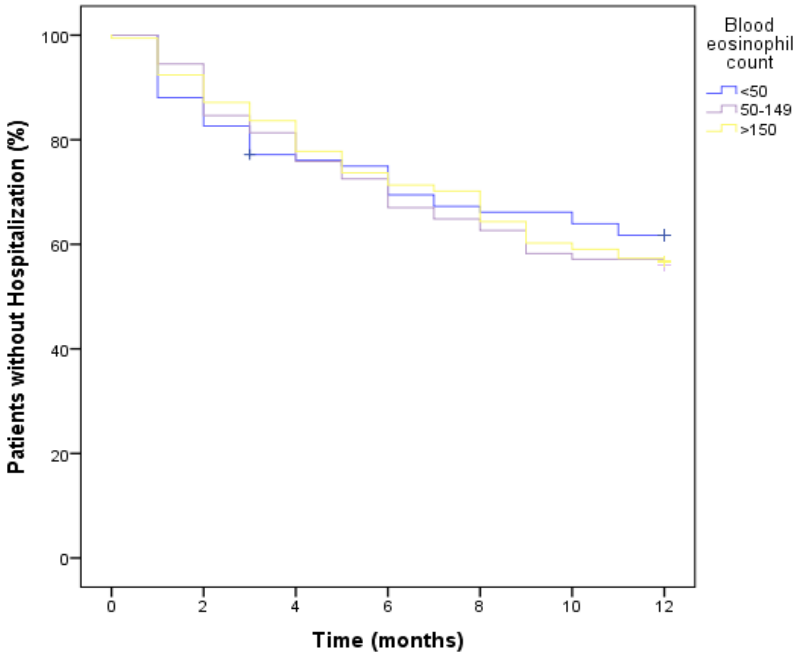
P<0.001 (log rank test)

~ Exacerbations



p=0.402 (log rank test)

~ Hospitalizations



p=0.811 (log rank test)

Kostikas K, et al. ERS 2019 (OA2147)

Eosinophils in COPD: myths and reality

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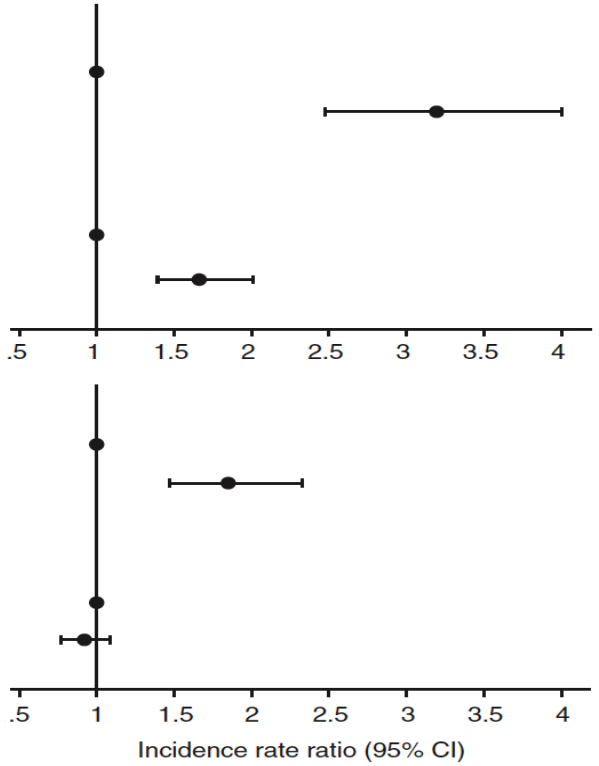
Blood EOS and increased exacerbation risk in COPD (Copenhagen)

Clinical COPD Blood eosinophils	N/Events	Person years of follow-up	IRR (95% CI)
Severe exacerbations			
< 0.34 ·10^9 cells/L (ref.)	165/194	593	1.00
≥ 0.34 ·10^9 cells/L	38/110	140	3.21 (2.49–4.14)
Moderate exacerbations			
< 0.34 ·10^9 cells/L (ref.)	165/492	593	1.00
≥ 0.34 ·10^9 cells/L	38/166	140	1.69 (1.40–2.04)
Severe exacerbations			
< 3.3% (ref.)	142/169	500	1.00
≥ 3.3%	61/135	233	1.84 (1.44–2.36)
Moderate exacerbations			
< 3.3% (ref.)	142/456	500	1.00
≥ 3.3%	61/202	233	0.92 (0.77–1.10)



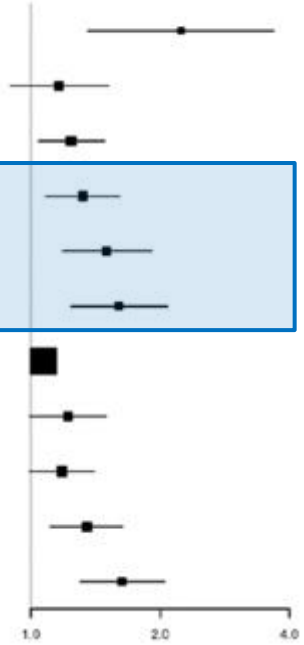
- 7225 COPD individuals in the Copenhagen General Population Study
- EOS ≥340 cells/μL (or 3.3%) was associated with increased risk of severe exacerbations both in the overall population and in those with a diagnosis of 'clinical COPD' (smoking history ≥ 10 pack years, FEV_1 < 70% of predicted and ≥ 1 moderate/severe exacerbation in previous year)

Vedel-Krogh S, et al. AJRCCM 2015;193(9):965-74.

Blood eosinophil thresholds and increased COPD exacerbation risk

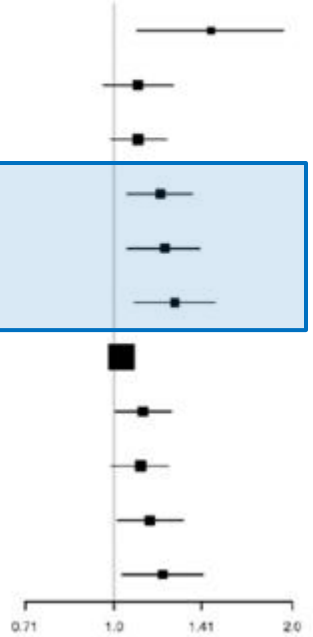
COPDGene

Eosinophil Cutoff	< n	≥ n	IRR	95% CI
cell/uL continuous	NA	1540	2.24	1.35-3.68
100 cells/uL	223	1330	1.16	0.90-1.52
200 cells/uL	814	739	1.24	1.04-1.48
300 cells/uL	1187	366	1.32	1.08-1.61
340 cells/uL	1350	203	1.5	1.18-1.91
400 cells/uL	1398	155	1.6	1.24-2.08
% continuous	NA	1540	1.07	1.02-1.11
2 %	408	1145	1.22	0.99-1.50
3 %	859	694	1.18	0.99-1.40
4 %	1166	387	1.35	1.11-1.63
5 %	1334	219	1.63	1.30-2.05



ECLIPSE

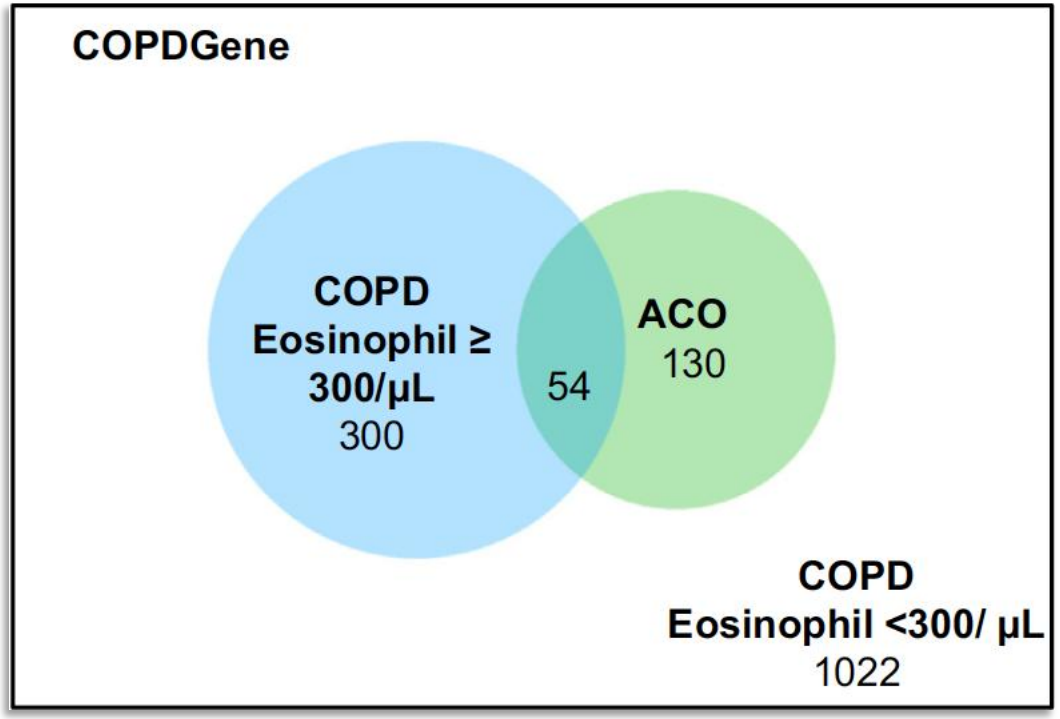
Eosinophil Cutoff	< n	≥ n	IRR	95% CI
continuous cells/uL	NA	1895	1.46	1.09-1.93
100 cells/uL	368	1527	1.1	0.96-1.26
200 cells/uL	1032	863	1.1	0.99-1.23
300 cells/uL	1477	418	1.2	1.05-1.36
340 cells/uL	1584	311	1.22	1.06-1.40
400 cells/uL	1668	227	1.27	1.08-1.48
continuous %	NA	1895	1.03	1.01-1.06
2 %	720	1175	1.12	1.00-1.25
3 %	1178	717	1.11	0.99-1.24
4 %	1476	419	1.15	1.01-1.31
5 %	1660	235	1.21	1.03-1.42

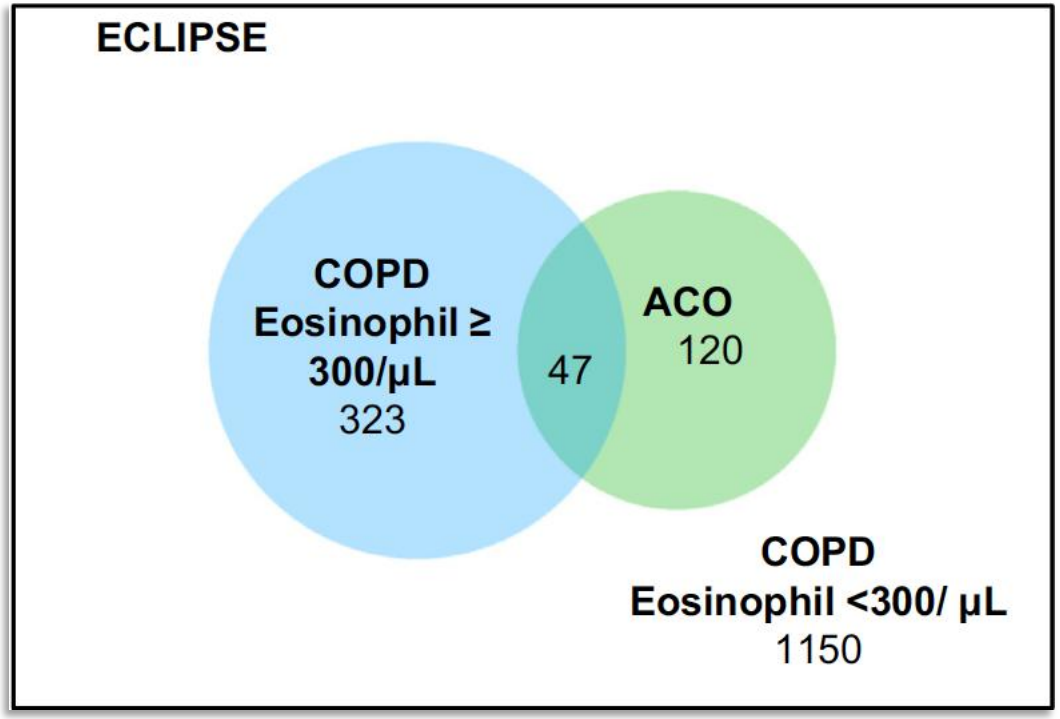


Yun JH et al., J All Clin Immunol 2018;141:2037-47

Blood eosinophilia vs. ACO - not interchangeable

COPD patients with blood EOS ≥300 cells/μL were more likely to have ACO
(OR 1.51 in COPDGene and 1.69 in ECLIPSE)



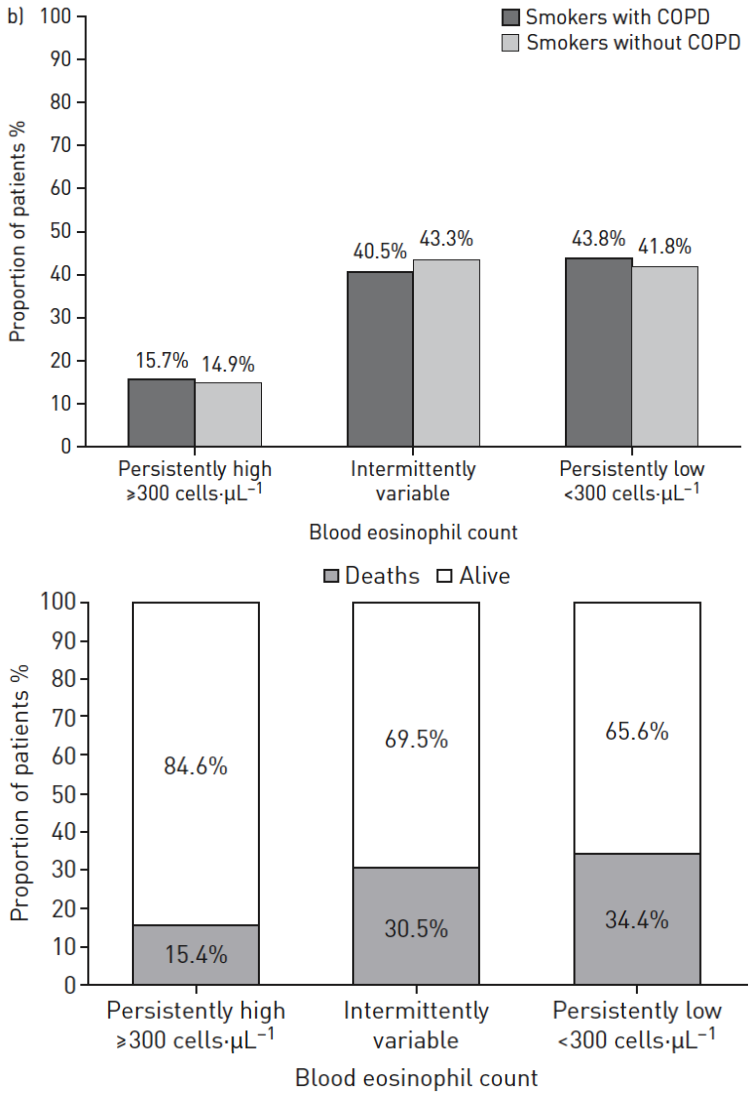


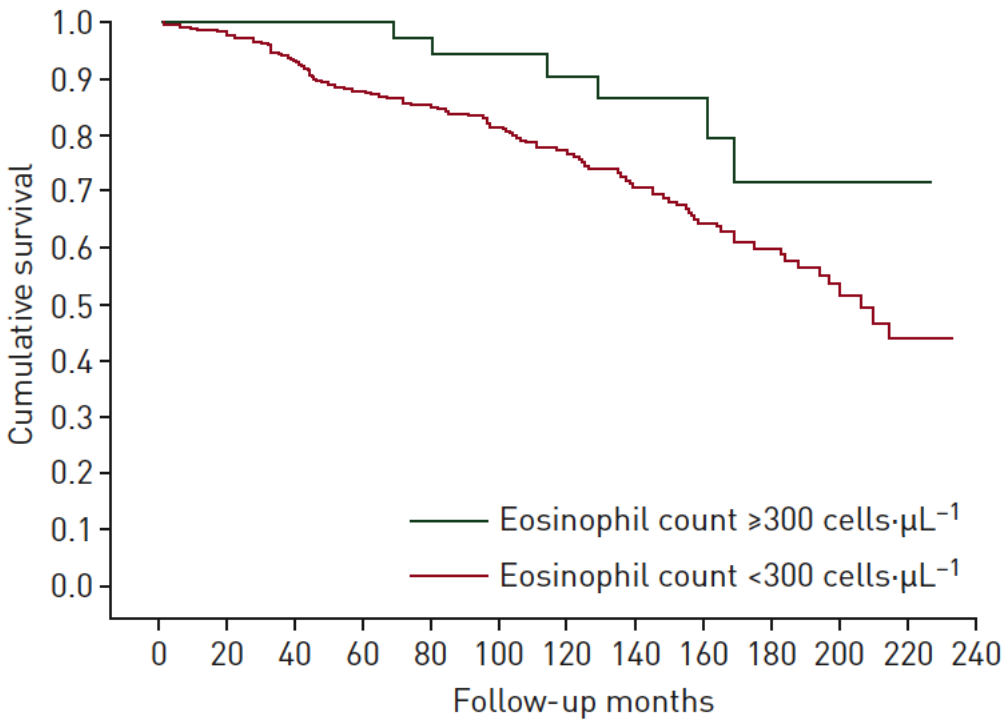
Both ACO and blood EOS ≥300 cells/μL were independent predictors of exacerbation risk

ACO defined by self-report of asthma diagnosis by a doctor before the age of 40 years

Yun JH et al., J All Clin Immunol 2018;141:2037-47

Persistent blood eosinophilia in stable COPD and reduced mortality





424 COPD patients and 67 smokers without COPD from the CHAIN cohort and 308 COPD patients from the BODE cohort with **3 eosinophil measurements over 2 years**

Persistent eosinophilia was not a risk factor for exacerbations (!)

Casanova C, et al, Eur Respir J 2017; 50: 1701162

Sputum (but not blood) EOS and COPD exacerbations (SPIROMICS)

	Blood eosinophils <200 per µL (n=1262)	Blood eosinophils ≥200 per µL (n=1237)	p value*	Sputum eosinophils <1·25% (n=656)	Sputum eosinophils ≥1·25% (n=171)	p value*
Total	311 (25%)	309 (25%)	0·35	125 (19%)	44 (26%)	0·05
Requiring health-care use	294 (23%)	291 (24%)	0·36	125 (19%)	43 (25%)	0·07
Antibiotic treatment	232 (18%)	240 (19%)	0·29	92 (14%)	34 (20%)	0·09
Corticosteroid treatment	199 (16%)	209 (17%)	0·27	66 (10%)	32 (19%)	0·002
Any drug treatment	265 (21%)	273 (22%)	0·29	105 (16%)	39 (23%)	0·033
Severe†	137 (11%)	162 (13%)	0·15	52 (8%)	22 (13%)	0·044

Data are n (% positive). *χ^2 test. †Exacerbations involving a trip to an emergency department or admission to hospital.

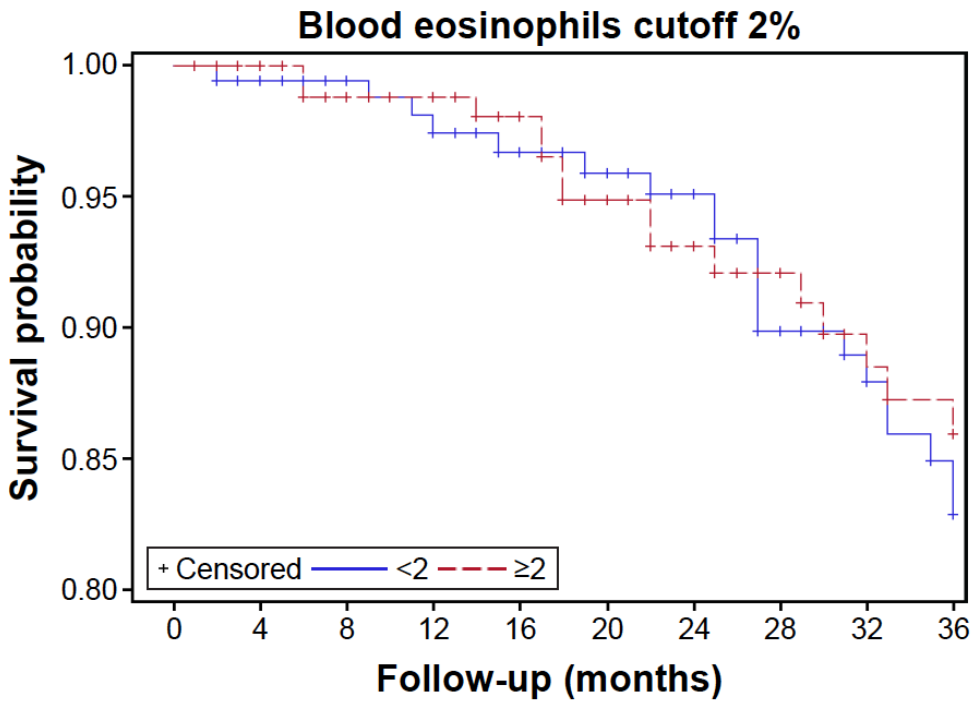
***Table 5*: Comparison of exacerbations occurring in the previous year for patients stratified by mean blood or sputum eosinophils**

Hastie AT, et al. Lancet Respir Med 2-17;5(12):956-967

Blood EOS not related to exacerbations (Initiatives BPCO - France)

Variables	Eos ≥2% (N=223)	Missing values	Eos <2% (N=235)	Missing values	*P*-values
Sex, M/F	72.6% (162)/27.4% (61)	0	71.5% (168)/28.5% (67)	0	0.783
Age, years	62 (55–70)	0	62 (55–70)	0	0.715
BMI (kg/m²)	25.3 (21.9–29.4)	0	24.2 (21.2–28.4)	0	0.093
Obesity (BMI >30 kg/m²)	22.0% (49)	0	18.3% (43)	0	0.326
Smoking habits		7		5	0.542
Former smoker	67.6% (146)		62.6% (144)		
Current smoker	29.6% (64)		34.3% (79)		
Never smoker	2.8% (6)		3.0% (7)		
Cumulative smoking (pack-years)	36.0 (24.0–54.0)	22	37.1 (22.5–52.5)	25	0.704
History of asthma	13.5% (30)	15	14.0% (33)	13	0.855
Hay fever	9.9% (22)	0	12.3% (29)	0	0.400
Eczema	7.6% (17)	0	8.1% (19)	0	0.854
Rhinitis/sinusitis	17.5% (39)	0	20.4% (48)	0	0.423
Occupational exposures	27.8% (62)	0	32.3% (76)	0	0.290
Chronic cough and sputum production	65.9% (147)	14	71.9% (169)	0	0.166
Exacerbation rate (per patient-year)	1.0 (0.0–2.0)	5	1.0 (0.0–3.0)	7	0.247
Severe (hospitalized) exacerbation rate (per patient-year)	0.0 (0.0–0.0)	5	0.0 (0.0–1.0)	7	0.174
mMRC dyspnea grade	2 (1–2)	18	2 (1–3)	21	0.211
Ischemic heart disease	11.2% (25)	0	11.5% (27)	0	0.925
Chronic heart failure	11.2% (25)	0	13.2% (31)	0	0.518
FEV_1% predicted	52 (37–68)	0	51 (34–70)	0	0.658
ICS outside fixed-dose combinations	21.5% (48)	5	23.0% (54)	10	0.709
ICS + long-acting beta-agonist	41.7% (93)	5	36.2% (85)	10	0.225
Long-acting antimuscarinic agents	30.5% (68)	5	34.0% (80)	10	0.299
Oral steroids	5.1% (12)	5	2.2% (5)	10	0.120
Follow-up duration (months)	45 (33–100)	1	51 (29–107)	1	0.641
Death rate	13.0% (29)	1	17.0% (40)	1	0.230

high EOS = less diabetes and lower SGRQ



Zysman M et al., Int J COPD 2017:12 1819–1824

Blood EOS predict exacerbation risk in ex-smokers (UK)

TABLE 1 Rate ratios for the association between elevated blood eosinophil count and chronic obstructive pulmonary disease (COPD) exacerbation during follow-up year in the total population of COPD patients and in subgroups of patients defined by gender, smoking status, inhaled corticosteroid (ICS) therapy and Global Initiative for Chronic Obstructive Lung Disease (GOLD) group. The rate of COPD exacerbation in patients with an elevated eosinophil count ($\geqslant 0.45\times10^9$ per L) relative to patients with a reference eosinophil count (0.05×10^9 per L to $<0.45\times10^9$ per L) is shown for each subgroup. Differences between subgroups are tested by including an interaction term of elevated eosinophil count and the variable used to define the categories of the subgroup in a multiple regression model (*e.g.* interaction term of elevated eosinophil count (yes/no)×gender (male/female) had a p-value of 0.11).

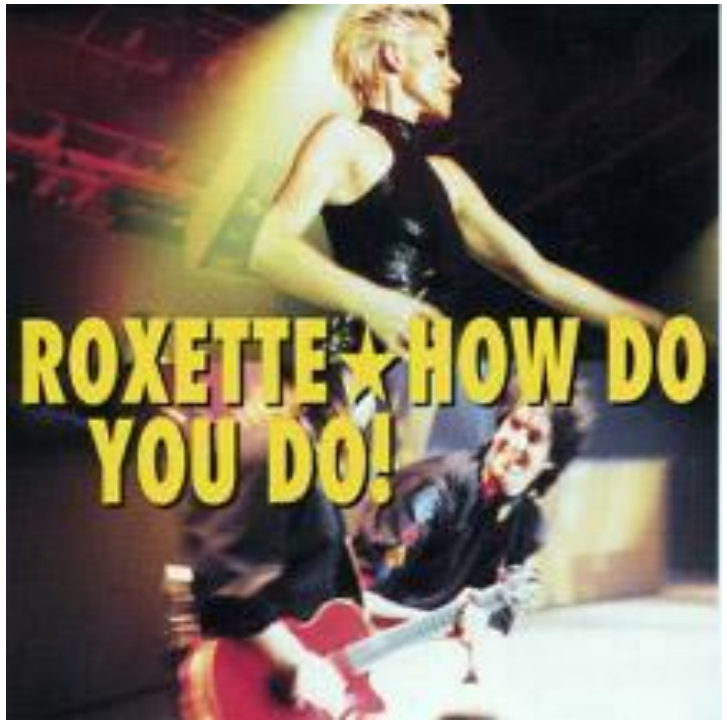
Study population	Subjects	Elevated eosinophil count	Rate ratio (95% CI)[#]	p-value	p-value interaction
Total population	8318 (100)	8.9	**1.13 (1.01–1.26)**	**0.03**	
Male	4695 (56.4)	11.6	**1.21 (1.06–1.38)**	**0.005**	0.11
Female	3623 (43.6)	5.5	0.98 (0.80–1.21)	0.88	
Current smokers	3610 (43.4)	8.7	0.86 (0.71–1.05)	0.14	**0.0002**
Ex-smokers	4708 (56.6)	9.1	**1.32 (1.15–1.51)**	**<0.0001**	
ICS[¶]	4082 (49.1)	9.4	**1.17 (1.02–1.35)**	**0.03**	0.29
No ICS	4236 (50.9)	8.5	1.02 (0.84–1.24)	0.82	
GOLD group[+]	6600 (79.3)				
A	2357 (35.4)	8.2	0.99 (0.77–1.29)	0.97	reference
B	1364 (20.5)	8.8	**1.33 (1.02–1.73)**	**0.04**	0.07
C	1379 (20.7)	7.9	1.27 (0.99–1.63)	0.06	0.12
D	1560 (23.4)	9.6	1.17 (0.95–1.44)	0.13	0.24

Data are presented as % or n (%) unless otherwise stated. Bold values indicate significant effects. ICS: inhaled corticosteroids; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 sec; FVC: forced vital capacity; MRC: Medical Research Council. [#]: adjusted for potential confounders; [¶]: maintenance treatment with ICS; [+]: GOLD groups (where data is available): for patients with FEV_1/FVC <0.70, defined based on an MRC score ⩾2 (yes, B or D; no, A or C), number of baseline exacerbations ⩾2 or leading to hospitalisation ⩾1 or FEV_1 (% predicted) <50% (yes, C or D; no, A or B). Obstruction defined as FEV_1/FVC <0.70 at spirometry measurement closest to index date within ⩽5 years.

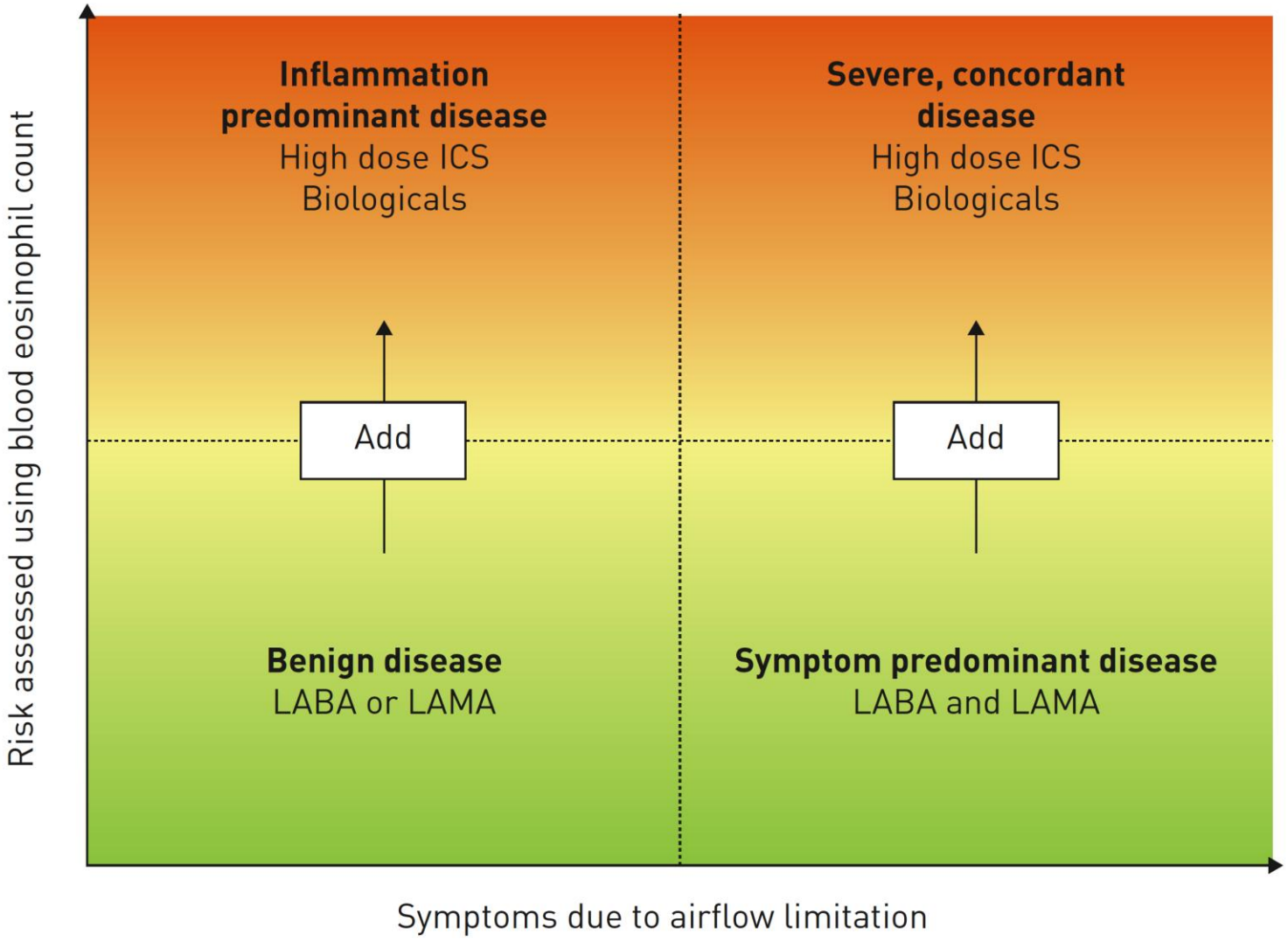
Kerkhof M, et al. Eur Respir J 2017; 50: 1700761

Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
- The early days: exacerbations et al.
- Predicting future risk
- **Identifying ICS responders**
- Real world evidence: the new must (?)
- An imperfect biomarker
- A more targeted approach?

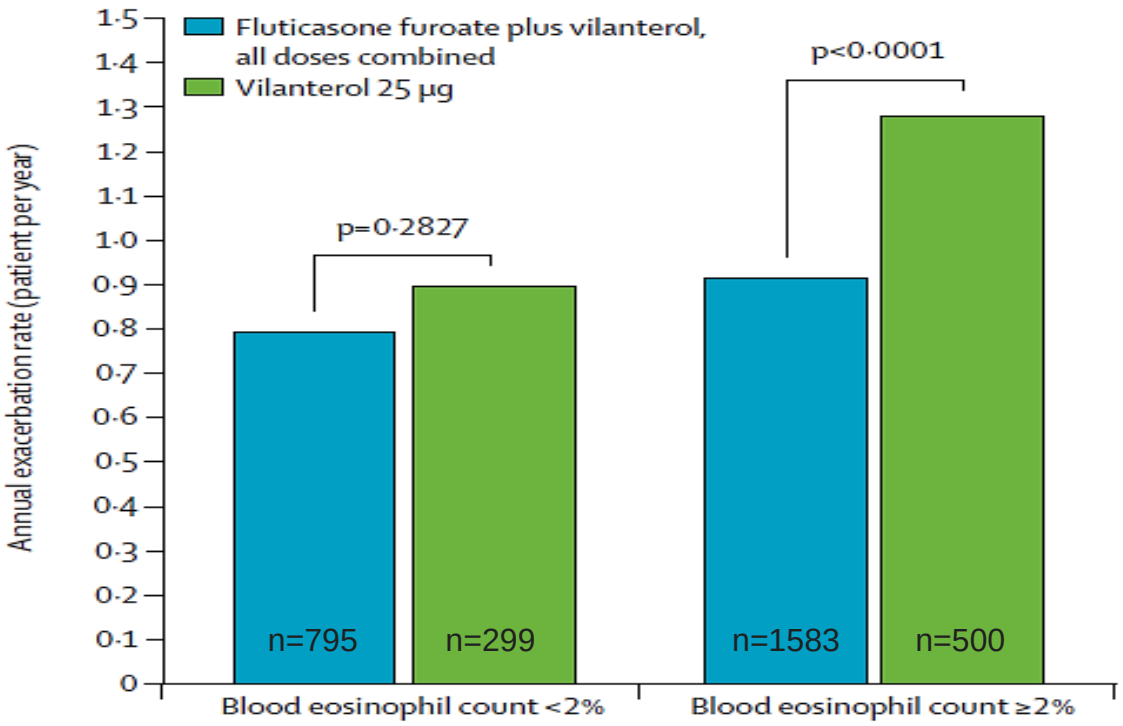


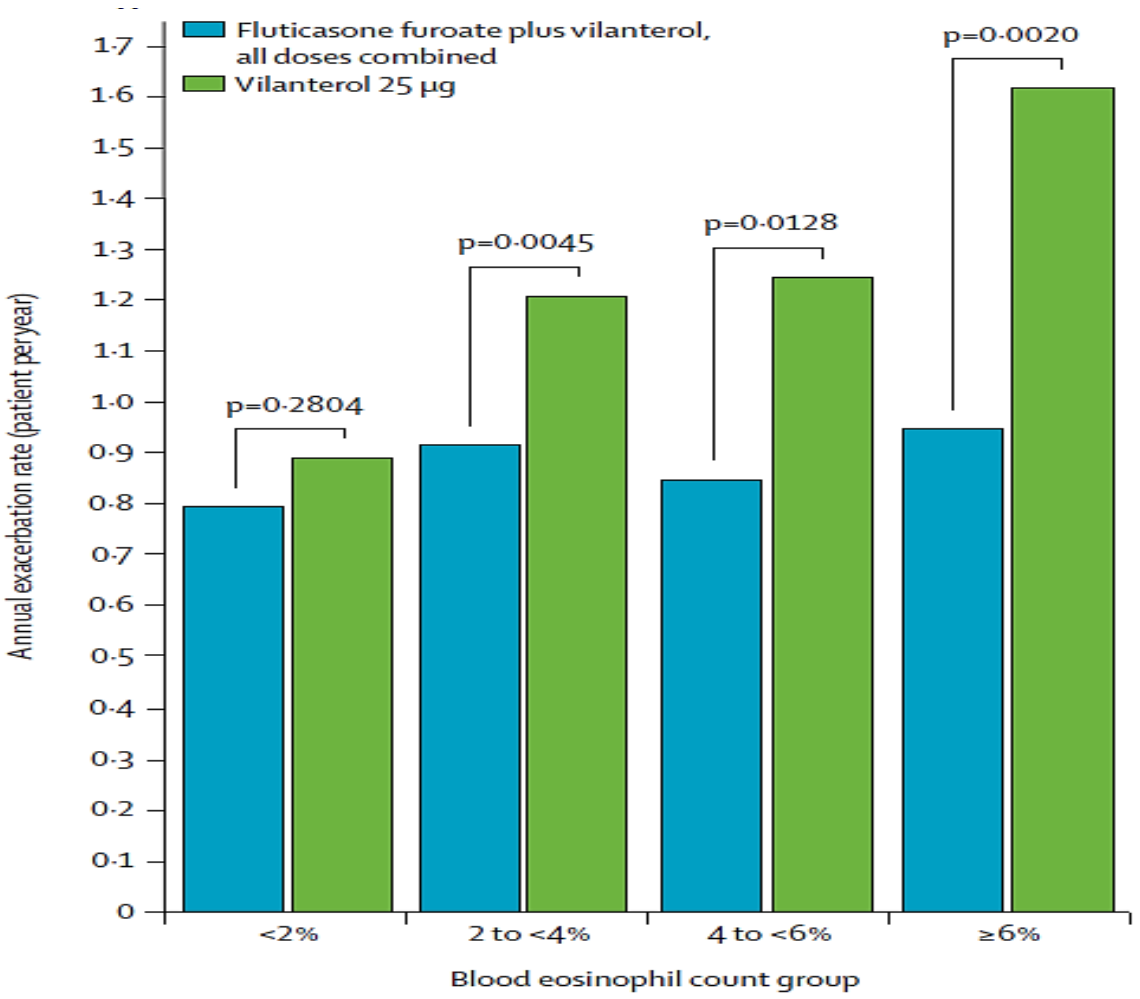
Risk assessment based on symptoms and blood EOS?



Pavord ID and Agusti A, Eur Respir J 2016; 47: 1299–1303

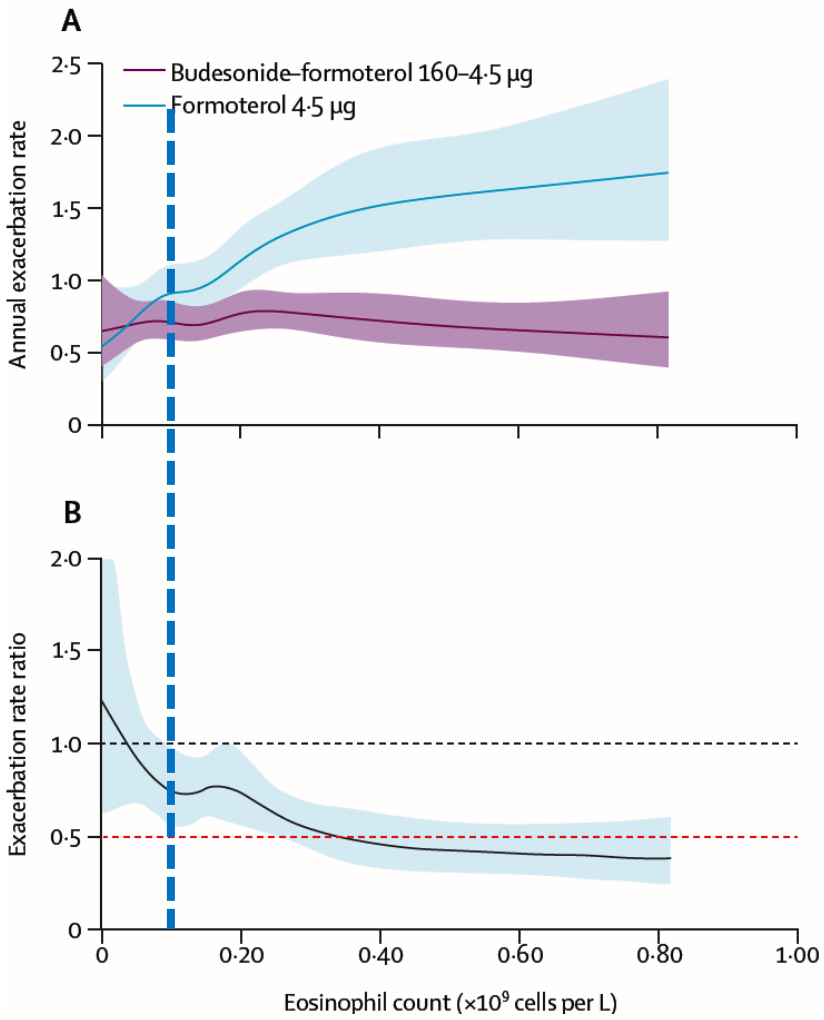
The first post-hoc analysis to show the way: FF/VI vs. VI

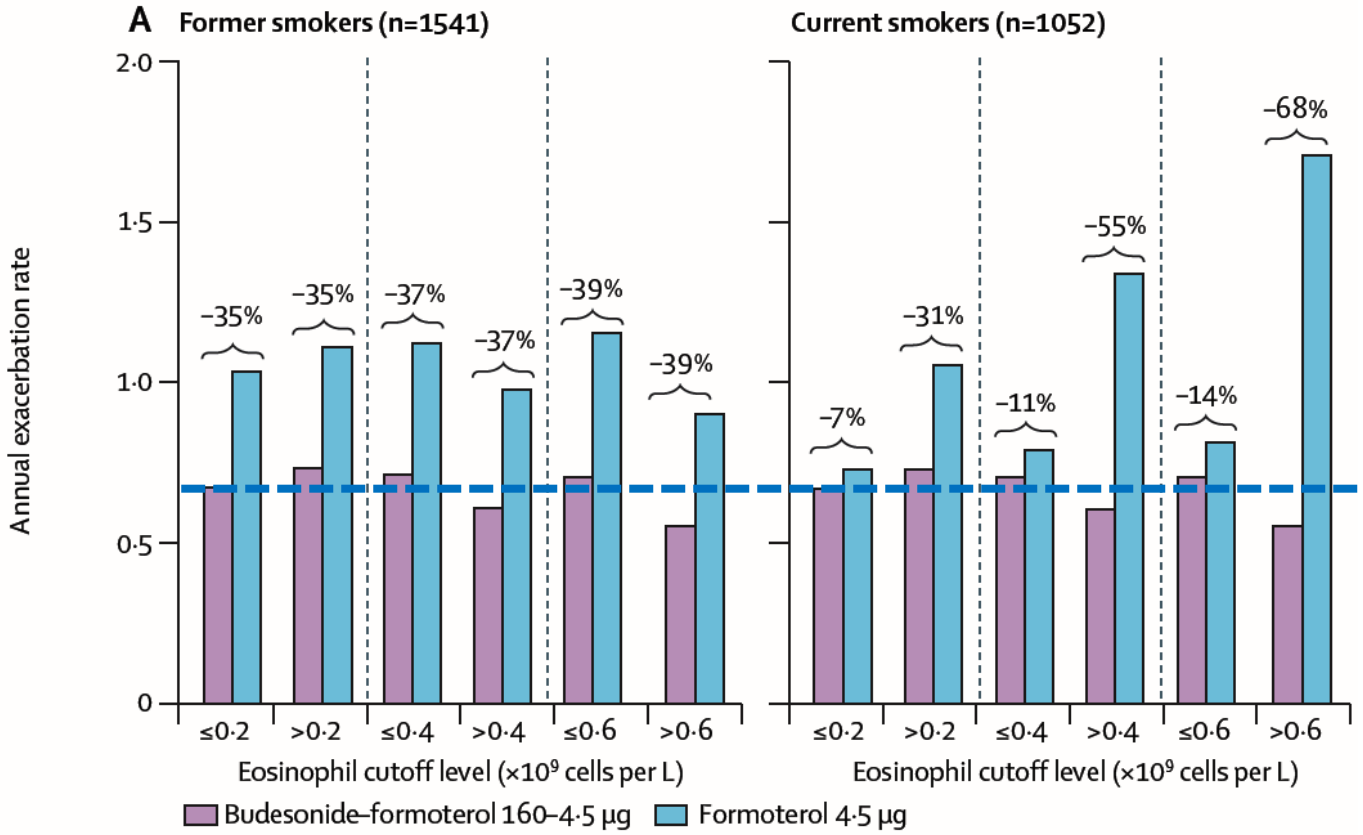




Pascoe S, et al. Lancet Respir Med 2015;3(6):435-42.

Blood EOS cut points: BUD/FORM vs. FORM

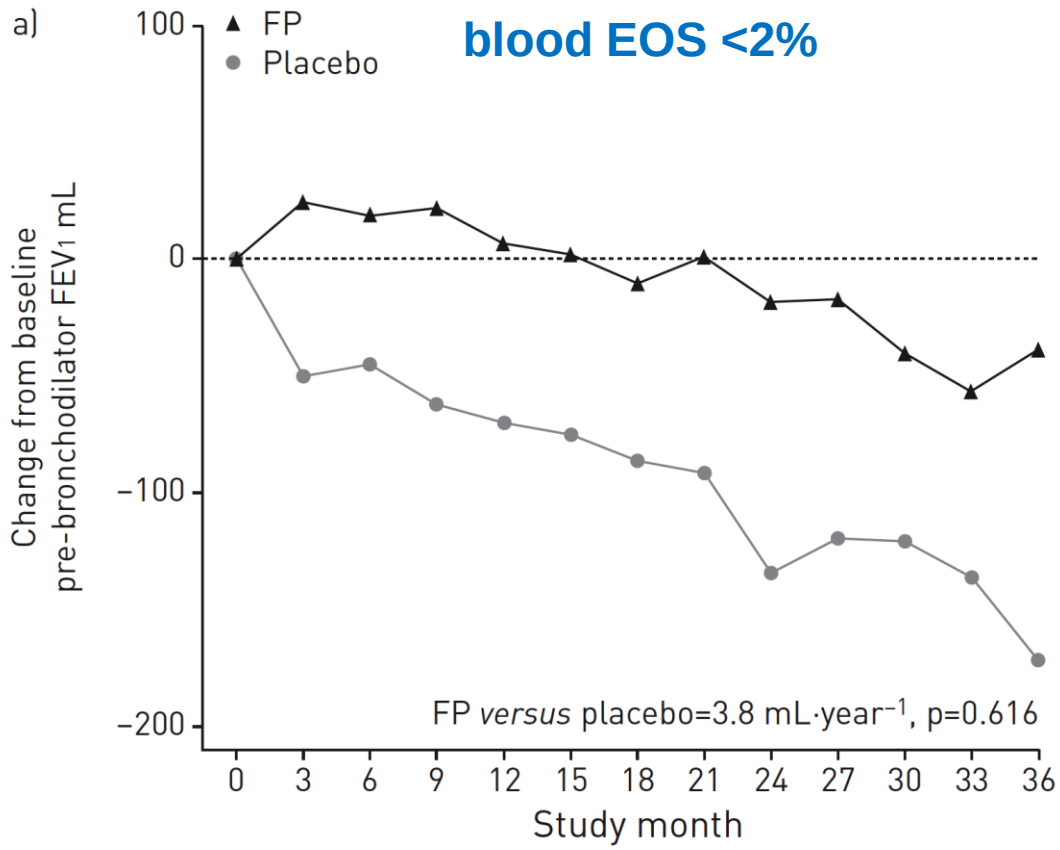


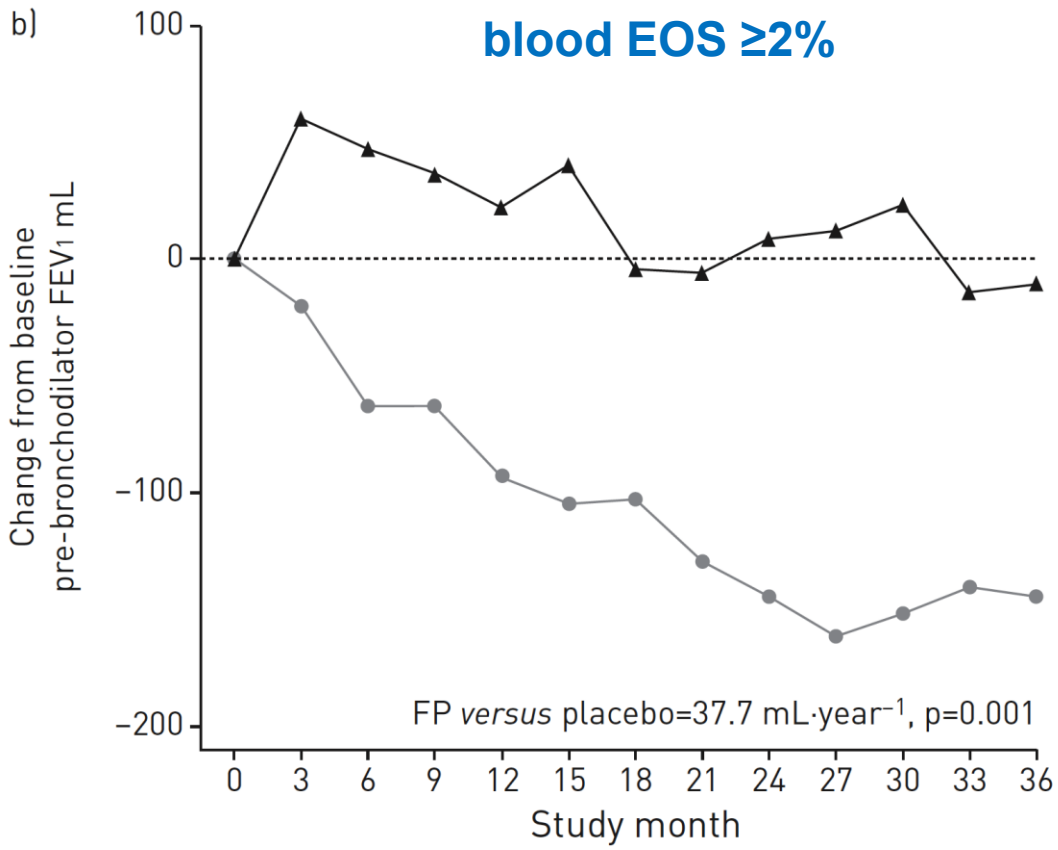


Bafadhel M et al., Lancet Respir Med 2018; 6: 117–26

ICS vs. placebo and FEV_1 decline by blood EOS

- Post-hoc analysis on data from ISOLDE study (N=751): FP vs PBO for 3 years
- **Lower exacerbation rates observed with FP vs placebo in both the high and low EOS groups**

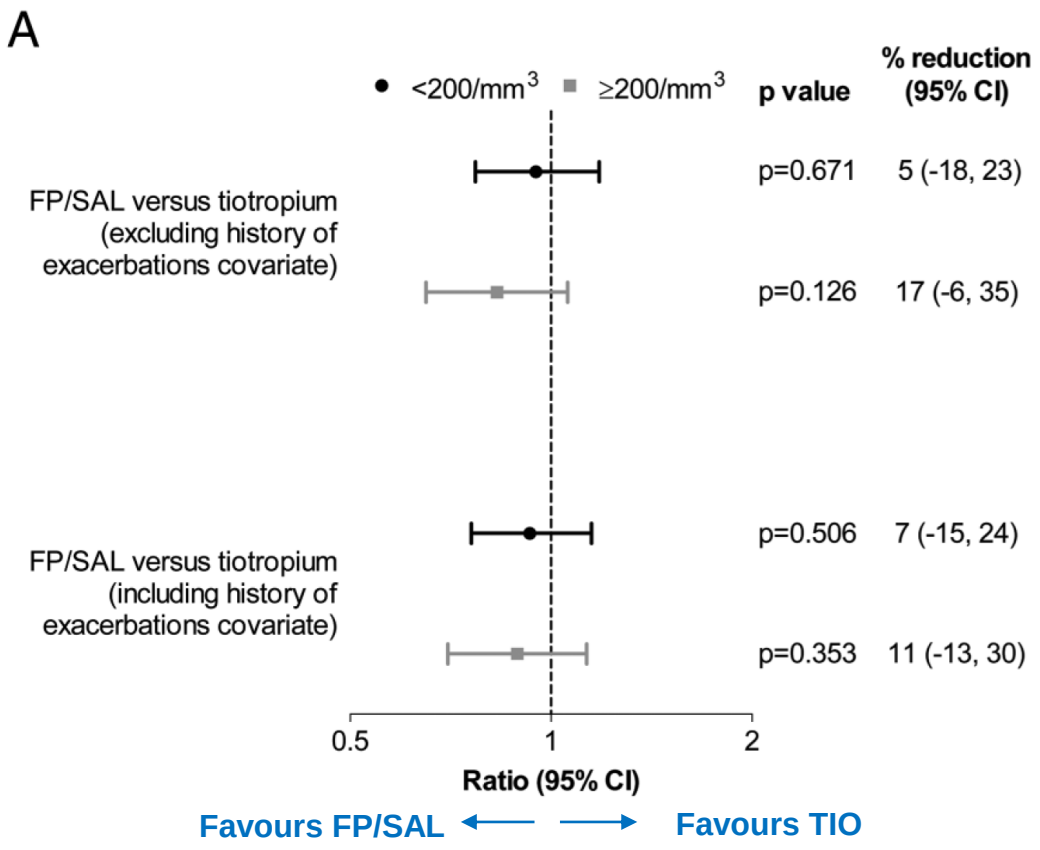


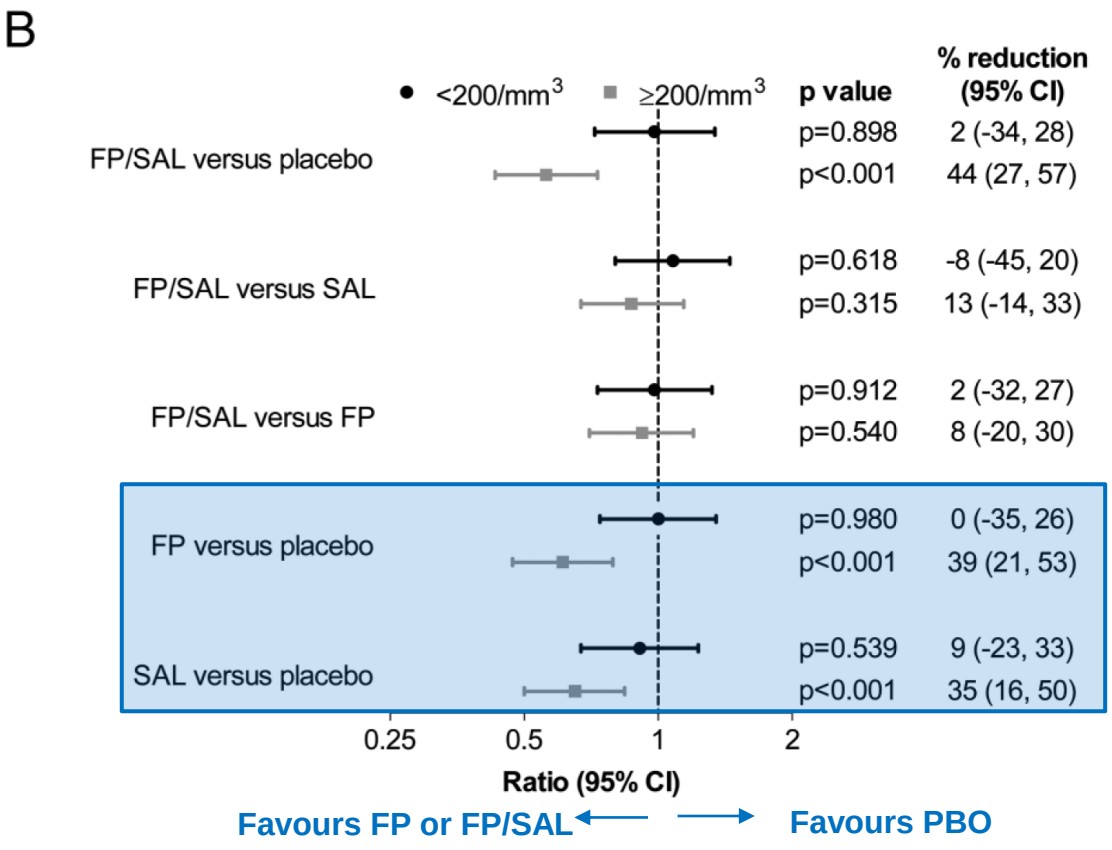


Barnes N, et al. Eur Respir J 2016;47(5):1374-82

ICS/LABA vs. TIO or mono-components and PBO on exacerbations

- Re-analysis of data from **INSPIRE** (FP/SAL vs. TIO) and **TRISTAN** (FP/SAL vs. mono-components and placebo)
- Stratification by % baseline EOS (**<200** vs. **≥200 cells/µL**)

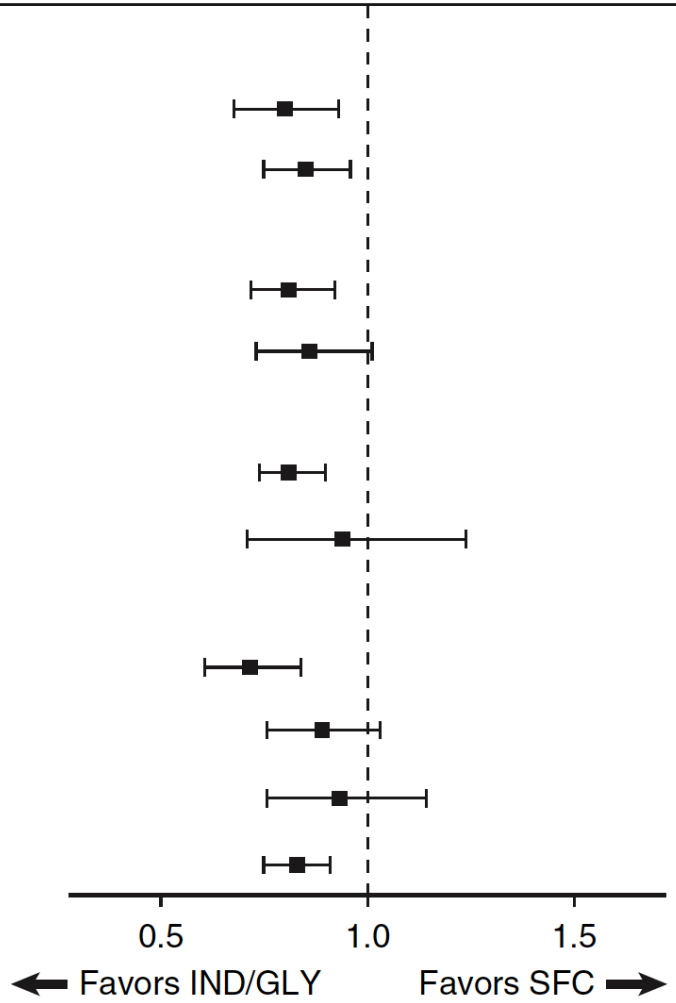




Pavord ID, et al. Thorax 2016;71:118–125

FLAME: IND/GLY vs. SFC by blood EOS

Subgroup	No. of patients IND/GLY	No. of patients SFC	Annualized rate IND/GLY	Annualized rate SFC	Rate ratio (95% CI)
Blood eosinophils count					
< 2 %	620	659	0.99	1.24	0.80 (0.68, 0.93)
≥ 2%	1,026	993	0.98	1.15	0.85 (0.75, 0.96)
Blood eosinophils count					
< 3 %	1,041	1,037	0.99	1.22	0.81 (0.72, 0.92)
≥ 3 %	605	615	0.98	1.14	0.86 (0.73, 1.01)
Blood eosinophils count					
< 5 %	1,442	1,444	0.98	1.20	0.81 (0.74, 0.90)
≥ 5 %	204	208	1.01	1.08	0.94 (0.71, 1.24)
Blood eosinophils count					
< 150 cells/μl	623	654	0.90	1.26	0.72 (0.61, 0.84)
150 to < 300 cells/μl	655	631	1.04	1.17	0.89 (0.76, 1.03)
≥ 300 cells/μl	368	367	1.03	1.11	0.93 (0.76, 1.14)
Overall	1,651	1,656	0.98	1.19	0.83 (0.75, 0.91)

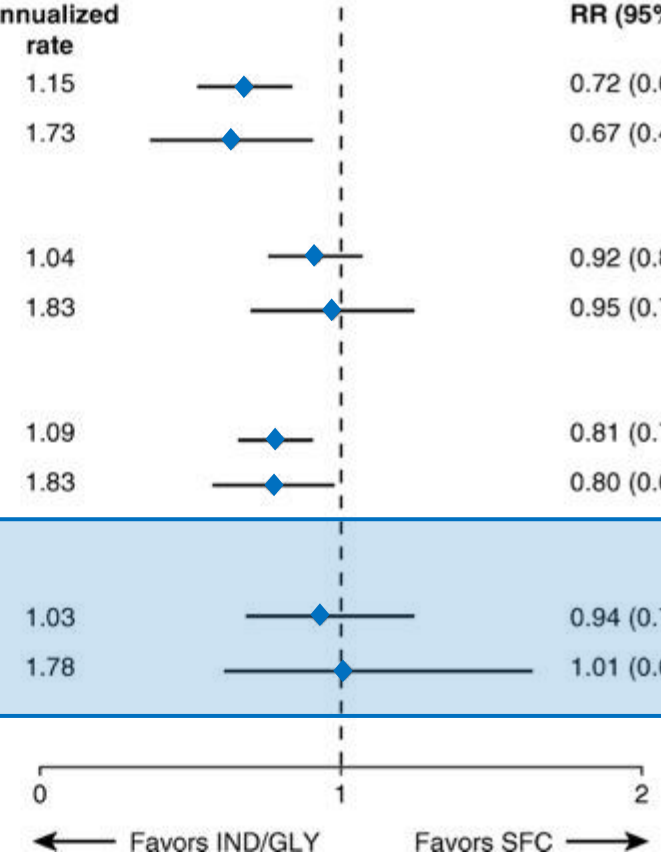


Roche N, et al, Am J Respir Crit Care Med 2017;195(9):1189-97

FLAME: exacerbation history and blood eosinophils

Rate ratios (95% CI) of moderate/severe chronic obstructive pulmonary disease exacerbations

	IND/GLY 110/50 µg o.d.		SFC 50/500 µg b.i.d.		
Eosinophil <150 cells/µL	**n**	**Annualized rate**	**n**	**Annualized rate**	**RR (95% CI); *P* values**
1 exacerbation	504	0.82	555	1.15	0.72 (0.60–0.86); *P* < 0.001
≥2 exacerbations	119	1.16	99	1.73	0.67 (0.48–0.94); *P* = 0.021
Eosinophil ≥150 cells/µL					
1 exacerbation	821	0.95	777	1.04	0.92 (0.80–1.06); *P* = 0.245
≥2 exacerbations	202	1.75	221	1.83	0.95 (0.75–1.21); *P* = 0.692
Eosinophil <300 cells/µL					
1 exacerbation	1,034	0.88	1046	1.09	0.81 (0.71–0.92); *P* < 0.001
≥2 exacerbations	244	1.46	239	1.83	0.80 (0.64–0.99); *P* = 0.038
Eosinophil ≥300 cells/µL					
1 exacerbation	291	0.96	286	1.03	0.94 (0.73–1.20); *P* = 0.612
≥2 exacerbations	77	1.79	81	1.78	1.01 (0.66–1.54); *P* = 0.973



b.i.d., twice daily; CI, confidence interval; IND/GLY, indacaterol/glycopyrronium; o.d., once daily; RR, rate ratio; SFC, salmeterol/fluticasone

Papi A, Kostikas K, et al. AJRCCM 2018 May 1;197(9):1223-1226

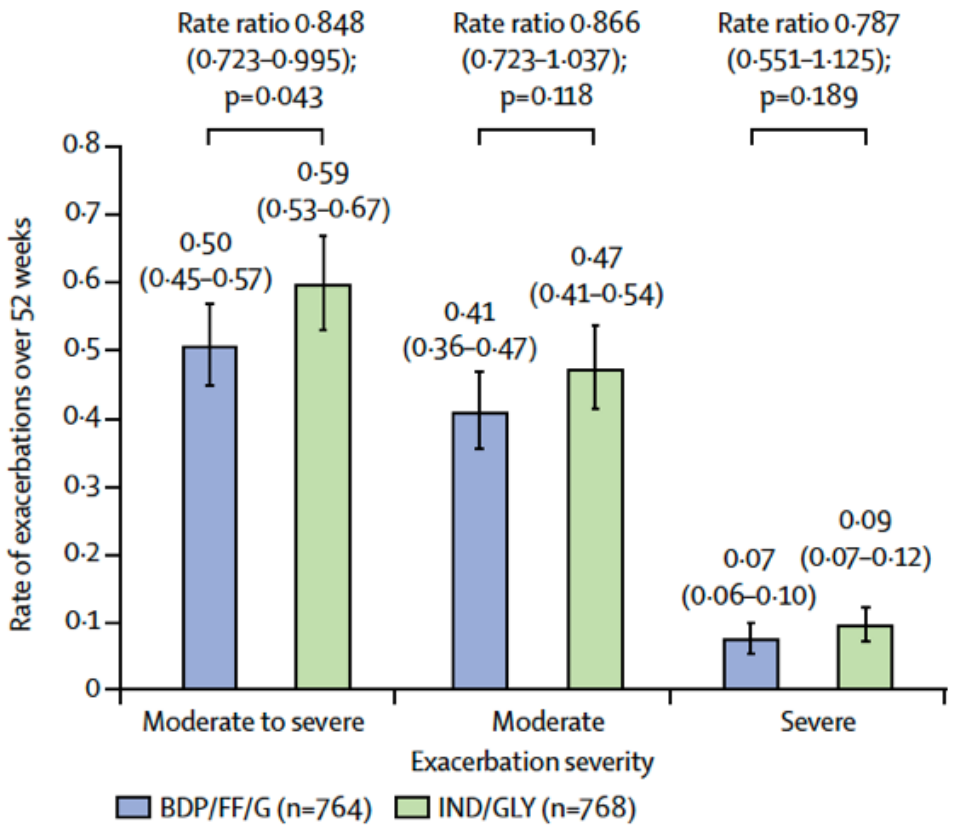
FLAME: minor changes in blood EOS from baseline to weeks 26 & 52

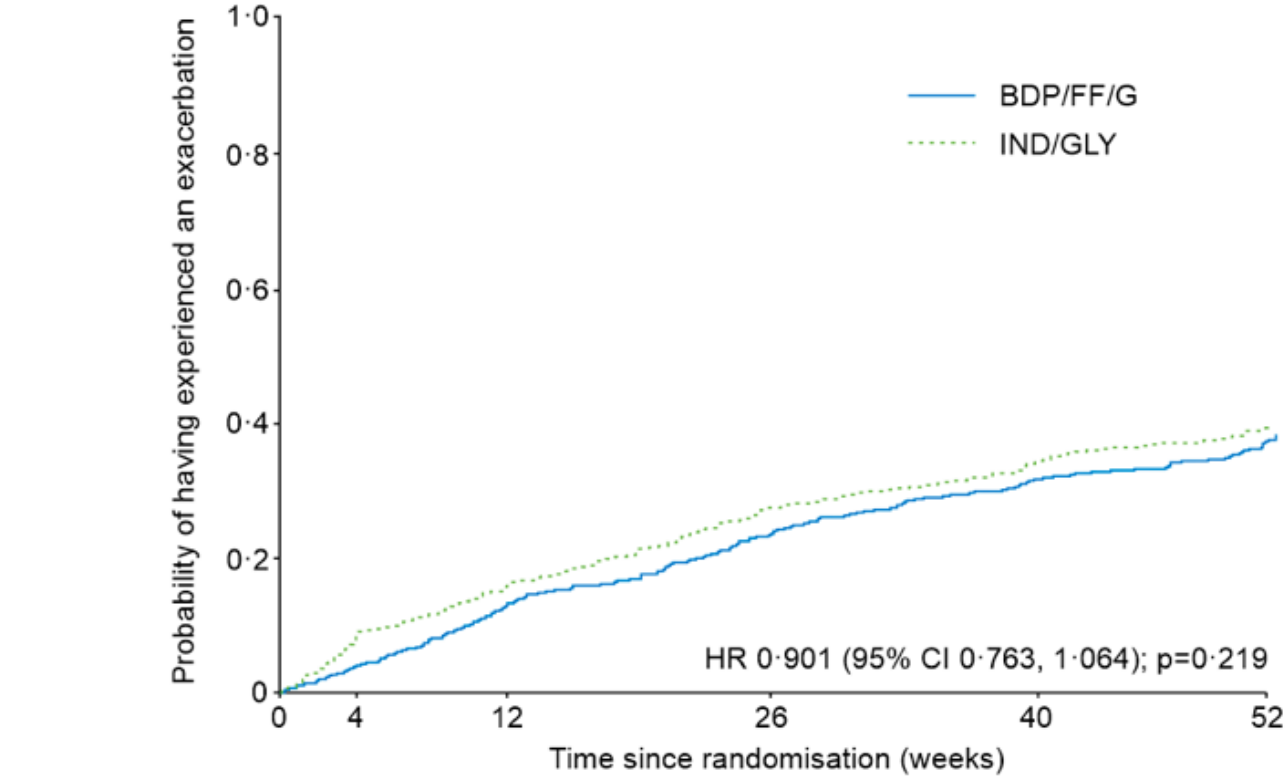
Visit and Treatment	LSM (SE)	Treatment Difference			
		Comparator	LSM (SE)	95% CI	*P* Value
Blood eosinophils, %					
Baseline					
All	2.835				
Week 26 CFB					
IND/GLY	−0.06 (0.047)	SFC	0.24 (0.066)	0.11–0.37	<0.001
SFC	−0.29 (0.047)				
Week 52 CFB					
IND/GLY	−0.05 (0.048)	SFC	0.32 (0.069)	0.18–0.45	<0.001
SFC	−0.37 (0.049)				
Blood eosinophils, cells/μl					
Baseline					
All	216				
Week 26 CFB					
IND/GLY	−3 (3.7)	SFC	16 (5.2)	6–26	0.002
SFC	−19 (3.7)				
Week 52 CFB					
IND/GLY	−3 (3.8)	SFC	22 (5.4)	11–33	<0.001
SFC	−25 (3.9)				

CFB = change from baseline; CI = confidence interval; GLY = glycopyrronium; IND = indacaterol; LSM = least-squares mean; SFC = salmeterol/fluticasone propionate combination.

Roche N, et al, Am J Respir Crit Care Med 2017;195(9):1189-97

TRIBUTE: rates and time to 1st moderate/severe exacerbation



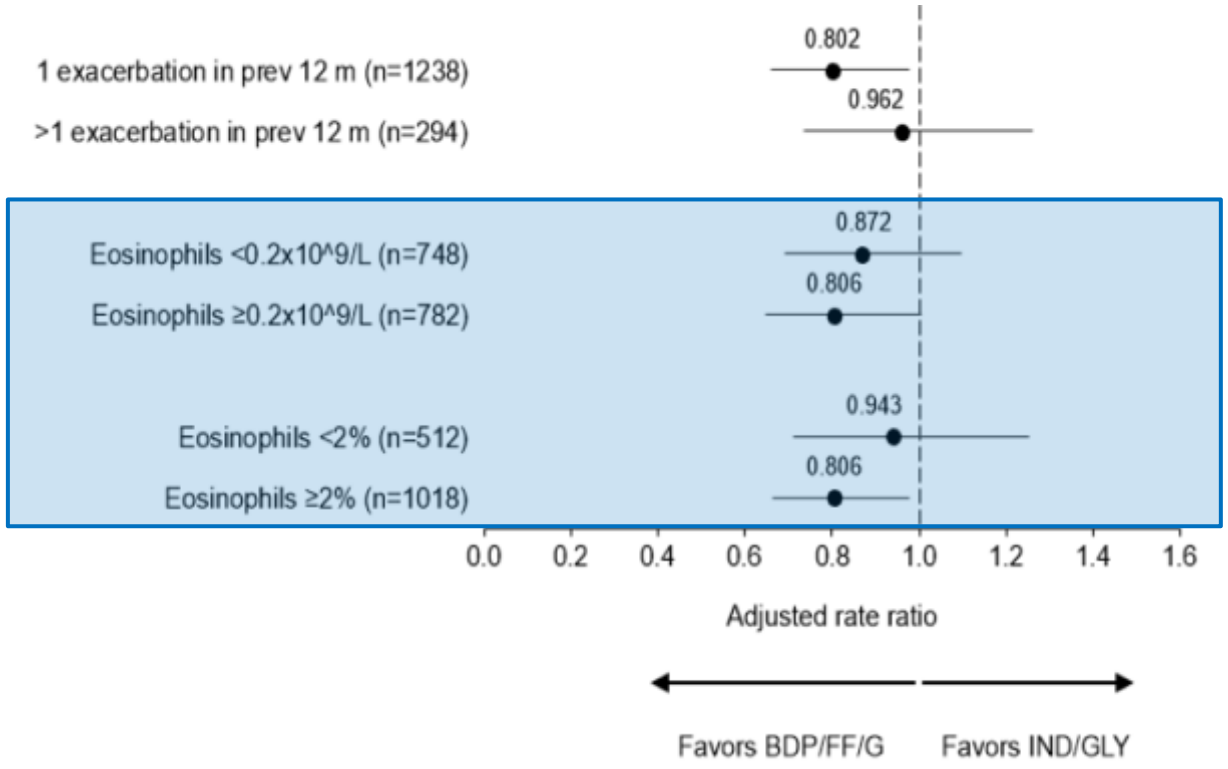


Number of patients at risk

BDP/FF/G	n=764	726	651	555	484	275
IND/GLY	n=768	704	633	523	456	288

Papi A et al. Lancet 2018; 391:1076–1084

TRIBUTE: responders in subgroup analyses

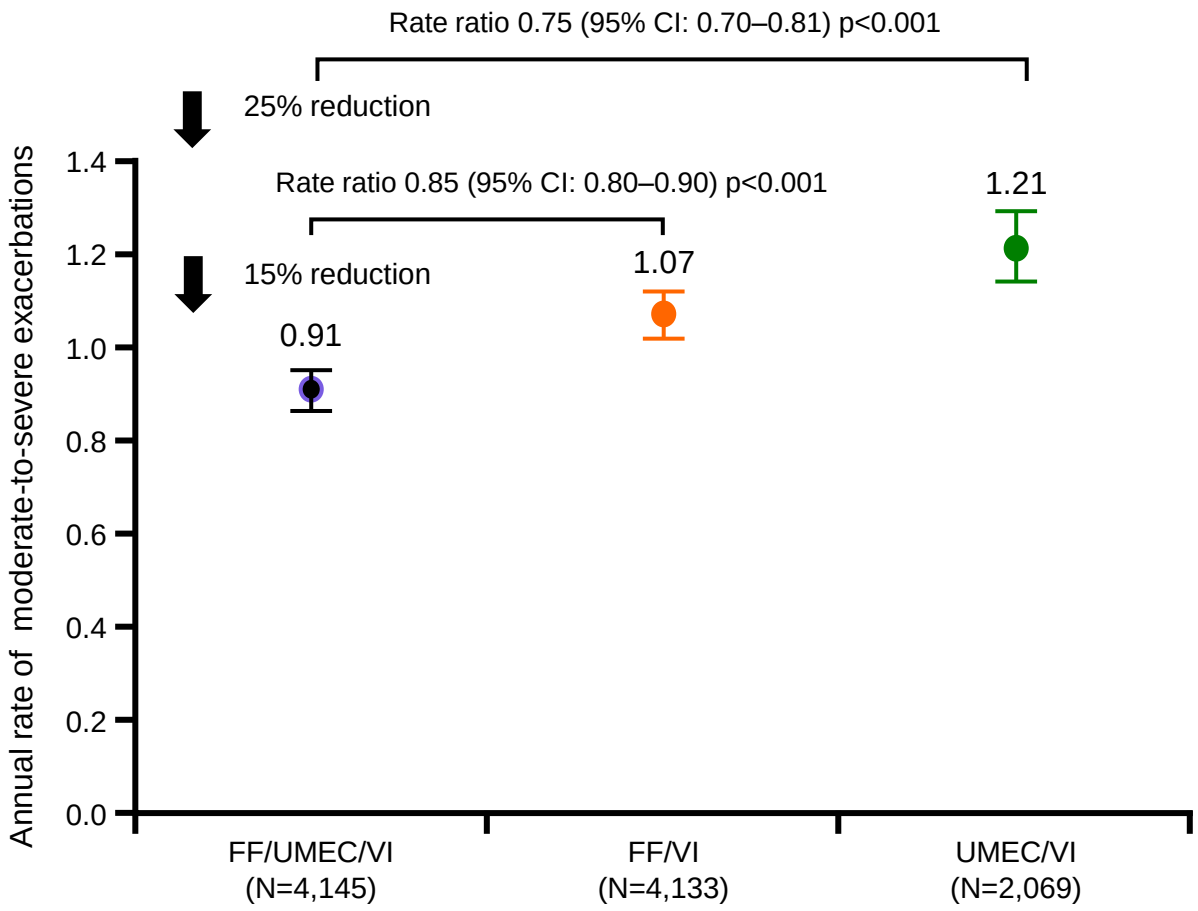


Modified from Papi A et al. Lancet 2018; 391:1076–1084 (Supplement)

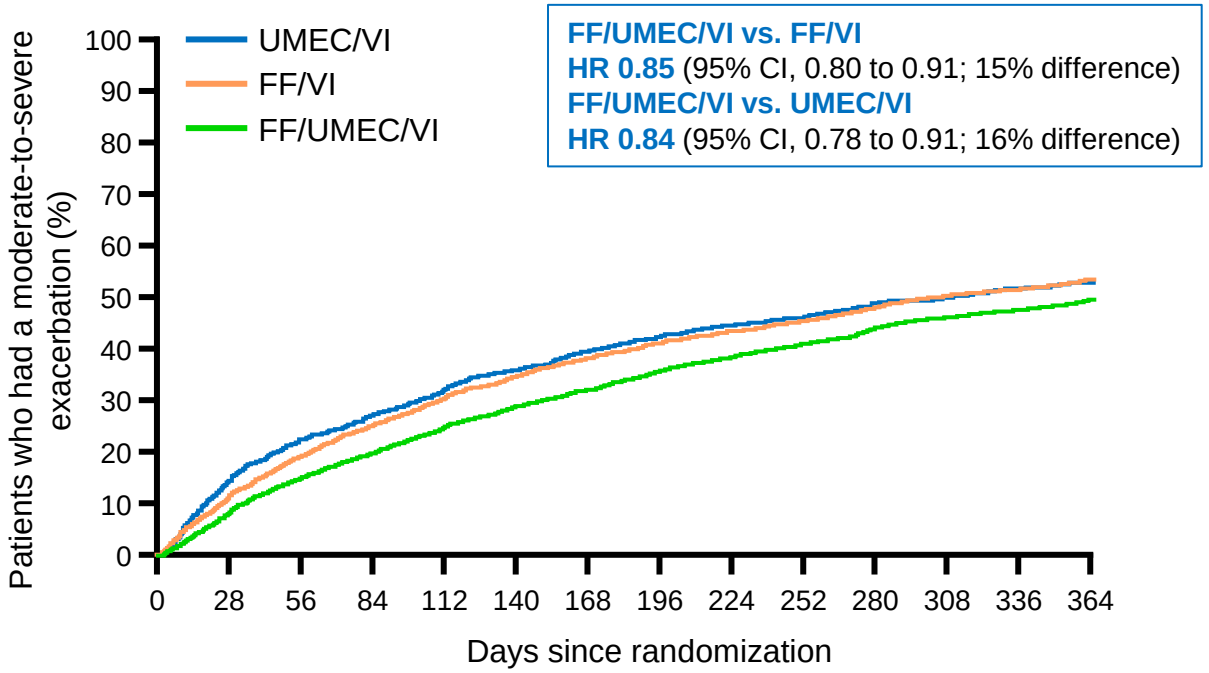
IMPACT: FF/UMEC/VI significantly reduced rate/risk of moderate-to-severe exacerbations versus FF/VI and UMEC/VI

Respiratory Ioannina

Model-estimated rate



Time-to-first-event analysis



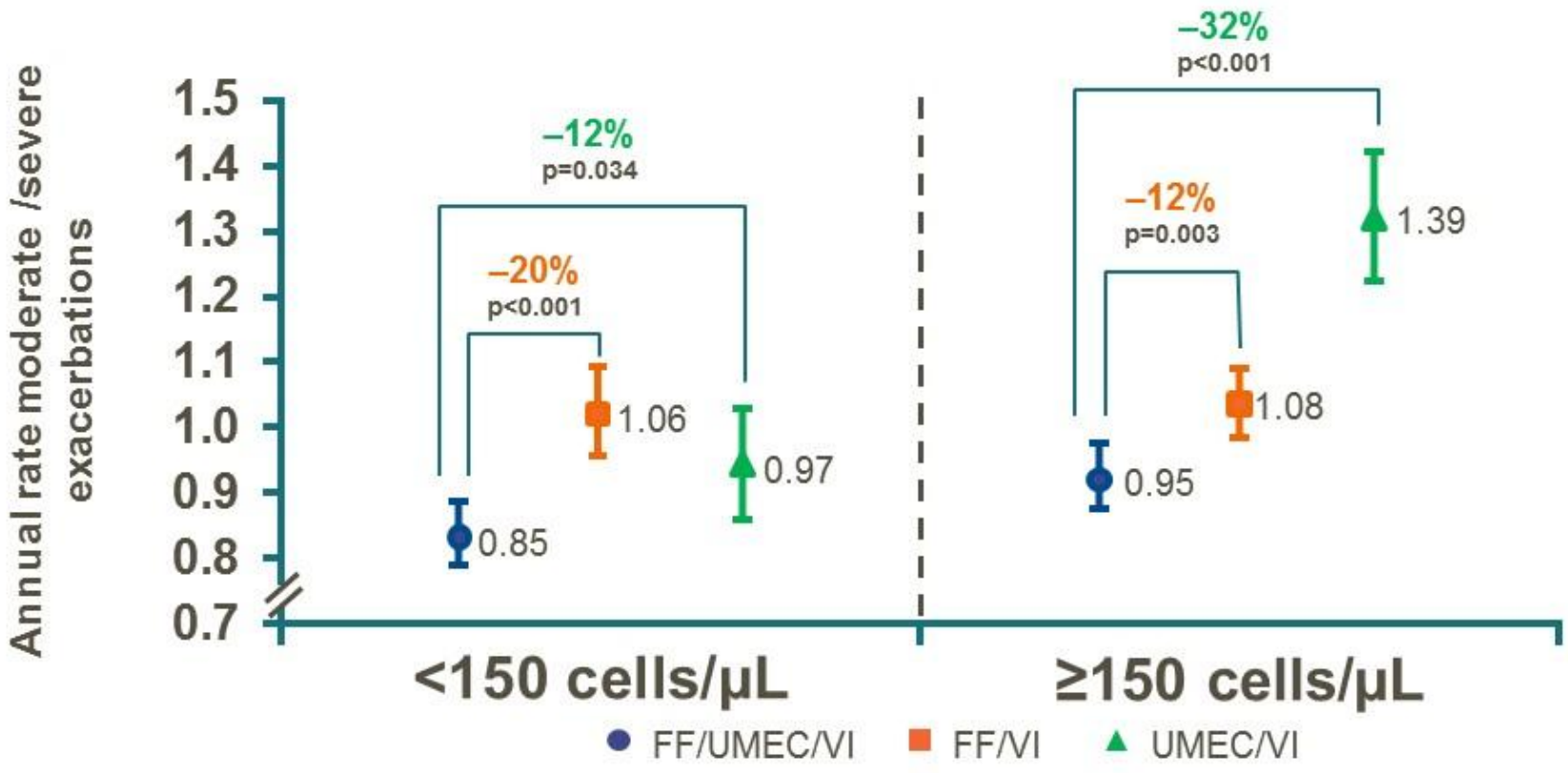
No. of patients at risk

UMEC/VI	2,070	1,721	1,516	1,406	1,301	1,201	1,123	1,059	1,001	971	917	884	851	642
FF/VI	4,134	3,554	3,133	2,838	2,620	2,410	2,250	2,120	2,004	1,823	1,823	1,729	1,671	1,228
FF/UMEC/VI	4,151	3,758	3,408	3,186	2,954	2,752	2,614	2,457	2,324	2,216	2,085	1,988	1,919	1,419

ITT population
Bars indicate 95% CI

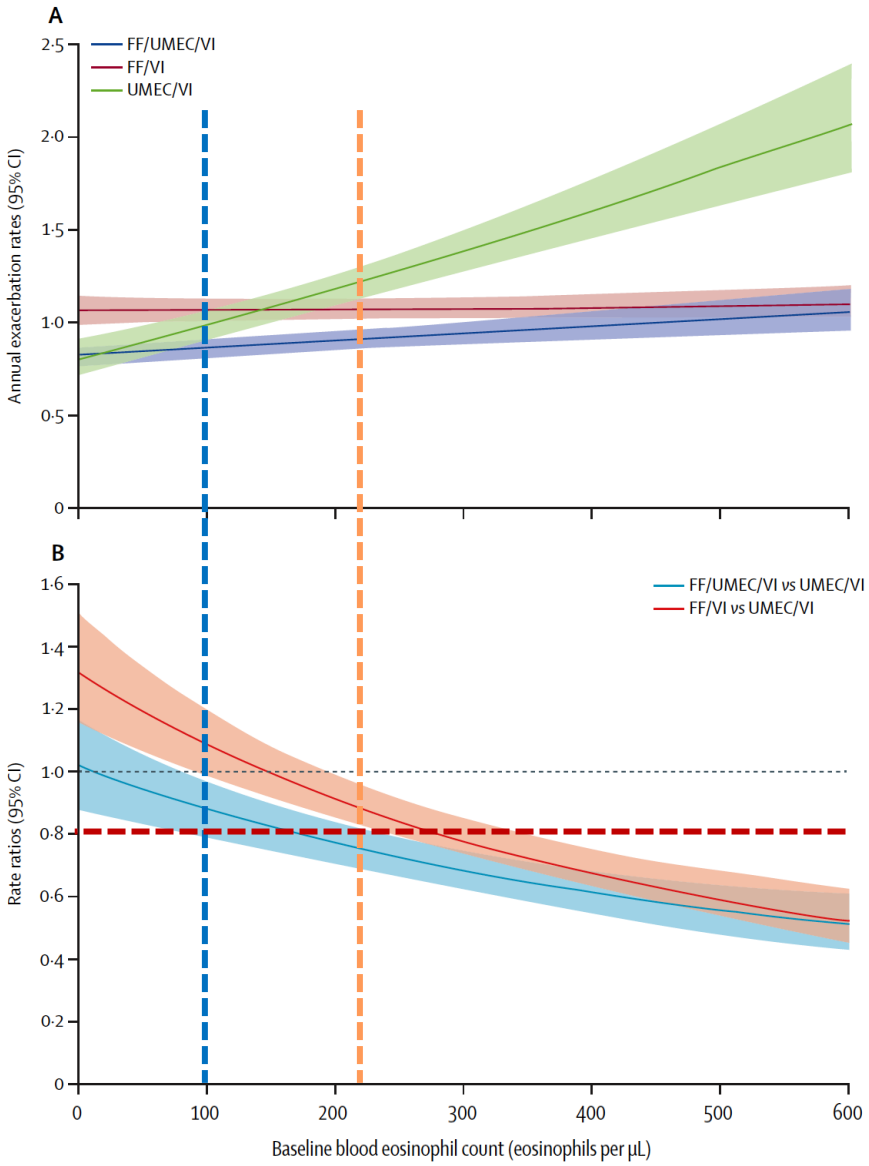
Lipson DA, et al. N Engl J Med 2018; 378:1671–1680

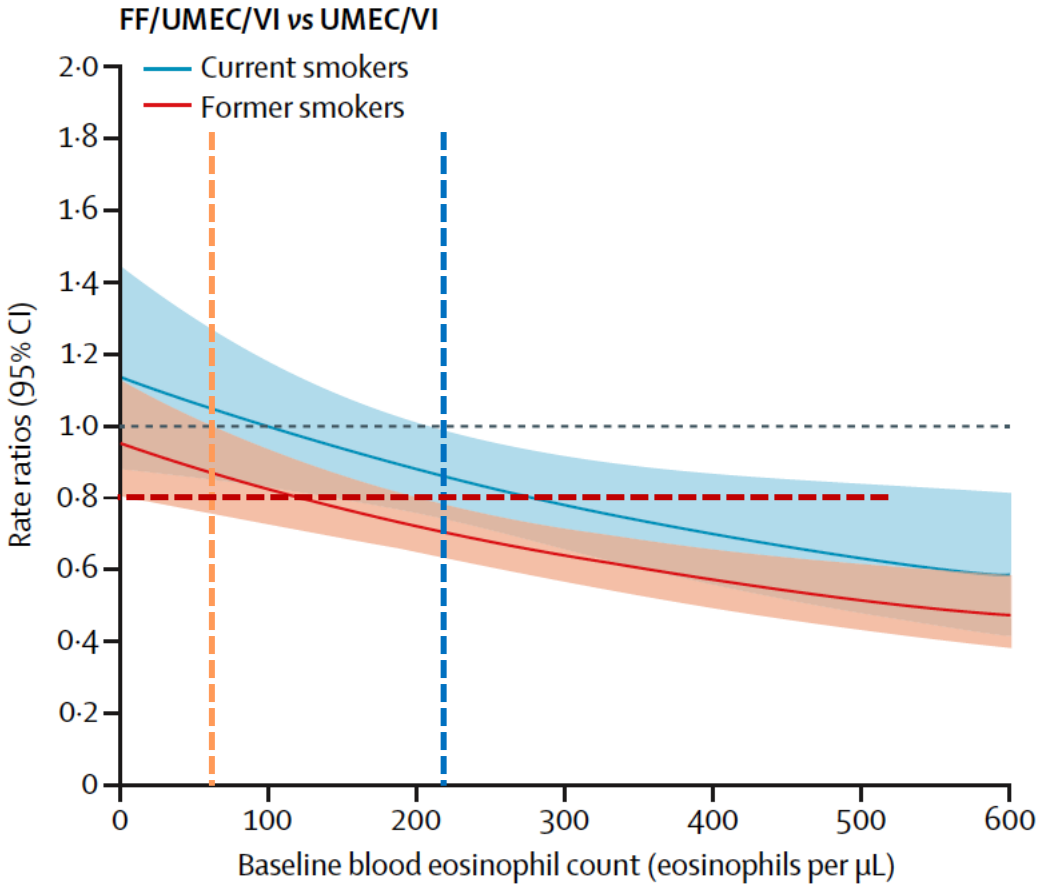
IMPACT: exacerbations by blood eosinophil counts



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

IMPACT: Blood EOS and ICS responsiveness - cut-points

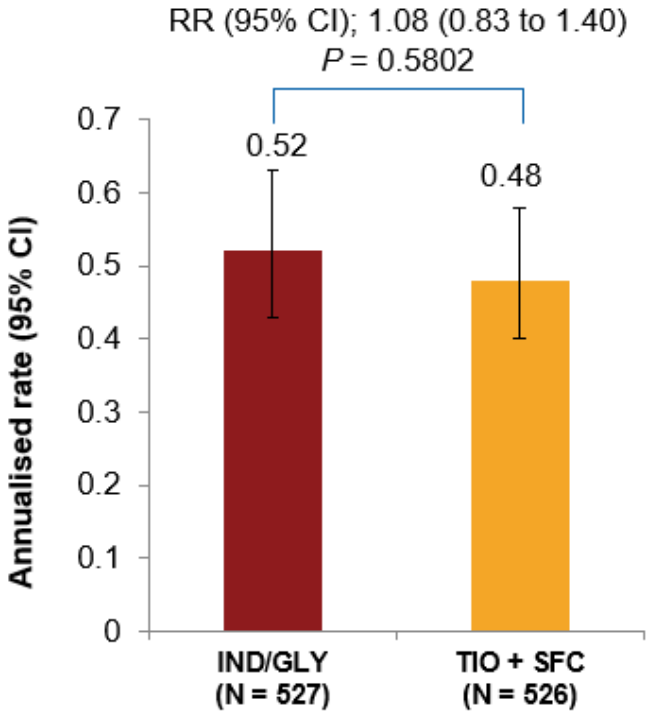




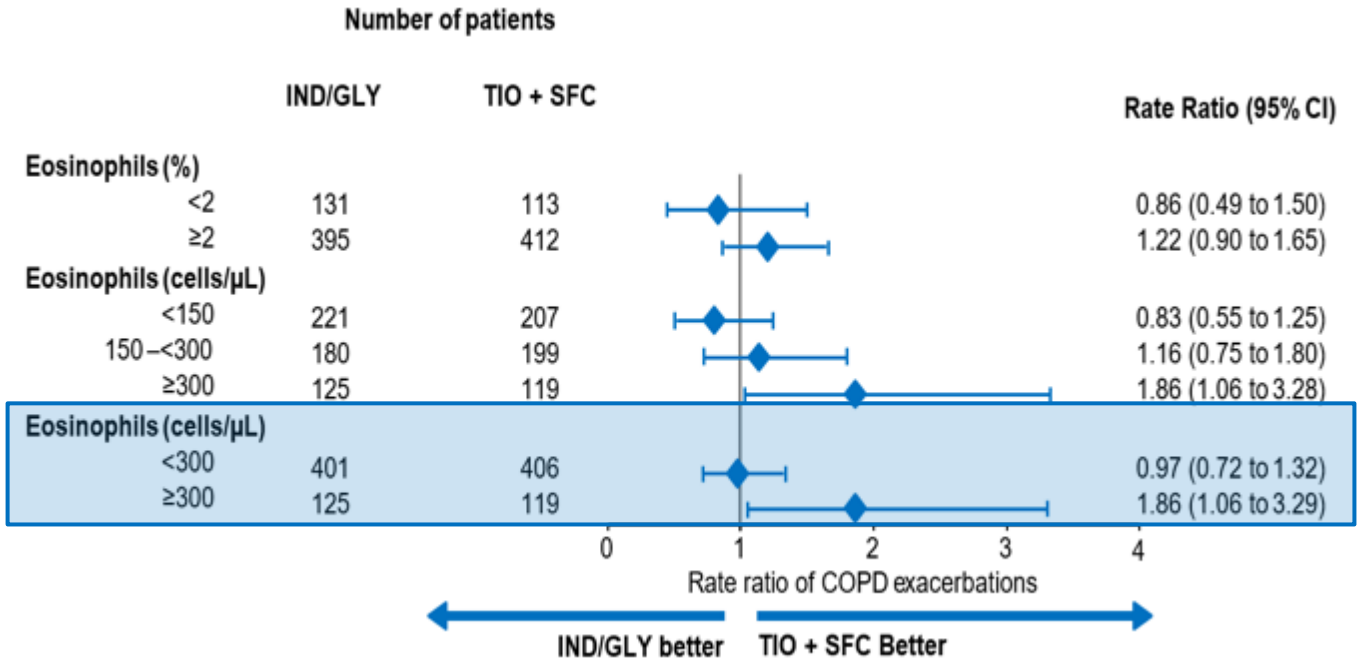
Pascoe S, et al. Lancet Respir Med 2019;7(9):745-756

SUNSET: Rate of moderate or severe exacerbations

Rate of moderate or severe exacerbations (overall population)



Rate of moderate or severe exacerbations by baseline eosinophil counts



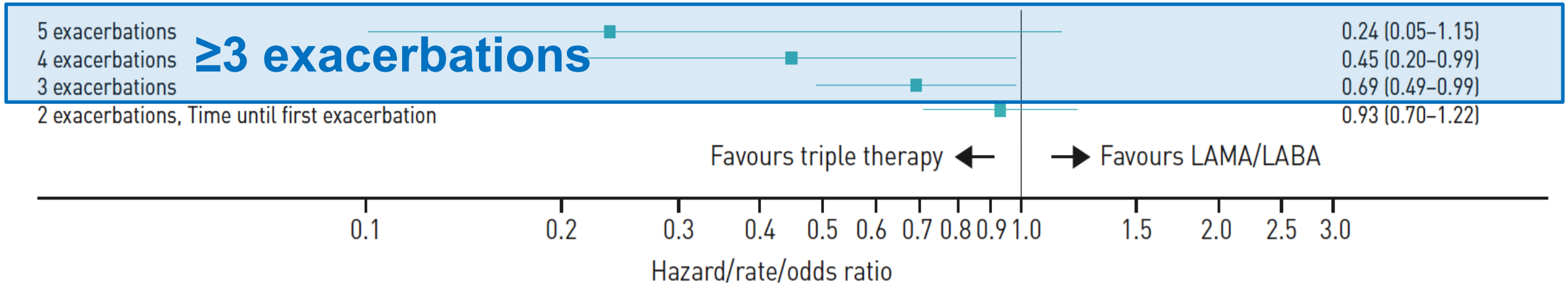
IND/GLY, indacaterol/glycopyrronium 110/50 µg once daily; SFC, salmeterol/fluticasone propionate 50/500 µg twice daily; TIO, tiotropium 18 µg once daily

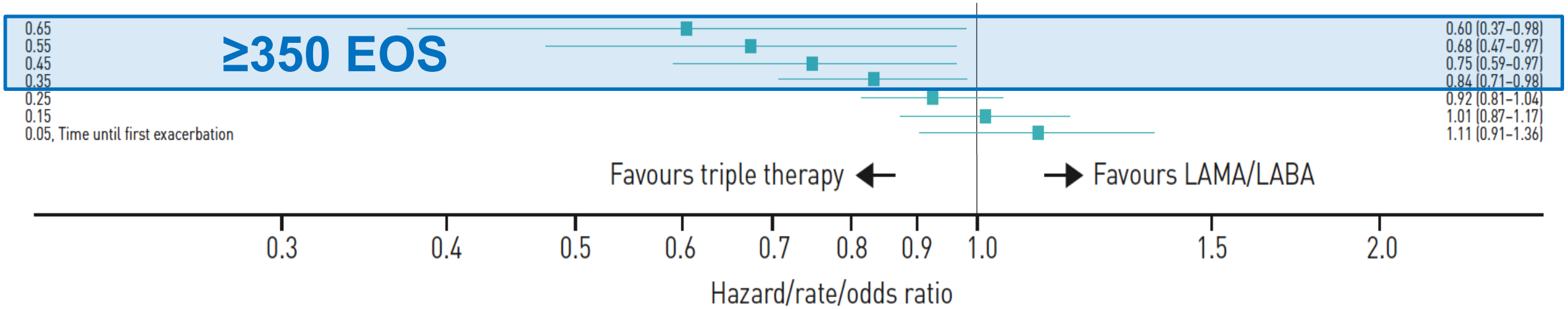
Chapman K,…, Kostikas K, and Wedzicha JA, Am J Respir Crit Care Med 2018; 198:329–339

Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
- The early days: exacerbations et al.
- Predicting future risk
- Identifying ICS responders
- **Real world evidence: the new must (?)**
- An imperfect biomarker
- A more targeted approach?

Real-life effectiveness of triple vs. LABA/LAMA (UK CPRD & OPCRD)





Patients with COPD aged ⩾40 years with a history of smoking were included if they initiated triple therapy or LABA/LAMA from no maintenance/LAMA therapy and had 2 or more exacerbations in the preceding year (matched 3:1)

Voorham J et al., ERJ Open Res 2019; 5: 00106-2019

Real-life effectiveness of triple vs. LABA/LAMA (UK CPRD)

	Number of patients	Number with events	Person-years	Rate per 100 per year	Crude* HR	Adjusted† HR (95% CI)
Moderate or severe exacerbation						
LAMA-LABA-ICS	5776	1615	2040	79.2	1.06	0.97 (0.86 - 1.09)
LAMA-LABA	1598	355	457	77.7	1.00	1.00 (Reference)
Stratified by eosinophil count						
< 2%						
LAMA-LABA-ICS	1984	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	2392	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	14[illegible]	1[illegible]1	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						
None						
LAMA-LABA-ICS	3827	583	1568	37.2	1.01	0.97 (0.80 - 1.17)
LAMA-LABA	1145	138	372	37.1	1.00	1.00 (Reference)
One						
LAMA-LABA-ICS	1656	523	560	93.5	1.07	1.09 (0.88 - 1.35)
LAMA-LABA	426	103	115	89.8	1.00	1.00 (Reference)
Two or more						
LAMA-LABA-ICS	1438	820	360	230.8	0.82	0.83 (0.70 - 0.98)
LAMA-LABA	361	177	55	320.1	1.00	1.00 (Reference)

≥6% EOS

≥2 exacerbations

Patients with COPD aged ⩾40 years with a history of smoking were included if they initiated triple therapy or LABA/LAMA from no maintenance/LAMA therapy and had 2 or more exacerbations in the preceding year (matched 3:1)

Suissa S et al., Chest 2019 (in press)

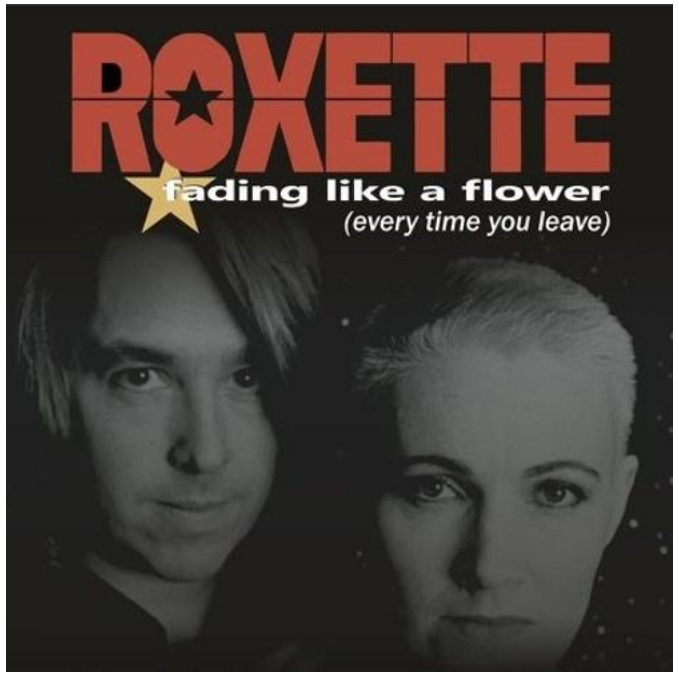
ICS use by blood EOS and exacerbation history in real life (Adelphi)

	0 exacerbations	1 exacerbation	≥2 exacerbations
Eosinophil count <150 cells/µL	n=46 34.8%	n=15 60.0%	n=23 82.6%
Eosinophil count ≥150 cells/µL	n=106 35.8%	n=63 60.3%	n=99 72.7%
Eosinophil count ≥300 cells/µL	n=38 23.7%	n=32 43.8%	n=48 75.0%

Vestbo J, Vogelmeier CF,…, and Kostikas K, Int J COPD 2019; 14: 853-861

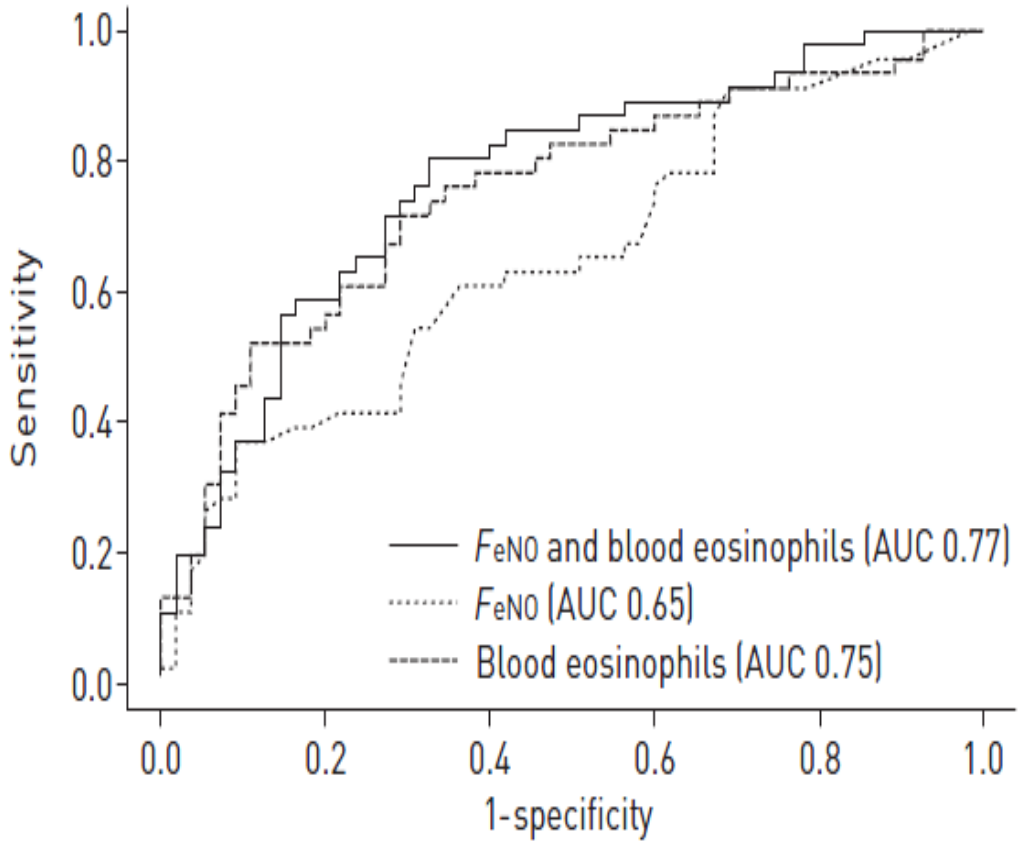
Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
- The early days: exacerbations et al.
- Predicting future risk
- Identifying ICS responders
- Real world evidence: the new must (?)
- **An imperfect biomarker**
- A more targeted approach?



Blood EOS (or FeNO) to predict sputum eosinophilia

- Retrospective analysis of 155 COPD patients
- EOS >162/μL (or 2.6%) identified patients with sputum EOS ≥3% with 71% (53%) sensitivity and 67% (83%) specificity



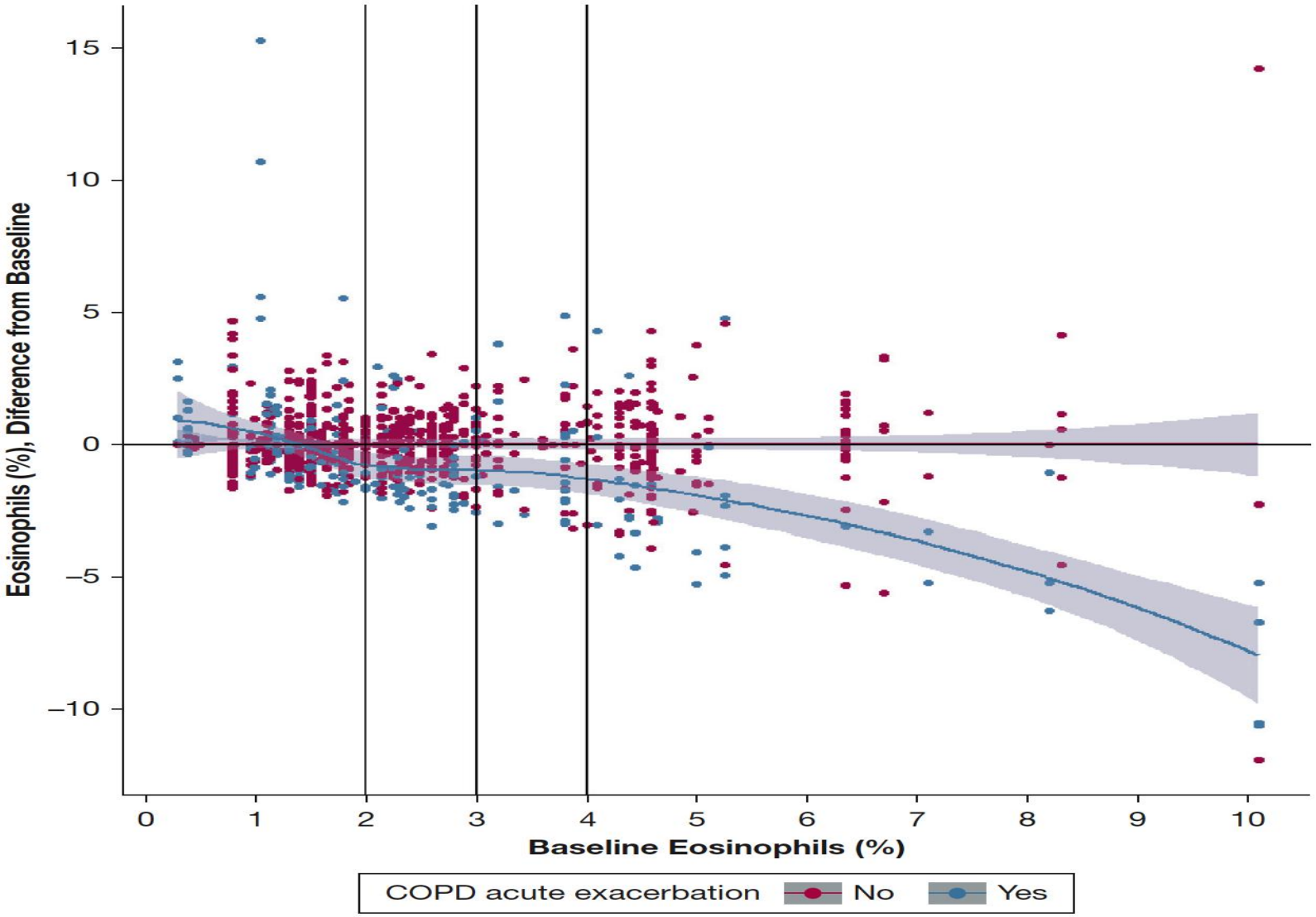
Schleich F, et al. Eur Respir J. 2016;47(5):1562-4

Stability of blood eosinophils over time (UK CPRD)

	Proportion with Stable Eosinophil Counts at Time Point (%)						
	6 mo	9 mo	1 yr	2 yr	4 yr	6 yr	8 yr
Patients with COPD	85	82	75	62	49	42	35
Absolute blood eosinophil count							
$<0.34 \times 10^9$, cells/L	95	93	90	86	80	77	75
$\geqslant 0.34 \times 10^9$, cells/L	80	70	63	45	30	23	18
Age							
40–59 yr	95	93	85	83	76	71	67
60–79 yr	93	90	80	79	70	65	60
$\geqslant$80 yr	91	89	77	73	66	61	58
Sex							
Female	94	92	89	81	75	70	68
Male	92	89	85	75	65	61	57
Smoking status							
Yes	95	90	88	81	72	69	62
No	95	90	88	79	72	69	62

Oshagbemi OA et al., Am J Respir Crit Care Med 2017;195(10):1402-1404

Stability of blood eosinophilia in stable and exacerbated COPD



Schumann D, Tamm M, Kostikas K, and Stolz D, Chest 2019; 156(3):456-465

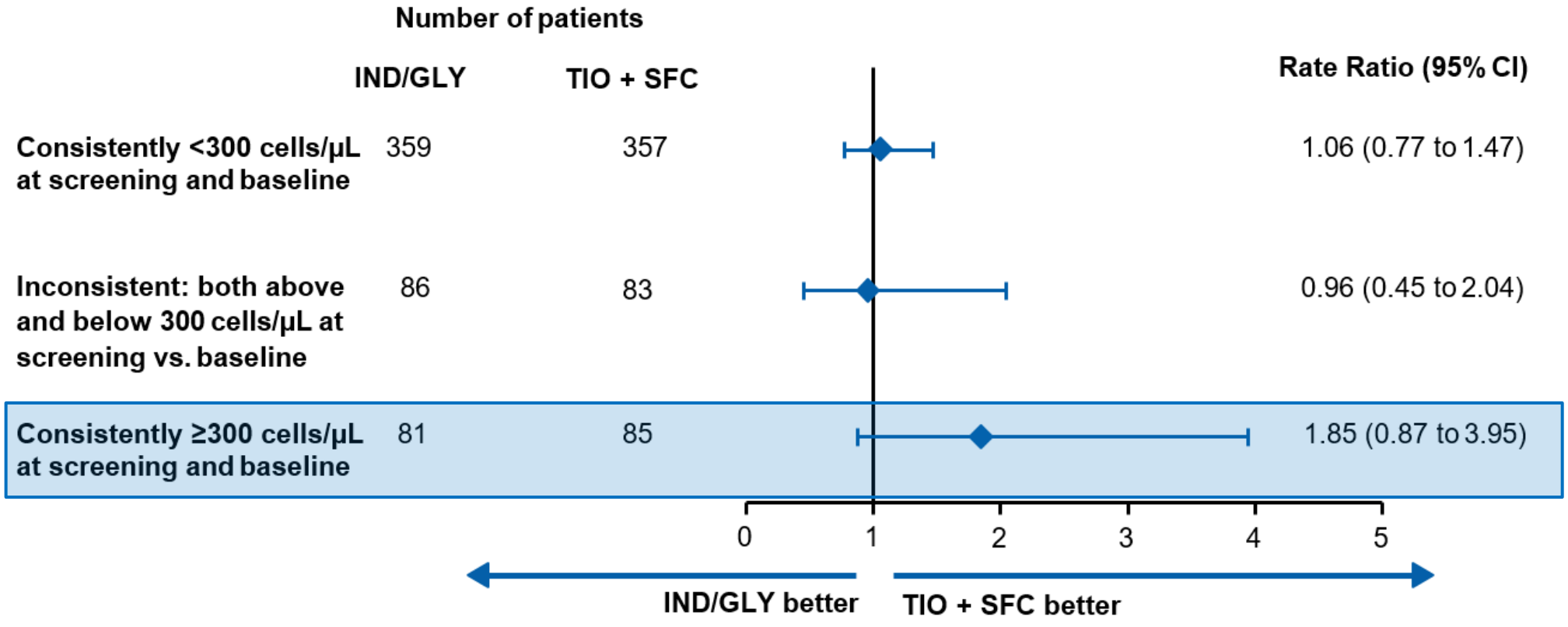
Stability of blood eosinophilia in stable and exacerbated COPD

Cutoff Point	Outcome	Ambulant		Hospitalization	
		Stable COPD	Moderate AECOPD	Severe AECOPD	Other Reason
2%	Concordant ≤ 2%	16 (14)	11 (23)	32 (48)	43 (30)
	Discordant 2%	73 (66)	26 (54)	32 (48)	90 (62)
	Concordant > 2%	22 (20)	11 (23)	3 (4)	12 (8)
3%	Concordant ≤ 3%	36 (32)	23 (48)	47 (70)	81 (56)
	Discordant 3%	63 (57)	22 (46)	17 (25)	60 (41)
	Concordant > 3%	12 (11)	3 (6)	3 (5)	4 (3)
4%	Concordant ≤ 4%	61 (55)	33 (69)	54 (81)	107 (74)
	Discordant 4%	49 (44)	15 (31)	11 (16)	34 (23)
	Concordant > 4%	1 (1)	0	2 (3)	4 (3)
150 cells/μL	Concordant ≤ 150 cells/μL	12 (11)	10 (21)	21 (31)	21 (14)
	Discordant 150 cells/μL	66 (59)	25 (52)	35 (52)	95 (66)
	Concordant > 150 cells/μL	33 (30)	13 (27)	11 (16)	29 (20)
300 cells/μL	Concordant ≤ 300 cells/μL	50 (45)	33 (69)	29 (51)	91 (63)
	Discordant 300 cells/μL	56 (50)	14 (29)	25 (44)	49 (34)
	Concordant > 300 cells/μL	5 (5)	1 (2)	3 (5)	5 (3)

Data are presented as No. (%). AECOPD = acute exacerbations of COPD.

Schumann D, Tamm M, Kostikas K, and Stolz D, Chest 2019; 156(3):456-465

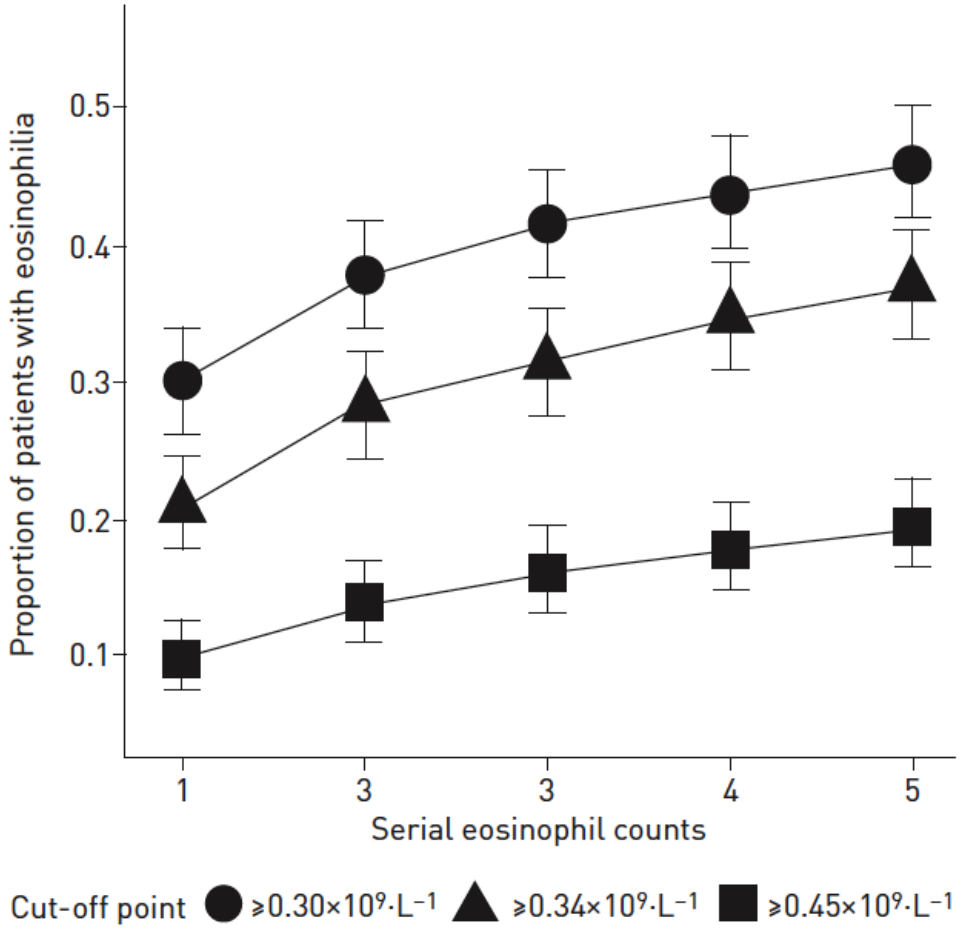
SUNSET: consistent eosinophilia and exacerbations



Do we need 2 or more blood EOS counts to decide long term ICS use?

Chapman K,…, Kostikas K, and Wedzicha JA, Am J Respir Crit Care Med 2018; 198:329–339

Eosinophils in COPD: how many swallows make a summer?



In conclusion, we would recommend that **a minimum of 2 or more eosinophil counts** should be taken into account to determine the eosinophilic status of COPD patients.

However, the eosinophil count should be considered in context, and not used as an absolute arbiter for decision making.

Biomarkers, however good, are no replacements for clinical judgement.

Hamad GA et al. Eur Respir J 2018; 51: 1702177

Eosinophils in COPD: myths and reality

- The quest for biomarkers in COPD
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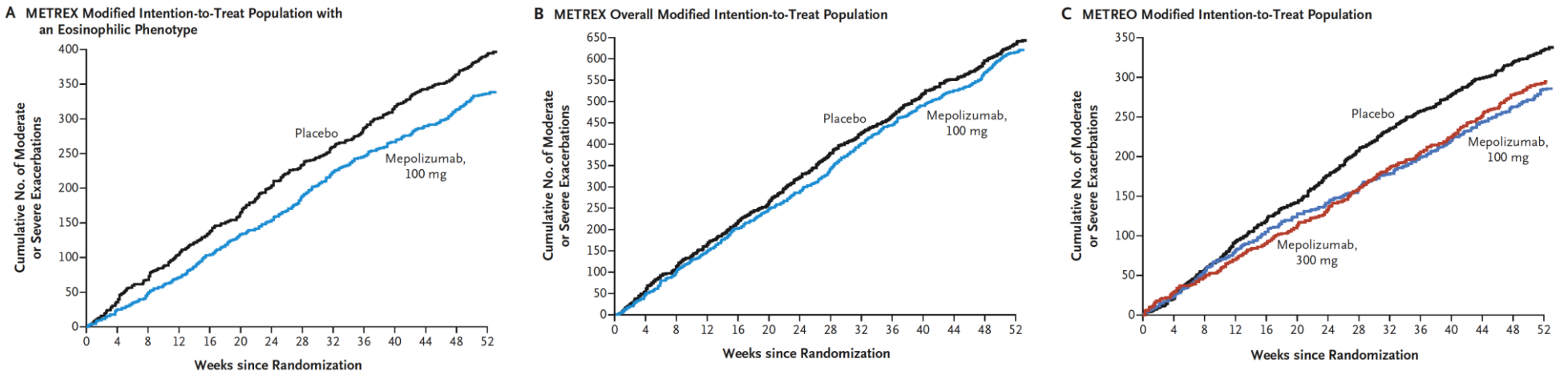
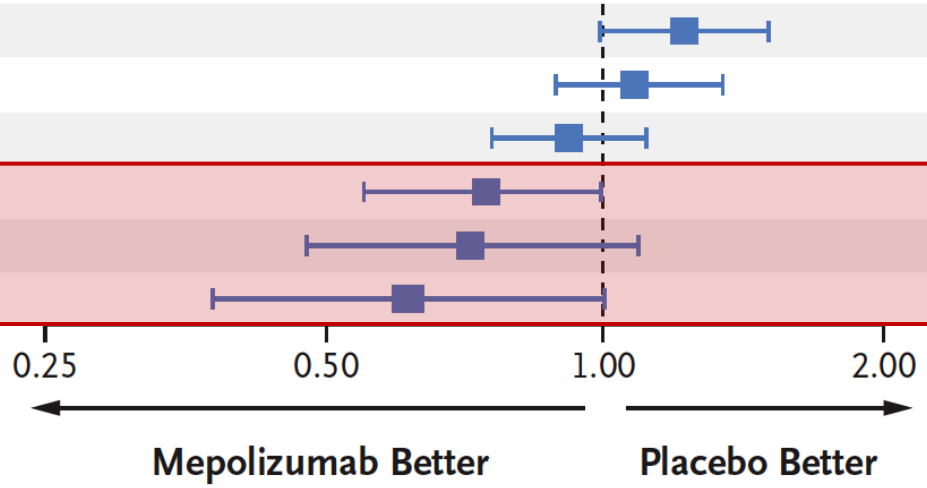
Mepolizumab for Eosinophilic COPD

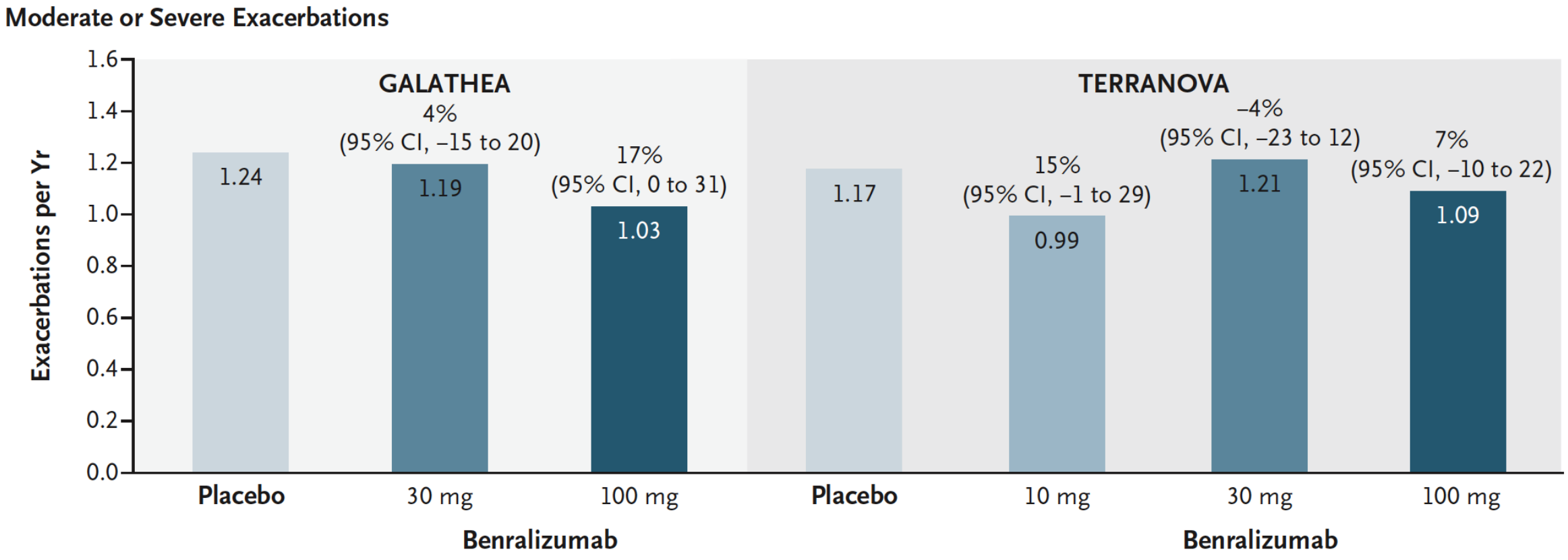


Blood Eosinophil Count	Mepolizumab Group	Placebo Group	Rate Ratio (95% CI)
cells/mm³	*no. of patients with event/total no. of patients*		
<150 with no historical count ≥300	184/184	190/190	1.23 (0.99–1.51)
<150 regardless of historical count	236/640	230/645	1.10 (0.91–1.34)
≥150 to <300	237/456	235/455	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)



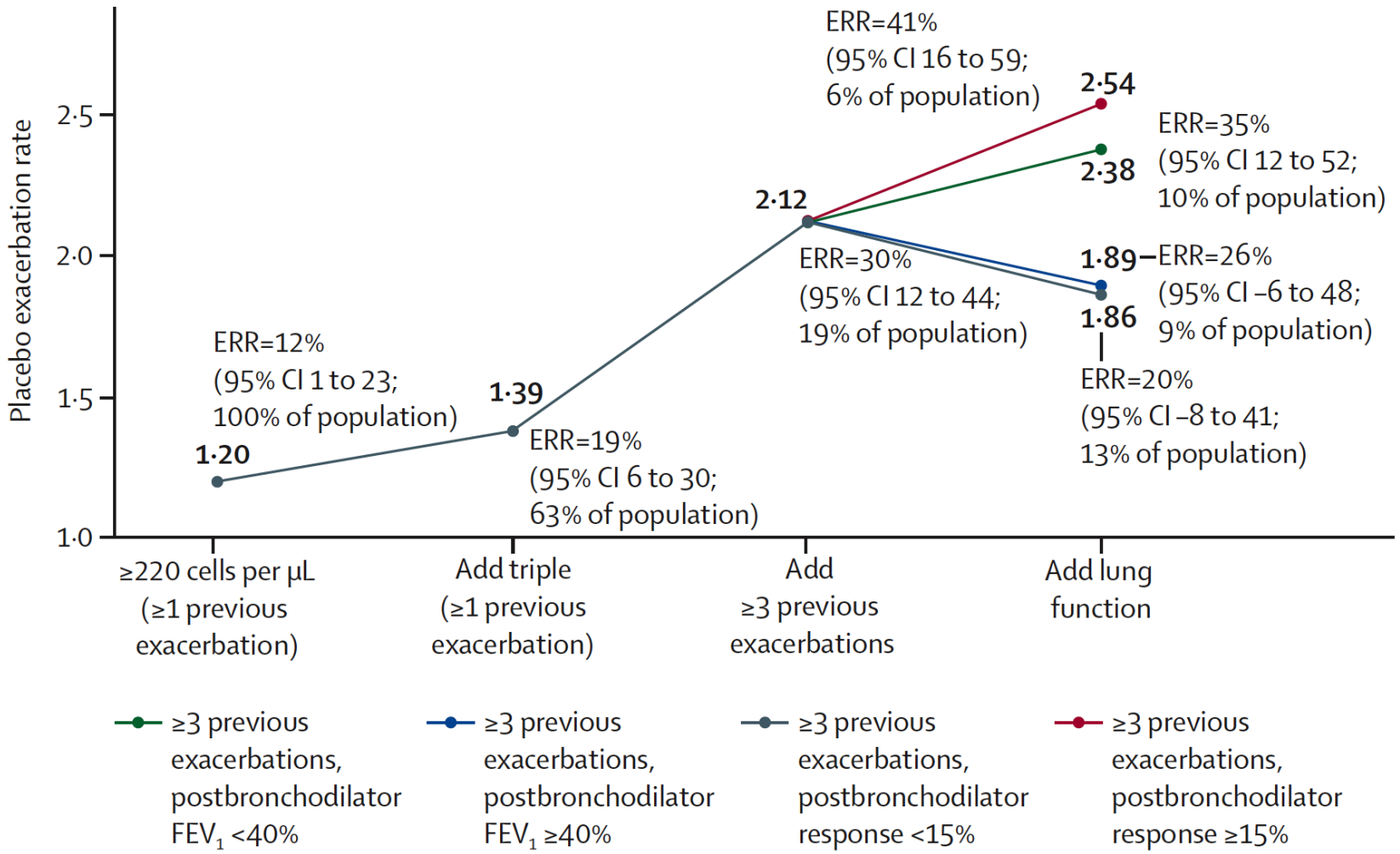
Pavord ID et al., N Engl J Med 2017;377(17):1613-29

Benralizumab for the prevention of COPD exacerbations



Criner GJ et al., N Engl J Med 2019;381:1023-34

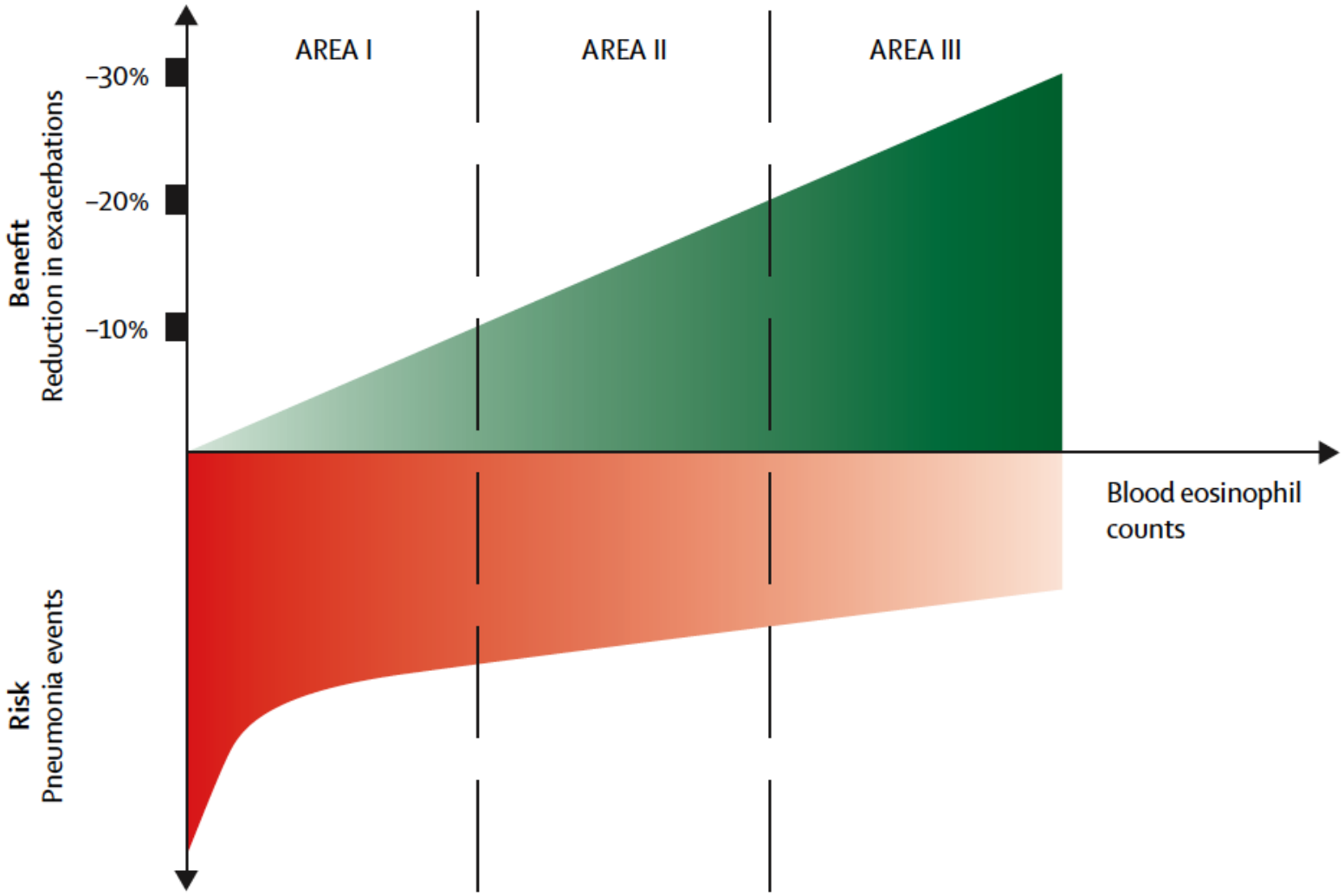
Responders to benralizumab and the future of anti-IL5/IL5Rα in COPD



RESOLUTE
(NCT04053634)
MATINEE
(NCT04133909)

Criner GJ et al., Lancet 2019 Sep 27 [Online ahead of print]; https://clinicaltrials.gov/ct2/show/NCT04053634; https://clinicaltrials.gov/ct2/show/NCT04133909

Risk-benefit of ICS use by blood EOS in COPD



Brusselle G, et al. Lancet Respir Med 2015;3(6):435-42.

Factors to consider when initiating **ICS treatment**

(in combination with one or two long-acting bronchodilators)

Respiratory Ioannina

STRONG SUPPORT	CONSIDER USE	AVOID USE
History 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/μ
History of, or concomitant, asthma		History of mycobacterial infection

**despite appropriate long-acting bronchodilator maintenance therapy*

GOLD 2020

A number of recent studies have shown that **blood eosinophil counts predict the magnitude of the effect of ICS** (added on top of regular maintenance bronchodilator treatment) **in preventing future exacerbations**.

ICS, inhaled corticosteroid; COPD, chronic obstructive pulmonary disease; ECOPD, COPD exacerbation

Agusti A, et al., Eur Respir J. 2018 Sep 6. pii: 1801219; GOLD 2020

Respiratory Ioannina

May guide treatment decisions on AECOPD?

Modest predictor of AECOPD risk - Better in non smokers?

May identify responders to ICS among exacerbators

A **TRIBUTE** to the **IMPACT** of blood EOS in COPD: the **SUNSET** of a biomarker or some elements of **WISDOM**?

Cut-point for effectiveness signal?

Repeatability poor – two measurements needed?

A potentially valid target for biologics in COPD

1882 *Current Drug Targets*, 2018, *19*, 1882-1896

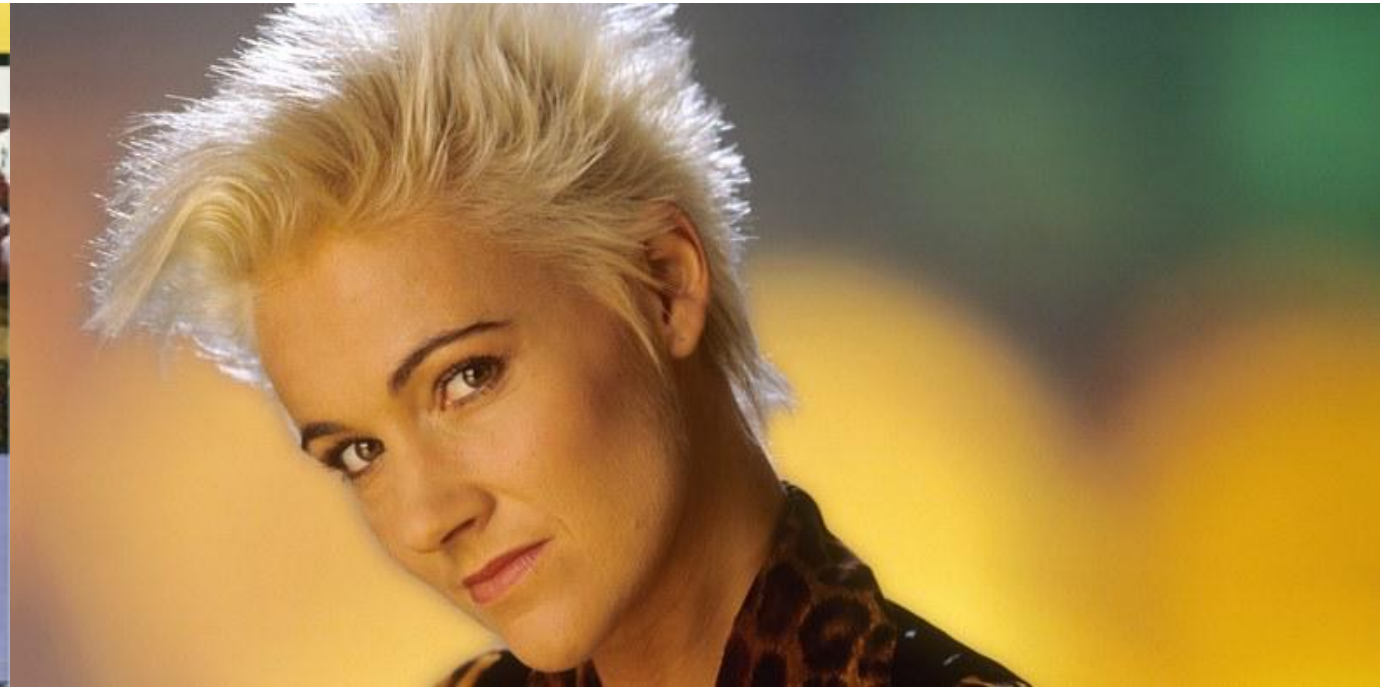
REVIEW ARTICLE

Blood Eosinophils as Biomarkers to Drive Treatment Choices in Asthma and COPD

Konstantinos Kostikas, Caterina Brindicci and Francesco Patalano*

Results: In asthma, the rationale for using blood eosinophils to guide treatment is clearly defined, backed by prospective, well-controlled studies. Higher eosinophil counts identify patients with more severe disease and poorer outcomes, patients for whom biologic therapies targeting allergic and/or eosinophilic pathways are recommended. In COPD, the evidence is less robust. High blood eosinophil counts are a modest predictor of future exacerbations, and may predict a favourable response to ICS on top of LABA/LAMA, especially in patients with a history of frequent exacerbations.

Conclusion: Before extensive application in clinical practice, further evaluation of these findings in prospective clinical studies, and standardization of the appropriate thresholds of clinically relevant eosinophilia are needed, together with establishing whether single or multiple measurements are required in different clinical settings.



R.I.P. Gun-Marie Fredriksson (30 May 1958 – 9 December 2019)

What is New in Respiratory Medicine

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