Eosinophlic COPD Phenotyping & Treatment Regimens

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Where today's science meets tomorrow's care™

INTERNATIONAL CONFERENCE

May 17- May 22, 2019

Dallas, Texas

Key words of COPD Issue on ATS 2019

Early COPD

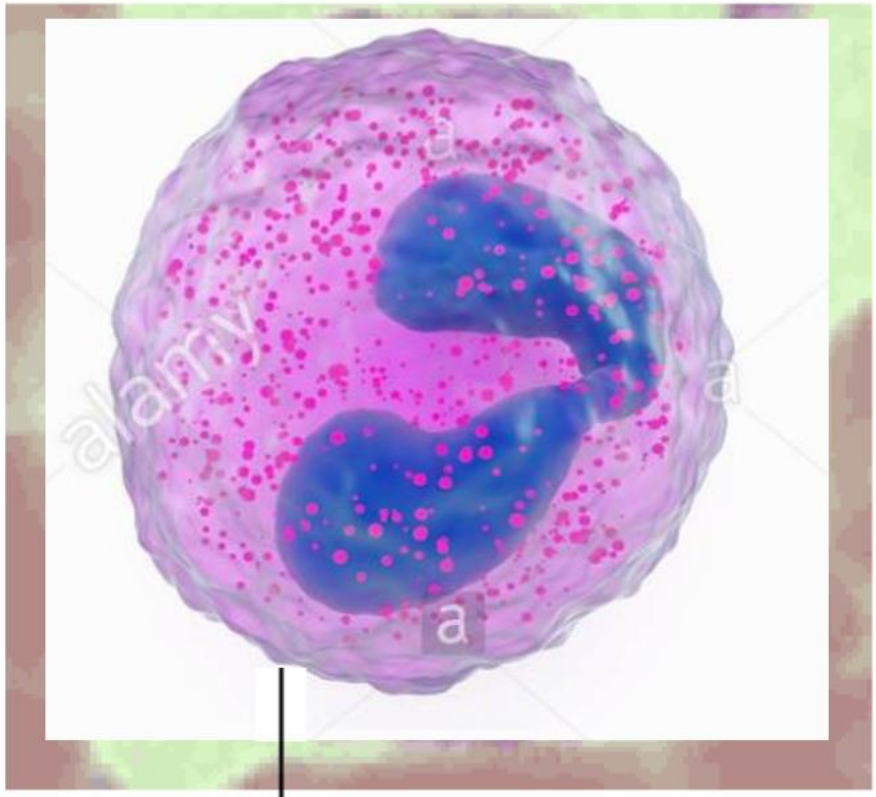
Phenotypes

Biomarkers-Eosinophils

Comorbidities

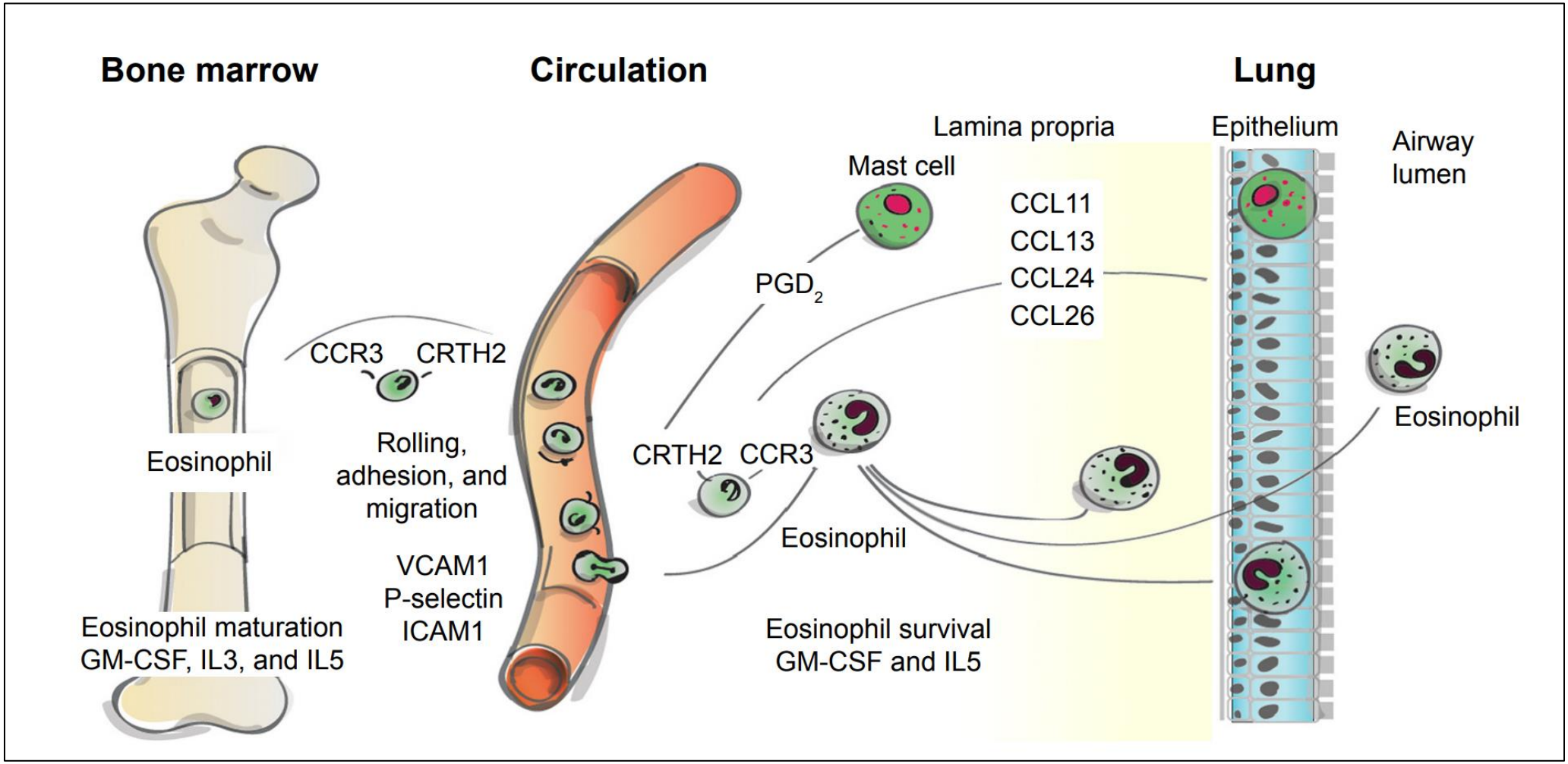
Risk Prediction & Prognosis

Eosinophil (Eos)



- Bilobed nucleus
- 2-4% of WBC
- Recruited to sites of inflammation
- Function: Involved in allergy, parasitic infections
- Contains: eosinophilic granules
- Granules contain: major basic protein
- Terminally differentiated

Recruitment of EOS into the lung tissue

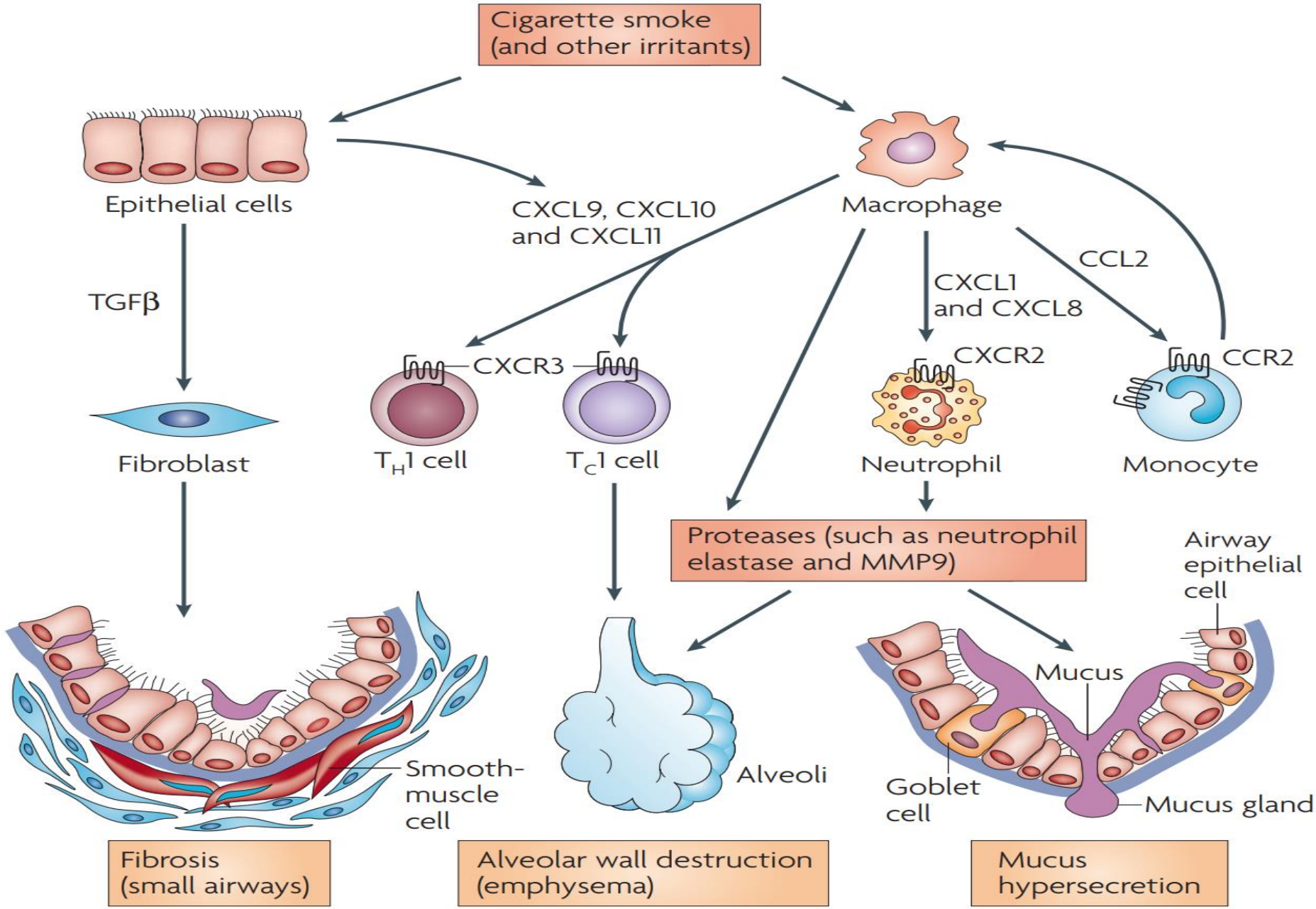


International Journal of COPD 2018:13

Role of Eosinophils in COPD

- Approximately **1/3** of **stable COPD** patients have evidence of **eosinophilic inflammation**.
- **Eosinophil counts-** a **potential biomarkers**
  - Benefit from **inhaled corticosteroid (ICS)** therapy
  - A **predictor of COPD AE**
  - May be a biomarkers to receive **Anti-IL5 therapy**?

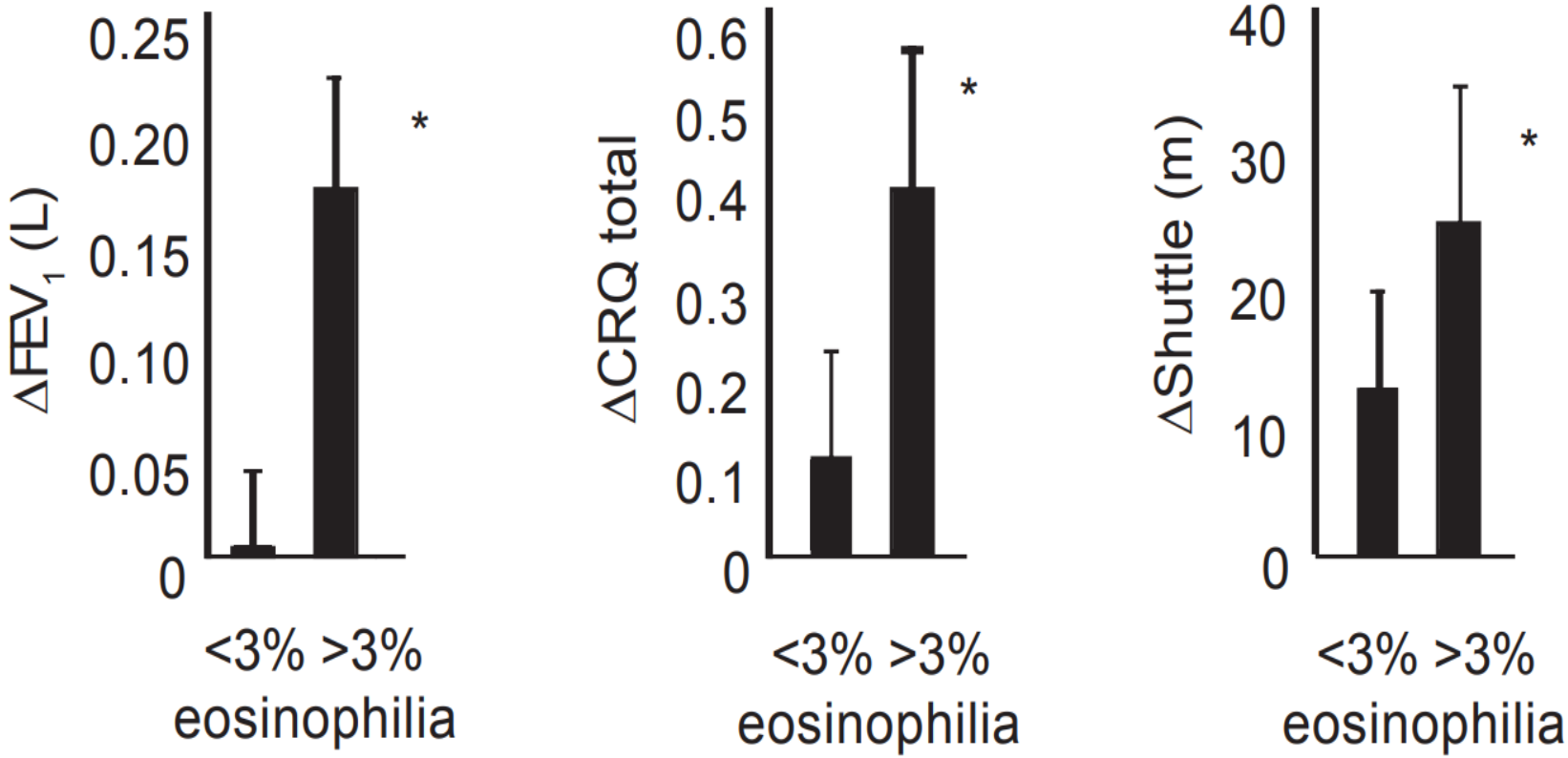
Eosinophils & COPD



Barnes PJ. Nat Rev Immunol. 2008 Mar;8(3):183-92.

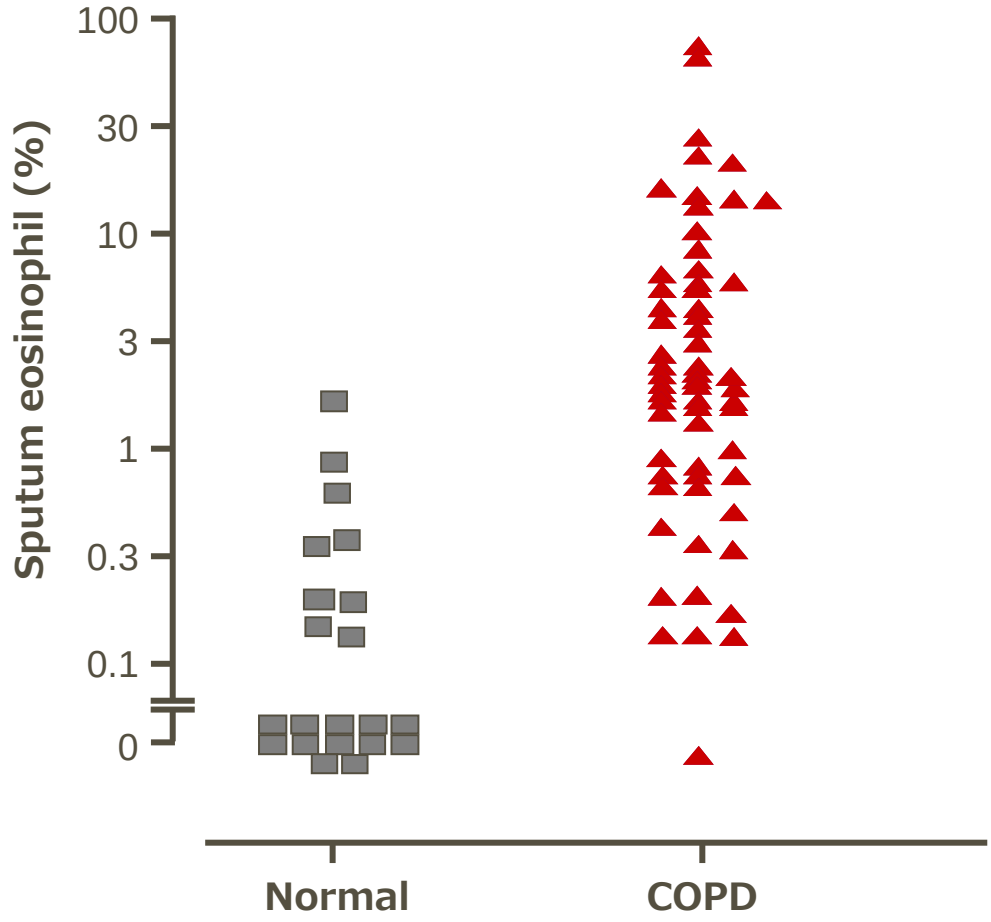
EOS >3% : good response to Prednisolone

Δ represents change after **prednisolone** compared with placebo



Lancet. ***2000*** *Oct 28;356(9240):1480-5*

Sputum EOS counts in stable COPD

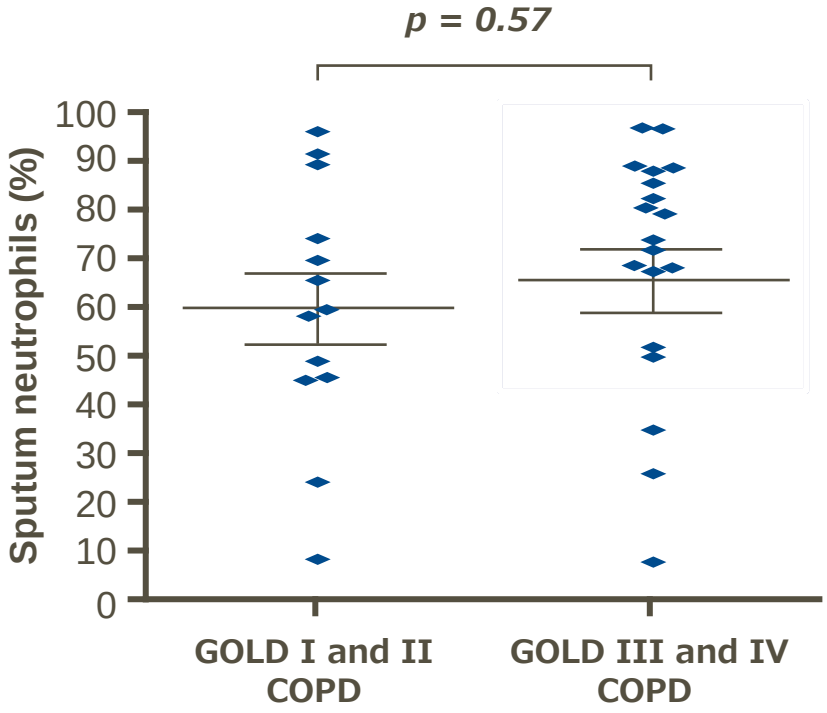


Up to 40% of COPD patients have an inflammatory pattern that includes higher EOS counts, known as EOS-associated COPD.

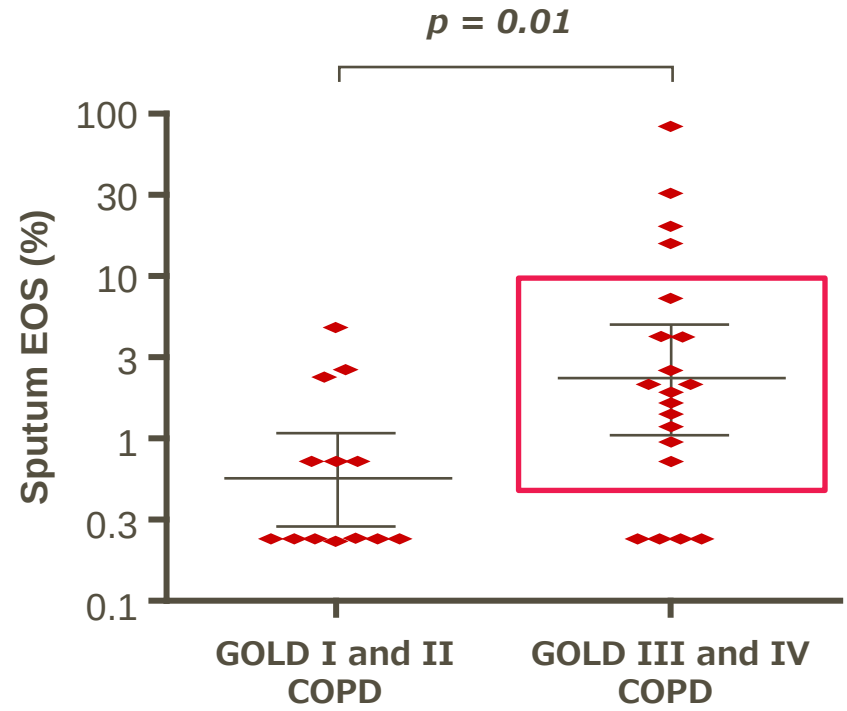
Int J Chron Obstruct Pulmon Dis. ***2006****;1(1):39-47.*

Sputum phenotypes in COPD

Neutrophilic airway inflammation



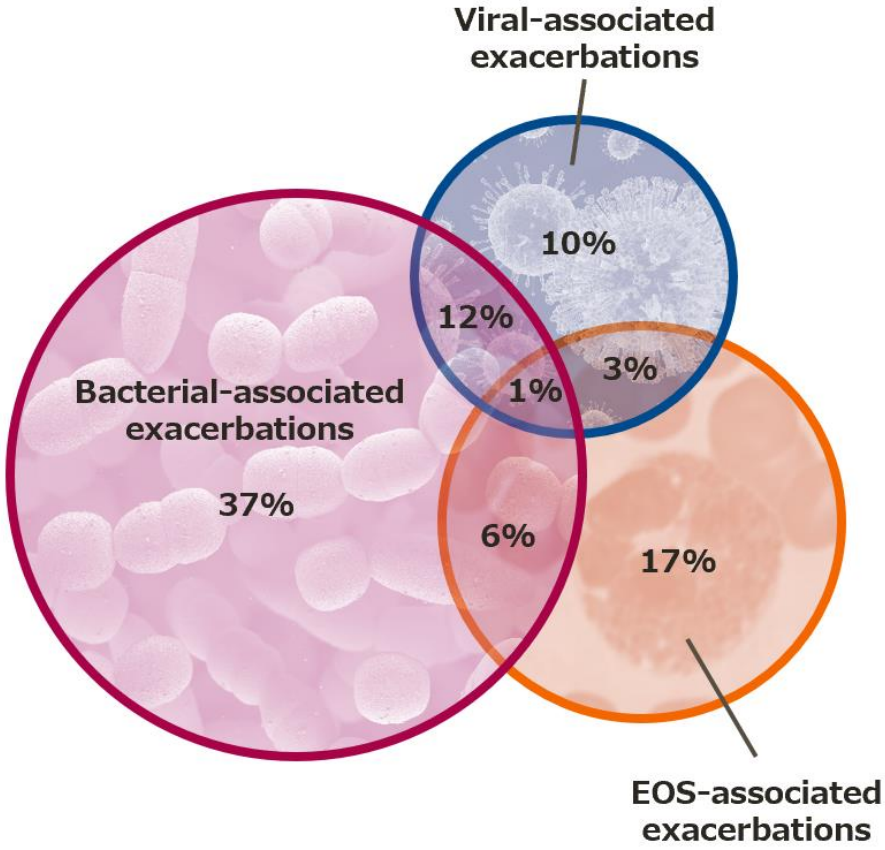
Eosinophilic airway inflammation



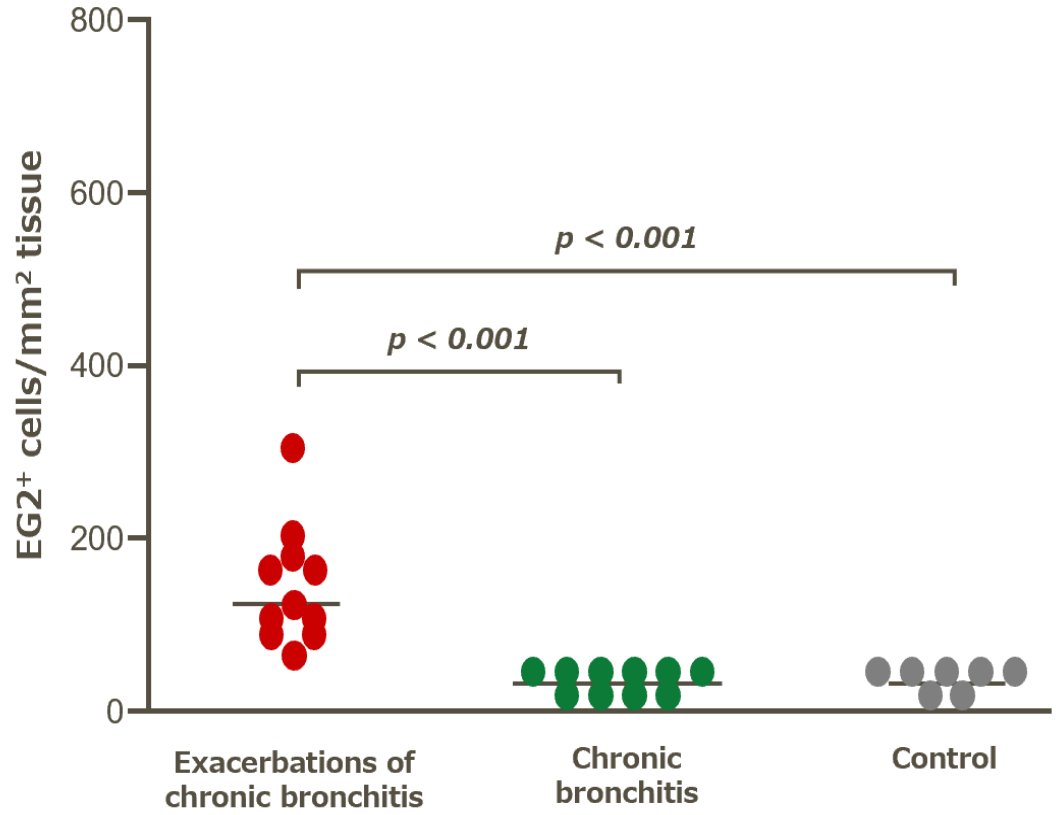
Respiration 2012; 83: 36–44

27% of AECOPD: associated with EOS

Aetiological causes of exacerbations



EG2+ cell counts in bronchial biopsies



Clin Exp Allergy. 1996 Jul;26(7):766-74.

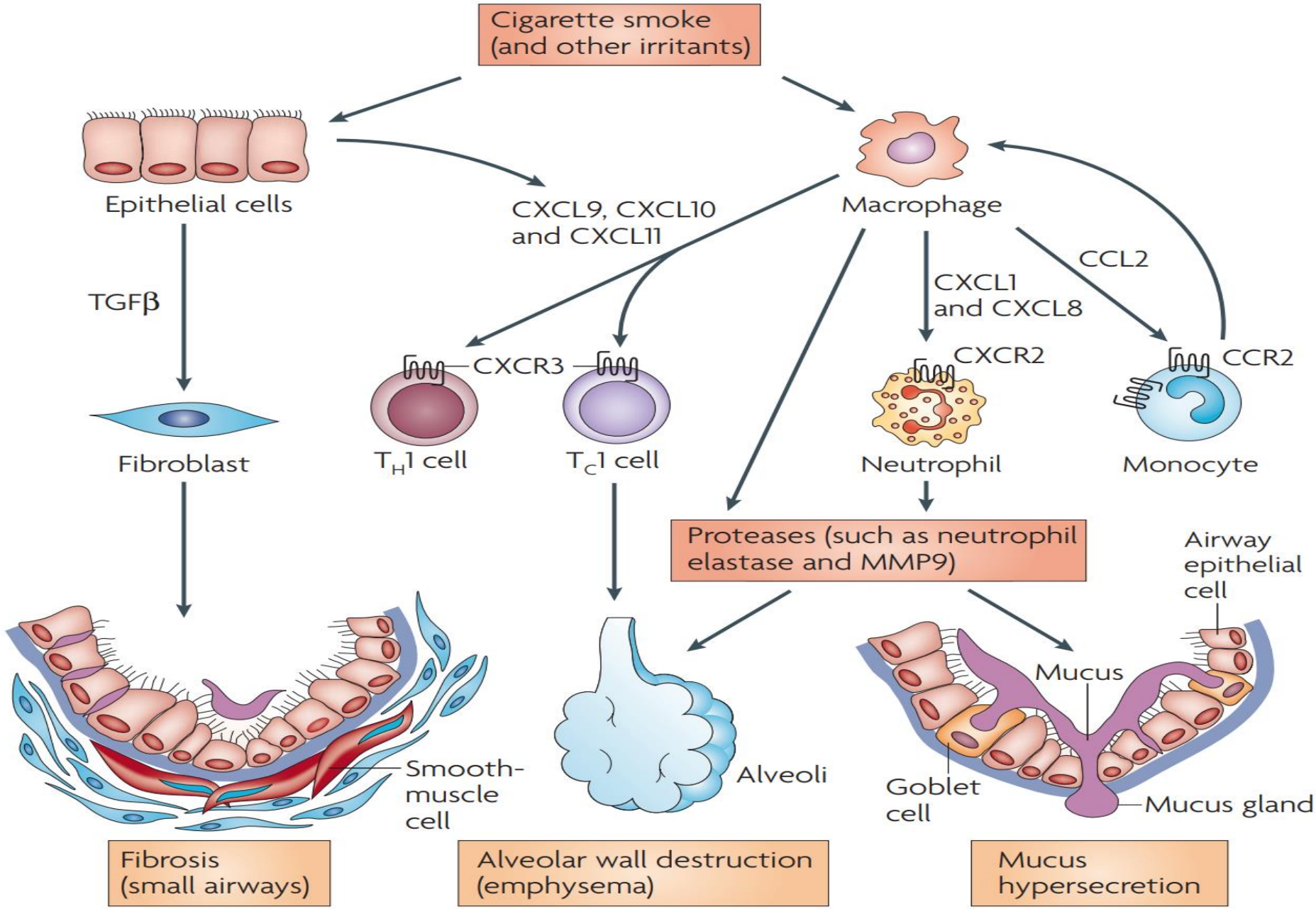
Am J Respir Crit Care Med. 2011 Sep 15;184(6):662-71

Inflammatory endotypes in COPD

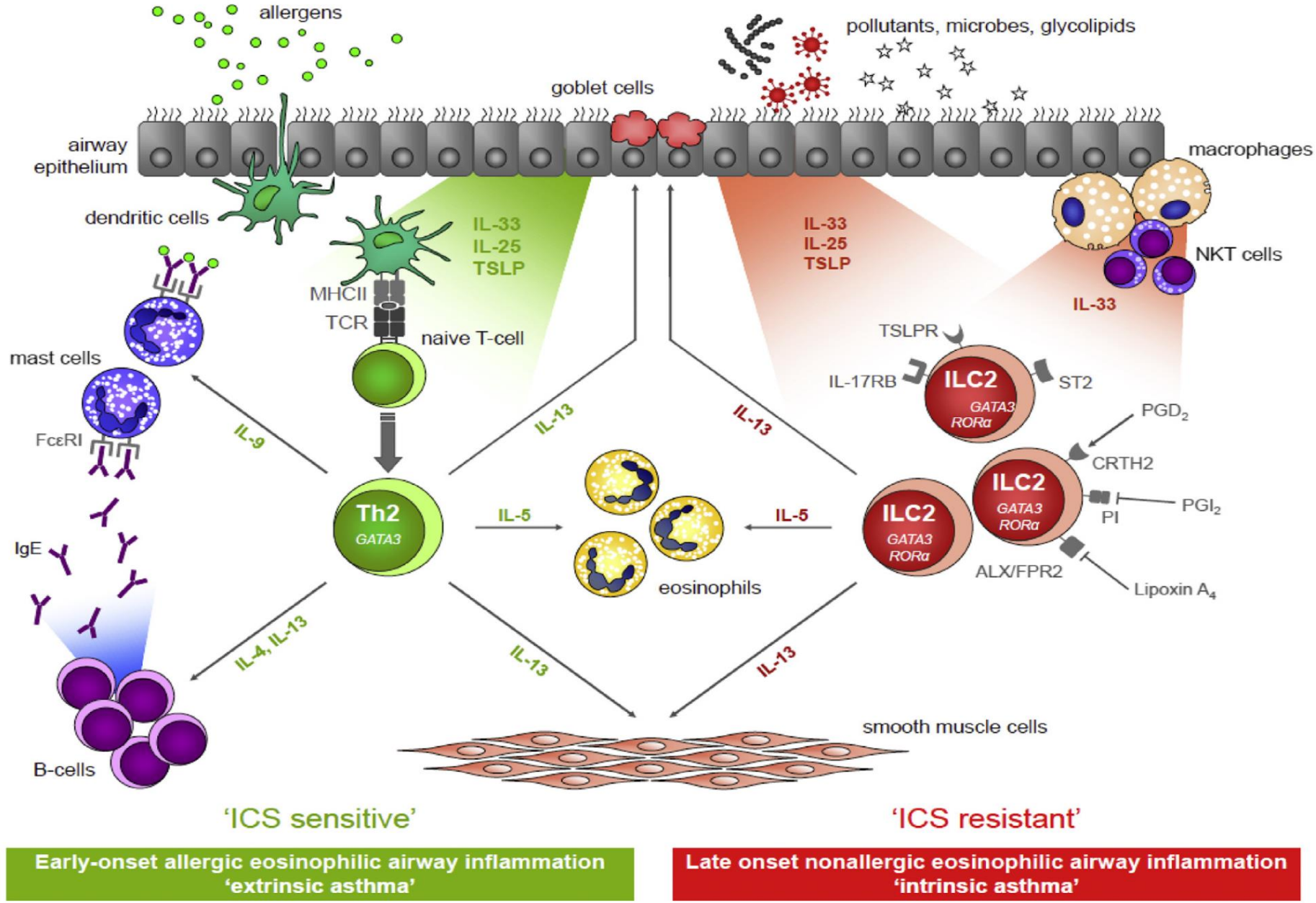
Peter J. Barnes

Allergy. 2019 Mar 4. doi: 10.1111/all.13760.

[Epub ahead of print]



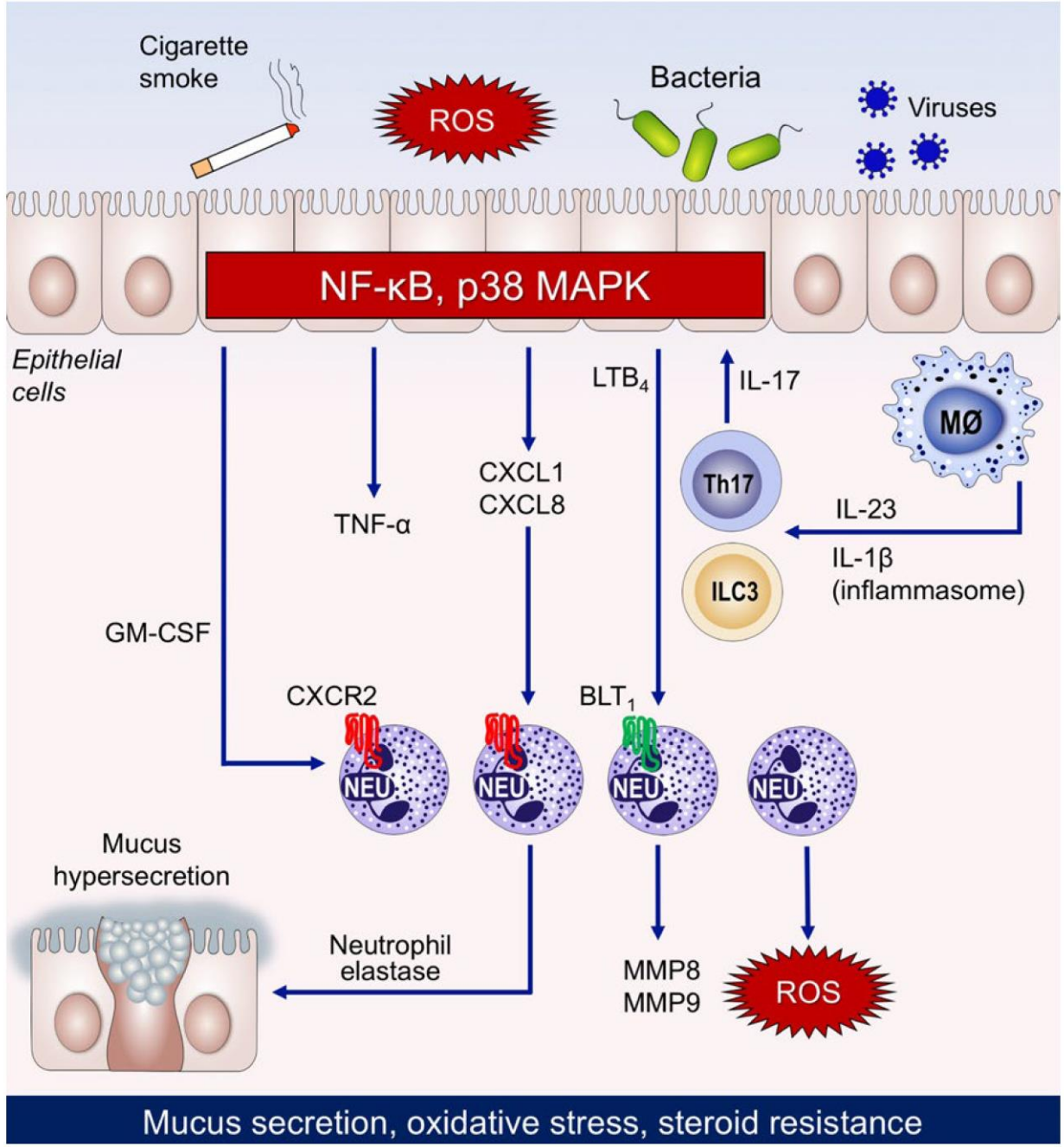
Barnes PJ. Nat Rev Immunol. 2008 Mar;8(3):183-92.



Ian Pavord. *J Allergy Clin Immunol 2018;141:1983-91*

Neutrophilic inflammation in COPD

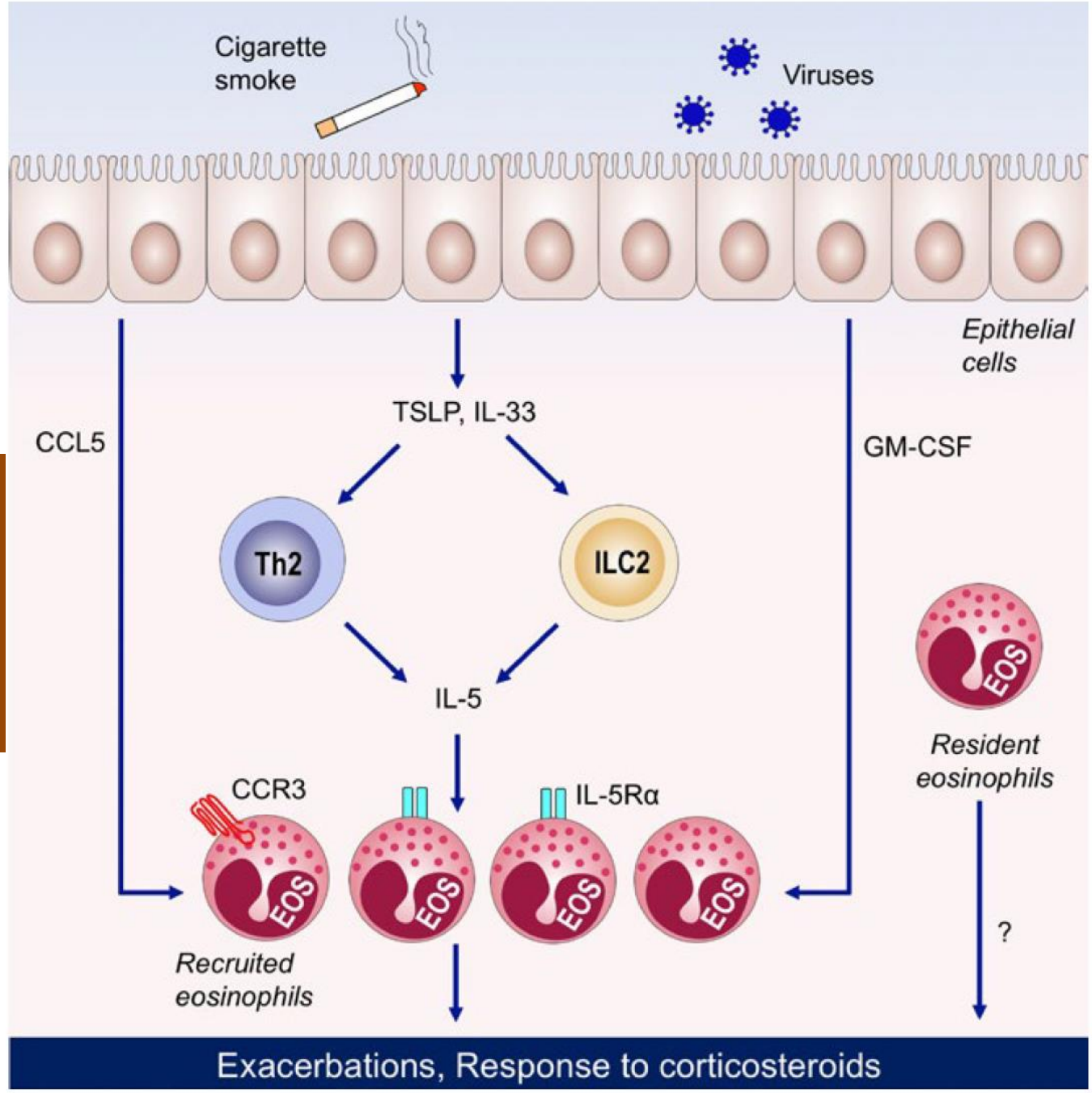
The neutrophilic inflammation in COPD is unresponsive to corticosteroids, even in high doses



Peter J. Barnes. Allergy. 2019 Mar 4. [Epub ahead of print]

Eosinophilic inflammation in COPD

Approximately 30% COPD:
-blood eos >340/μL
Approximately 15% COPD:
-blood eos consistently >300/μL x 2y
Add on ICS may reduced AECOPD
-blood eos >300/μL or >4%



Peter J. Barnes. Allergy. 2019 Mar 4. [Epub ahead of print]

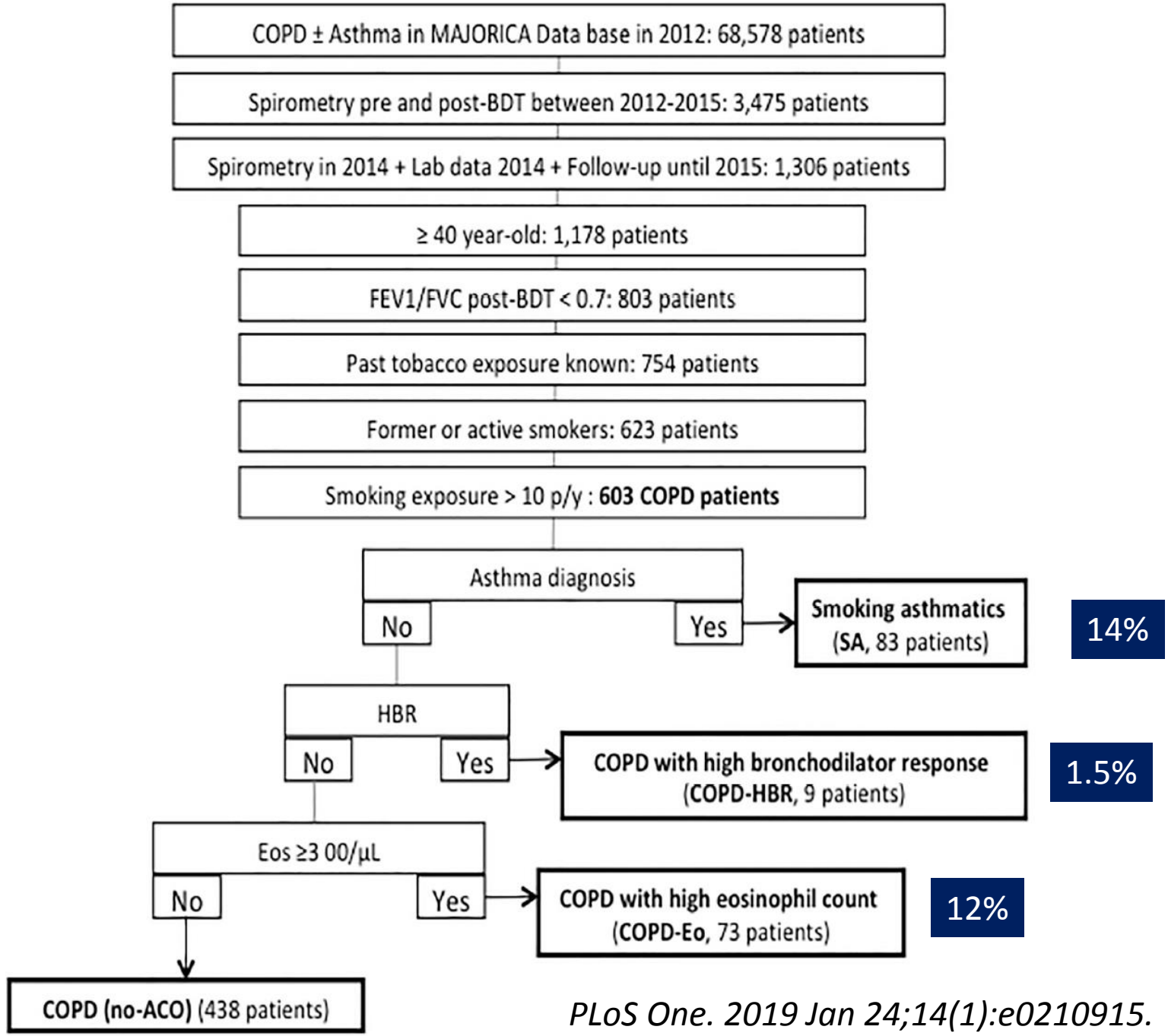
PLOS ONE

RESEARCH ARTICLE

ACO: Time to move from the description of different phenotypes to the treatable traits

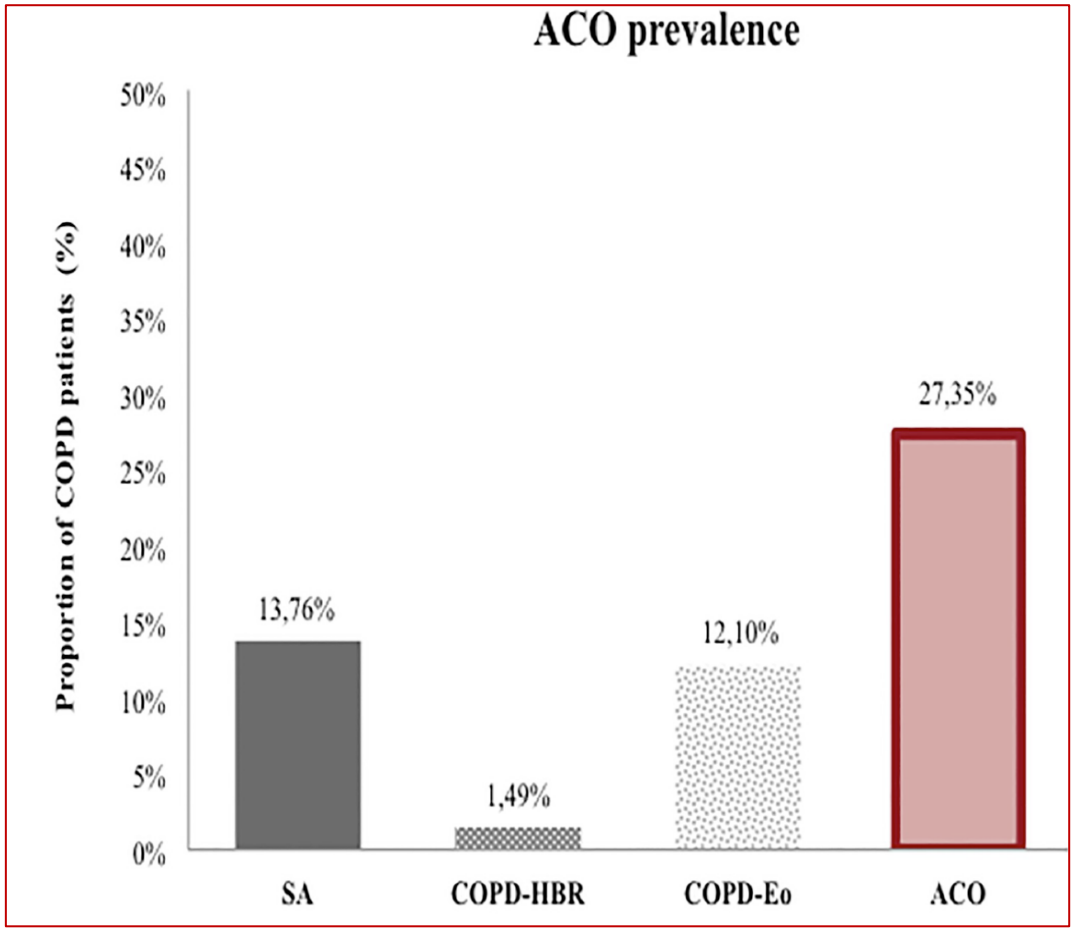
- **Aim:** to compare the **different phenotypes** inside the ACO definition in a real-life population cohort.
- **Materials:** MAJORICA cohort (N=603)
- Results:
  - Prevalence of **smoking asthmatics (SA) was 14%;**
  - COPD patients with **high BD response 1.5**%;
  - **Eosinophilic COPD** patients **12%** (eos. $\geqq$ 300).

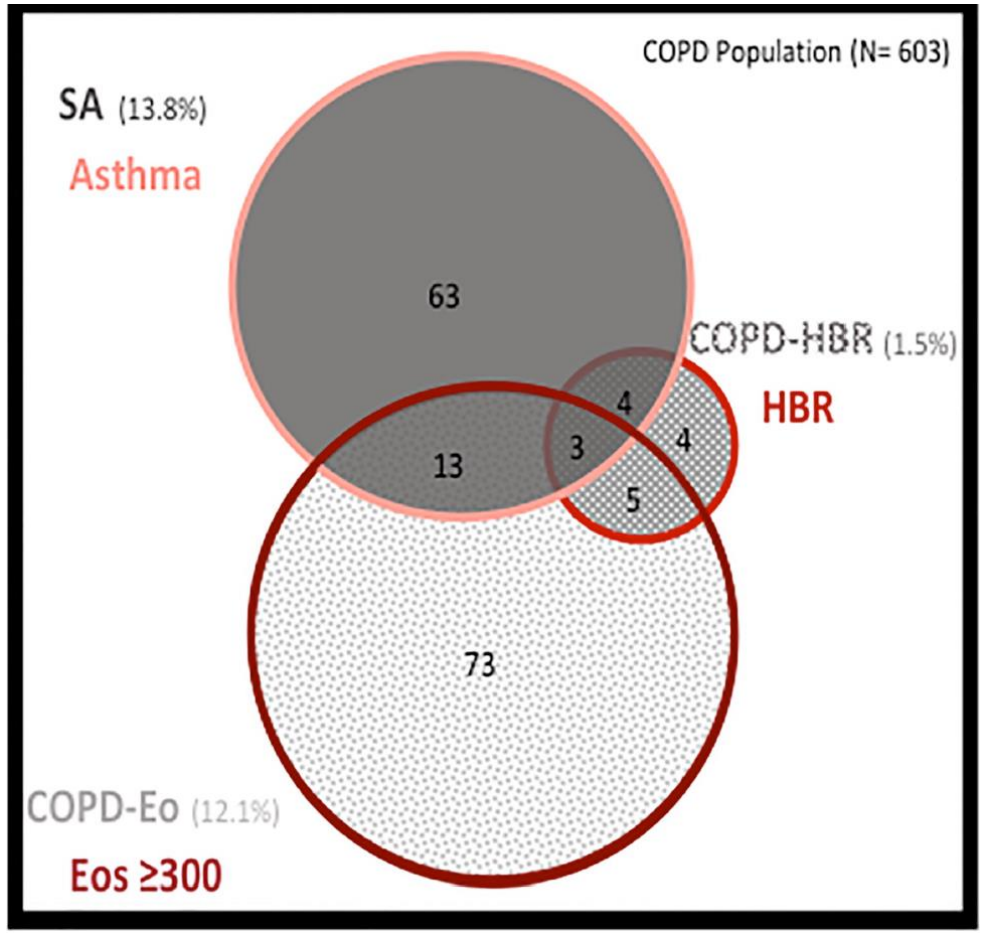
PLoS One. 2019 Jan 24;14(1):e0210915.



PLoS One. 2019 Jan 24;14(1):e0210915.

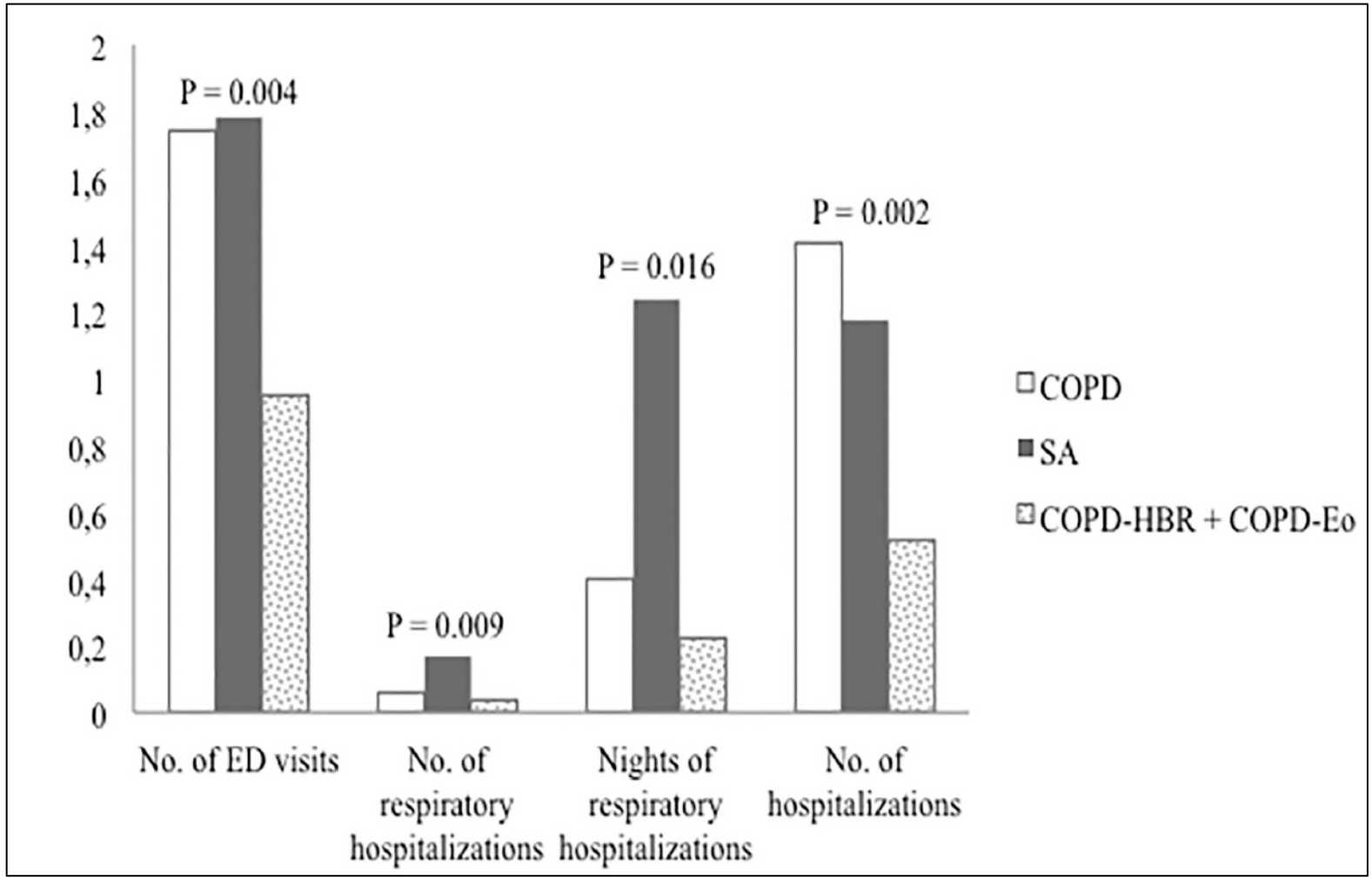
Comparison of the three ACO phenotypes





PLoS One. 2019 Jan 24;14(1):e0210915.

Use of health resources: SA & COPD↑



PLoS One. 2019 Jan 24;14(1):e0210915.

Biomarkers in COPD

Risk of AE prediction

Treatment response prediction

Biomarkers of eosinophilic airway inflammation

Biomarker	Association with treatment response	Invasiveness	Comments
FeNO	CS, anti-IL-13, anti-IL-4/IL-13, anti-IgE	Noninvasive	Easy, quick, cheap, generally available
Serum IgE	*Not associated*	Minimal	Omalizumab decreases free IgE
Sputum piriostin	Anti-IL-13, anti-IgE	Minimal	Limited availability
Blood EOS count	Anti-IL-5, anti-IL4/IL13 (?)	Minimal	Generally available, *predicts ICS response and anti-IL-5 responses* in COPD; associated with *increased risk of exacerbations in COPD*
Sputum EOS count	CS, anti-IL-5, anti-IL-4/IL-13 (?)	Moderate	Specialist centers, tissue specific, time consuming, good therapeutic marker for OCS, ICS and biologics

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

[Original Research]

CHEST

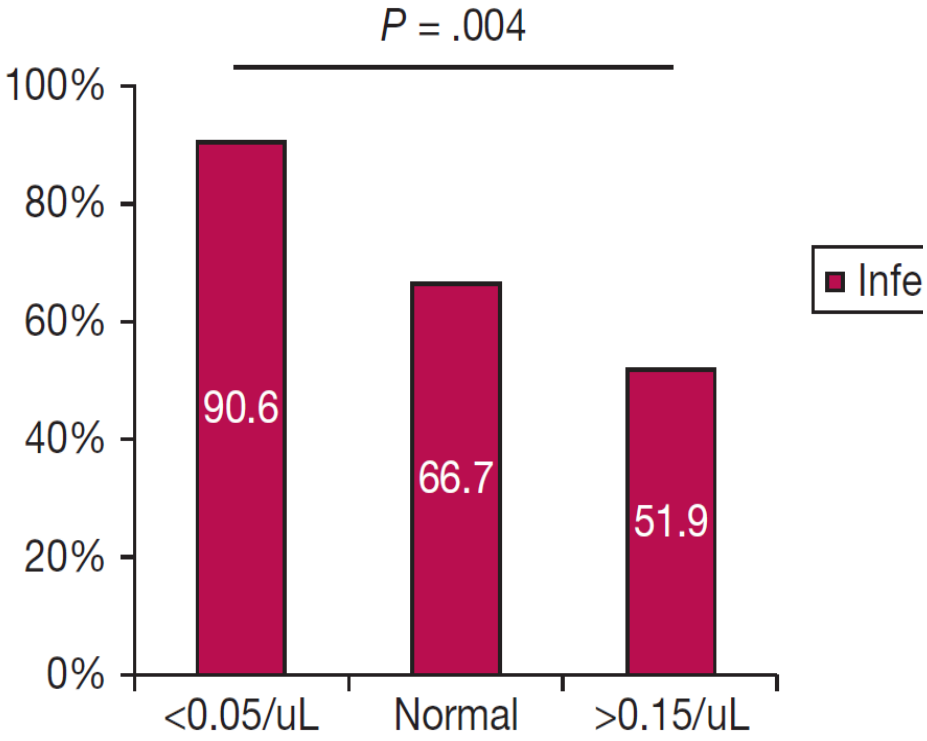
Low and High Blood Eosinophil Counts as Biomarkers in Hospitalized Acute Exacerbations of COPD

- A Derivation (n = 242) and validation (n = 99) cohort studies of patients hospitalized for AECOPD.
- **Exacerbations were grouped by blood eos counts**:
  - **low (<50/μL), normal (50-150/μL),** or **high (>150/μL).**
- **AE associated with infection:**
  - CRP ≧20 mg/L
  - Positive of Virus test or culture.

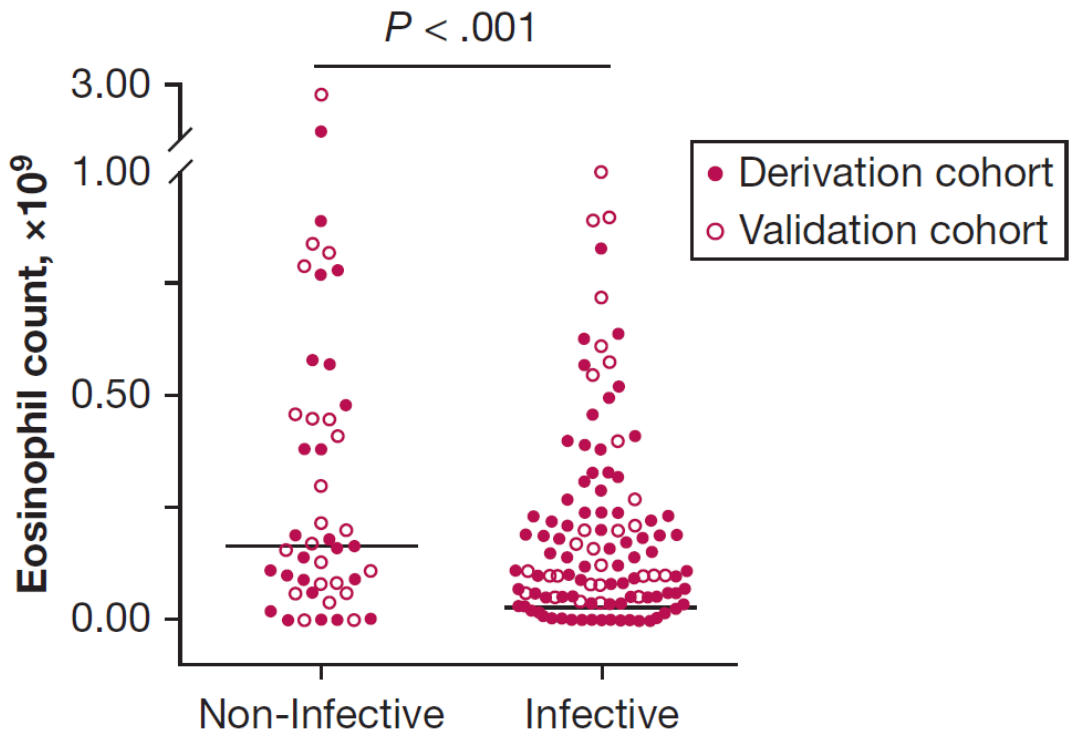
Chest. ***2019*** *Apr 9. pii: S0012-3692(19)30822-0. [Epub ahead of print]*

AE due to Infection: 84.2% retrospective & 71.4% validation cohort

Infection was far less common across increasing blood eos groups



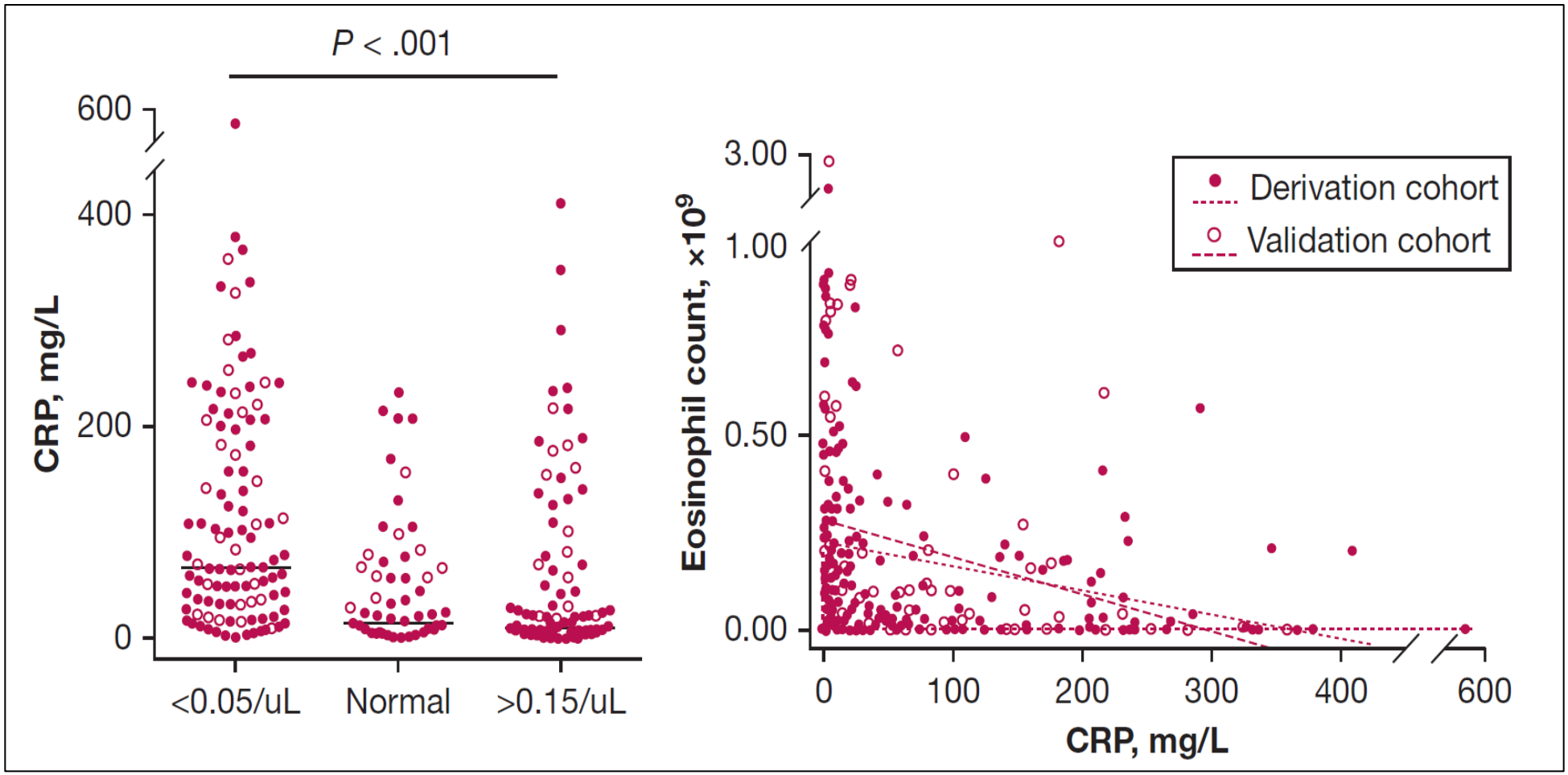
Eosinophil counts were significantly higher in the AECOPD group not associated with infection



median 185/mL vs 40/mL respectively, P < .001

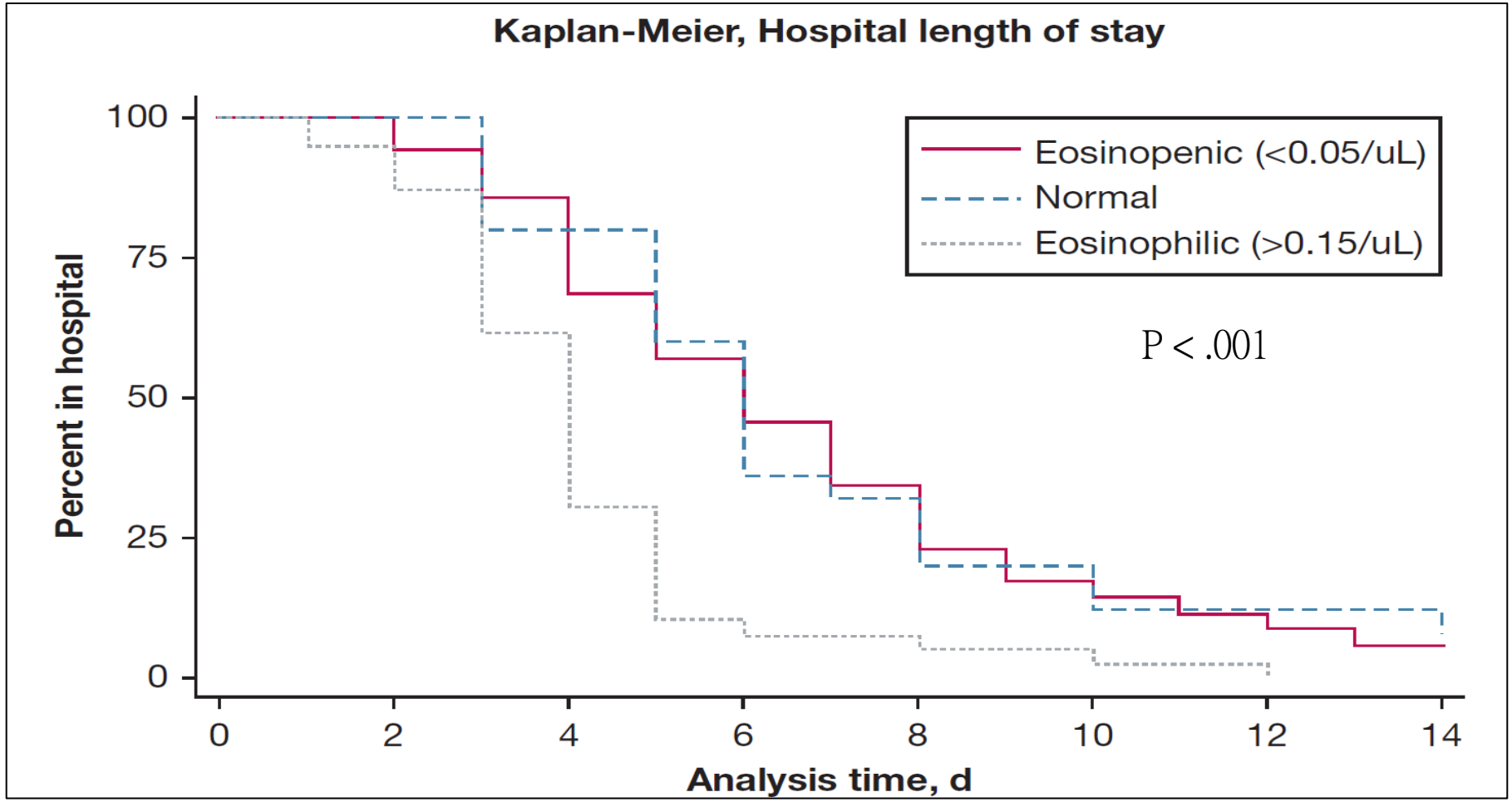
Chest. 2019 Apr 9. pii: S0012-3692(19)30822-0. [Epub ahead of print]

Blood eosinophil counts correlated negatively with CRP



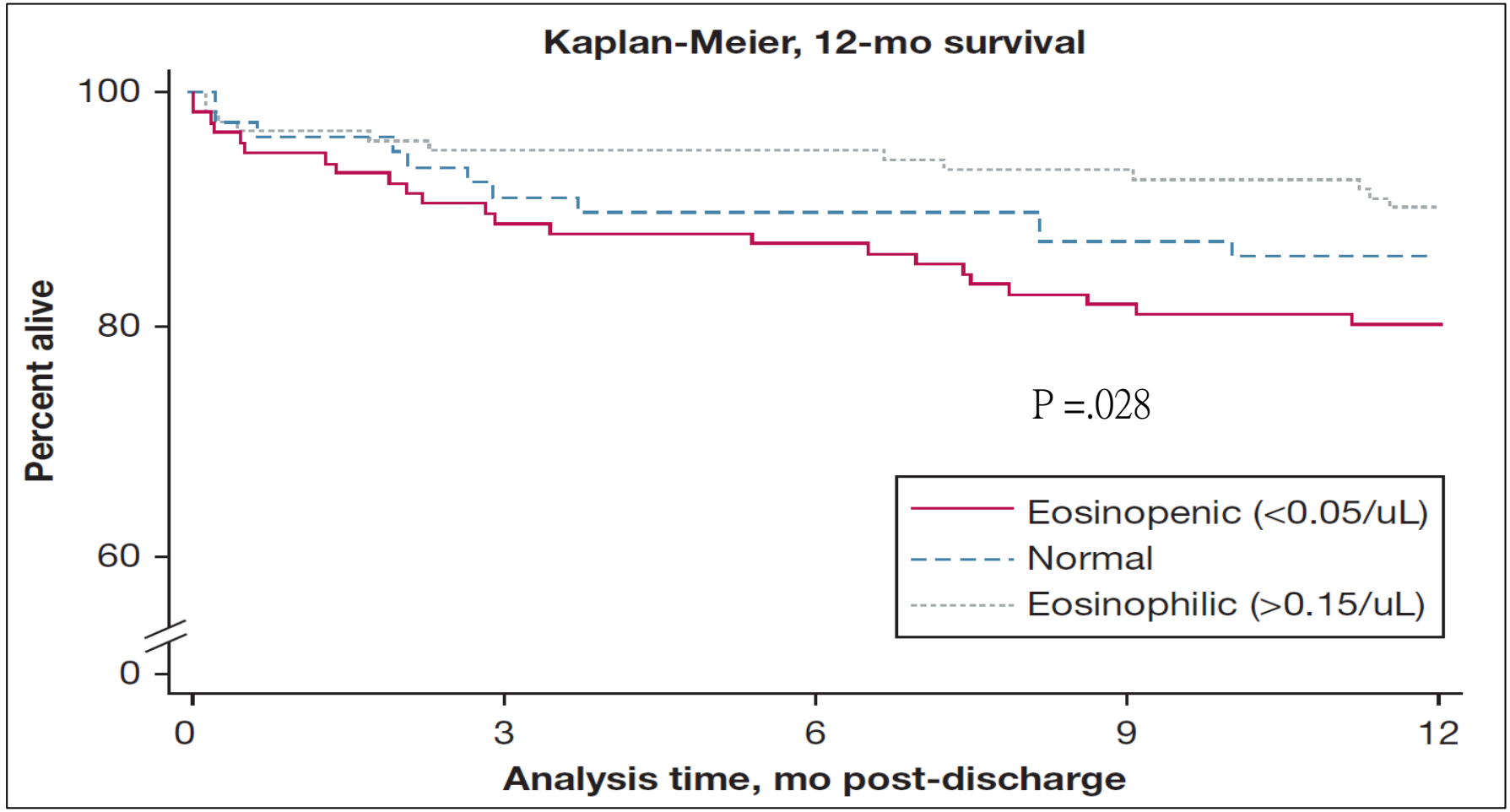
Chest. 2019 Apr 9. pii: S0012-3692(19)30822-0. [Epub ahead of print]

Length of hospital stay according to blood eosinophil group



Chest. 2019 Apr 9. pii: S0012-3692(19)30822-0. *[Epub ahead of print]*

12 months survival according to blood eosinophil group



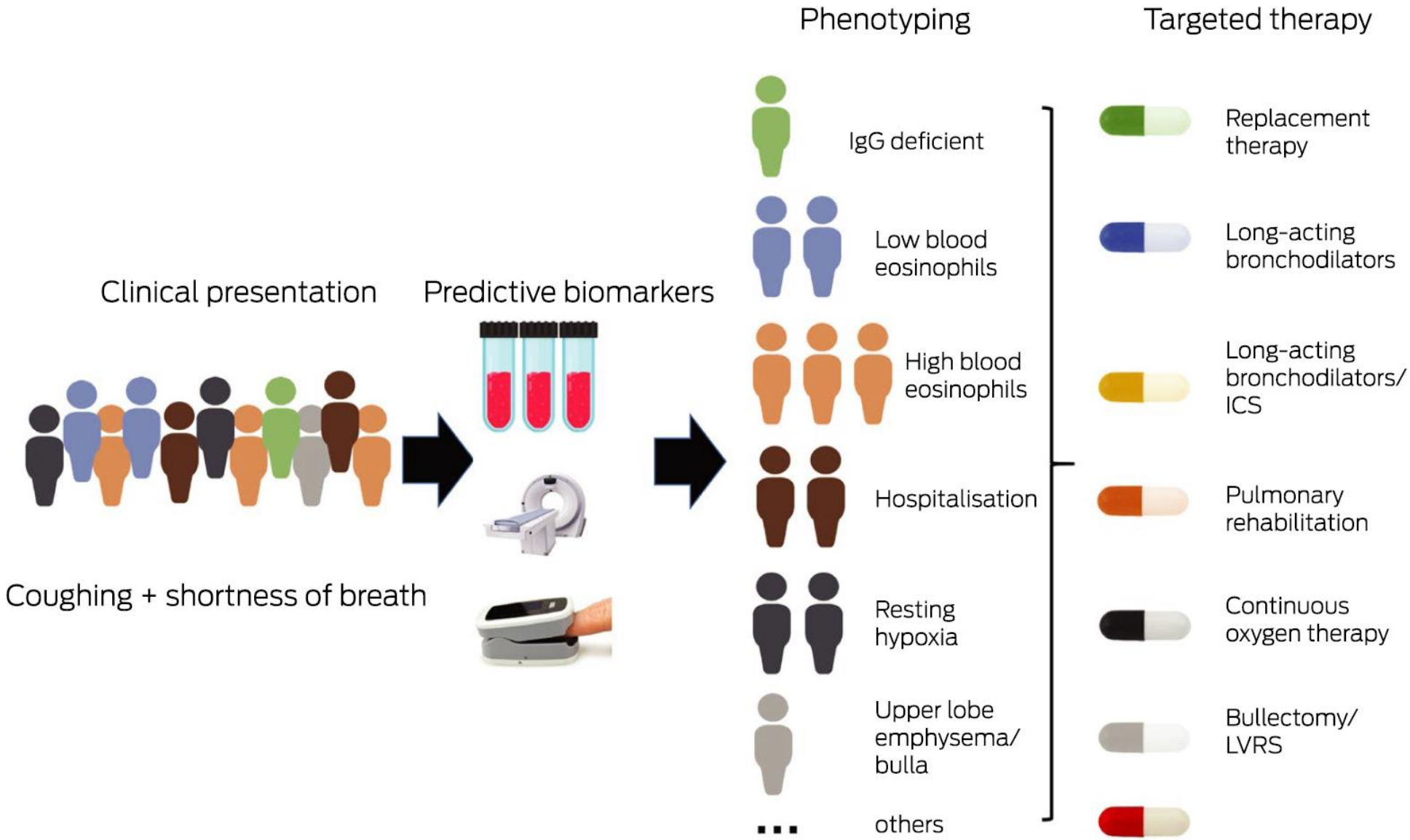
Chest. 2019 Apr 9. pii: S0012-3692(19)30822-0. [Epub ahead of print]

Precision Medicine and Treatable Trait in COPD

Eosinophilic inflammation is Treatable trait in COPD

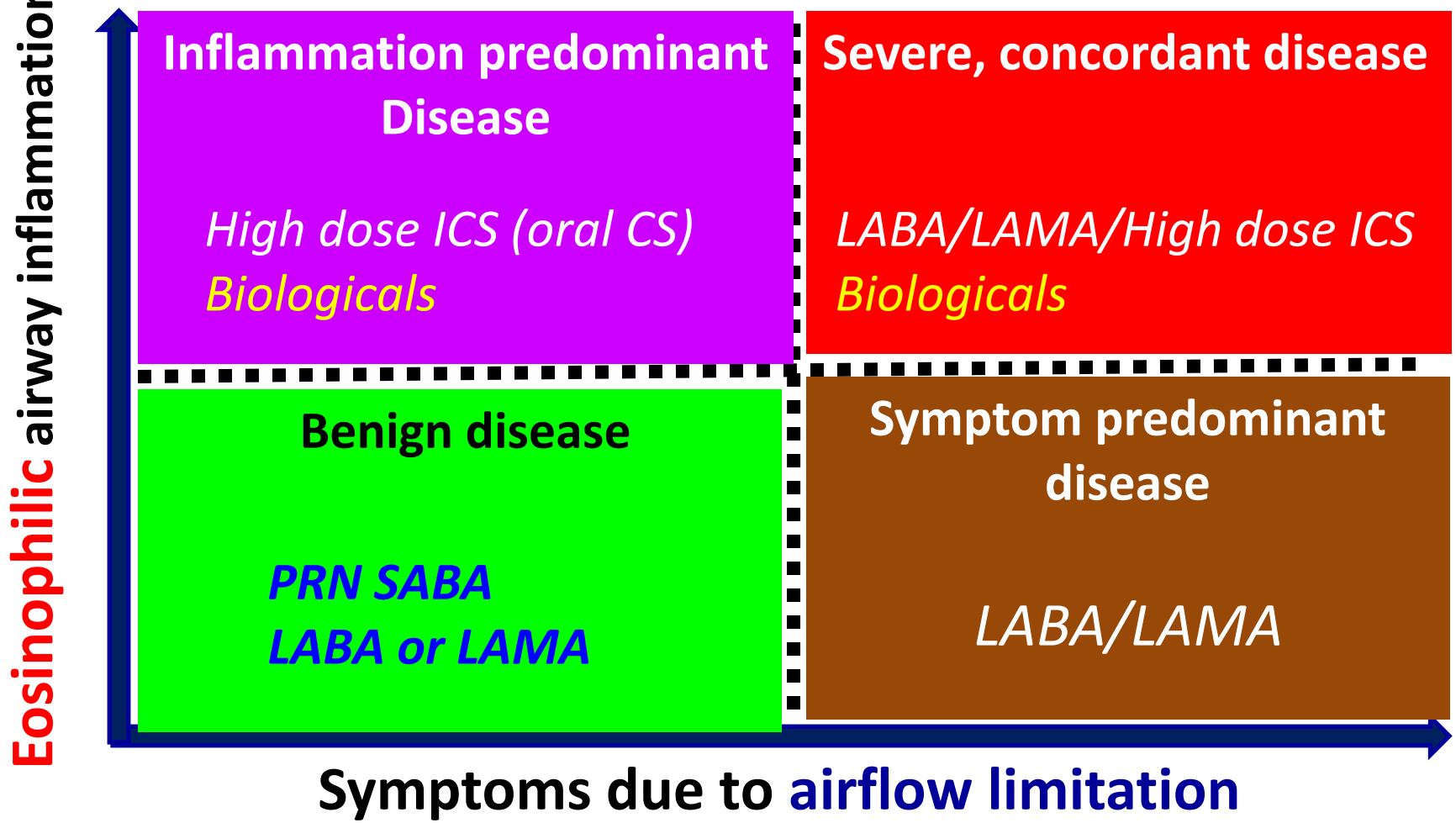
Corticosteroid | Anti-IL5 | Other Biologics

1 Implementing precision health for patients with chronic obstructive pulmonary disease



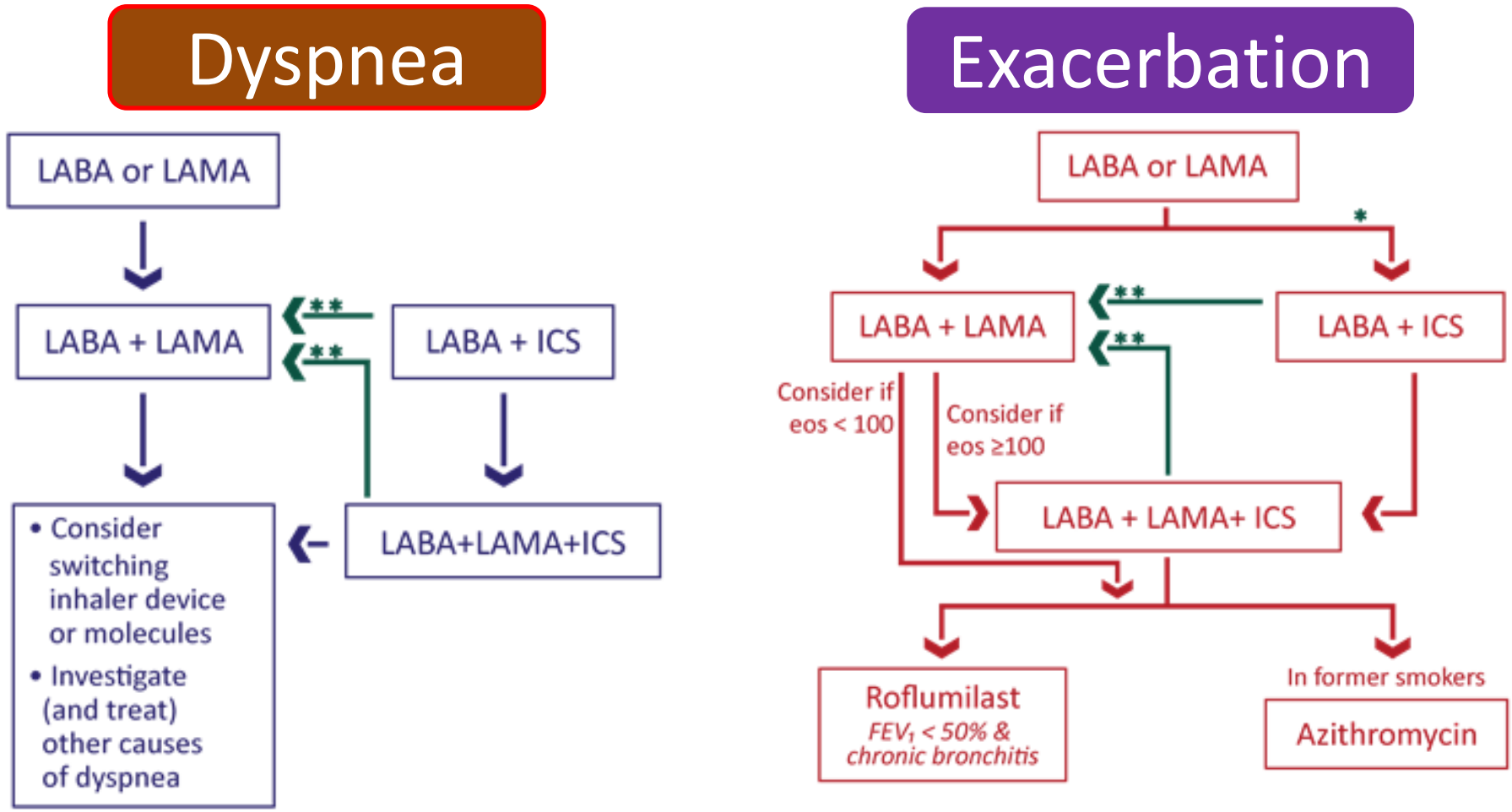
Med J Aust. 2019 May;210(9):424-428.

Eosinophilic inflammation & Airflow obstruction



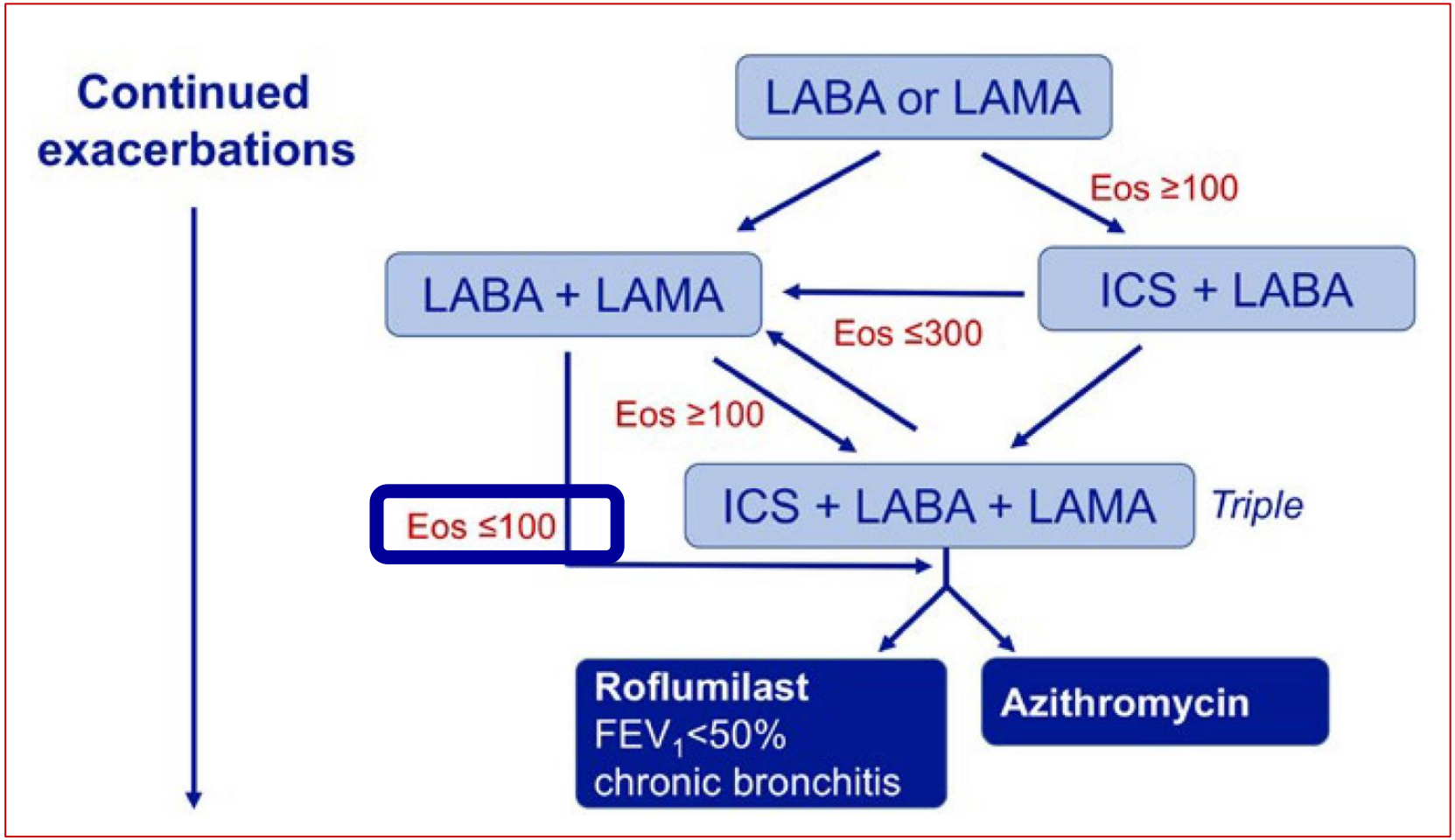
Clin Sci 2017 1;131:1027-1043

Treatable trait in GOLD 2019



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*

Importance of blood eosinophils in determining COPD therapy



Peter J. Barnes. Allergy. 2019 Mar 4. [Epub ahead of print]

Precision Treatment in COPD by Biomarkers

2 Examples of precision health in subgroups of patients with chronic obstructive pulmonary disease identified through the use of clinical traits or blood or bioimaging markers

Intervention	Subgroup	NNT	Endpoint prevented	Treatment period (years)
LAMA *v* LABA[22]	Overall	24	Exacerbation	1
	BMI ≤ 20 kg/m^2	8	Exacerbation	1
	GOLD 4*	7	Exacerbation	1
ICS–LABA–LAMA *v* LABA–LAMA[23]	Overall	38	Exacerbation	1
	Blood eosinophil ≥ 300 cells/μL	9	Exacerbation	1
LVRS *v* no LVRS[9]	Overall	245	Mortality	5
	Upper lobe predominant emphysema and low exercise capacity†	6	Mortality	5
Domiciliary oxygen *v* no oxygen therapy	Overall[24]	56	Mortality	1–6
	PaO_2 < 60 mmHg[10]	5	Mortality	3

BMI = body mass index; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LVRS = lung volume reduction surgery; NNT = number needed to treat to prevent at least one endpoint in one patient; PaO_2 = oxygen tension on room air. * Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 4 represents FEV_1 < 30% of predicted. † 25 W for women and 40 W for men on cardiopulmonary exercise test.

Med J Aust. 2019 May;210(9):424-428.

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.

J Allergy Clin Immunol 2018;141:1983-91

	Effect on clinical measures				
	FEV_1	Symptoms	Exac	PC_{20}	OCS sparing
Oral steroids	+	+	++	++	NA
Anti–IL-5	+	+	++	0	++
Anti–IL-13	+	+	+	?	0
Anti–IL-4/IL-13	++	++	++	?	?
Anti-IgE	+	+	+	0	?
Anti-TSLP	++	++	++	?	?

	Effect on biomarkers			
	Bl eos	Sp eos	FENO	IgE
Oral steroids	↓↓	↓↓	↓	↓
Anti–IL-5	↓↓	↓↓	↔	↔
Anti–IL-13	↑	↓	↓↓	↓
Anti–IL-4/IL-13	↑	↓	↓↓	↓↓
Anti-IgE	↔	↓	↓↓	↓↓
Anti-TSLP	↓	↓	↓↓	↓

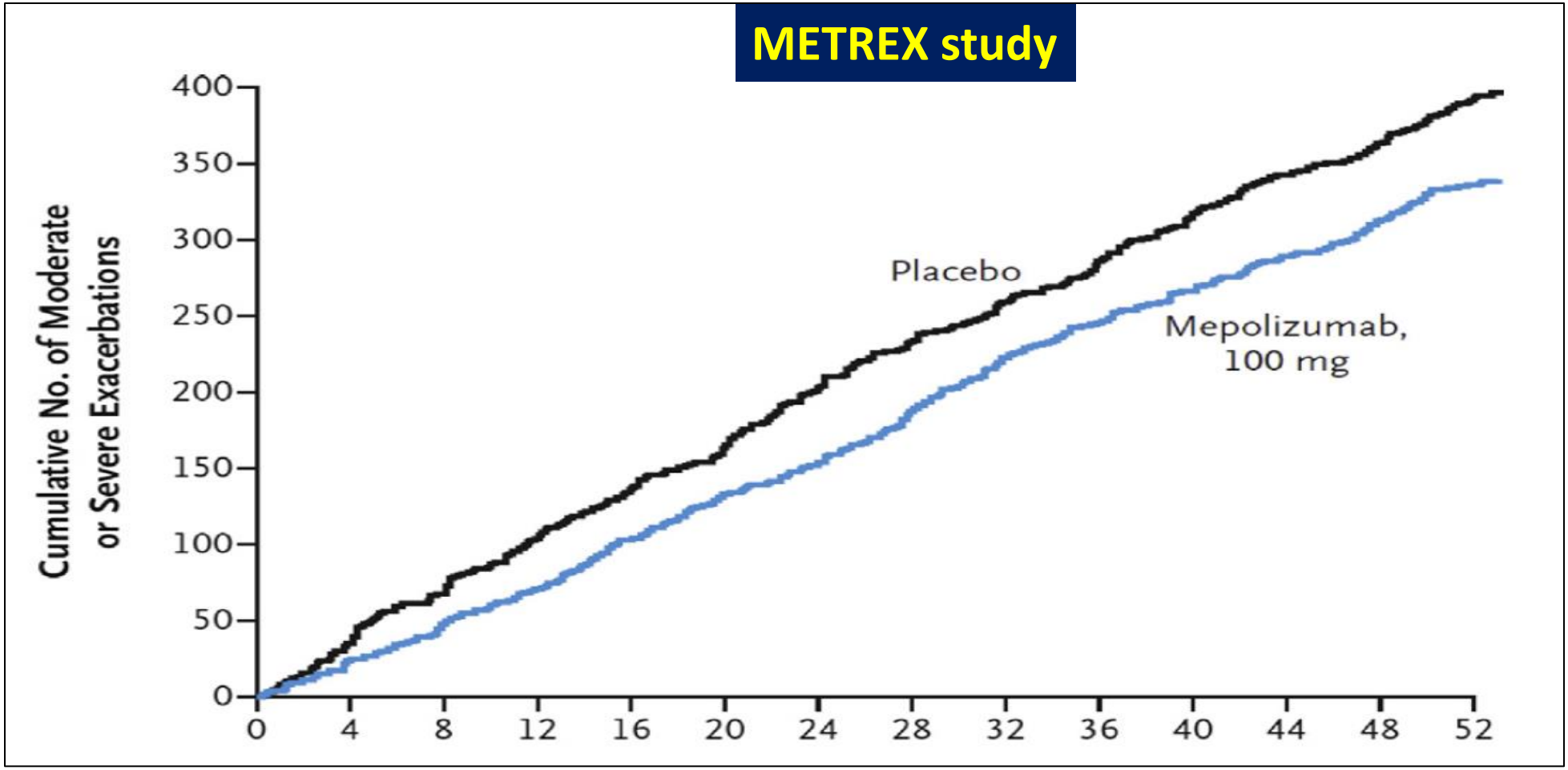
++ and ↓↓, Marked effect; 0, no effect; ?, no information.

OCS, Oral corticosteroid; *TSLP*, thymic stromal lymphopoietin.

J Allergy Clin Immunol 2018;141:1983-91

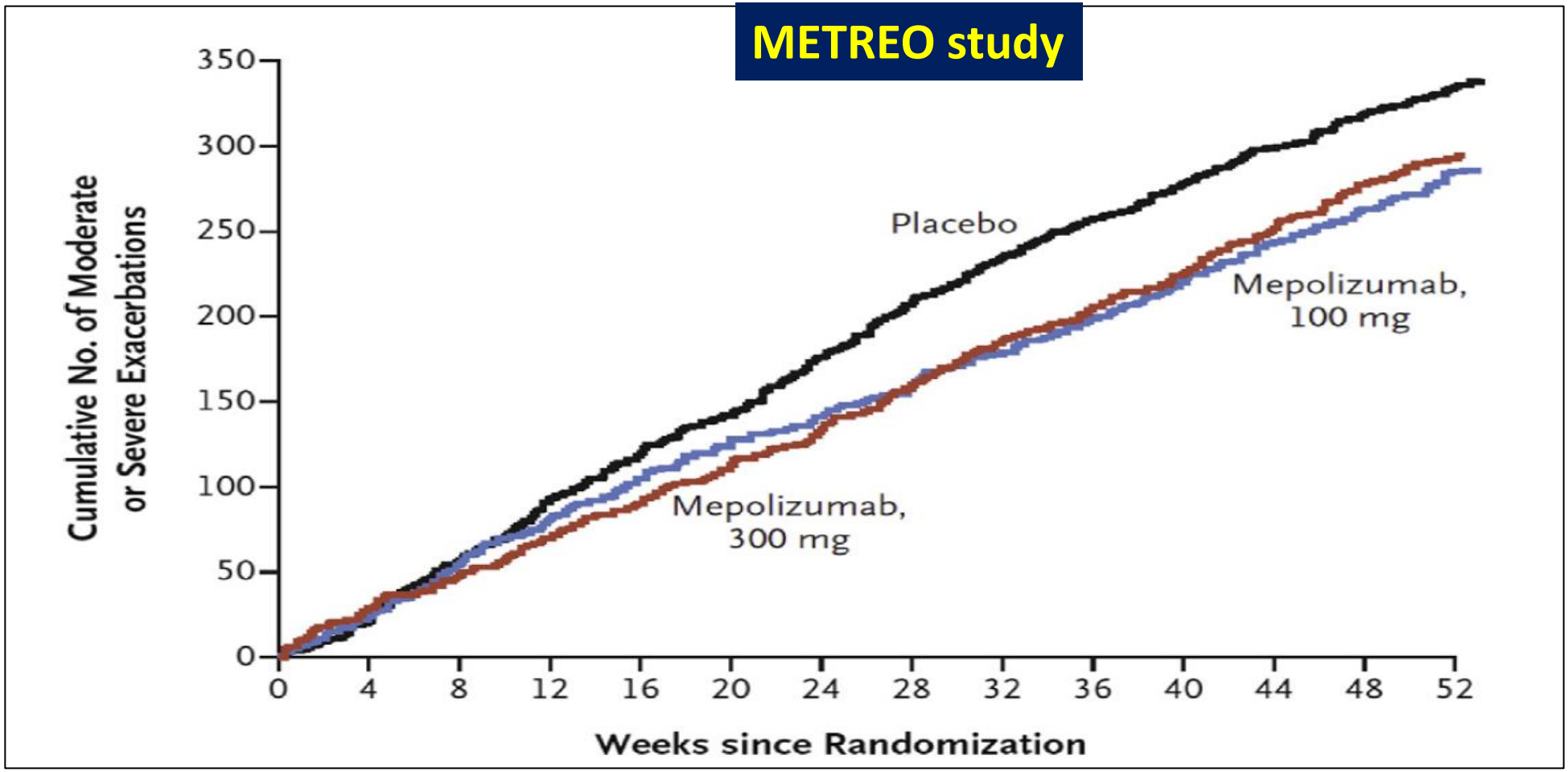
Biologics in chronic obstructive pulmonary disease

Anti-IL5 in COPD: METREX & METREO

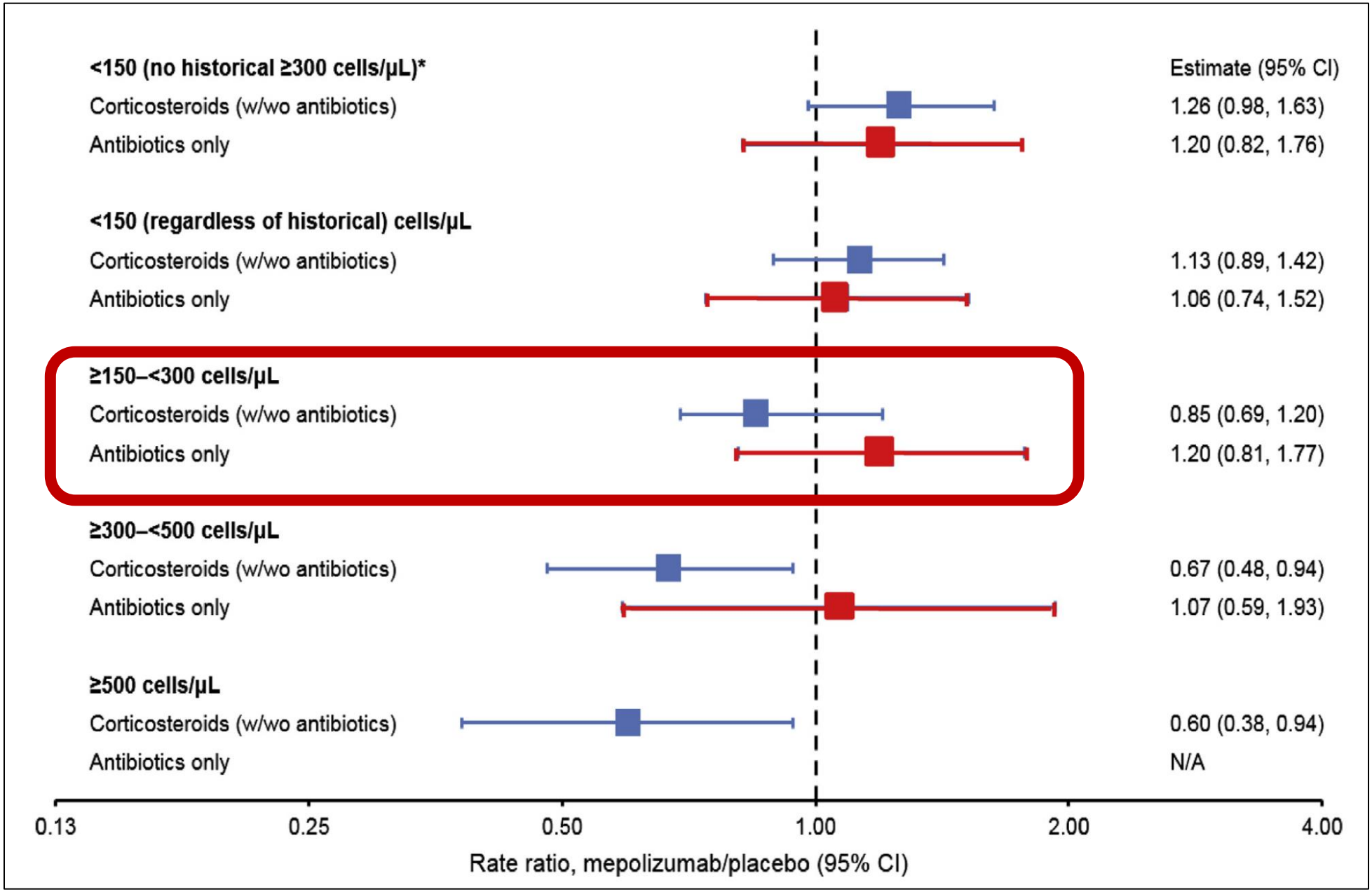


J Allergy Clin Immunol 2018;141:1983-91

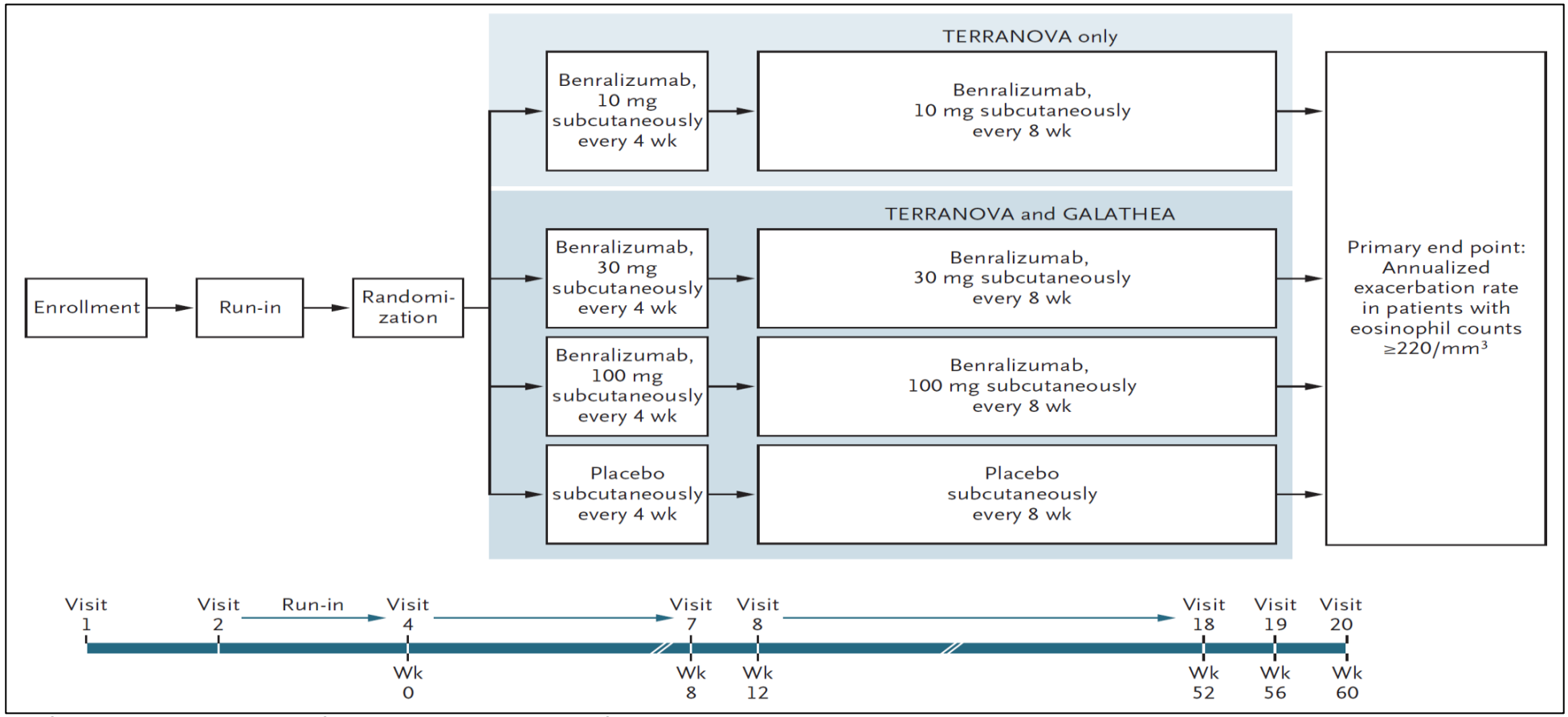
Anti-IL5 in COPD: METREX & METREO



J Allergy Clin Immunol 2018;141:1983-91


<150 (no historical ≥300 cells/μL)*
Corticosteroids (w/wo antibiotics)
Antibiotics only
<150 (regardless of historical) cells/μL
Corticosteroids (w/wo antibiotics)
Antibiotics only
≥150–<300 cells/μL
Corticosteroids (w/wo antibiotics)
Antibiotics only
≥300–<500 cells/μL
Corticosteroids (w/wo antibiotics)
Antibiotics only
≥500 cells/μL
Corticosteroids (w/wo antibiotics)
Antibiotics only
Estimate (95% CI)
1.26 (0.98, 1.63)
1.20 (0.82, 1.76)
1.13 (0.89, 1.42)
1.06 (0.74, 1.52)
0.85 (0.69, 1.20)
1.20 (0.81, 1.77)
0.67 (0.48, 0.94)
1.07 (0.59, 1.93)
0.60 (0.38, 0.94)
N/A
0.13
0.25
0.50
1.00
2.00
4.00
Rate ratio, mepolizumab/placebo (95% CI)

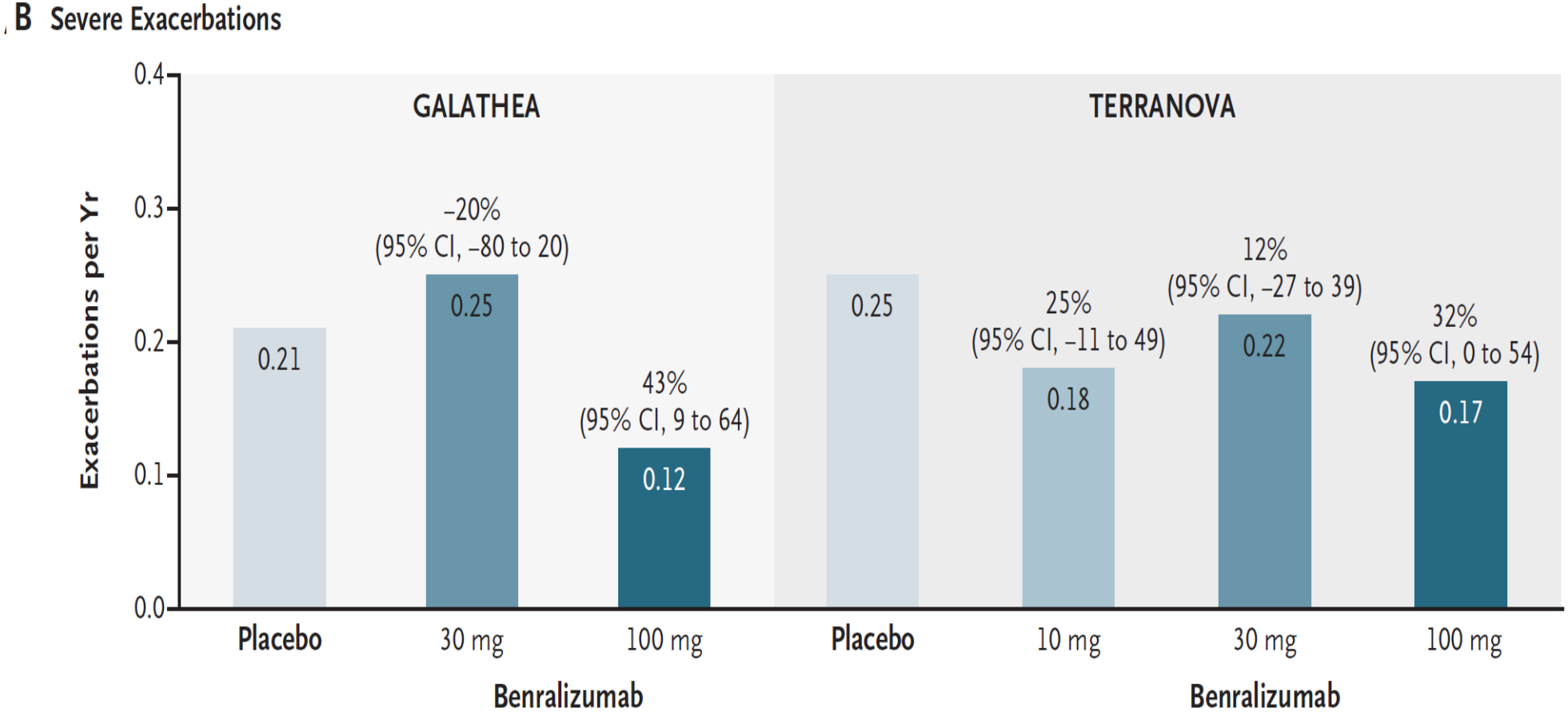
Benralizumab for the Prevention of COPD Exacerbations



the GALATHEA and TERRANOVA Study Investigators

N Engl J Med. 2019 May 20. [Epub ahead of print]

None of the annualized COPDAE RR for any dose of benralizumab reached significance



N Engl J Med. 2019 May 20. [Epub ahead of print]

No Significant difference in any endpoints

Table 2. Analysis of Efficacy in Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.*

End Point	GALATHEA			TERRANOVA			
	Benralizumab, 30 mg (N=382)	Benralizumab, 100 mg (N=379)	Placebo (N=359)	Benralizumab, 10 mg (N=377)	Benralizumab, 30 mg (N=394)	Benralizumab, 100 mg (N=386)	Placebo (N=388)
Exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	1.19 (1.04–1.36)	1.03 (0.90–1.19)	1.24 (1.08–1.42)	0.99 (0.87–1.13)	1.21 (1.08–1.37)	1.09 (0.96–1.23)	1.17 (1.04–1.32)
Rate ratio, benralizumab vs. placebo (95% CI)†	0.96 (0.80–1.15)	0.83 (0.69–1.00)	—	0.85 (0.71–1.01)	1.04 (0.88–1.23)	0.93 (0.78–1.10)	—
Unadjusted P value	0.65	0.05	—	0.06	0.66	0.40	—
Severe exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	0.25 (0.19–0.33)	0.12 (0.08–0.17)	0.21 (0.15–0.28)	0.18 (0.14–0.25)	0.22 (0.17–0.28)	0.17 (0.13–0.22)	0.25 (0.19–0.32)
Rate ratio, benralizumab vs. placebo (95% CI)‡	1.20 (0.80–1.80)	0.57 (0.36–0.91)	—	0.75 (0.51–1.11)	0.88 (0.61–1.27)	0.68 (0.46–1.00)	—
Lung function							
No. of patients with data	329	326	317	325	322	347	344
Change from baseline to wk 56 in prebronchodilator FEV_1 — liters	0.014±0.282	0.031±0.294	0.010±0.275	0.021±0.346	0.011±0.289	0.033±0.291	0.016±0.292
Health-related quality of life							
No. of patients with data	338	331	317	331	329	354	349
Change from baseline to wk 56 in SGRQ total score§	−5.025±14.677	−6.723±15.723	−3.913±15.039	−7.733±14.996	−8.674±17.910	−7.257±15.989	−6.863±16.344

Add on Benralizumab for COPD

- ***Not associated*** with a lower annualized rate of COPD exacerbations than placebo among patients:
  - with **moderate to very severe COPD**,
  - a history of **frequent moderate or severe exacerbations**
  - **Blood eosinophil counts of 220 per cumm** or greater

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Take Home Messages

- Approximately **1/3** of **stable COPD** patients have evidence of eosinophilic inflammation.
- **Role of Eosinophils in COPD:**
  - Benefit from **inhaled corticosteroid (ICS)** therapy **>=300**
  - A **predictor of COPD AE** **>=100, 2AE,1Ad**
  - May be a biomarkers to receive **Anti-IL5 therapy** **>=150**
- **Biomarkers of eosinophilic airway inflammation:**
  - **Blood Eos, Sputum Eos**, **FeNO**, Piriotin, Serum IgE
- **CRP and Blood eosinophil level** could be a guidance to **manage AECOPD**.