Biomakers in asthma management

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Conflict of interests

- Grants from GSK, AZ, Novartis and Chiesi
- Adbaord fees from GSK, AZ, Novartis

Presentation outline

1. What is a biomarker?
2. Sputum eosinophils as relevant biomarker in asthma
3. Are « proxy » of sputum eosinophils a solution?
4. Can blood be more relevant than sputum to guide treatment in severe asthma?
5. The future of biomarkers

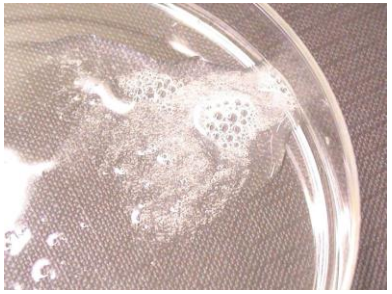
What is a biomarker?

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

National Institute of Health

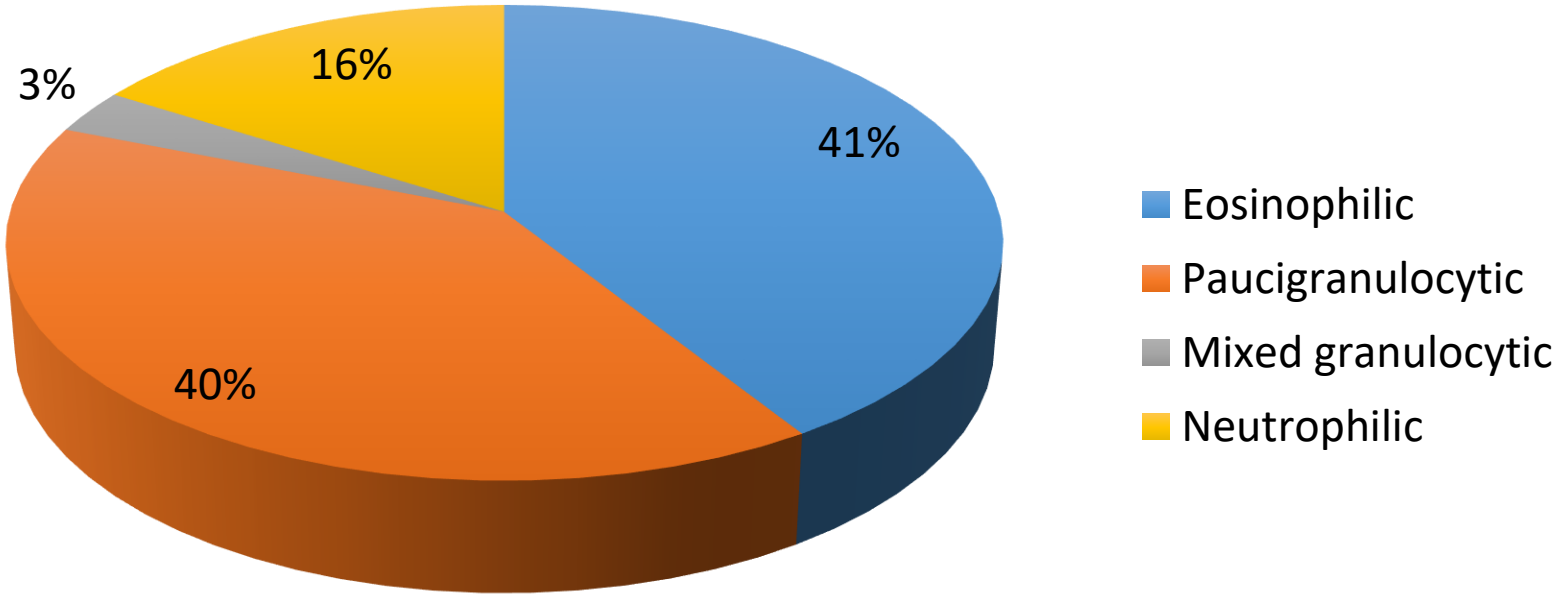
Sputum eosinophils as a model of useful biomarker in asthma

Airway inflammatory phenotypes in asthma



Induced sputum

N=508

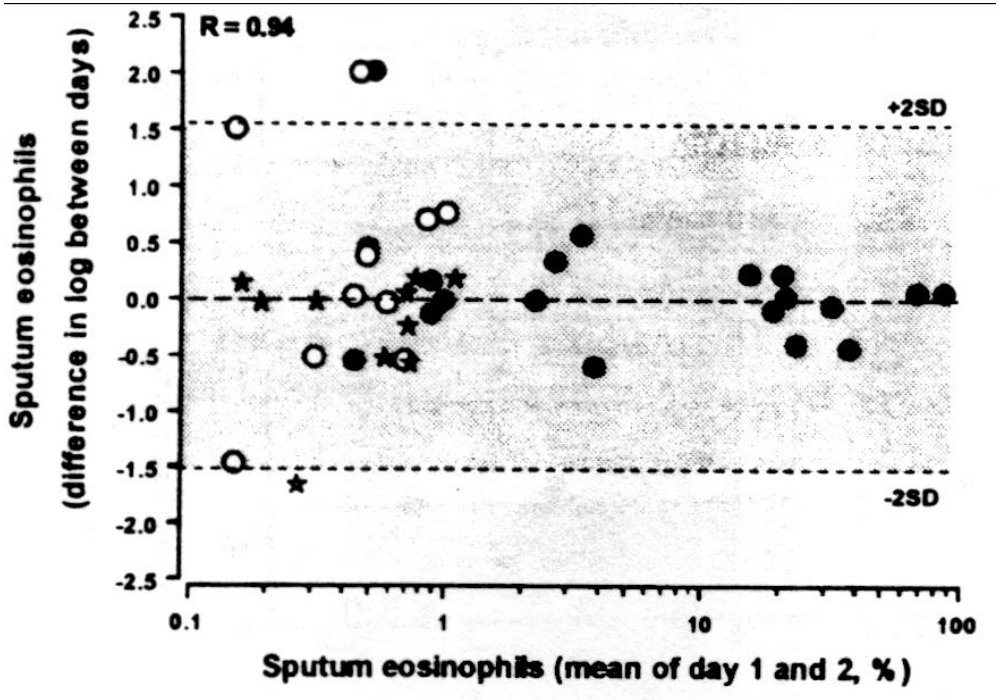


Eosinophilic and paucigranulocytic: most frequent phenotypes

Schleich F et al BMC Pulm Med 2013

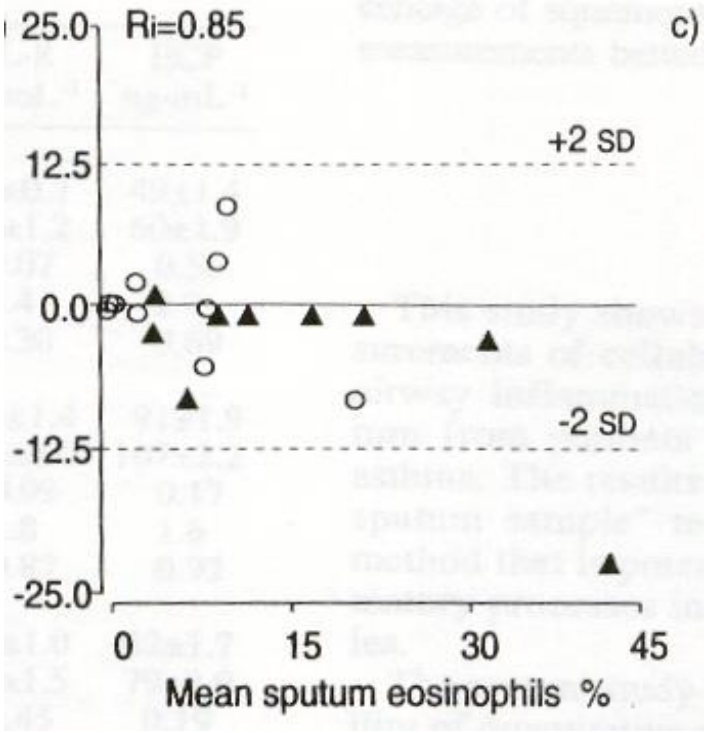
Reproducibility of sputum eosinophil counts in asthmatics

Plug



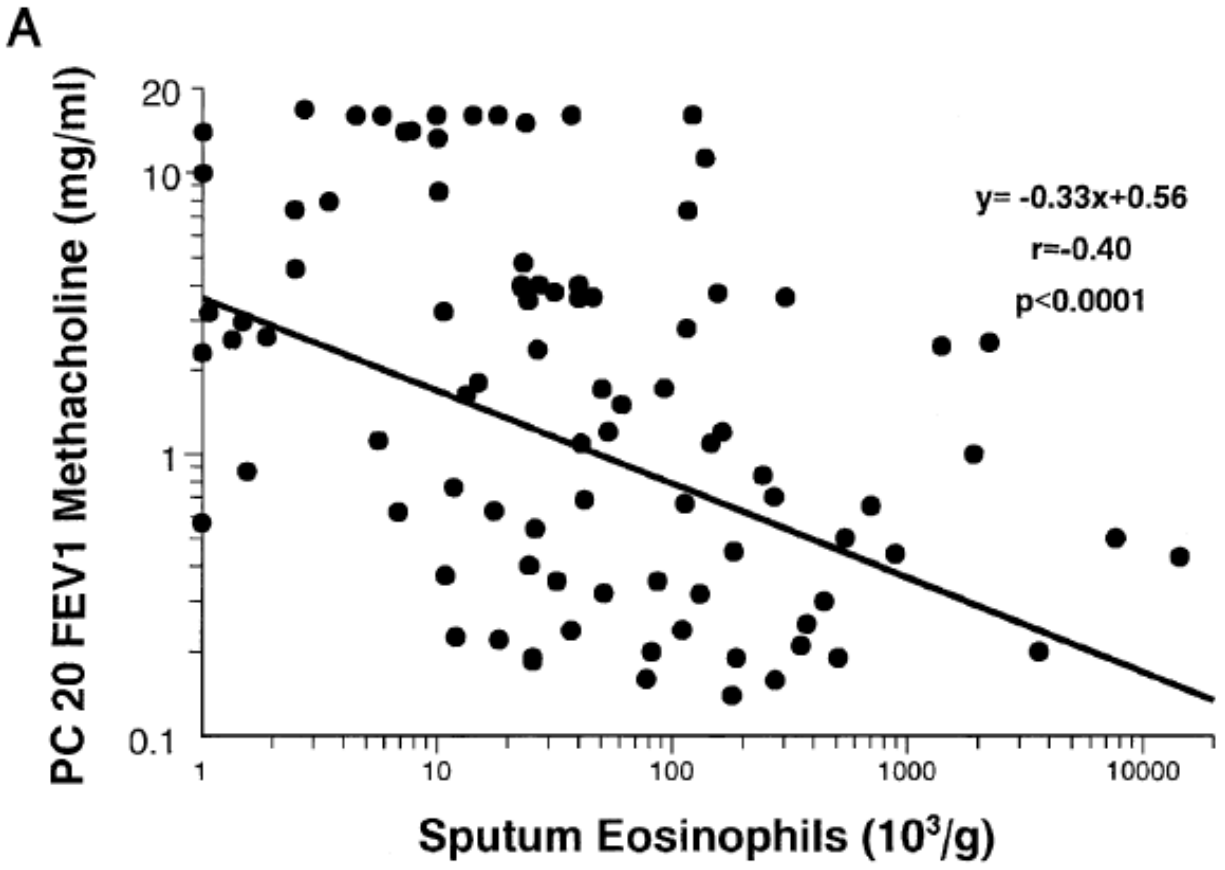
Pizzichini E et al Am J Respir Crit Care Med 1996

Whole sample



Int'veen J et al Eur Respir J1996

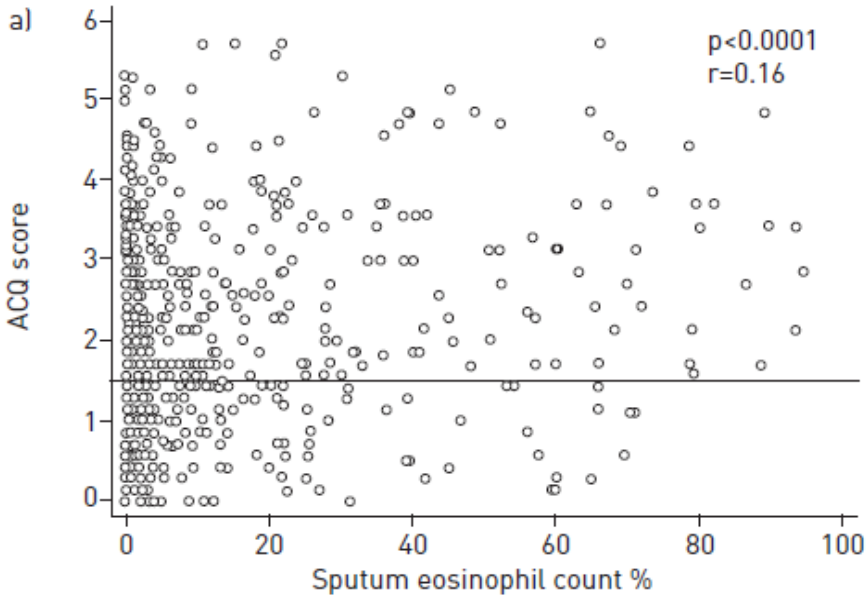
Sputum eosinophil counts and BHR

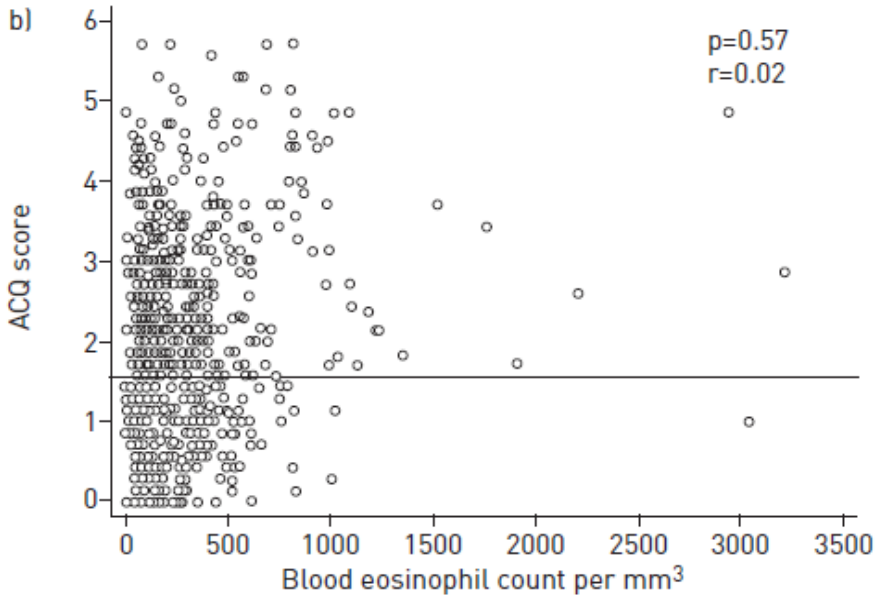


Louis R et al Allergy 2002

Correlation between ACQ and eosinophil trait (sputum vs blood)

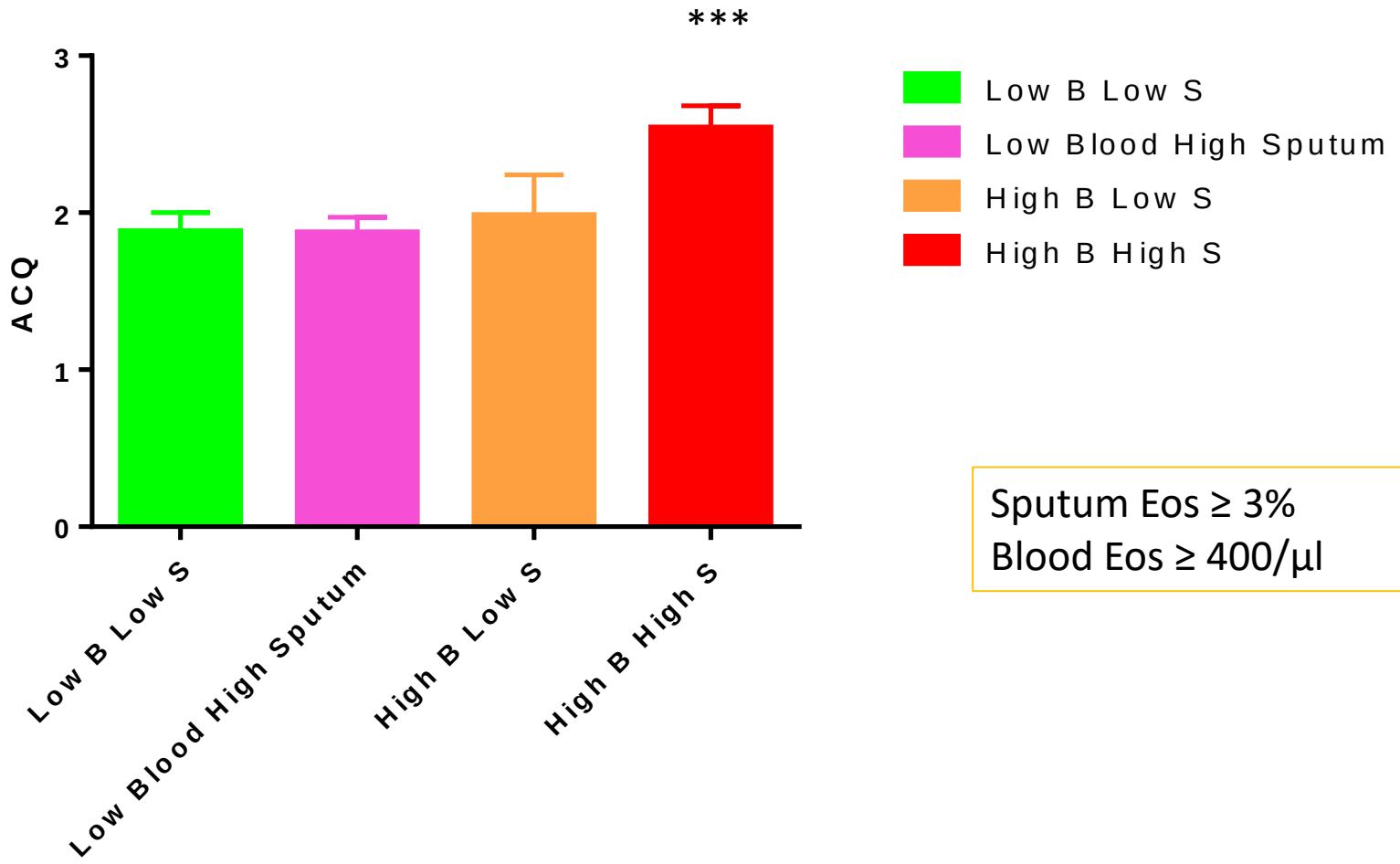
N=758





Schleich F et al ERJ 2014

Eosinophilic inflammation and Asthma control
Retrospective cohort of asthmatics (N=508)



Sputum Eos ≥ 3%
Blood Eos ≥ 400/µl

Schleich F et al ERJ 2014

* p< 0.05 Compared to Low Low

Eosinophilic inflammation and Asthma control
Retrospective longitudinal study

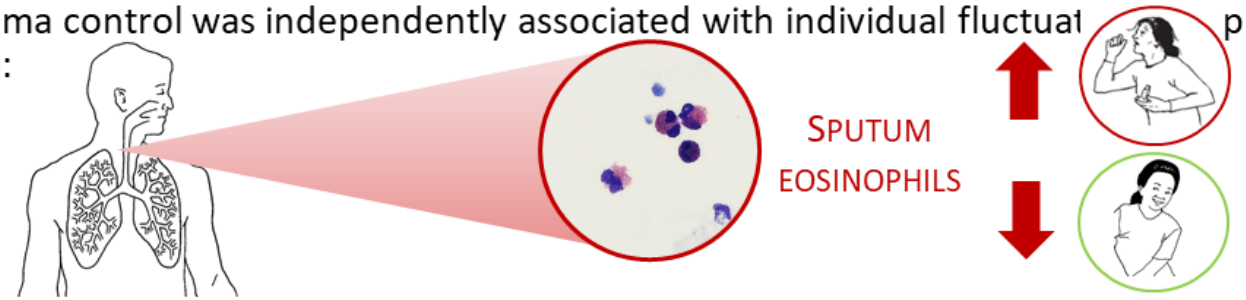
- Results:

TABLE II. Linear mixed models assessing the relationship between ACQ-6 and within-subject variations in sputum eosinophils as well as potentially confounding or causal factors

	Initial cohort N = 187, total number of visits with a value of ACQ-6 = 507				Validation cohort N = 79, total number of visits with a value of ACQ-6 = 175			
	Univariate		Multivariate* N = 187, O = 495		Univariate		Multivariate* N = 79, O = 174	
ACQ-6	Coef. (SE)	*P*	Coef. (SE)	*P*	Coef. (SE)	*P*	Coef. (SE)	*P*
Time (d)	0.000069 (0.000072)	.34	0.000082 (0.000072)	.26	0.00012 (0.00011)	.27	0.000092 (0.000101)	.37
Baseline sputum eosinophils (%							0014 (0.01004)	.99
Within-subject variations in sp							0.016 (0.006)	.005
Within-subject variations in pr							0.020 (0.010)	.044
Within-subject variations in FE							0.012 (0.018)	.52
Within-subject variations in ICS dose†‡	−0.00011 (0.00006)	.048	0.000024 (0.000048)	.61	−0.00022 (0.00012)	.076	−0.00013 (0.00012)	.30
Within-subject variations in OCS dose†§	0.0027 (0.0134)	.84	0.011 (0.011)	.34	−0.041 (0.034)	.23	0.017 (0.034)	.61

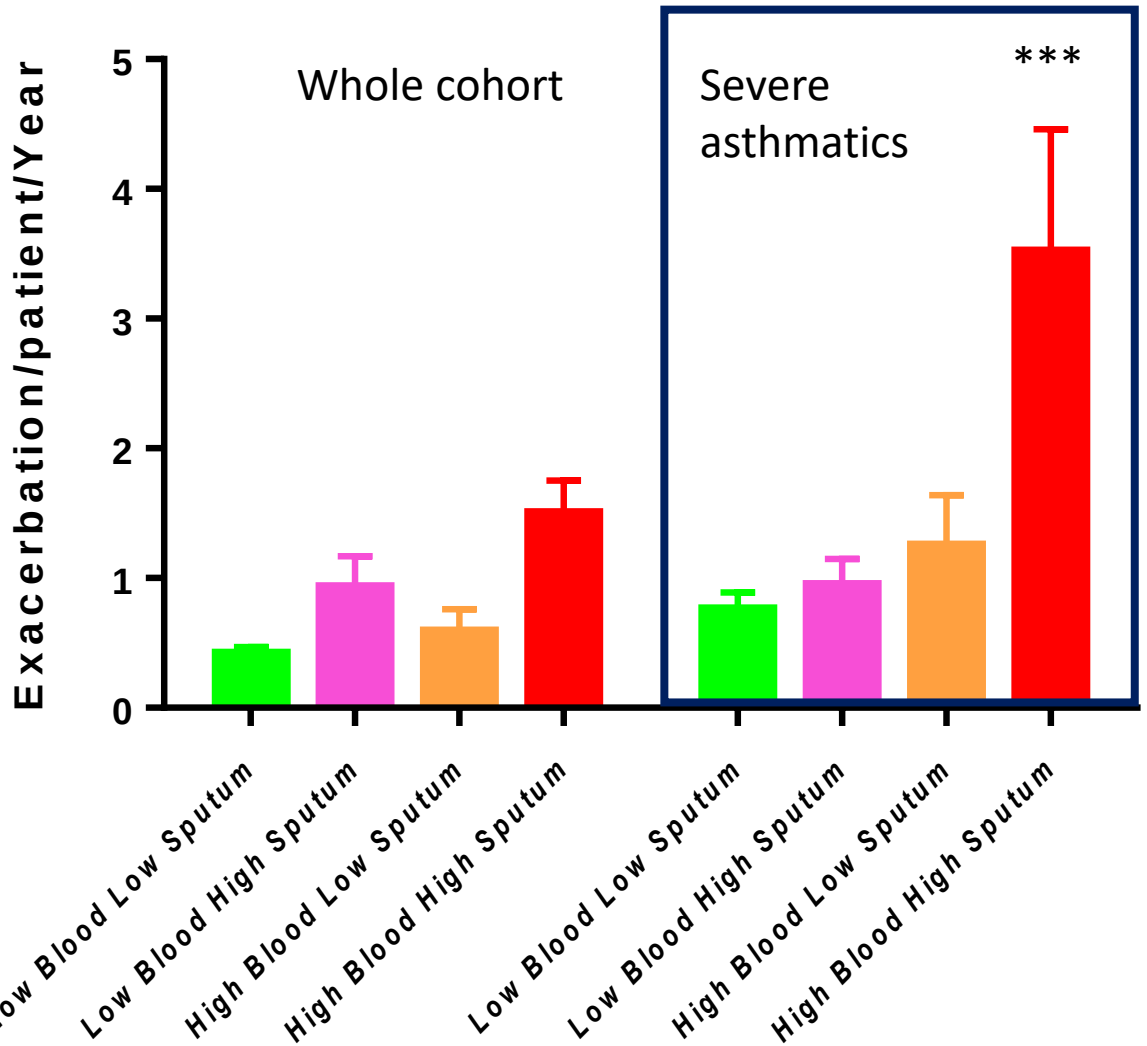
Both fluctuation in Sputum eosinophils and in FEV1 independently contribute to change in asthma control

- Asthma control was independently associated with individual fluctuat putum eosinophils over time:



Demarche S et al JACI Pract 2017

Eosinophilic inflammation and exacerbation rate
Retrospective cohort of severe asthmatics (N=144)



Schleich F et al ERJ 2014

* p< 0.05 Compared to Low Low

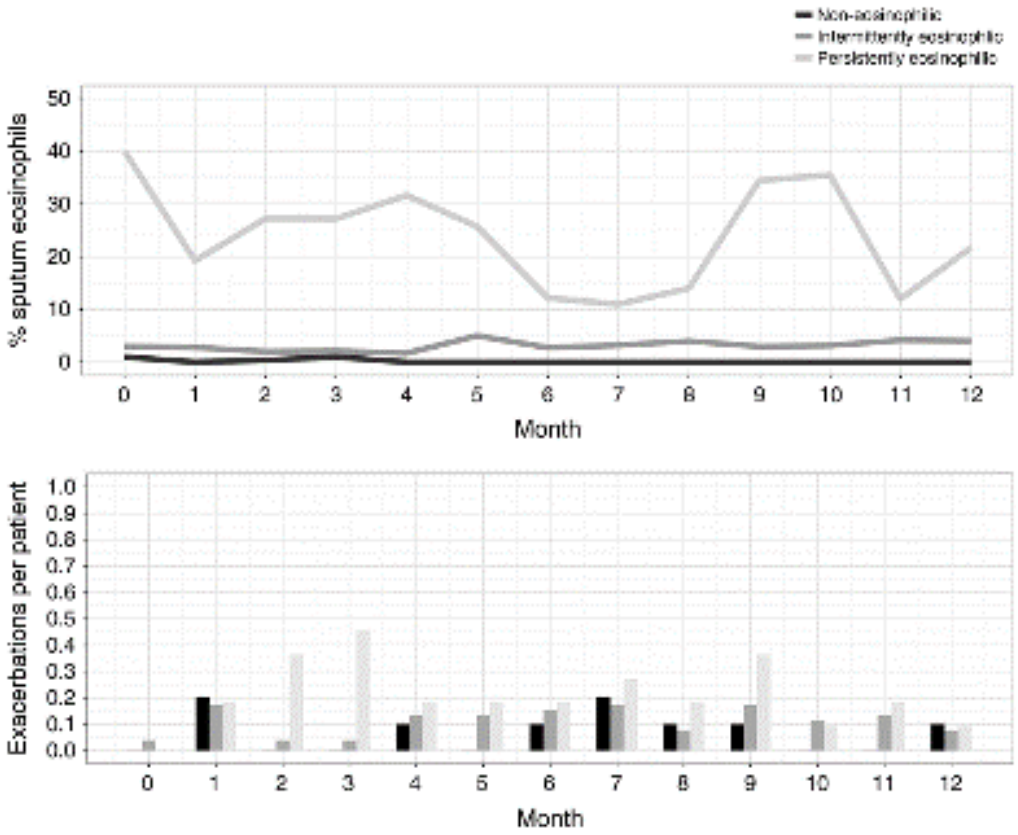
Detection of exacerbations in asthma based on electronic diary data: results from the 1-year prospective BIOAIR study

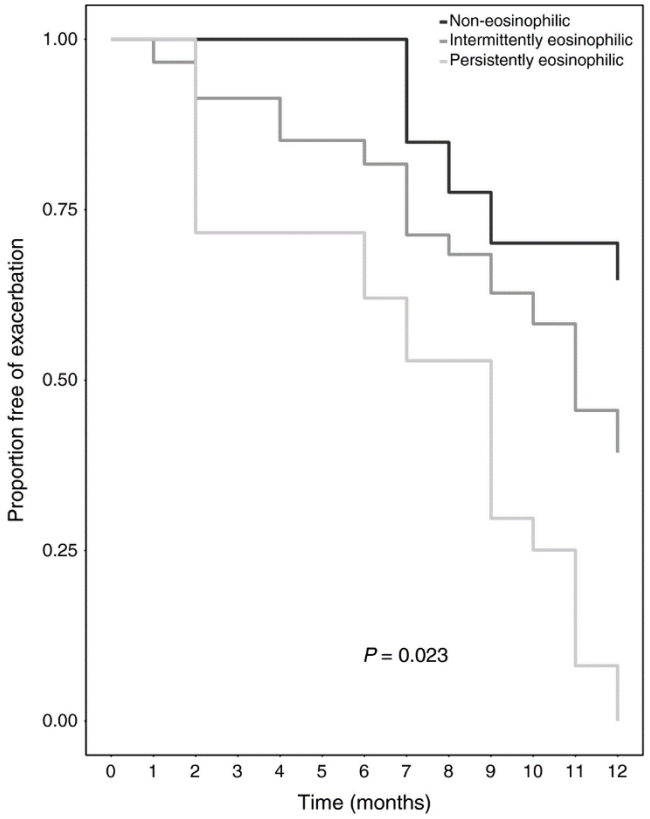
Table 4 Adjusted ORs in multivariate logistic regression models for factors associated with the development of severe exacerbations and any exacerbations in the whole asthma cohort and severe asthma group

Factor	OR	95% CI	p Value	Comments
Severe exacerbations				
Juniper ACQ >1.36 (median)	3.61	1.7 to 7.65	0.001	Adjusted for age, gender, smoking and atopy
Sputum eosinophils ≥3%	3.27	1.13 to 9.42	0.028	As above
BMI >25	2.9	1.3 to 6.5	0.01	As above
SGRQ >34.6 (median)	2.22	1.03 to 4.8	0.042	As above

Kupczyk et al Thorax 2013

Sputum eosinophils as a risk factor for exacerbation
A prospective study in severe asthma (N=73)

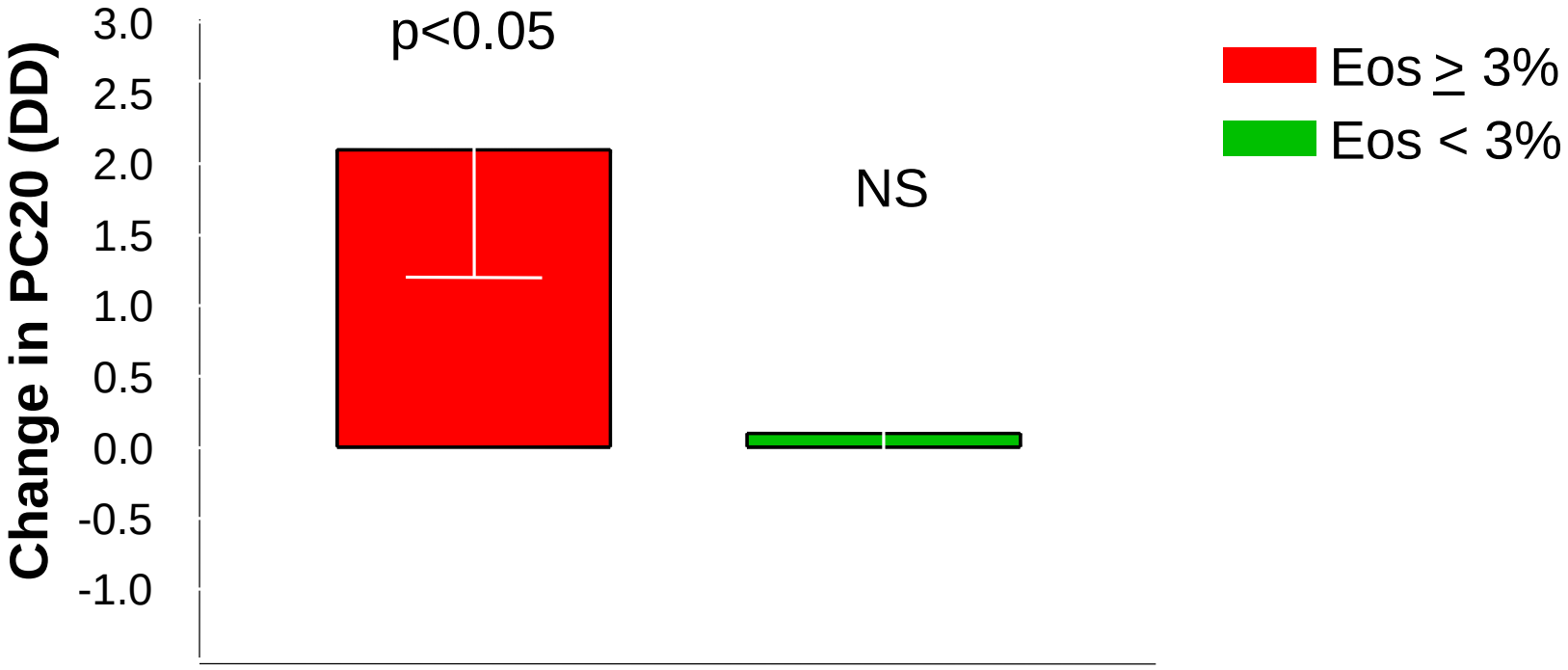




Walsh J et al Clin Exp Allergy 2016

Sputum eosinophilia as a predictive factor for response to inhaled corticoids in asthma

(inhaled budesonide 800 µg/d for 6 weeks)



Pavord I et al Lancet 1999

Non eosinophilic asthma better responds to LAMA

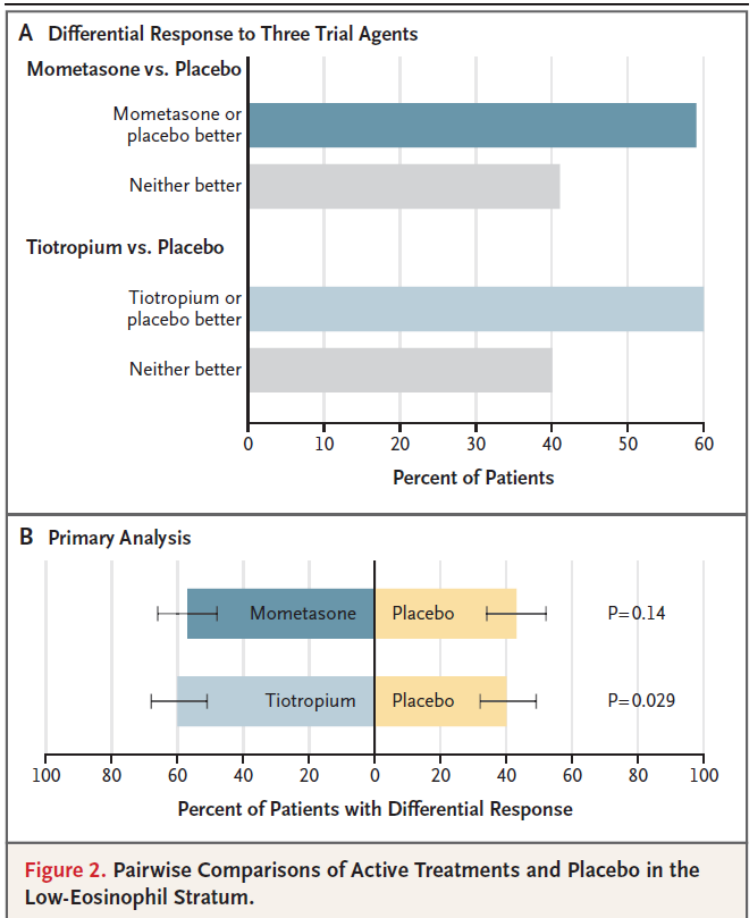
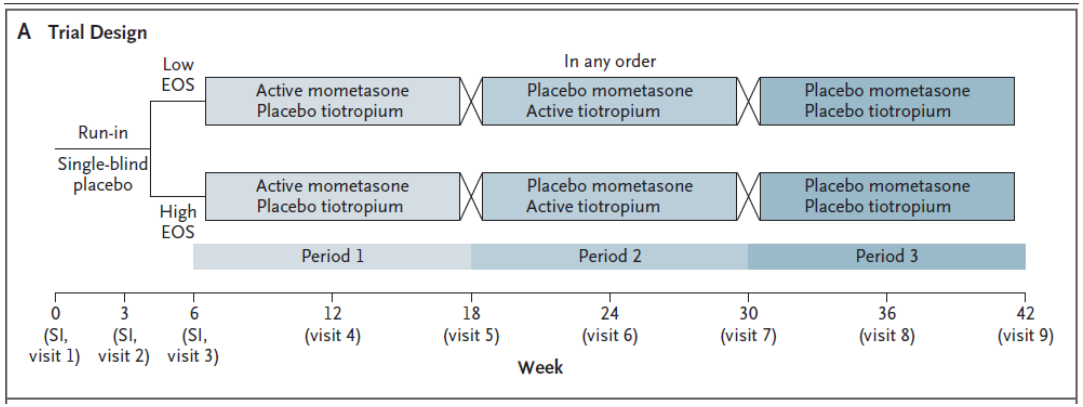
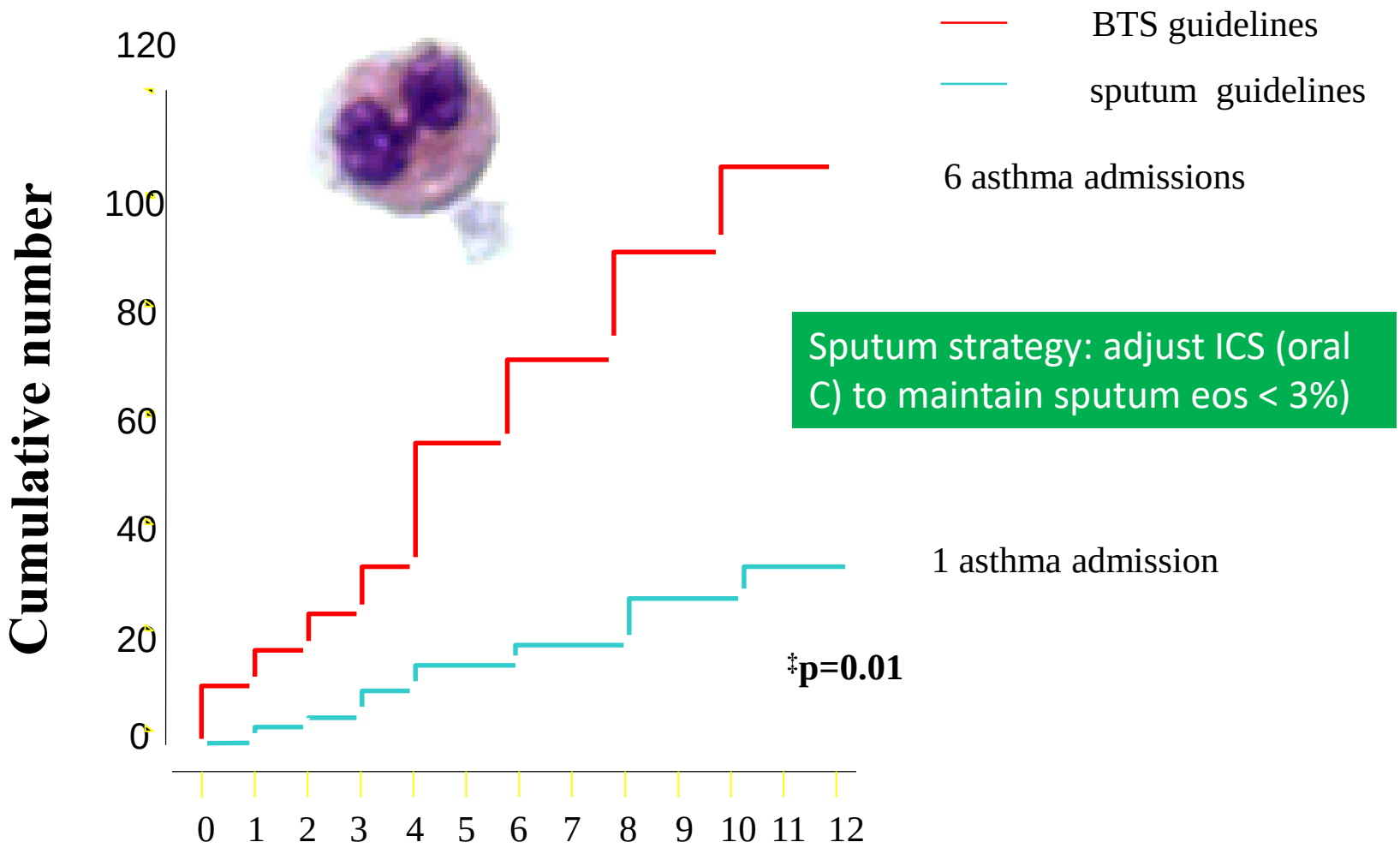


Figure 2. Pairwise Comparisons of Active Treatments and Placebo in the Low-Eosinophil Stratum.



Lazarus et al N Engl J Med 2019

Monitoring sputum eosinophils help to reduce severe exacerbation in severe asthma



Sputum strategy: adjust ICS (oral C) to maintain sputum eos < 3%)

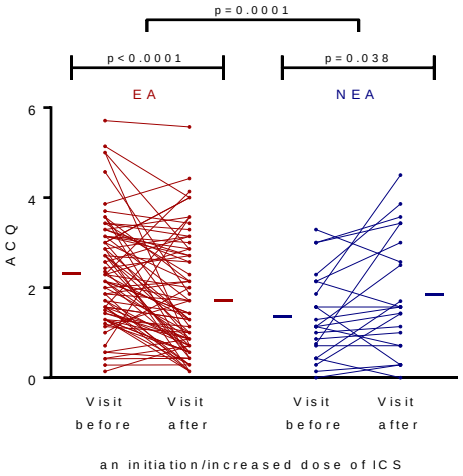
Green R et al Lancet 2002

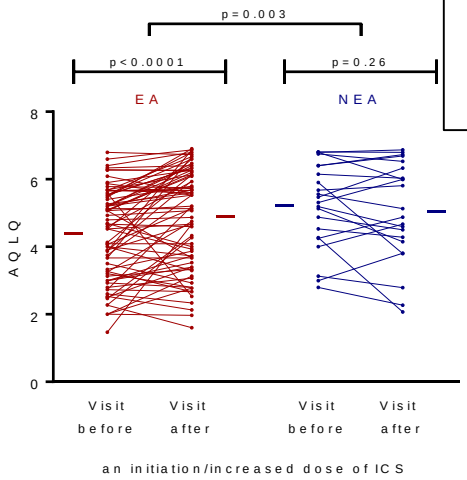
Retrospective study in real life N=224	Patients with an initiation/increaseddose of ICS between 2 visits N= 101	Patients with a cessation/decreased dose of ICS between 2 visits N=60	Patients with non ICS or stable dose of ICS between 2 visits N=63
Time between 2 visits (years)	1 (0.5-2.6)	1.5 (0.9-2.6)	2 (0.7-3.8)
Women, N (%)	56 (55)	33 (55)	41 (65)
Age (years)	53 (40-63)	51 (37-62)	53 (44-66)
BMI (Kg/m2)	26±5.1	26.4±4.7	26.8±49
Atopy, N (%)	52 (51)	35 (58)	32 (51)
Age of asthma onset (years)	41 (16-57)	31 (8-53)	46 (27-55)
Smoking status NS CS Ex S	 53 (52) 11 (11) 37 (37)	 31 (52) 11 (18 18 (30)	 32 (51) 15 (24) 16 (25)
Variation in ICS dose	800 (400-1200)	900 (500-1200)	0

Sputum eosinophilia as a predictive factor for response to inhaled corticoids in asthma in real life

Median increase in beclomethasone 800µg/d from 400 to 1000µg/d

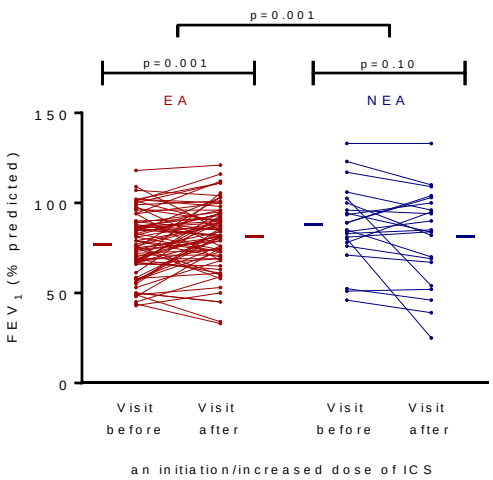
EA: ≥3%
n=79

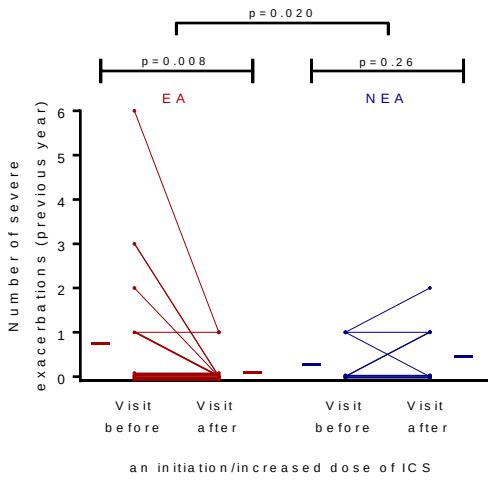




Mean

NEA: < 3%
n=22



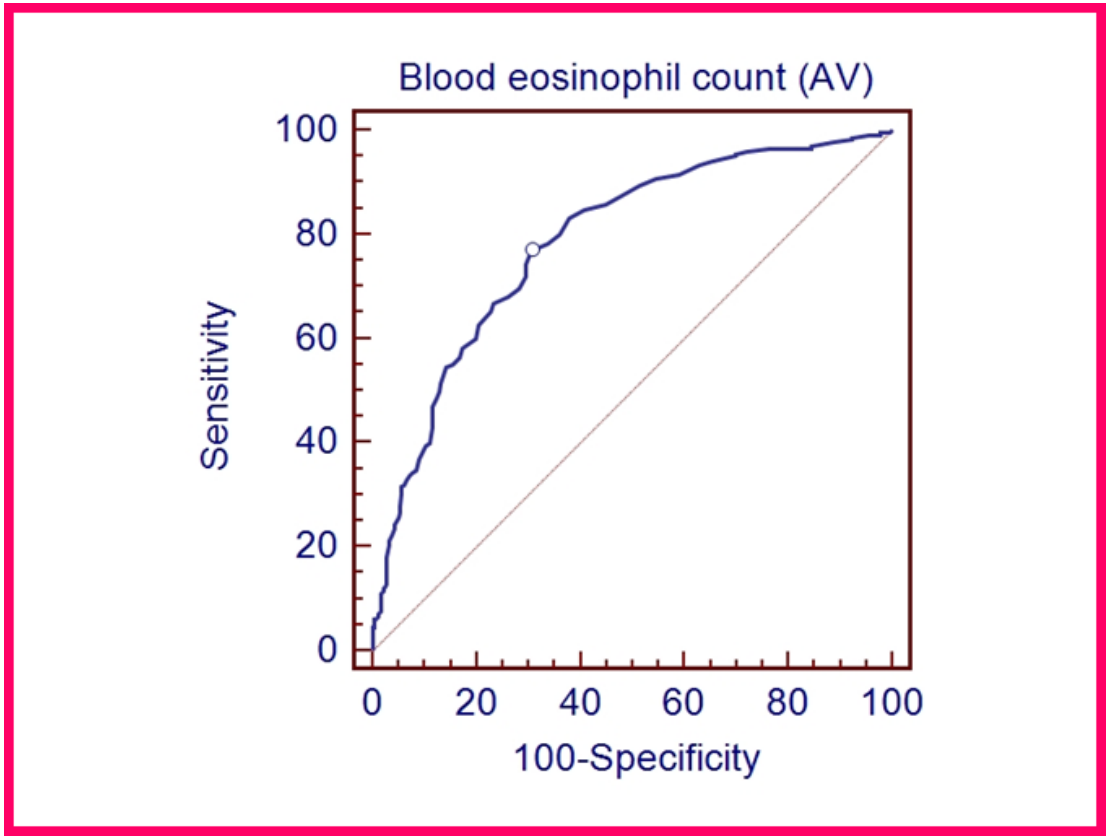


Demarche S et al BMJ open 2017

Can « proxy »reflect sputum eosinophils ?

- Blood Eosinophils
- FeNO
- IgE

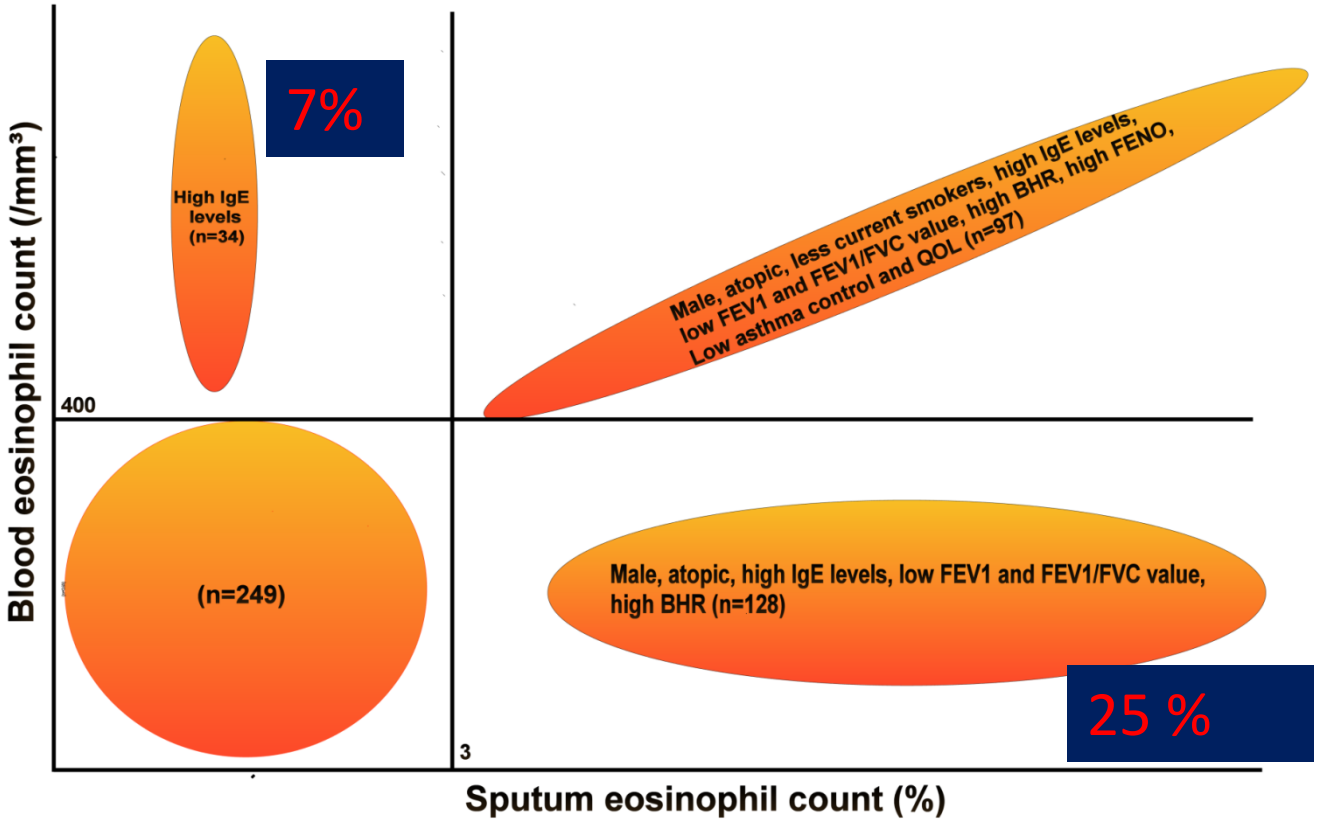
Blood eosinophils to identify sputum eosinophils ≥ 3%



Cut off: **≥ 220/mm³**
Sensitivity: 77%
Specificity: 70%
AUC: 0.79,
p<0.0001

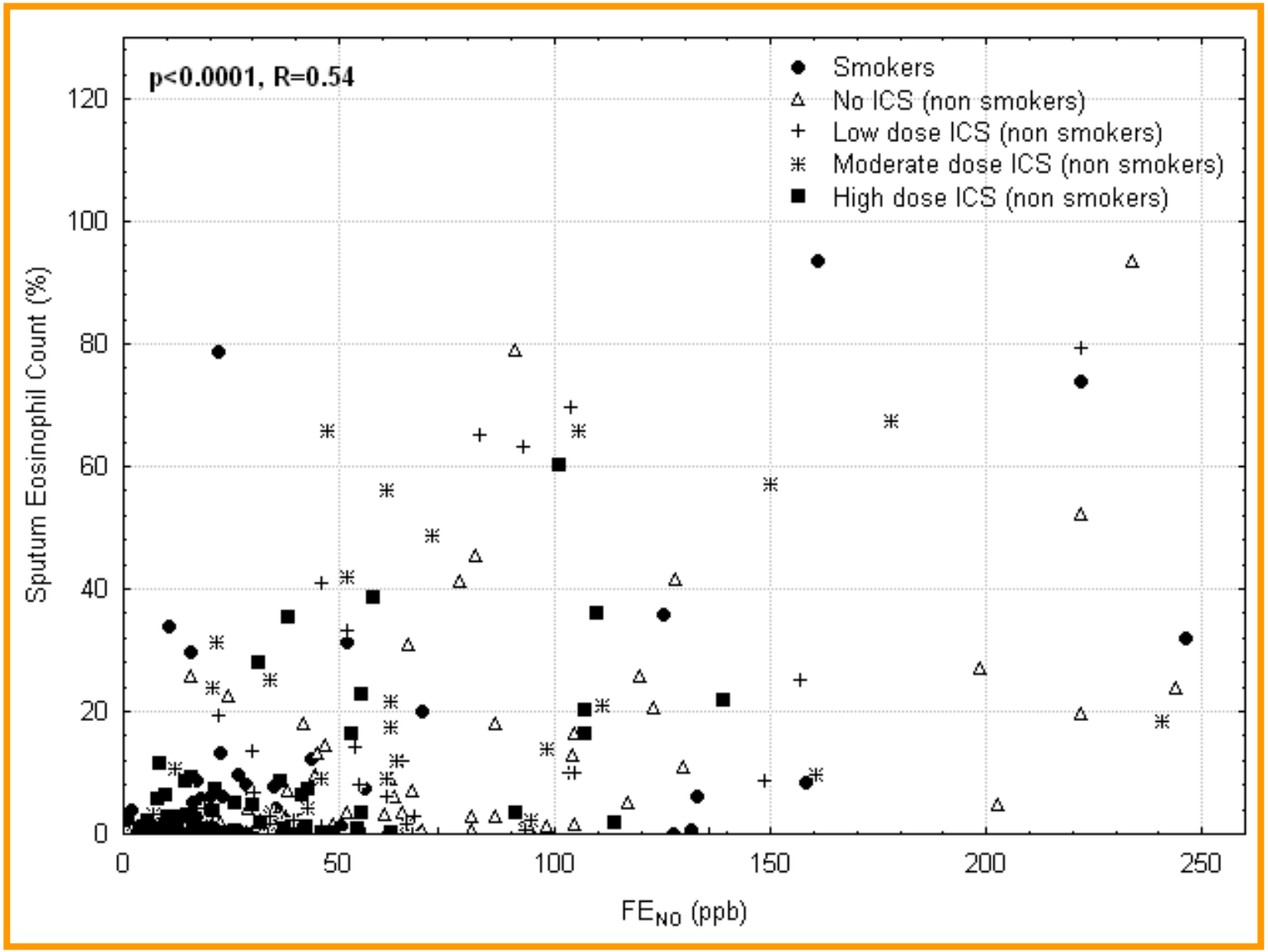
Schleich F et al BMC Pulm Med 2013

Discordance between blood and sputum eosinophils



Schleich F et al ERJ 2014

Relationship between exhaled NO and sputum eosinophil count in asthma



F Schleich et al Thorax 2010

FENO: surrogate marker for sputum eosinophilia?

Smoking	Atopy	High dose of ICS	FENO cut-off (ppb)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
No	No	No	38	74	66	65	75
No	No	Yes	24	59	78	58	79
No	Yes	No	**58**	88	48	74	70
No	Yes	Yes	35	71	70	64	76
Yes	No	No	23	58	78	58	78
Yes	No	Yes	**15**	37	94	52	89
Yes	Yes	No	33	68	70	62	76
Yes	Yes	Yes	20	54	85	58	83

Schleich et al., Thorax 2010

Biomarkers	Number of studies	AUC included	Number of patients	AUC
FeNO	17	19	3216	0.75
Blood Eos	14	14	2405	0.78
Serum IgE	7	7	942	0.65
Serum Periostin	2	3	204	0.65
Serum ECP	2	2	174	0.72
EBC Ph	2	2	96	0.74
Exhaled VOCS	1	1	18	0.98
EBC	1	1	53	0.69
Nasal lavage Eosinophils	1	1	130	0.88

Korevaar D et al Lancet Respir Med 2015

What is the best tool to predict sputum Eos ≥ 3% ?

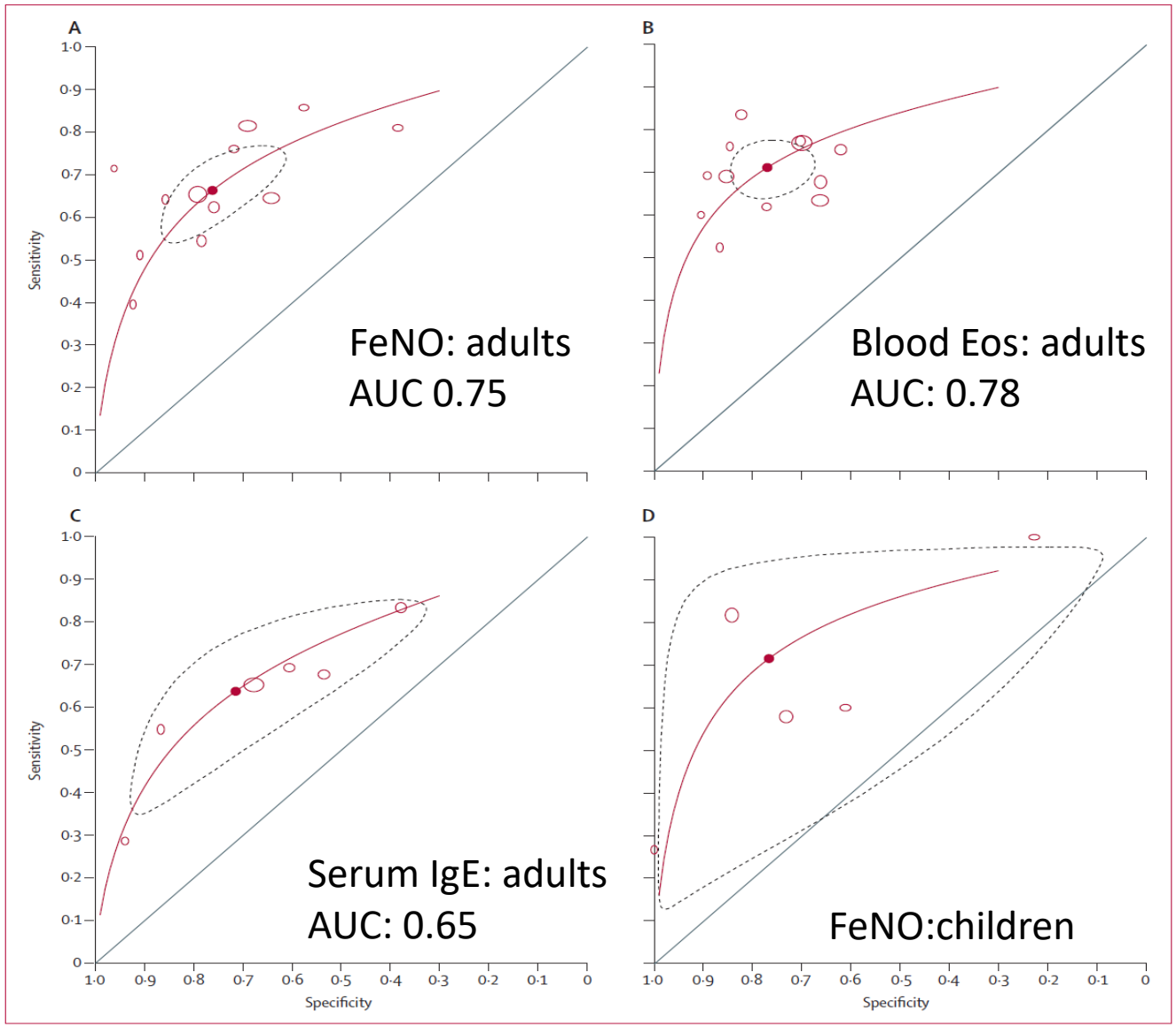
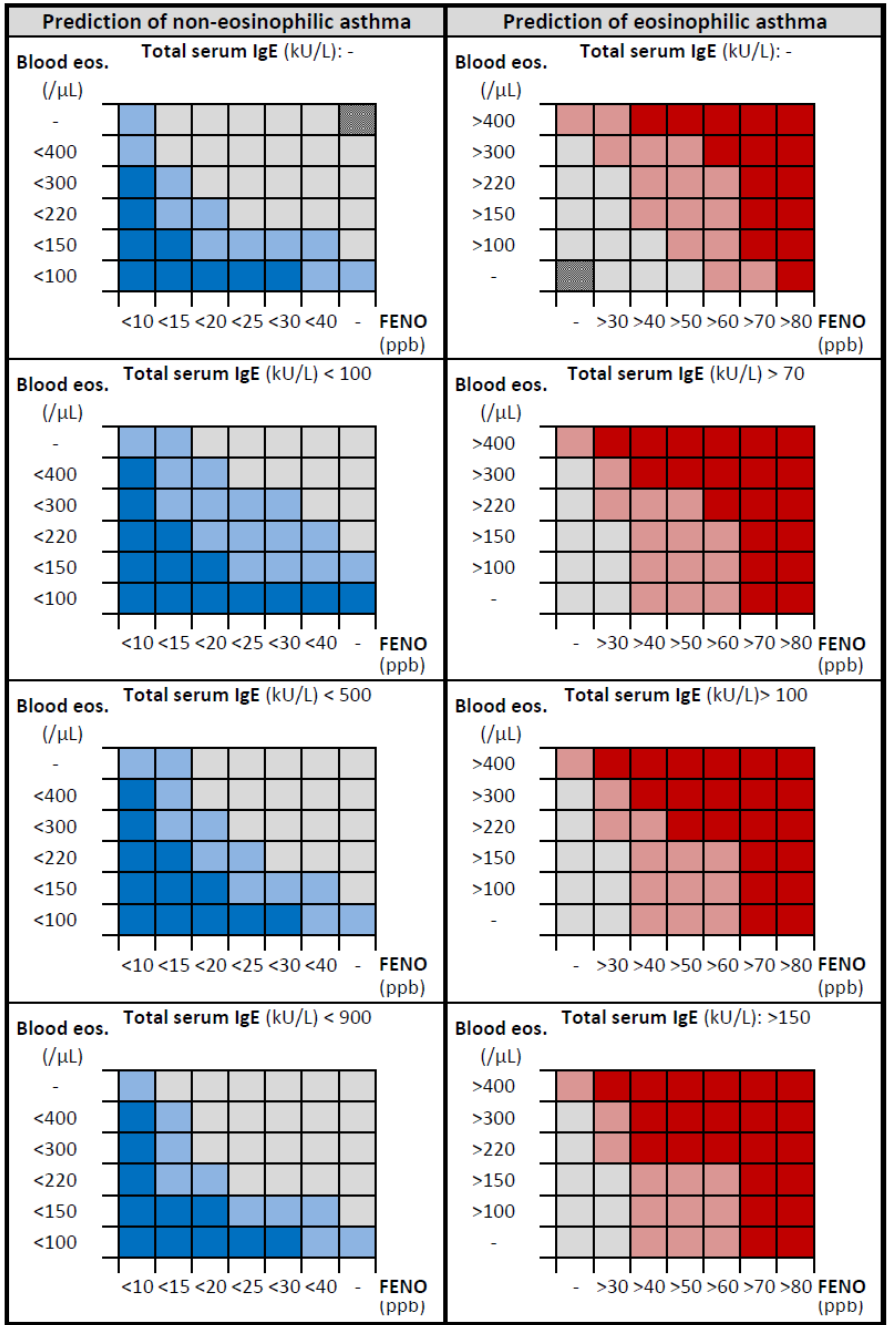


Figure 4: Summary receiver operating characteristics curve for detecting sputum eosinophils of 3% or more in adults, and 2·5% or more or 3% or more in children

(A) FeNO (ppb) in adults, (B) blood eosinophils (per µL) in adults, (C) IgE (IU/mL) in adults, and (D) FeNO (ppb) in children. Each open circle is the result from a single study. Closed circles are summary estimates. Dotted ellipses are 95% confidence regions around summary estimates. ppb=parts per billion.

Korevaar D et al Lancet Respir Med 2015



Combination of biomarkers to indentify sputum eosinophils ≥3%

A table to help in practice

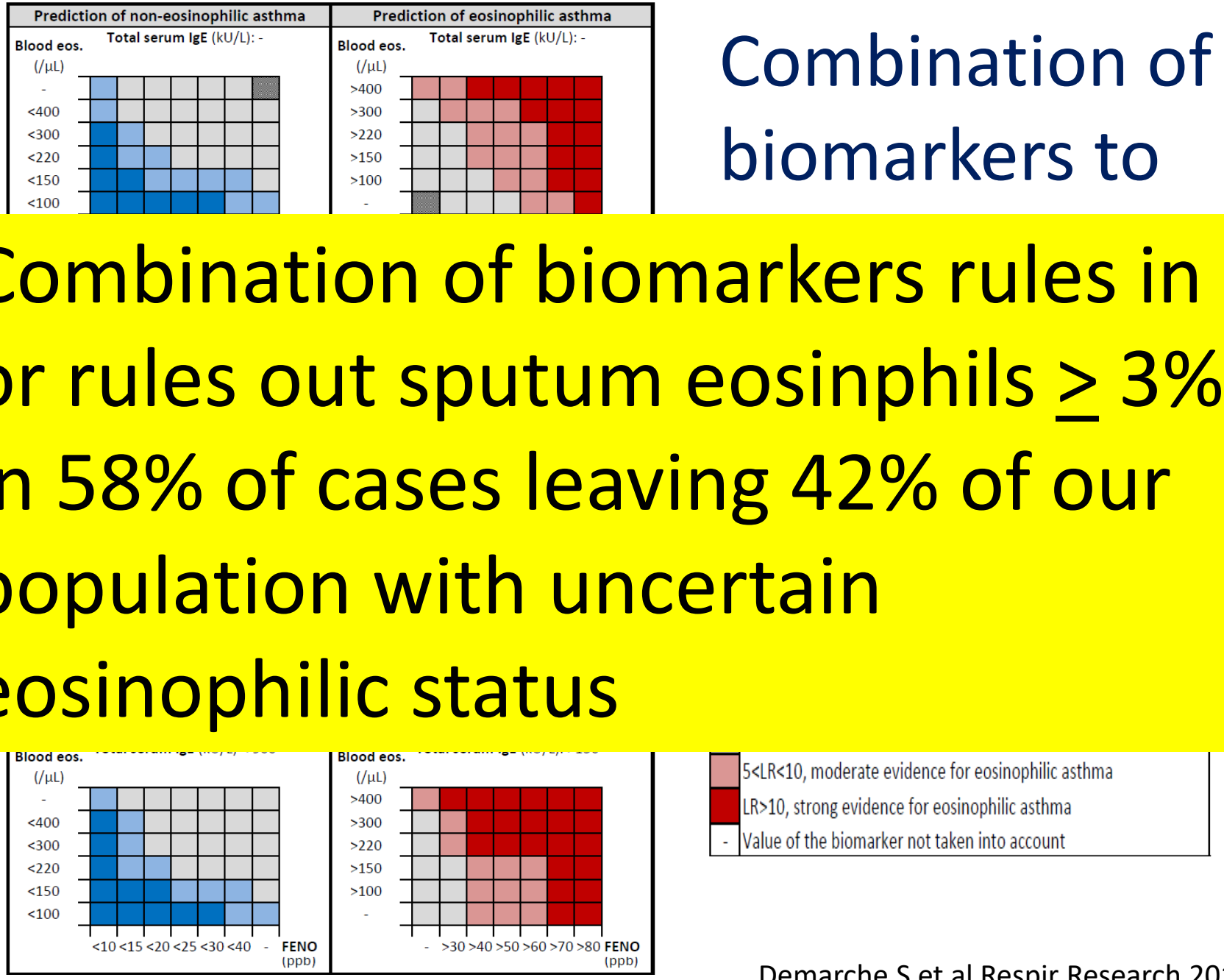
N=869

	LR<0.1, strong evidence for non-eosinophilic asthma
	0.1<LR<0.2, moderate evidence for non-eosinophilic asthma
	0.2<LR<5
	5<LR<10, moderate evidence for eosinophilic asthma
	LR>10, strong evidence for eosinophilic asthma
-	Value of the biomarker not taken into account

Demarche S et al Respir Research 2017

Combination of biomarkers to

Combination of biomarkers rules in or rules out sputum eosinphils ≥ 3% in 58% of cases leaving 42% of our population with uncertain eosinophilic status



Demarche S et al Respir Research 2017

Can blood be more relevant than sputum/FeNO to guide treatment in severe asthma?

Impact of blood eosinophil counts on mepolizumab effect on exacerbation

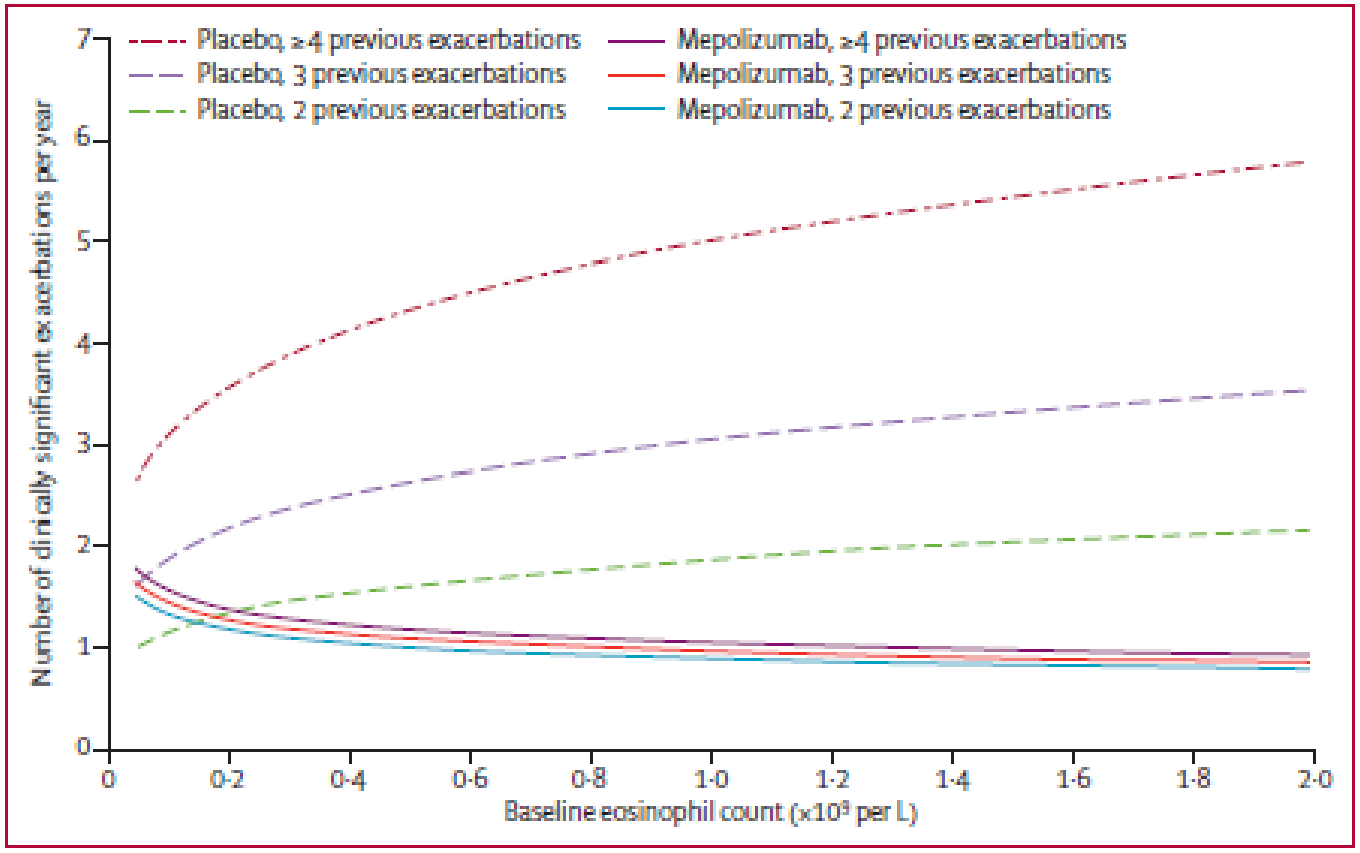
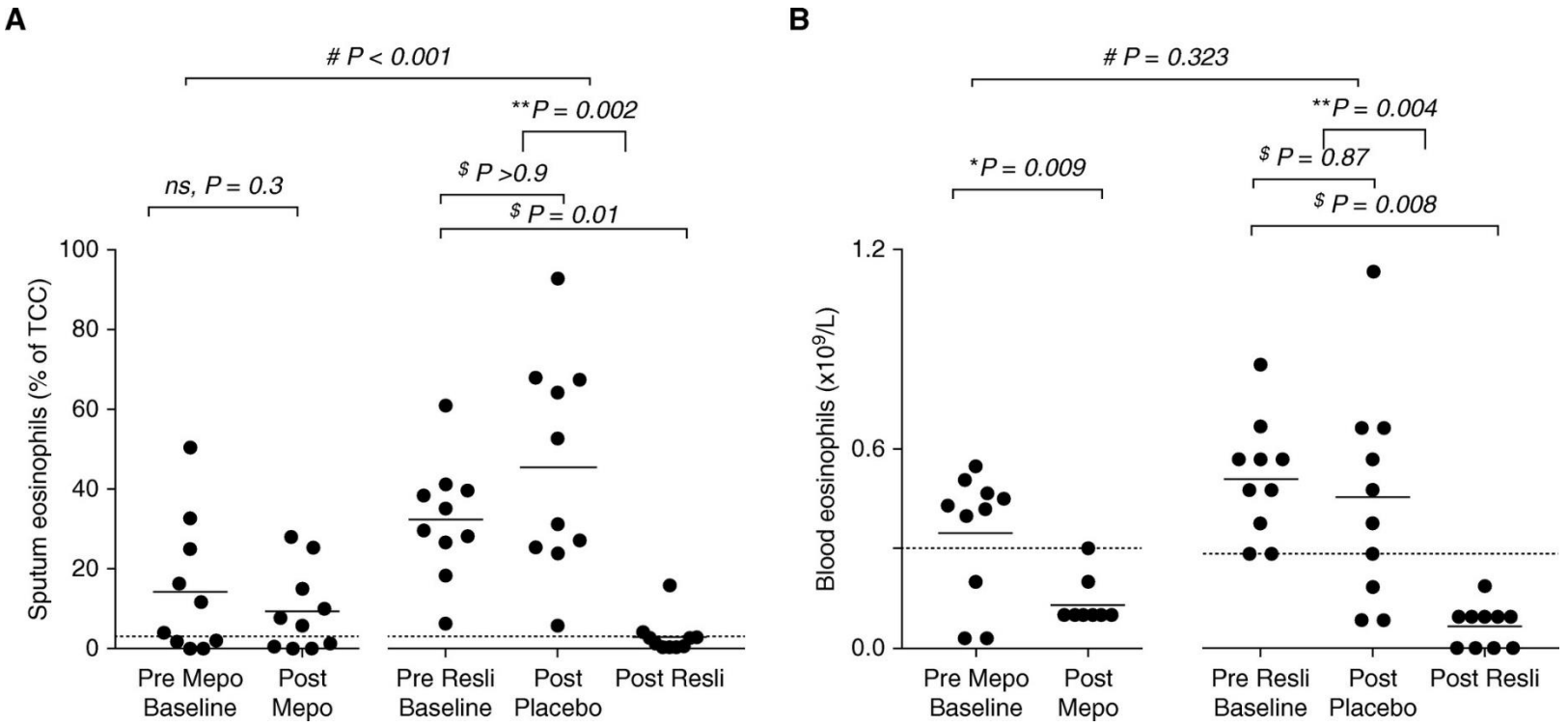


Figure 4: **Predictive modelling of rate of exacerbations**
Done on the basis of blood eosinophil count at baseline, history of exacerbations, and treatment with mepolizumab or placebo.

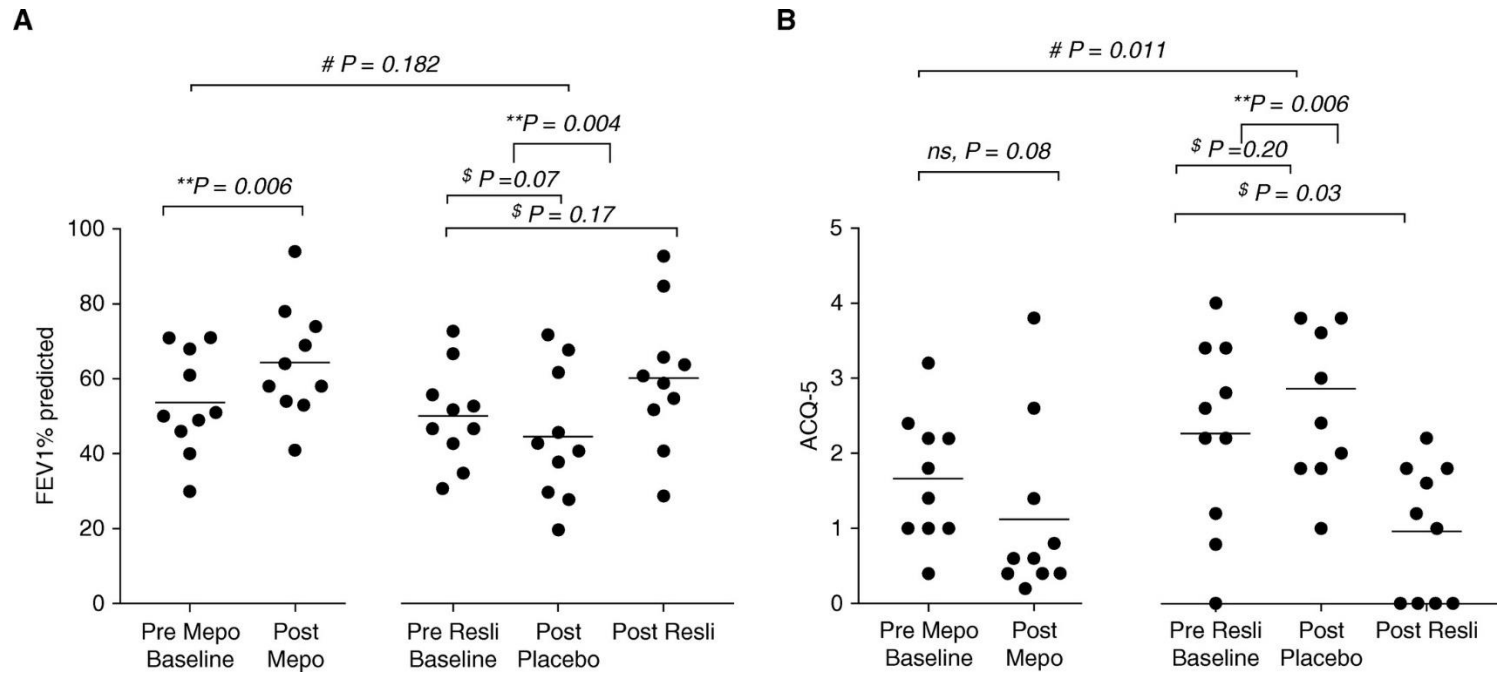
Pavord I et al Lancet 2012

Reslizumab 3mg/Kg is more potent than mepolizumab 100 mg SC for lowering sputum eosinophils



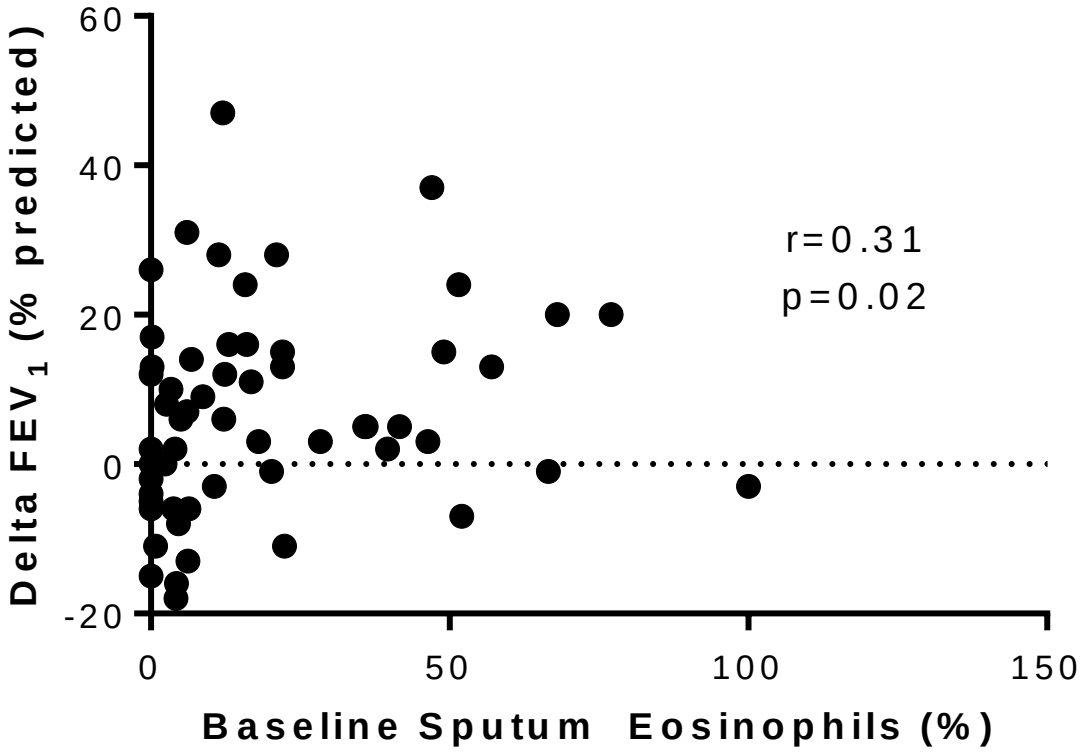
Mukherjee M et al Am J Respir Crit Care Med 2018

Sputum eosinophils may be more important than blood to improve lung function and asthma control



Mukherjee M et al Am J Respir Crit Care Med 2018

High sputum eosinophils predicts improvement in FEV1 after mepolizumab in a real life setting



CHU Liege Asthma Clinic 2019

Impact of serum IgE on omalizumab effect on exacerbation

Table 3 Efficacy outcomes in subgroups of patients divided in quartiles according to baseline IgE in the pooled population.

Outcome measure	Baseline IgE subgroup							
	0–75 IU/mL		76–147 IU/mL		148–273 IU/mL		⩾274 IU/mL	
	Omal. ($n = 602$)	Control ($n = 453$)	Omal. ($n = 659$)	Control ($n = 421$)	Omal. ($n = 634$)	Control ($n = 444$)	Omal. ($n = 616$)	Control ($n = 465$)
Annualized asthma exacerbation rate	1.28	1.48	0.85	1.47	0.80	1.47	0.76	1.43
Δ*	Δ–13.8%		Δ–41.9%		Δ–45.4%		Δ–46.5%	
P-value	0.227		< 0.001		< 0.001		< 0.001	
Annualized severe exacerbation rate	0.09	0.22	0.07	0.11	0.07	0.20	0.05	0.17
Δ*	Δ–59.7%		Δ–38.0%		Δ–66.4%		Δ–68.8%	
P-value	< 0.05		0.218		< 0.001		< 0.001	
Annualized total emergency visit rate	0.44	0.64	0.32	0.60	0.35	0.89	0.33	0.55
Δ*	Δ–31.0%		Δ–46.3%		Δ–60.9%		Δ–40.8%	
P-value	0.141		< 0.05		< 0.01		< 0.05	
FEV_1 net benefit†, %	4.1	–0.5	11.7	3.4	7.9	0.5	22.3	2.9
P-value	0.289		0.057		0.099		< 0.001	
AQLQ improvement ⩾ 0.5 points, %	58.7	54.2	67.5	54.0	68.7	50.0	68.9	52.5
P-value	0.298		< 0.001		< 0.001		< 0.001	
Physician's overall assessment‡, %	49.3	40.2	59.3	42.9	66.6	36.1	67.1	36.2
P-value	< 0.05		< 0.001		< 0.001		< 0.001	

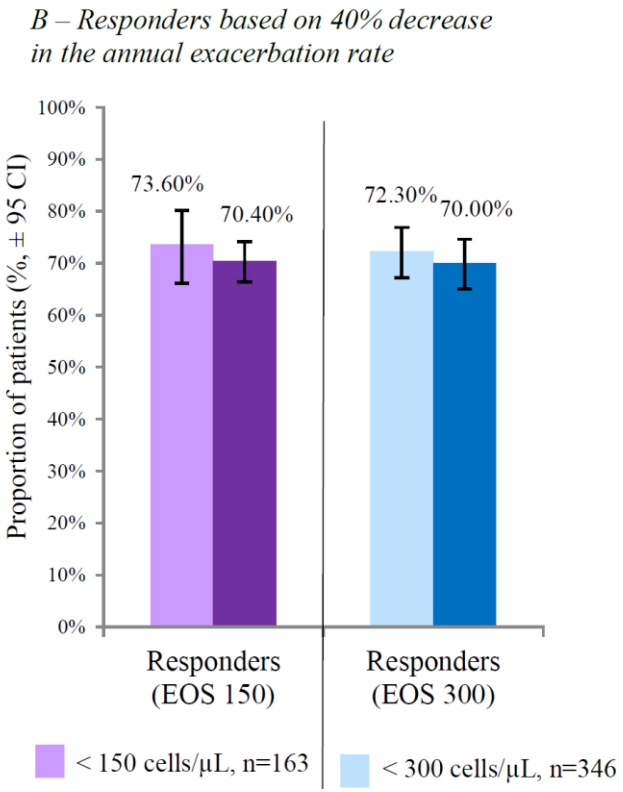
*Δ denotes the reduction in rate for omalizumab vs. placebo.

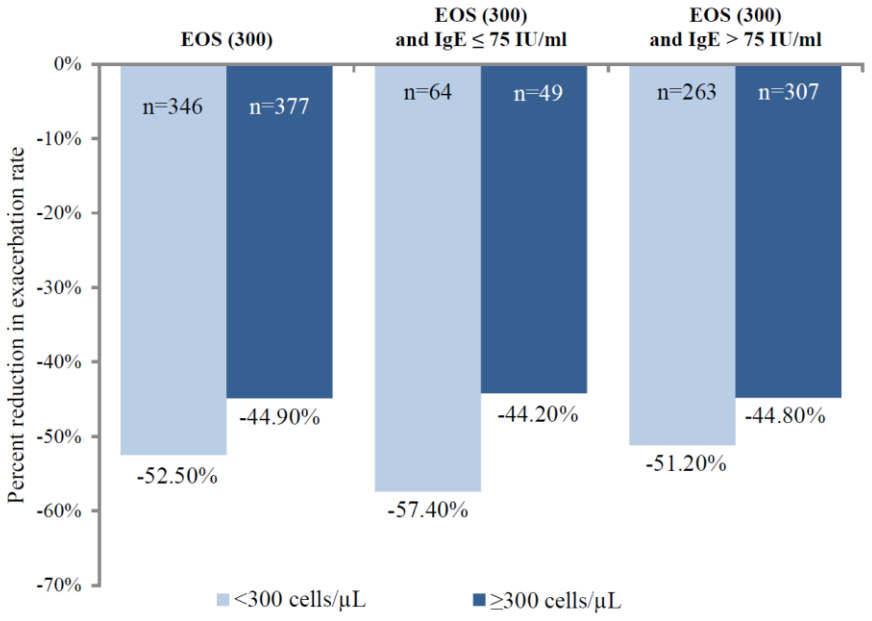
†Patients with improvement in $FEV_1 \geqslant 200$ mL minus those with worsening ⩾200 mL, statistical testing was performed using proportions of patients with an improvement, a worsening, or no meaningful change.

‡Complete control or marked improvement, *P*-value for the overall distribution of physician's overall assessment. Not all endpoints were assessed in each study.

Bousquet J et al Respir Med 2007

Impact of blood eosinophils and serum IgE on response to omalizumab in real life
The Stellair Study (N=723)





Humbert M et al ERJ 2018

LE CONCEPT D'EXACERBATION DANS L'ASTHME ET LA BPCO :

ENQUÊTE SUR LES CRITÈRES DE PRESCRIPTION DE CORTICOÏDES SYSTÉMIQUES ET D'ANTIBIOTIQUES CHEZ LES GÉNÉRALISTES ET LES PNEUMOLOGUES

LOUIS R (1), ZIANT S (2), DUCHESNES C (3), GIET D (4), SCHLEICH F (5), CORHAY JL(6)

RÉSUMÉ : Les exacerbations dans l'asthme et la bron-

généralistes ou pneumologues.

MOTS-CLÉS : ***Asthme - BPCO - Exacerbations - Corticoïdes systémiques - Antibiotiques***

There is wide variation in the clinical parameters which trigger the prescription of OCS in asthmatics among chest physicians and among GP alike

EXACERBATIONS IN ASTHMA AND CHRONIC OBSTRUCTIVE

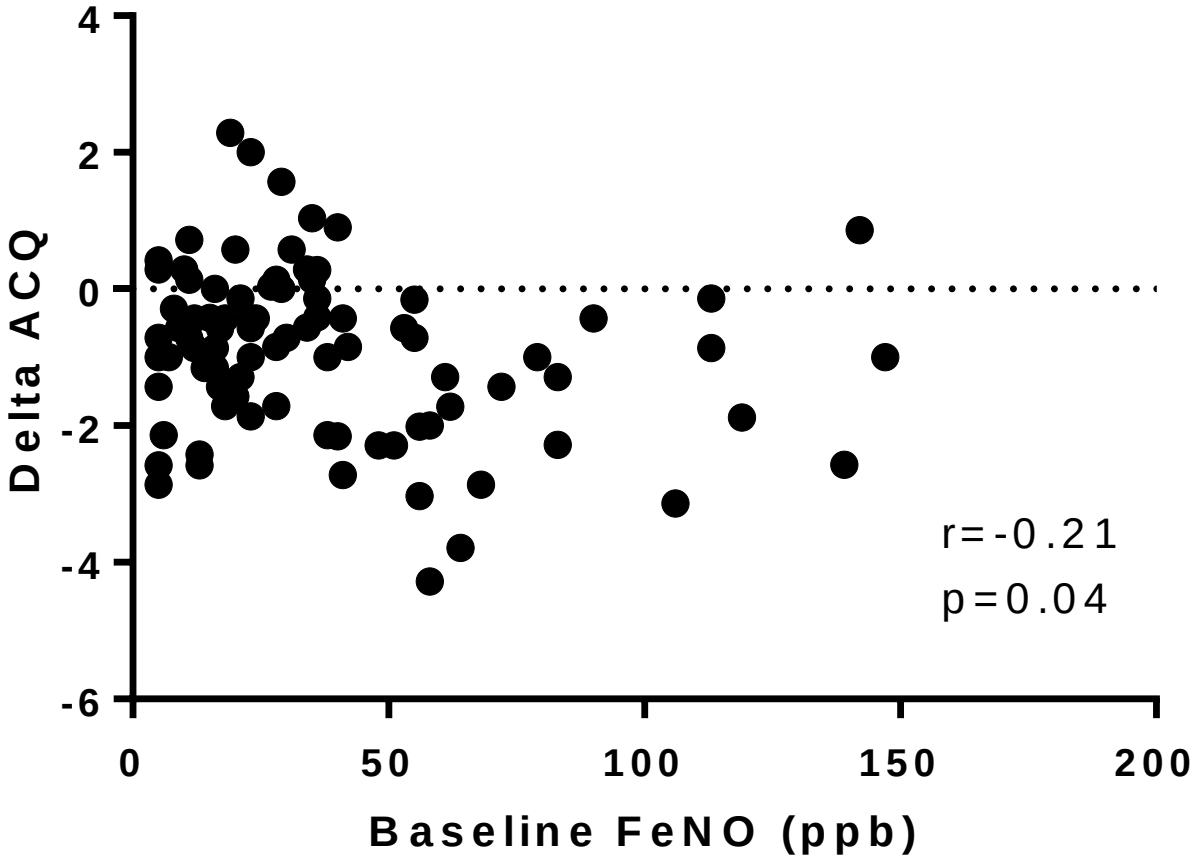
pancy between GP and chest physicians regarding systemic corticoids but also, more surprisingly, within the same professional group. In contrast, criteria to prescribe antibiotics are more coherent between and within the groups.

KEYWORDS : ***Asthma - COPD - Exacerbations - Systemic corticoids - Antibiotics***

INTRODUCTION

Louis R et al Rev Med Liege 2018

High FeNO predicts improvement in asthma control at 1 year after omalizumab in a real life setting



CHU Liege Asthma Clinic 2019

The future of biomarkers ?

VOCS analysis in vivo

Teflon bag

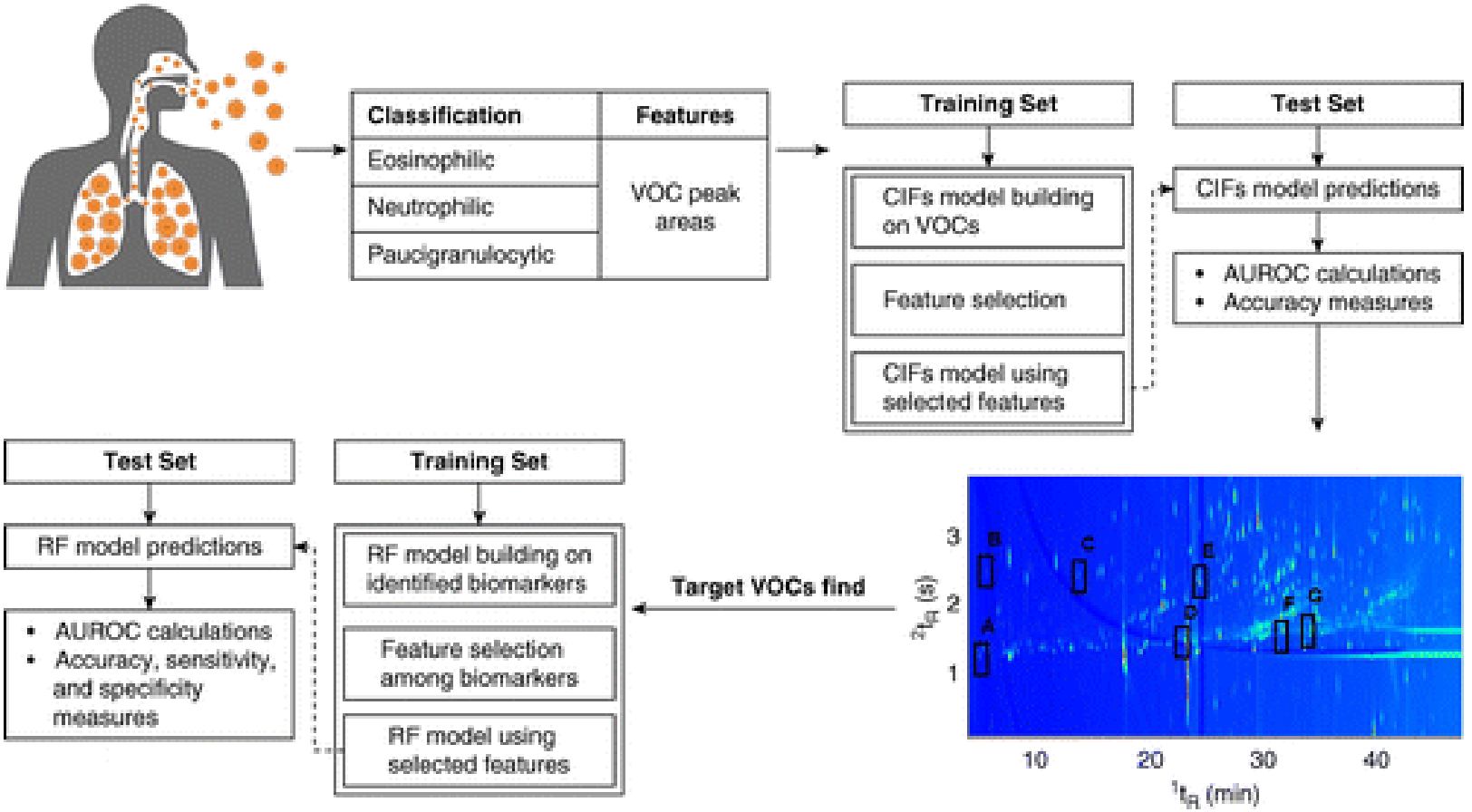
Sampling

Transport sample to desorption tubes

Desorption tubes

GC-MS analysis of samples

Data analysis



Schleich F et al AJRCCM 2019

Table 1. Demographic and Functional Characteristics of Patients with Asthma Recruited for the VOC Study

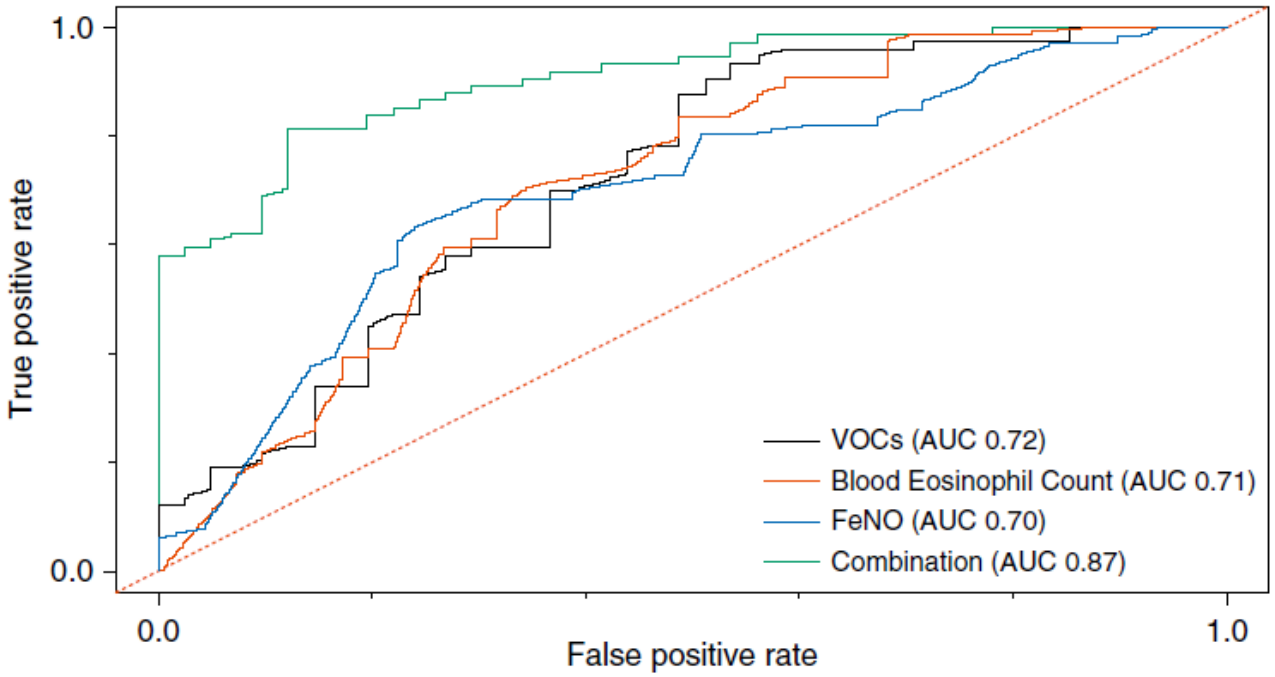
Characteristics	Discovery Cohort	Validation Cohort	*P* Values
N	276	245	
Age, yr	50 ± 15	54 ± 15	0.02
Sex, F, %	59	53	0.19
Height, cm	168 ± 10	168 ± 9	0.35
Weight, kg	73 ± 16	77 ± 16	0.003
Smokers, %	18.5	15	0.20
Exsmokers, %	36	34	0.86
Nonsmokers, %	45.5	50	0.15
Age of onset, %			
<12 yr	22	20	0.26
12–40 yr	36	35	0.30
⩾40 yr	42	45	0.03
Atopy, %	60	55	0.50
ICS therapy, yes, %			
Steroid naive	32	41	0.01
Low-dose ICS	15	11	0.18
Moderate-dose ICS	26	17	0.01
High-dose ICS	27	31	0.90
FEV_1, % predicted	84 (30–128)	88 (15–148)	0.1
FEV_1/FVC, %	70 ± 14	77 ± 14	6×10^{-4}
Blood eosinophil count, mm^{-3}	197 (0–1,133)	192 (0–1,547)	0.37
F_{ENO}	26 (6–340)	24 (5–191)	0.08
Sputum eosinophils, %	2.9 (0–91)	2 (0–67)	0.07
Sputum neutrophils, %	50 (3–100)	58 (1–98)	0.0001

Definition of abbreviations: F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; VOC = volatile organic compound.

Low dose of ICS, <200 μg beclomethasone dipropionate equivalent. Moderate dose of ICS, >200 to 400 beclomethasone dipropionate equivalent. High dose of ICS, >400 μg beclomethasone dipropionate equivalent (Global Initiative for Asthma guidelines) (17). Parametric data are shown as mean ± SD, and nonparametric data are shown as median (range).

Schleich F et al AJRCCM 2019

VOCS measured by GCMS to identify eosinophilic asthma (n=250)

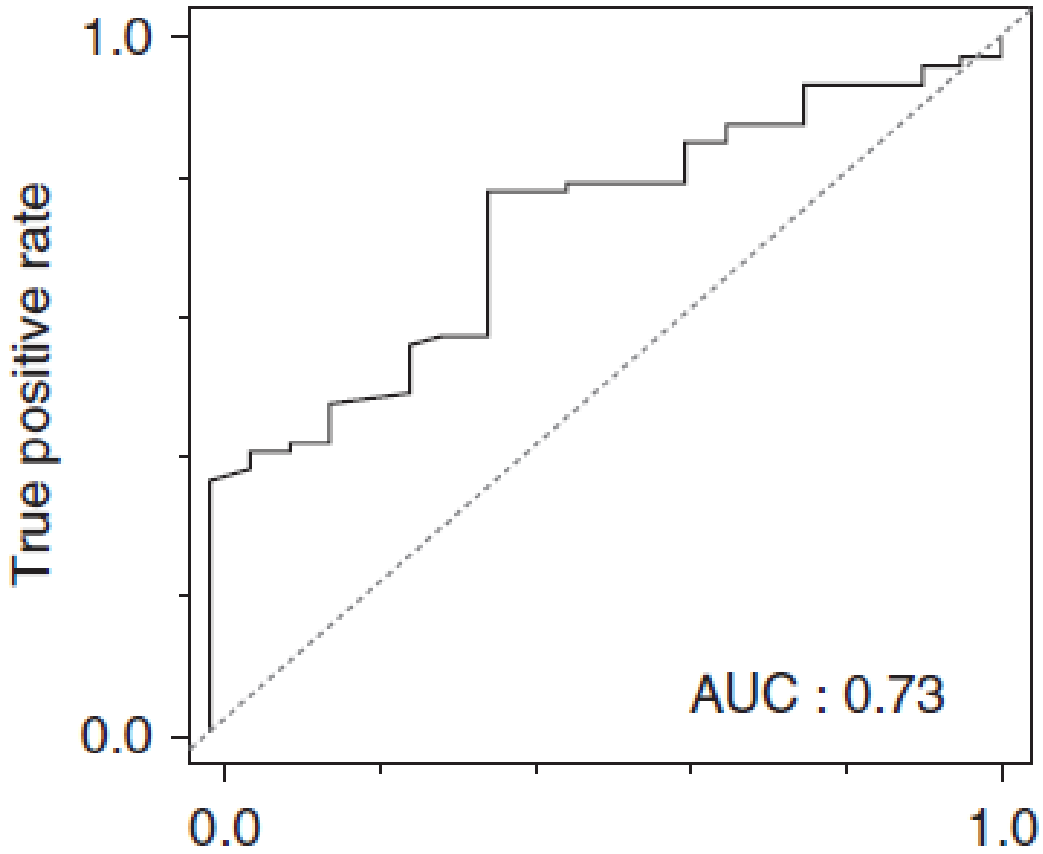


Hexane
2-Hexanone

Percentage Eosinophils ≥ 3%

Schleich F et al AJRCCM 2019

VOCS measured by GCMS to identify neutrophilic asthma (n=250)



Nonanal
Hexane
1-Propanol

Schleich F et al AJRCCM 2019

Take home messages

- Sputum eosinophils is a reliable biomarker predicting the response to ICS that can only be approached in 60% by combining “proxy”
- The technique of induced sputum should be implemented in any severe asthma clinic
- FeNO is a user friendly biomarker which may help in diagnosing and predicting ICS responsiveness in mild to moderate asthma but less suitable to manage severe asthma
- Blood is not necessarily the best compartment to choose biomarkers to predict response to biologics in asthma
- There is potential in measuring VOCs in exhaled air to phenotypes and monitor asthma

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CHU Liege Asthma Clinic

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Is FeNO by itself a reliable biomarker?

Stabilility of FeNO over time (ADEPT study)

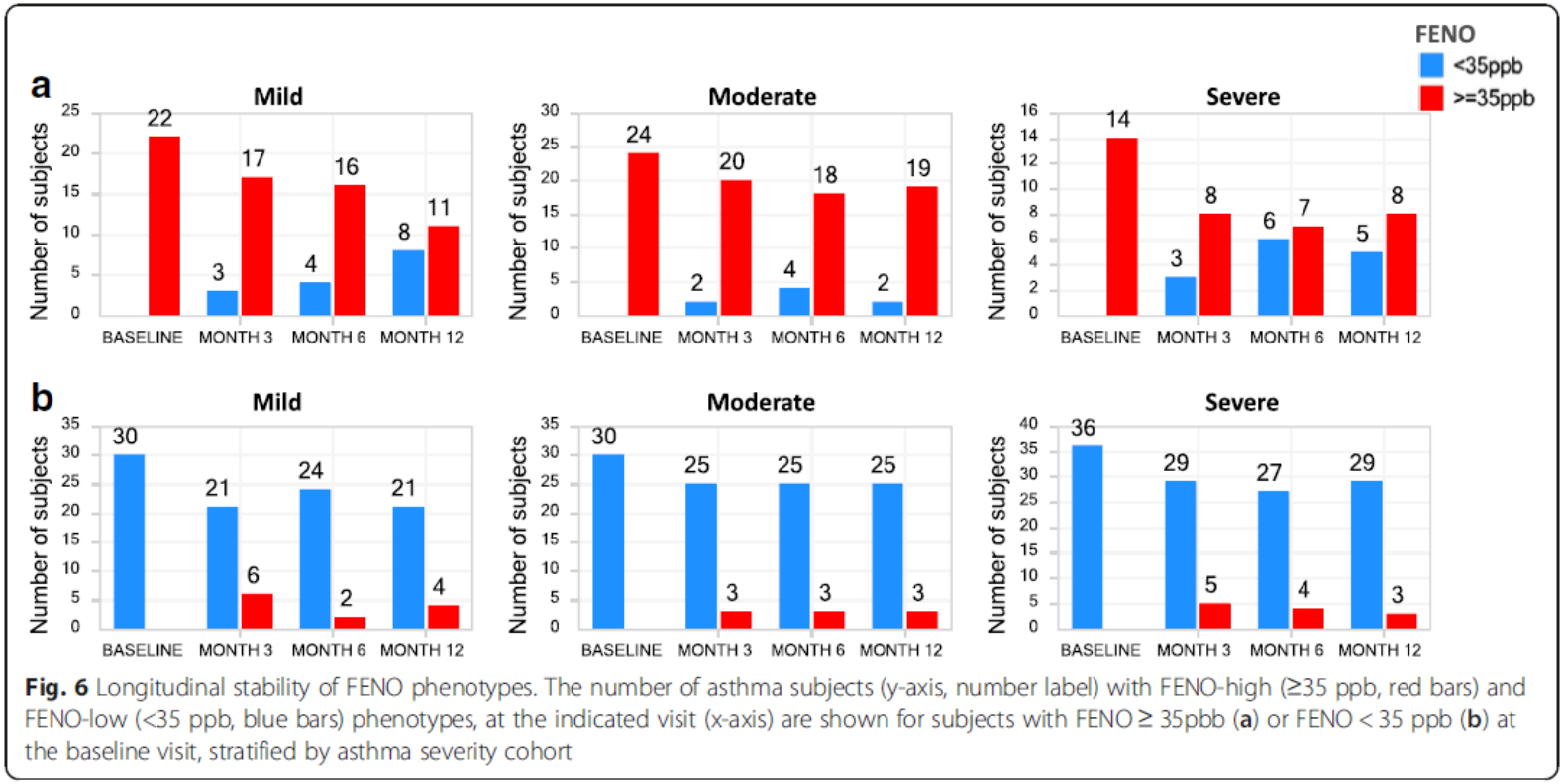


Fig. 6 Longitudinal stability of FENO phenotypes. The number of asthma subjects (y-axis, number label) with FENO-high (≥35 ppb, red bars) and FENO-low (<35 ppb, blue bars) phenotypes, at the indicated visit (x-axis) are shown for subjects with FENO ≥ 35pbb (**a**) or FENO < 35 ppb (**b**) at the baseline visit, stratified by asthma severity cohort

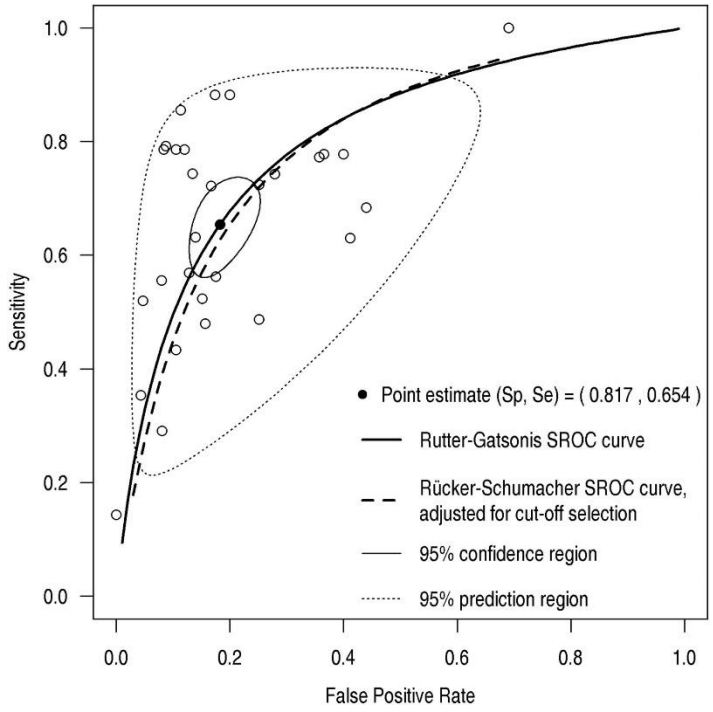
Silkoff et al Respir Research 2016

Accuracy of FE_{NO} for diagnosing asthma: a systematic review

Stefan Karrasch,[1,2,3] Klaus Linde,[1] Gerta Rücker,[4,5] Harriet Sommer,[4,5] Marlies Karsch-Völk,[1] Jos Kleijnen,[6,7] Rudolf A Jörres,[3] Antonius Schneider[1]

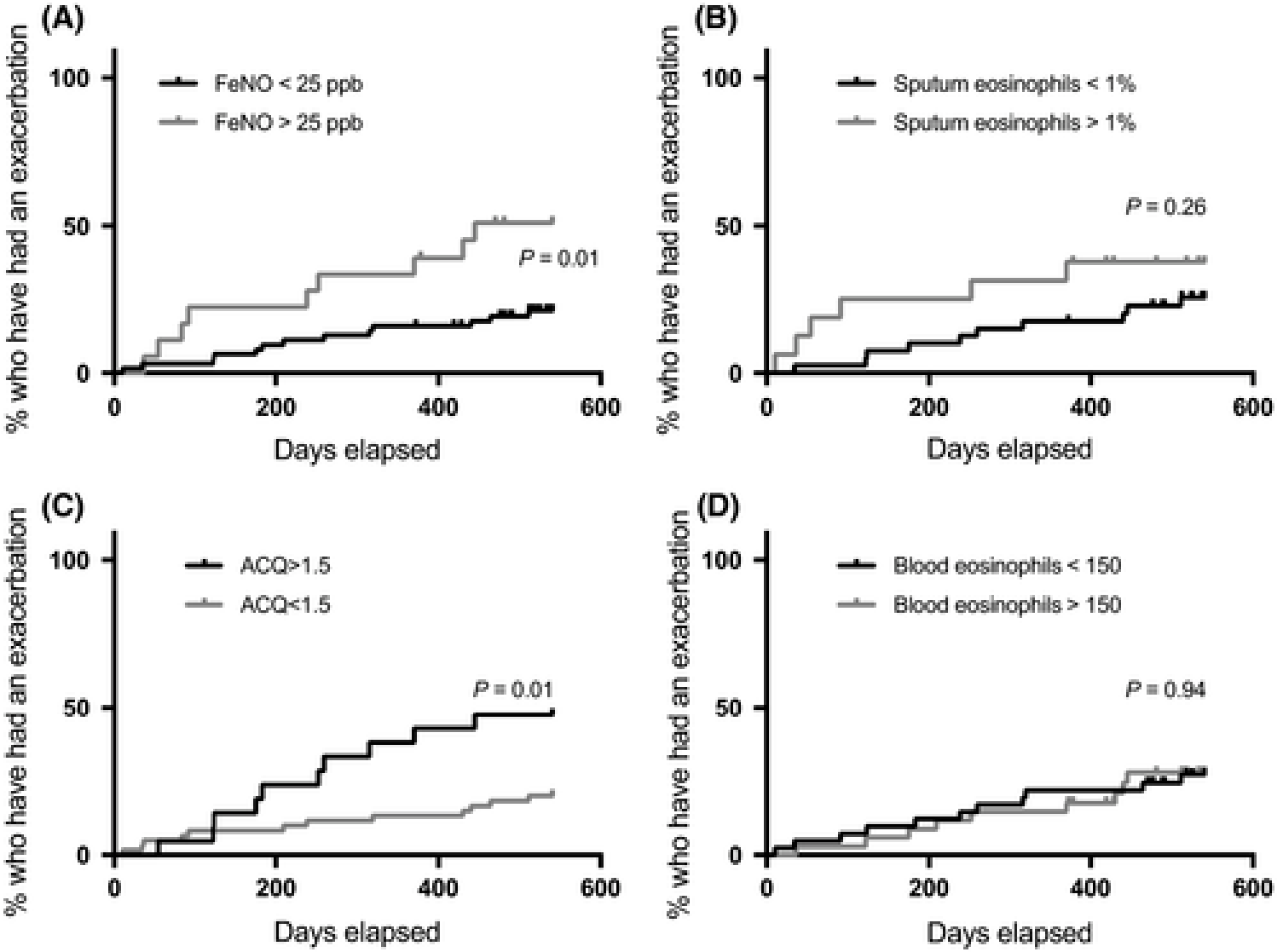
Conclusions There appears to be a fair accuracy of FE_{NO} for making the diagnosis of asthma. The overall specificity was higher than sensitivity, which indicates a higher diagnostic potential for ruling in than for ruling out the diagnosis of asthma.

Threshold ranging from 11 ppb to 55 ppb with an average of 30 ppb



Karrasch et al Thorax 2017

High exhaled NO levels predicts increased risk of exacerbation



Bjerregaard A et al Clin Exp Allergy2017

High exhaled NO levels predicts increased risk of viral induced exacerbation

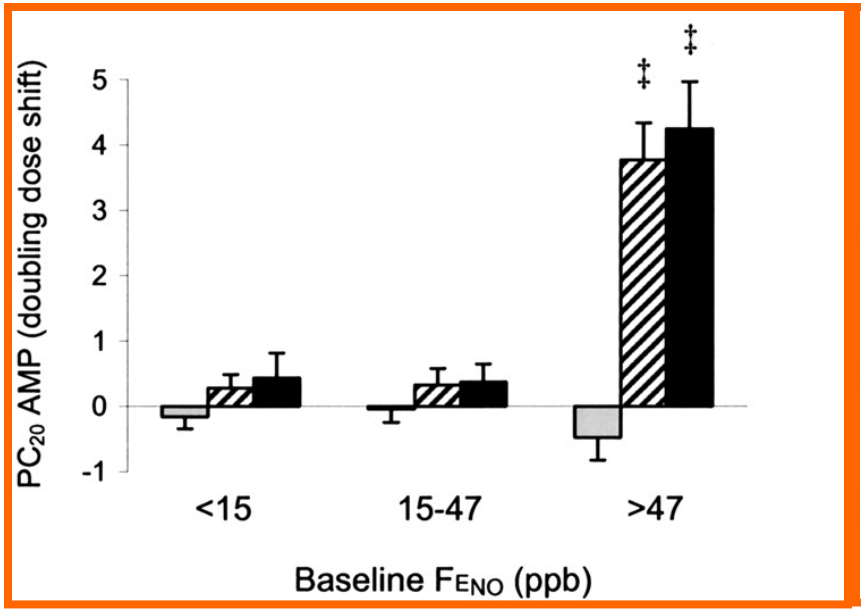
TABLE 2 Proportional hazards models of inflammatory markers at baseline and risk (hazard ratio, HR) of exacerbation (all exacerbations, and virus-induced exacerbations)

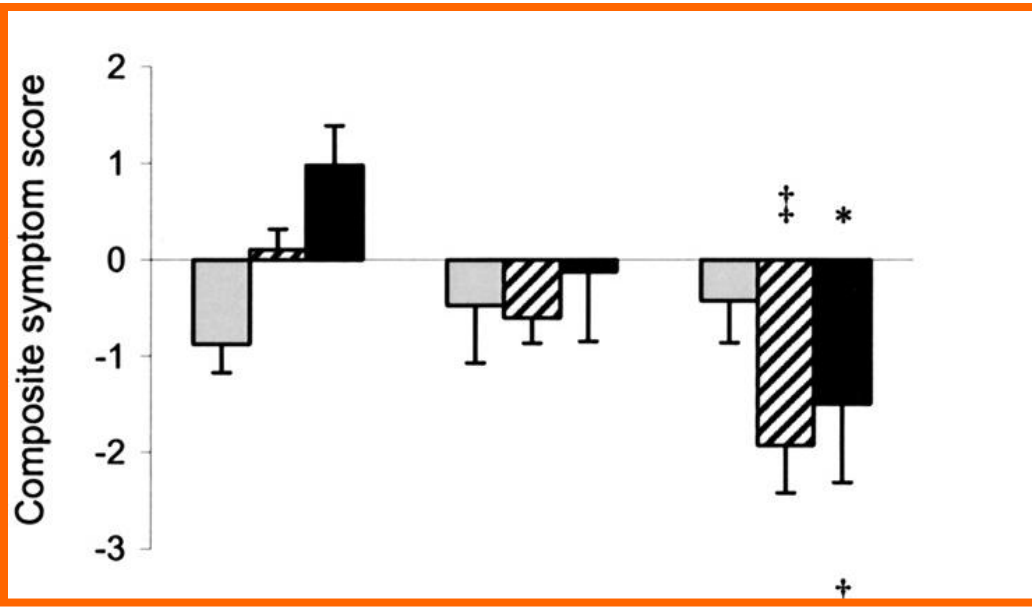
	Any exacerbation (n=22)		Virus pos. exacerbation (n=15)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
FeNO >25 ppb	3.1 (1.2-7.8)	.015	3.4 (1.1-10.4)	.033
Sputum eosinophils >1%	4.1 (1.2-13.8)	.024	7.6 (1.6-35.2)	.010
Blood eosinophils >150 ($\times 10^9$ cells/L)	1.2 (0.5-2.9)	.720	1.0 (0.3-3.0)	.941
Atopy (positive SPT)	0.5 (0.2-1.2)	.129	0.6 (0.2-1.6)	.269
IgE >150 ($\times 10^3$ IU/L)	1.3 (0.5-3.3)	.648	1.4 (0.4-4.5)	.555

Each HR in the table represents a regression model adjusted for ICS dose, smoking status, ACQ score and % predicted FEV1 at baseline.

Bjerregaard A et al Clin Exp Allergy2017

High exhaled NO levels predict good response to inhaled corticoids in patients with respiratory symptoms without established respiratory diagnosis





Baseline FeNO provided greater sensitivities and negative predictive values than:

12% FEV1 reversibility to salbutamol

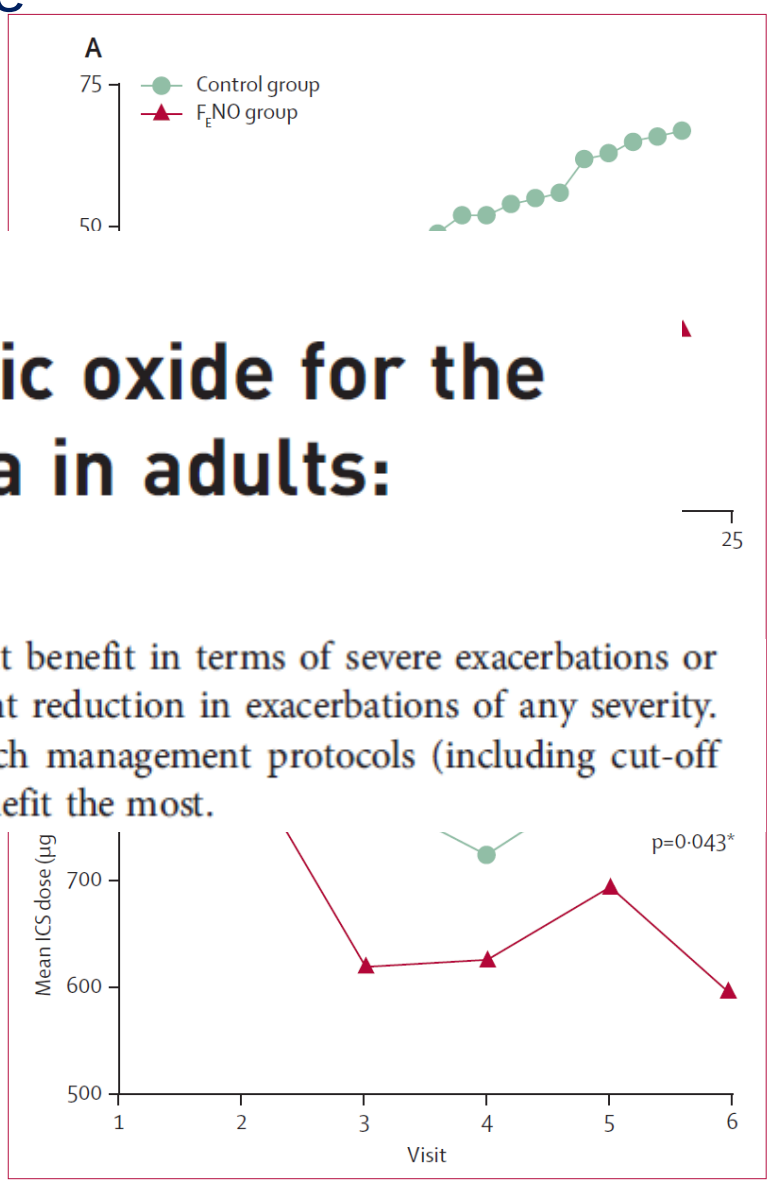
FEV1 < 80% predicted

PD20 methacholine < 8µmol

PEFR variation > 20%

Smith A et al Am J Respir Crit Care Med 2005

FeNO guided management may reduce asthma exacerbation in mild asthma



Fractional exhaled nitric oxide for the management of asthma in adults: a systematic review

FeNO guided management showed no statistically significant benefit in terms of severe exacerbations or inhaled corticosteroid use, but showed a statistically significant reduction in exacerbations of any severity. However, further research is warranted to clearly define which management protocols (including cut-off points) offer best efficacy and which patient groups would benefit the most.

Step 3	Budesonide 200 µg twice per day	Formoterol 12 µg twice per day
Step 4	Budesonide 400 µg twice per day	Formoterol 2 × 12 µg twice per day
Step 5	Budesonide 800 µg twice per day	Formoterol 2 × 12 µg twice per day

F_ENO=fraction of exhaled nitric oxide. ICS=inhaled corticosteroid.

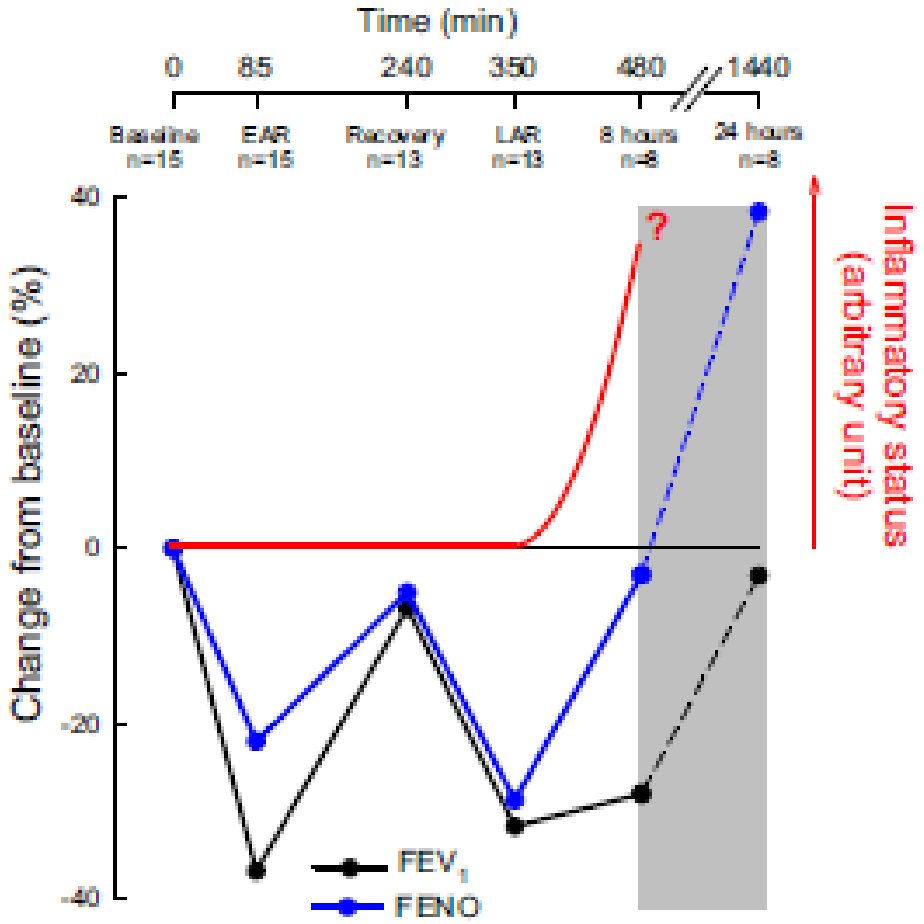
Table 2: **F_ENO algorithm treatment steps**

Figure 2: **Effect of F_ENO-guided asthma management during pregnancy on number of asthma exacerbations (A) and maintenance mean daily ICS dose (B)**
ICS=inhaled corticosteroids. F_ENO=fraction of exhaled nitric oxide. *From generalised linear mixed model model analysis.

Powell H et al Lancet 2011
Essat et al ERJ 2016

Exhaled nitric oxide: A biomarker integrating both lung function and airway inflammation changes

Amaryllis Haccuria, MD,[a,b] Alain Michils, MD, PhD,[a] Sébastien Michiels, MD,[a] and Alain Van Muylem, PhD[a] *Brussels and Namur, Belgium*



Change in FeNO after a bronchial allergenic challenge

Haccuria A et al JACI 2014