The Lancet Commission on Asthma

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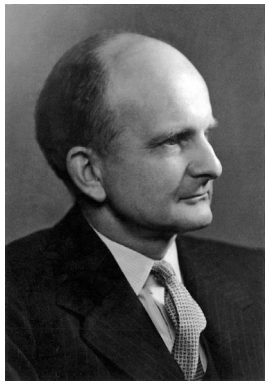
Disclosures

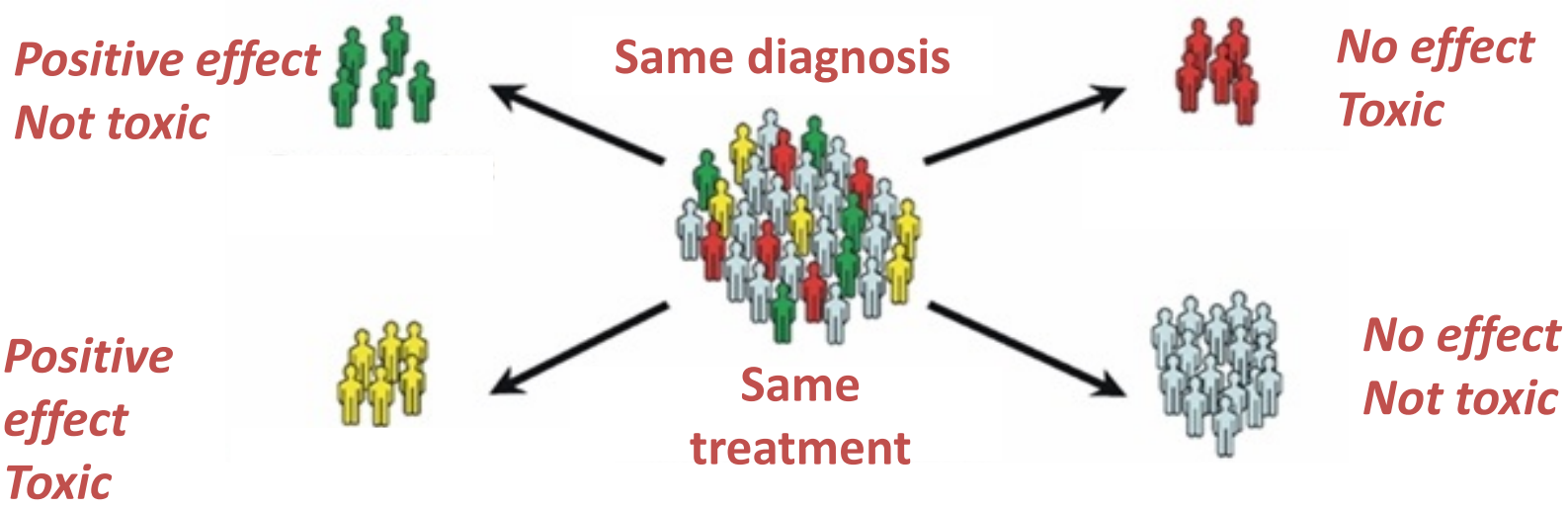
- **Speaker's Honoraria:** AstraZeneca, Boehringer Inglehiem, Aerocrine, Chiesi, Novartis and GSK.
- **Advisory Panels:** Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp, Regeneron.
- **Sponsorship:** Boehringer Ingelheim, GSK, AstraZeneca, Chiesi and Napp.

Time to reform taxonomy of airways disease

….. once we have cast diseases into these vast receptacles, these aetiological dustbins, they are satisfactorily accounted for. I believe that those brave enough to lift the lids off these bins and poke about among the rubbish there may find clinical salvage of inestimable value.

Asher et al. British Medical Journal 1954;ii:460-62





C. Vogelmeier (with permission)

PERSPECTIVE
PRECISION MEDICINE FOR AIRWAY DISEASES

Treatable traits: toward precision medicine of chronic airway diseases

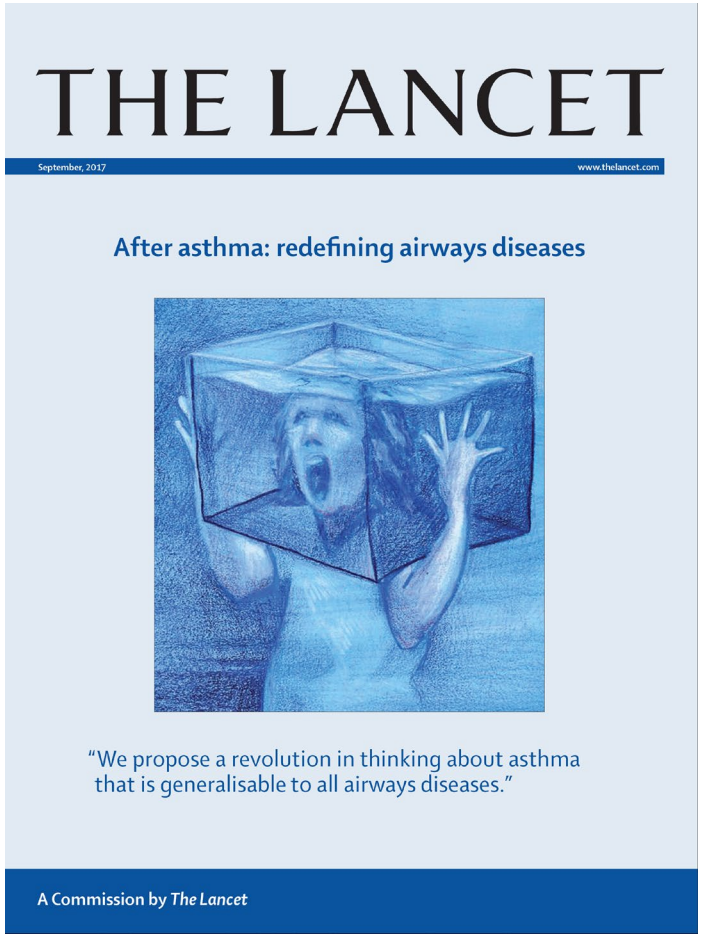
Alvar Agusti[1], Elisabeth Bel[2], Mike Thomas[3], Claus Vogelmeier[4], Guy Brusselle[5,6], Stephen Holgate[7], Marc Humbert[8], Paul Jones[9], Peter G. Gibson[10], Jørgen Vestbo[11], Richard Beasley[12] and Ian D. Pavord[13]

•*Agusti et al. European Respiratory Journal 2016;47:410-9*

The Lancet Commissions

After asthma: redefining airways diseases

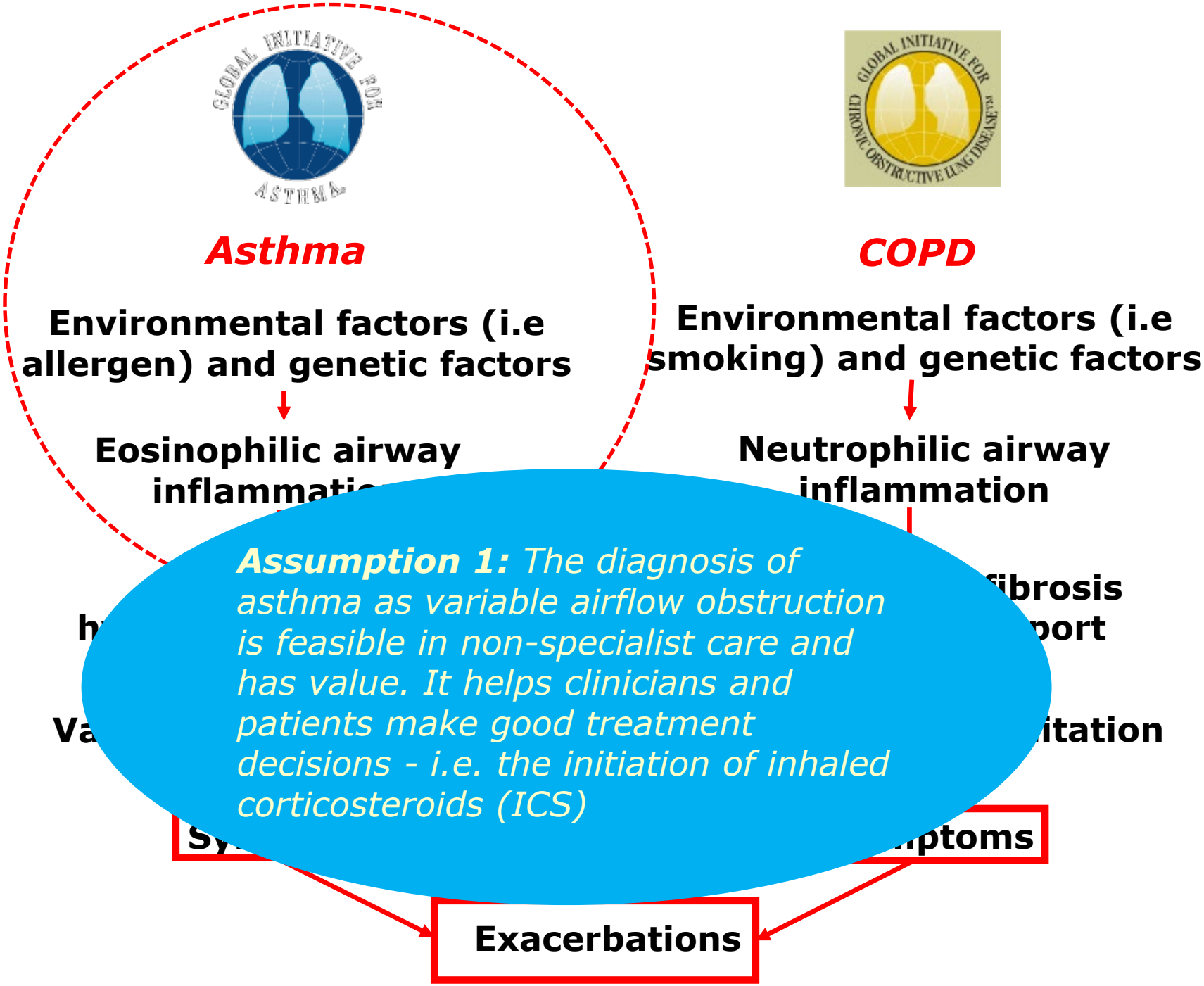
Ian D Pavord, Richard Beasley, Alvar Agusti, Gary P Anderson, Elisabeth Bel, Guy Brusselle, Paul Cullinan, Adnan Custovic, Francine M Ducharme, John V Fahy, Urs Frey, Peter Gibson, Liam G Heaney, Patrick G Holt, Marc Humbert, Clare M Lloyd, Guy Marks, Fernando D Martinez, Peter D Sly, Erika von Mutius, Sally Wenzel, Heather J Zar, Andy Bush



•*Pavord et al. Lancet 2018; 391:350-400*

What has changed? Why is mechanism based management ready for the big-time?

- Progress against key outcomes has stopped
- New methods to measure airway inflammation have exposed several damaging assumptions/over-simplifications
- Management guided by these measures looks feasible and more effective than our current approach.
- New treatment options have inflammatory phenotype-specific benefits.


Asthma
COPD
Environmental factors (i.e allergen) and genetic factors
Environmental factors (i.e smoking) and genetic factors
Eosinophilic airway
Neutrophilic airway
inflammation
Assumption 1: The diagnosis of asthma as variable airflow obstruction is feasible in non-specialist care and has value. It helps clinicians and patients make good treatment decisions - i.e. the initiation of inhaled corticosteroids (ICS)
Exacerbations

Asthma diagnosis. Problems in non-specialist care

- Available tests have low sensitivity, meaning that it is difficult to rule out the diagnosis
- There is pressure to make an early diagnosis
- There are few options other than a trial of treatment
- Conditions confused with asthma commonly improve spontaneously; this could create the illusion that a trial of treatment has been successful so treatment will be continued unnecessarily

Over-diagnosis of asthma

https://www.express.co.uk/life-style/health/658376/Aiagnosis-asthma-trivialised-Inhalers-handed-fashion-accessories-health/amp

inhalers handed out like fashion accessory

Are asthma diagnoses TRIVI...

EXPRESS

NEWS SHOWBIZ FOOTBALL COMMENT FINAN

Life & Style Health

Is asthma being TRIVIALISED accessories'

ASTHMA Inhalers are being dished out like "fashi that medics are over-diagnosing the condition in c

PUBLISHED: 23:30, Tue, Apr 5, 2016

'Bright and bubbly' teen dies from asthma attack while waiting for paramedics

A TROUBLED ambulance service is under investigation after a 14-year-old girl died from an asthma attack while waiting for paramedics.

By ANIL DAWAR

PUBLISHED: 15:55, Tue, Aug 6, 2013

SHARE TWEET 0

alternative diagnosis

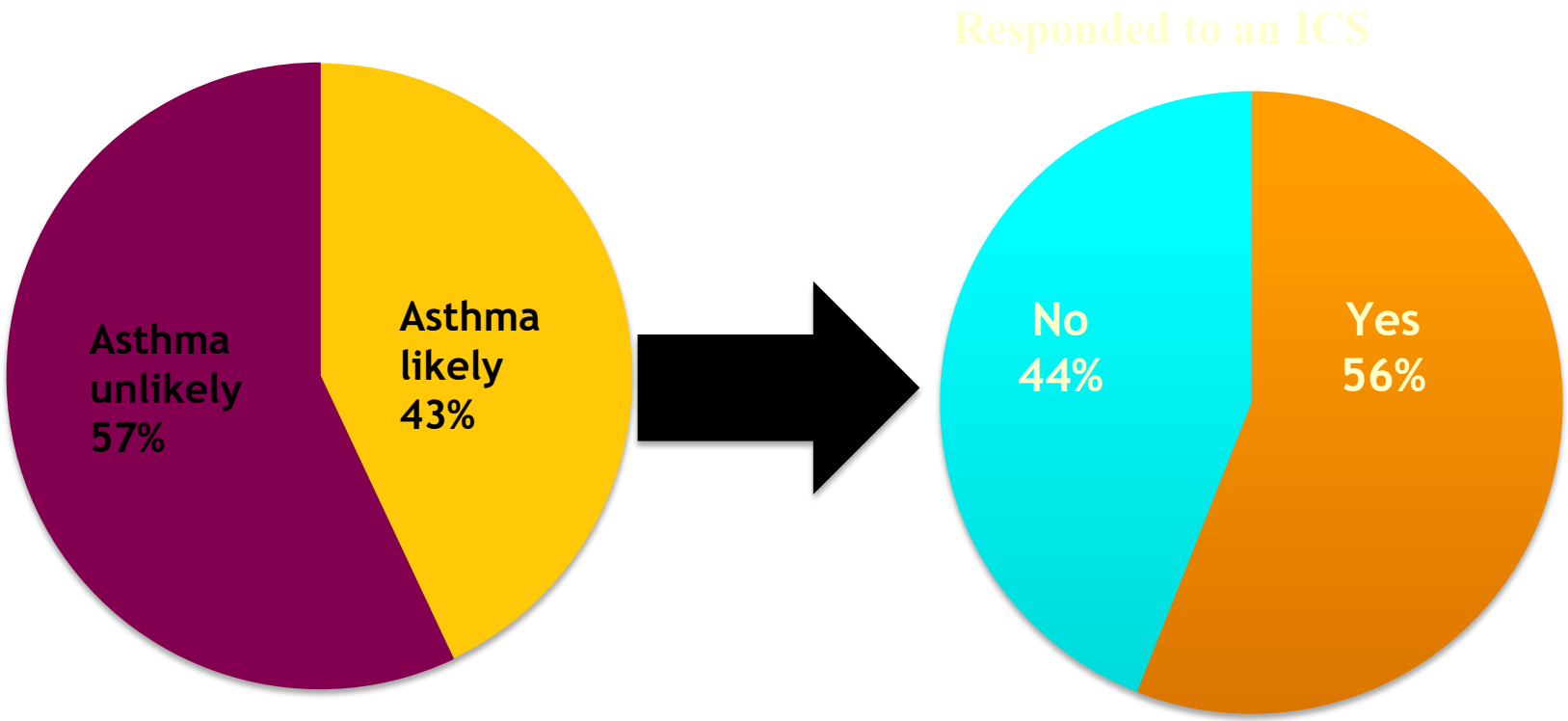
Participant enters 12-mo follow-up, and all asthma medications are held; bronchial challenge tests at 6 and 12 mo

Aaron et al. JAMA 2017;317:269-79

Asthma diagnosis. Being clear about the question

- What is the risk of a poor outcome (i.e. severe asthma attack, decline in lung function)?
- How likely is this patient to respond to inhaled corticosteroids and how hard should I push?
- Is it asthma? vs What asthma do they have?

FeNO as a predictive biomarker: response to ICS



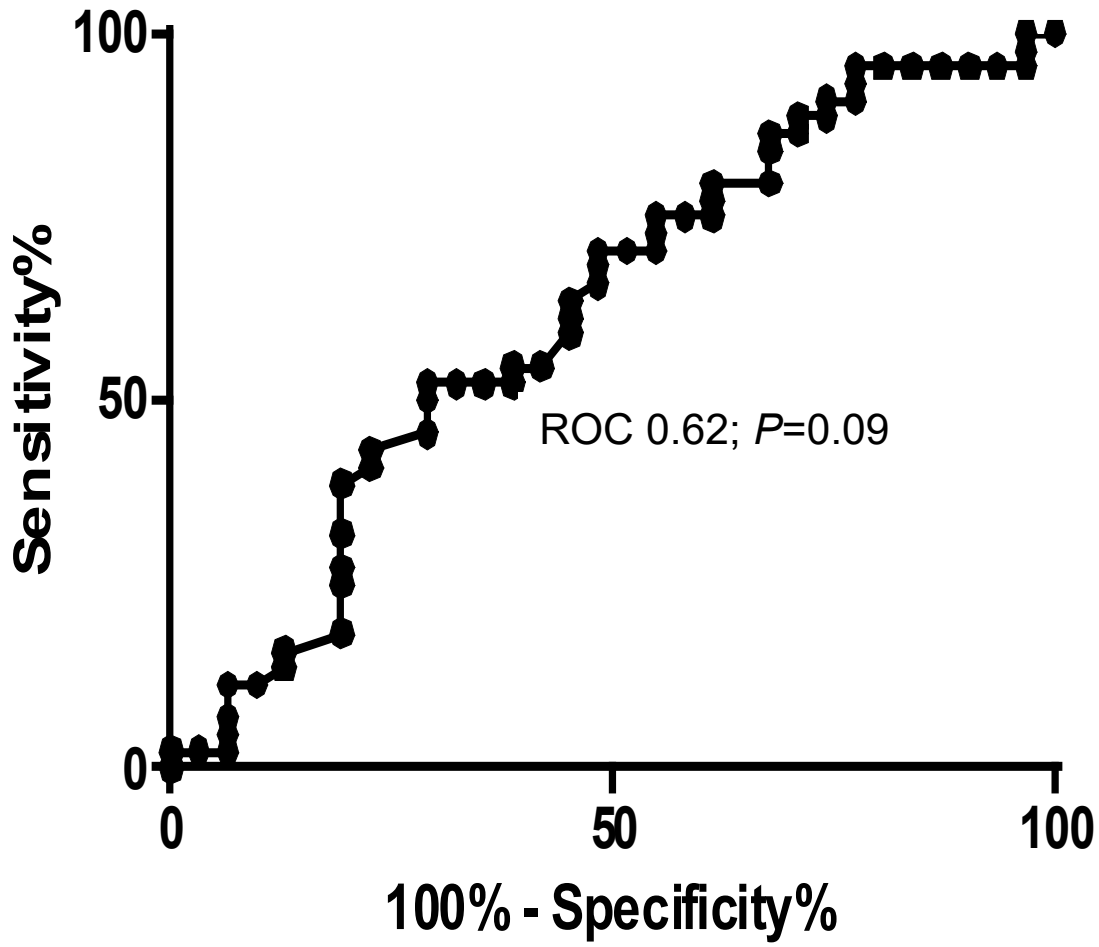
(N=76)

16 patients with asthma and 12 without benefitted from the ICS they were prescribed

FeNO, fractional exhaled nitric oxide; GP, general practitioner

Martin MJ, et al. Thorax 2016;71:562-564

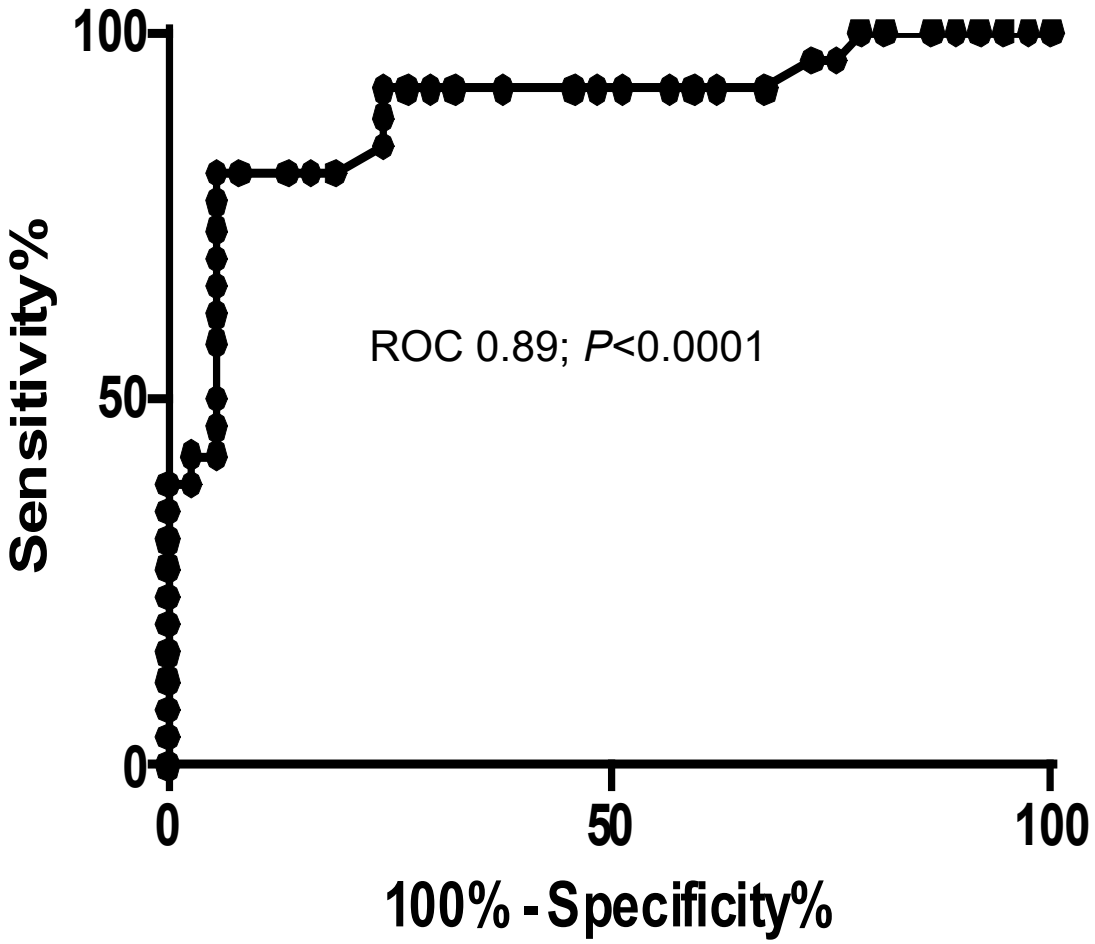
ROC curve for FeNO and asthma diagnosis



FeNO, fractional exhaled nitric oxide; ROC, receiver operating characteristics

Martin MJ, et al. Thorax 2016;71:562-564.

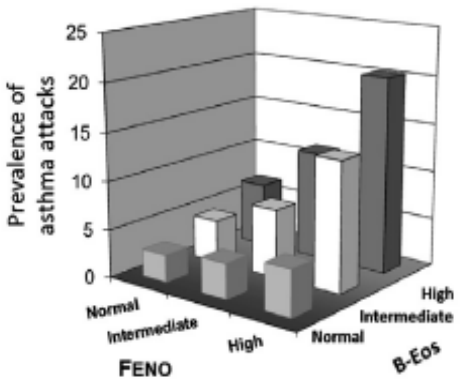
ROC curve for FeNO and response to ICS at 4 weeks

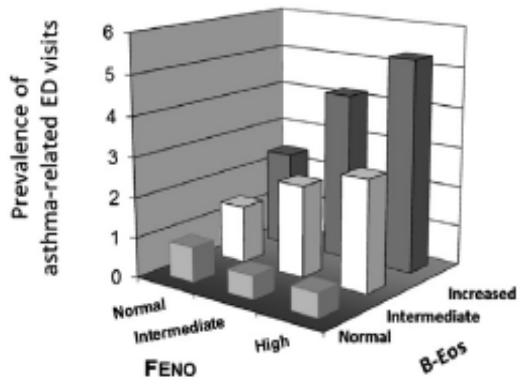


FeNO, fractional exhaled nitric oxide; ROC, receiver operating characteristics

Martin MJ, et al. Thorax 2016;71:562-564

Markers of Type-2 inflammation and risk



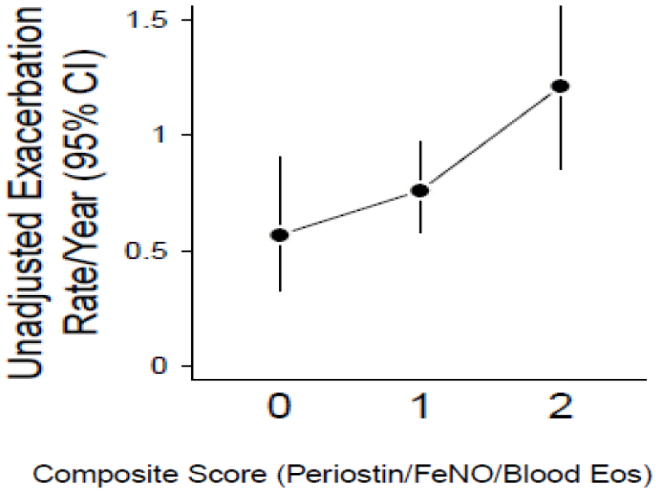


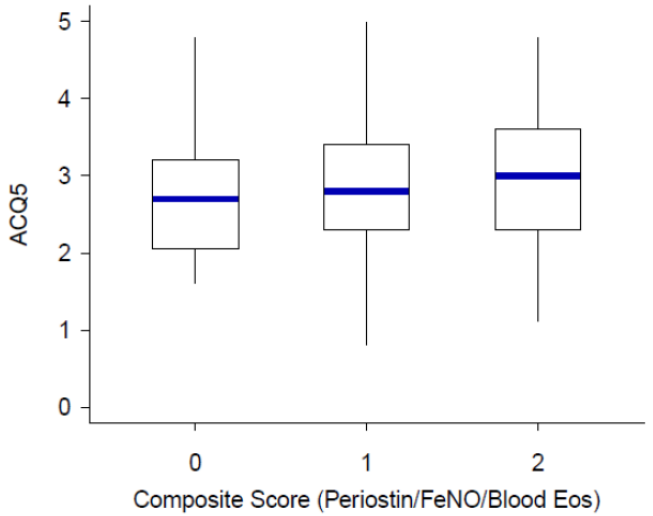
Number of subjects per group (n), according to levels of FENO and B-Eos.

7,827	1,042	167	Normal B-Eos
1,806	478	215	Intermediate B-Eos
498	168	207	High B-Eos
Normal FENO	Intermediate FENO	High FENO	

<0.3 x 10^9/L
>0.3-0.5 x 10^9/L
>0.5 x 10^9/L

<25 ppb *25-50 ppb* *>50 ppb*





Malinovschi et al. J Allergy Clin Immunol 2013;132:821-7

Heaney et al. Thorax 2015

Meta-analysis of studies investigating FeNO guided management of asthma

Analysis 1.1. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 1 Number of participants who had ≥ 1 exacerbations over study period.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

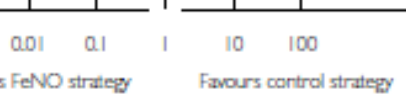
Outcome: 1 Number of participants who had ≥ 1 exacerbations over study period

Study or subgroup	FeNO strategy N	Control strategy N	log [Odds Ratio] (SE)	Odds Ratio M,Fixed,95% CI	Weight	Odds Ratio M,Fixed,95% CI
Honkoop 2014	189	203	-0.4463 (0.4546)		14.3 %	0.64 [0.26, 1.56]
Powell 2011	111	109	-0.7344 (0.2926)		34.4 %	0.48 [0.27, 0.85]
Shaw 2007	58	60	-0.5746 (0.4267)		16.2 %	0.56 [0.24, 1.30]
Smith 2005	46	48	0.3863 (0.4697)		13.4 %	1.47 [0.59, 3.69]
Syk 2013	93	88	-0.7244 (0.3679)		21.8 %	0.48 [0.24, 1.00]
Total (95% CI)	**497**	**508**			**100.0 %**	**0.60 [0.43, 0.84]**

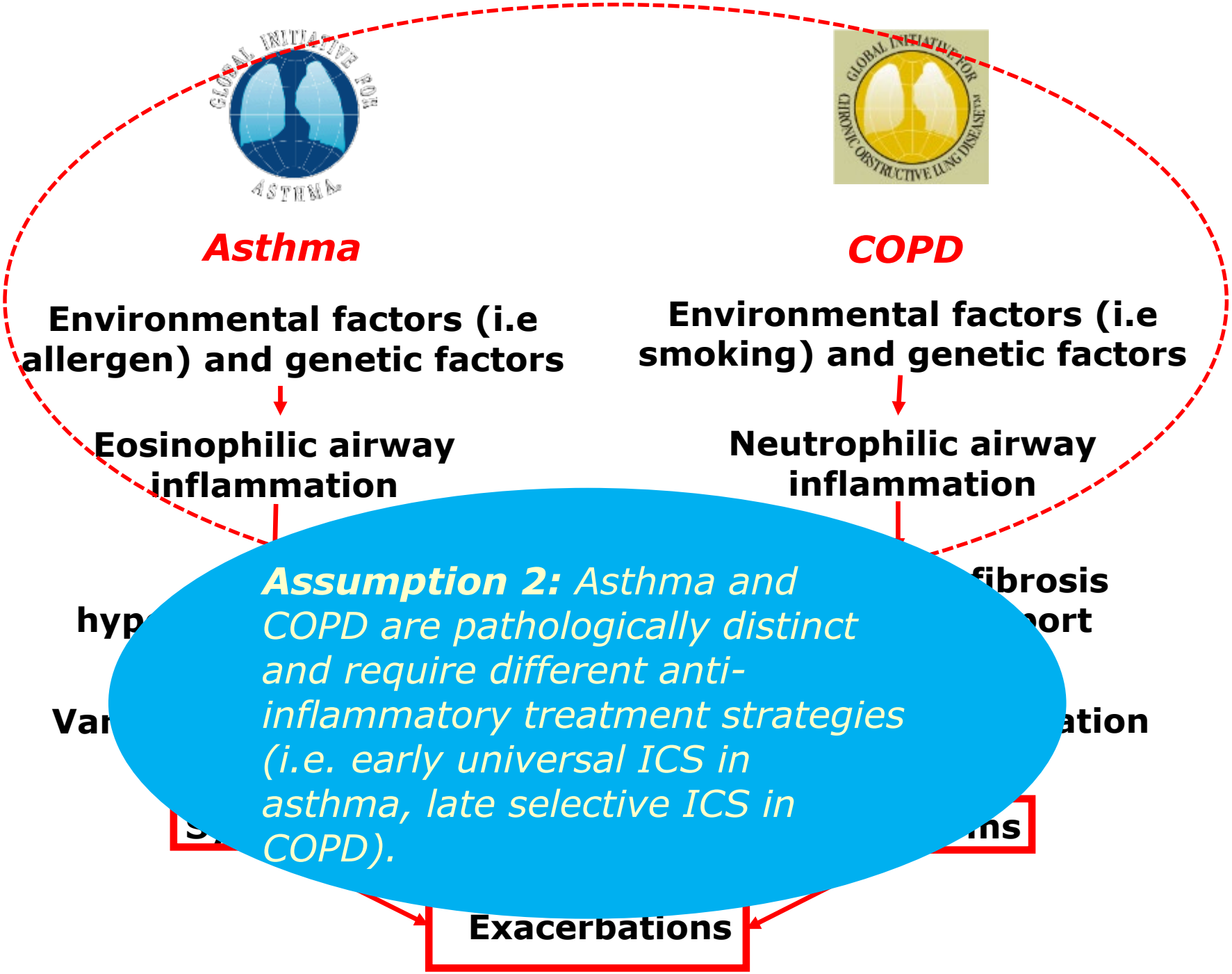
Heterogeneity: $Chi^2 = 4.61$, df = 4 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 3.00 (P = 0.0027)

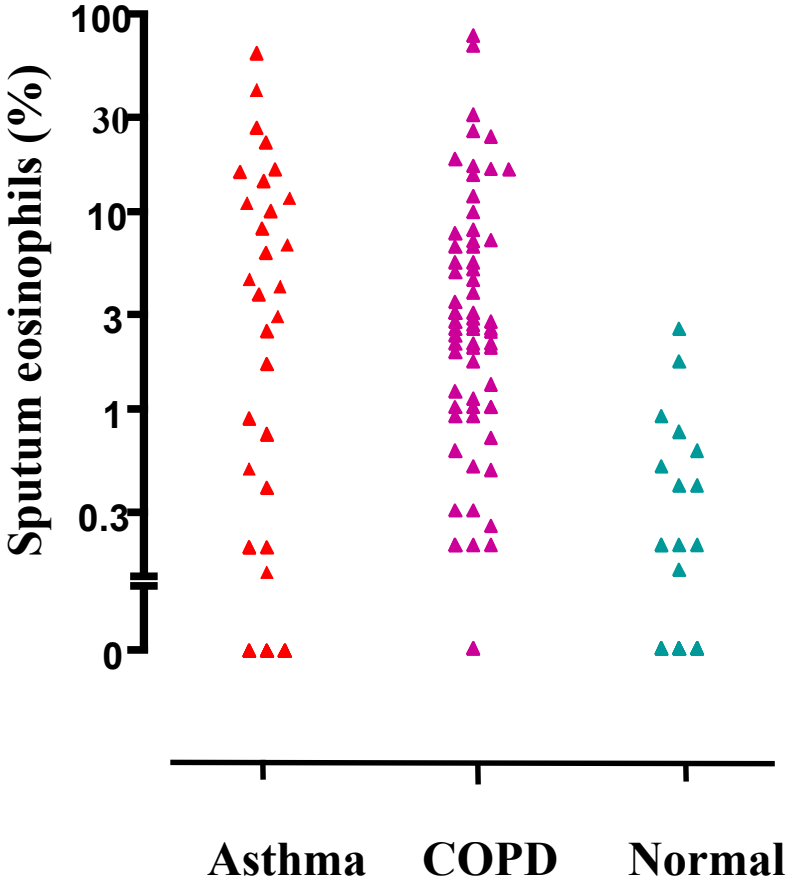
Test for subgroup differences: Not applicable



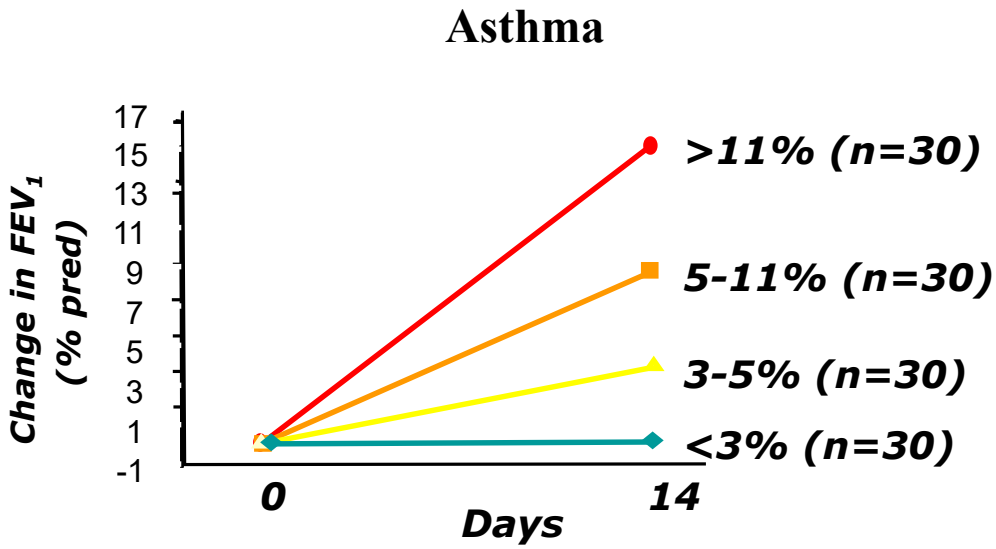
Petsky HL, Kew KM, Turner C, Chang AB.
Exhaled nitric oxide levels to guide treatment for adults with asthma.
Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011440.
DOI: 10.1002/14651858.CD011440.pub2.


Asthma
COPD
Environmental factors (i.e allergen) and genetic factors
Environmental factors (i.e smoking) and genetic factors
Eosinophilic airway inflammation
Neutrophilic airway inflammation
Assumption 2: Asthma and COPD are pathologically distinct and require different anti-inflammatory treatment strategies (i.e. early universal ICS in asthma, late selective ICS in COPD).
Exacerbations

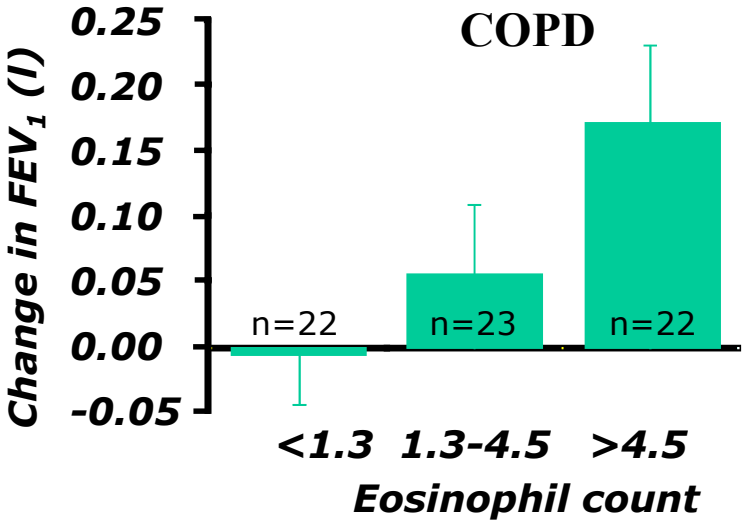
Sputum eosinophil counts in asthma and COPD



Brightling et al. Lancet 2000;356:1480-85;
Green et al. Thorax 2002; 57:875-879

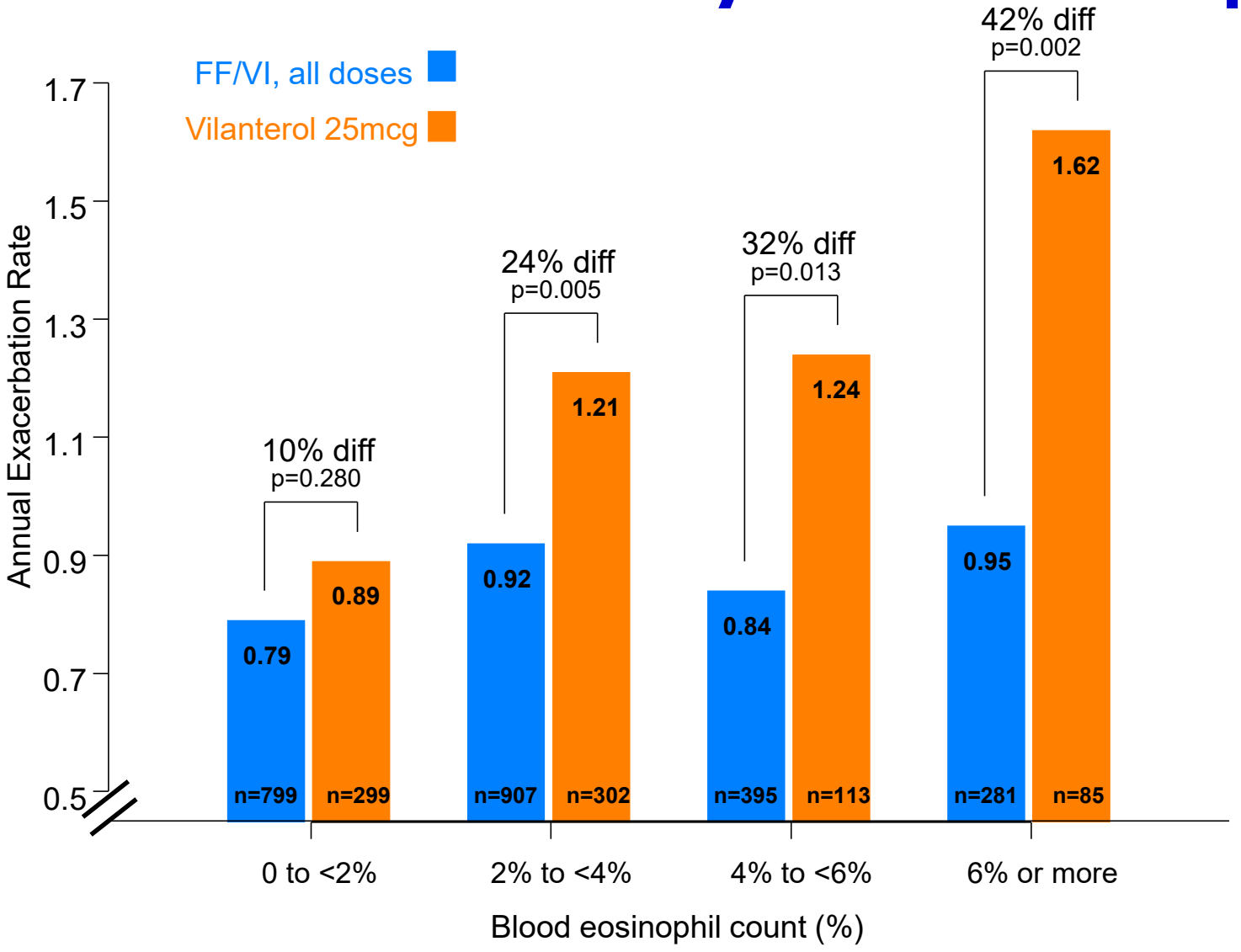


Meijer et al . CEA 2002;32:1096-03



Brightling et al. Lancet 2000;356:1480-85

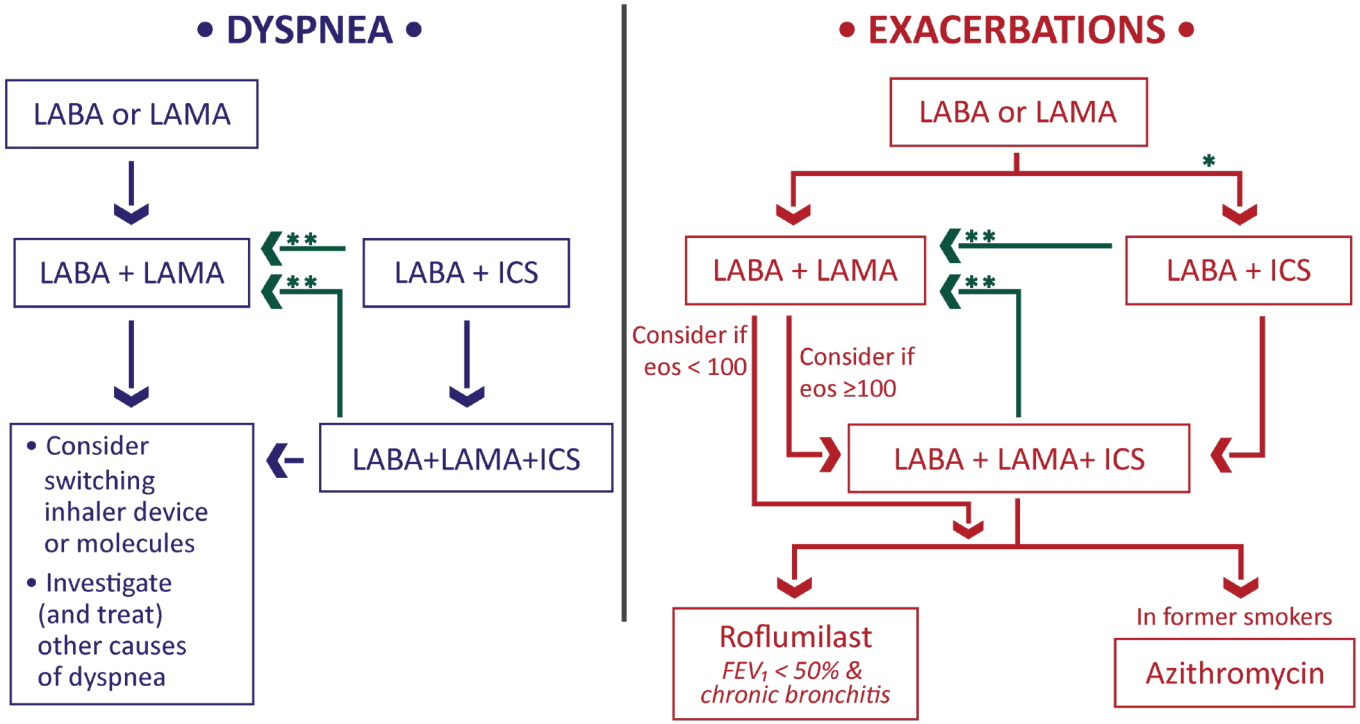
The effect of addition of fluticasone furoate to vilanterol by blood eosinophils



Pascoe et al. Lancet Resp Med 2015;3:435-42

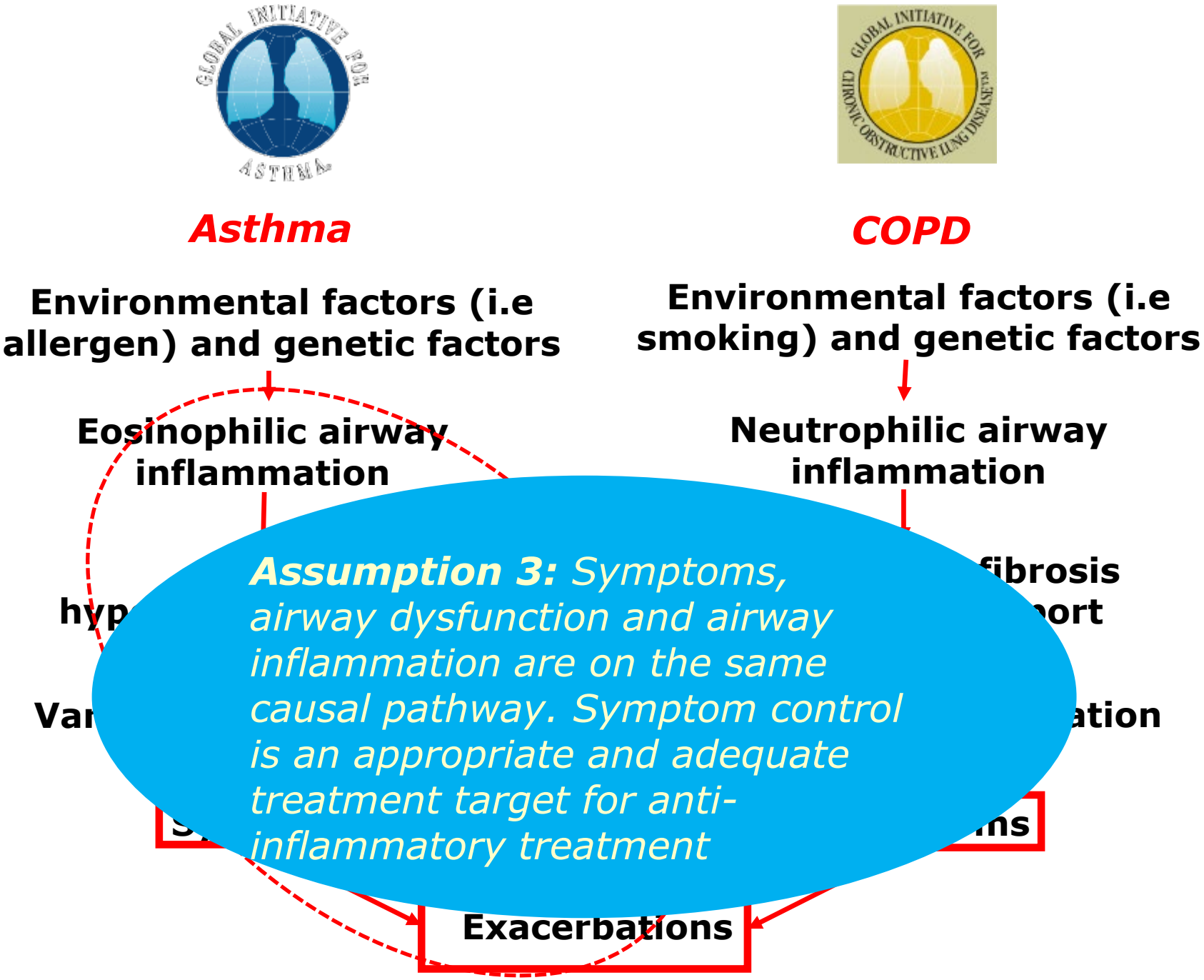
FOLLOW-UP PHARMACOLOGICAL TREATMENT

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

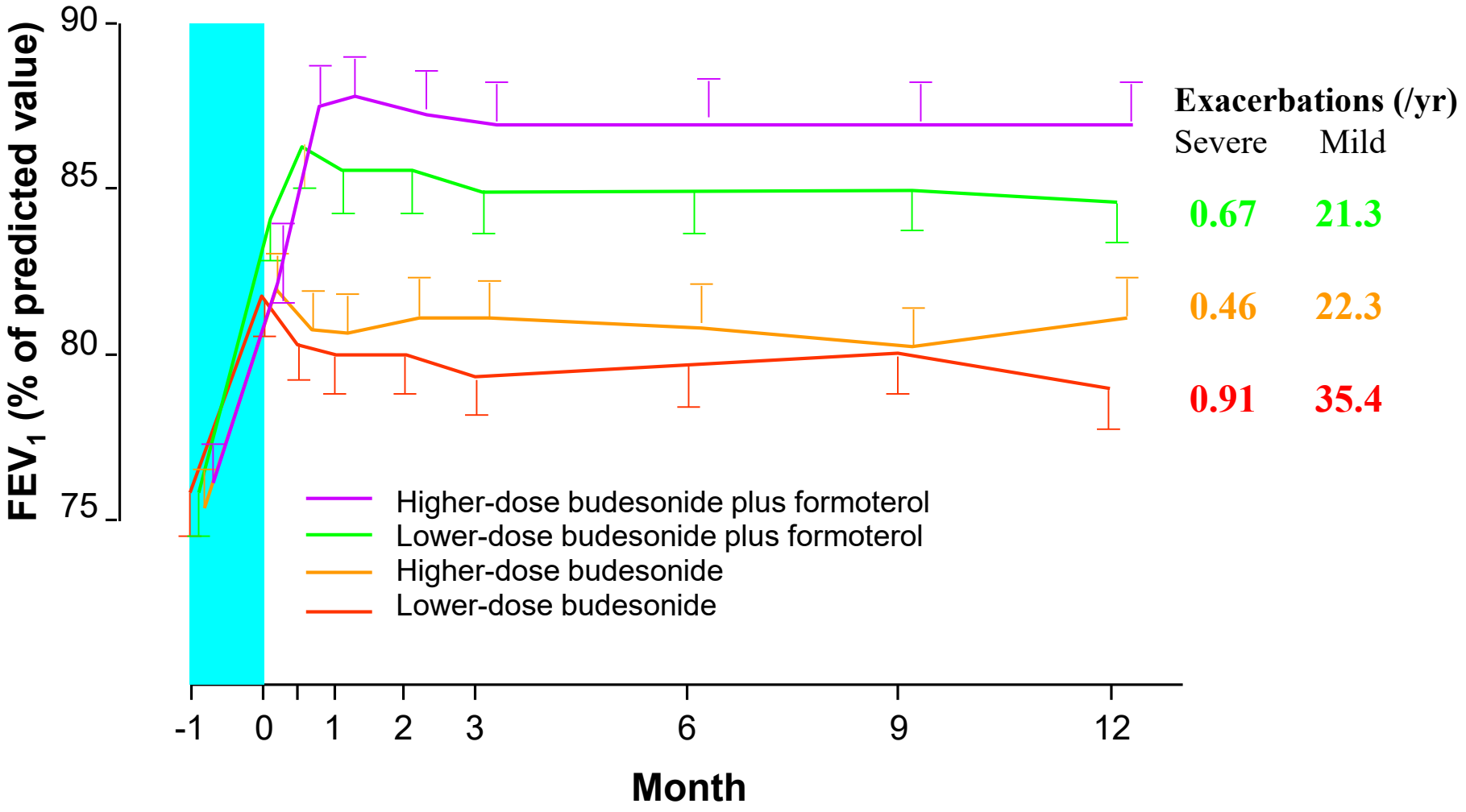


eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

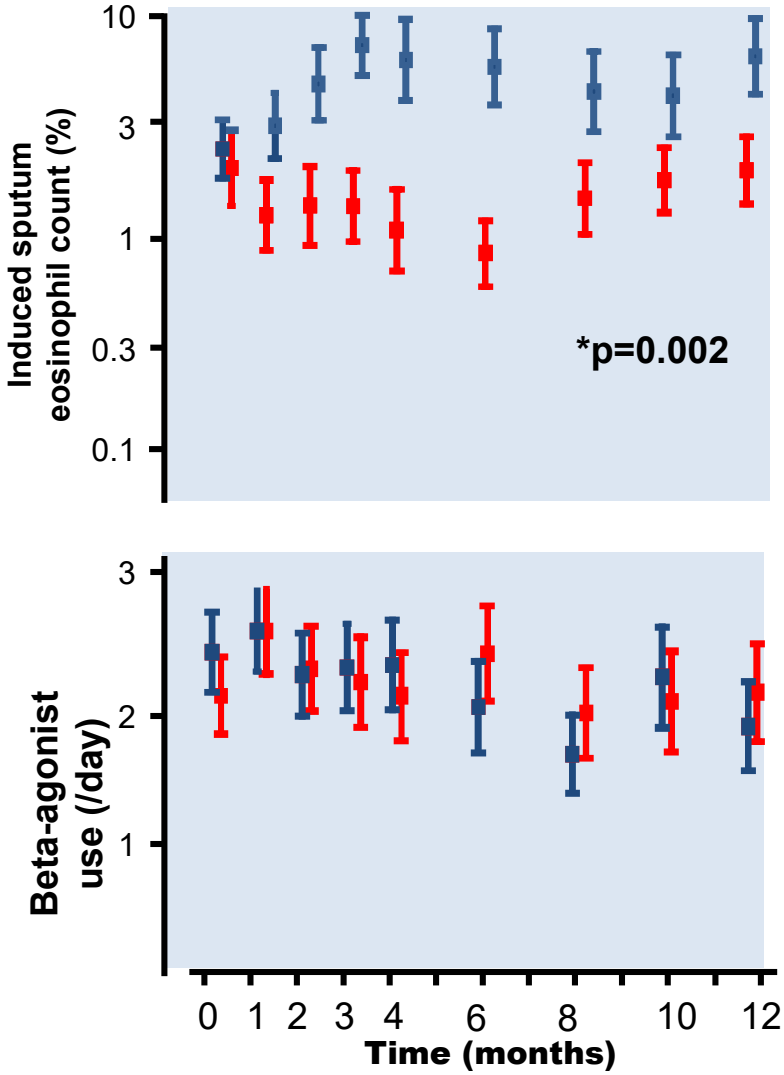

Asthma
COPD
Environmental factors (i.e allergen) and genetic factors
Environmental factors (i.e smoking) and genetic factors
Eosinophilic airway inflammation
Neutrophilic airway inflammation
Assumption 3: Symptoms, airway dysfunction and airway inflammation are on the same causal pathway. Symptom control is an appropriate and adequate treatment target for anti-inflammatory treatment
Exacerbations

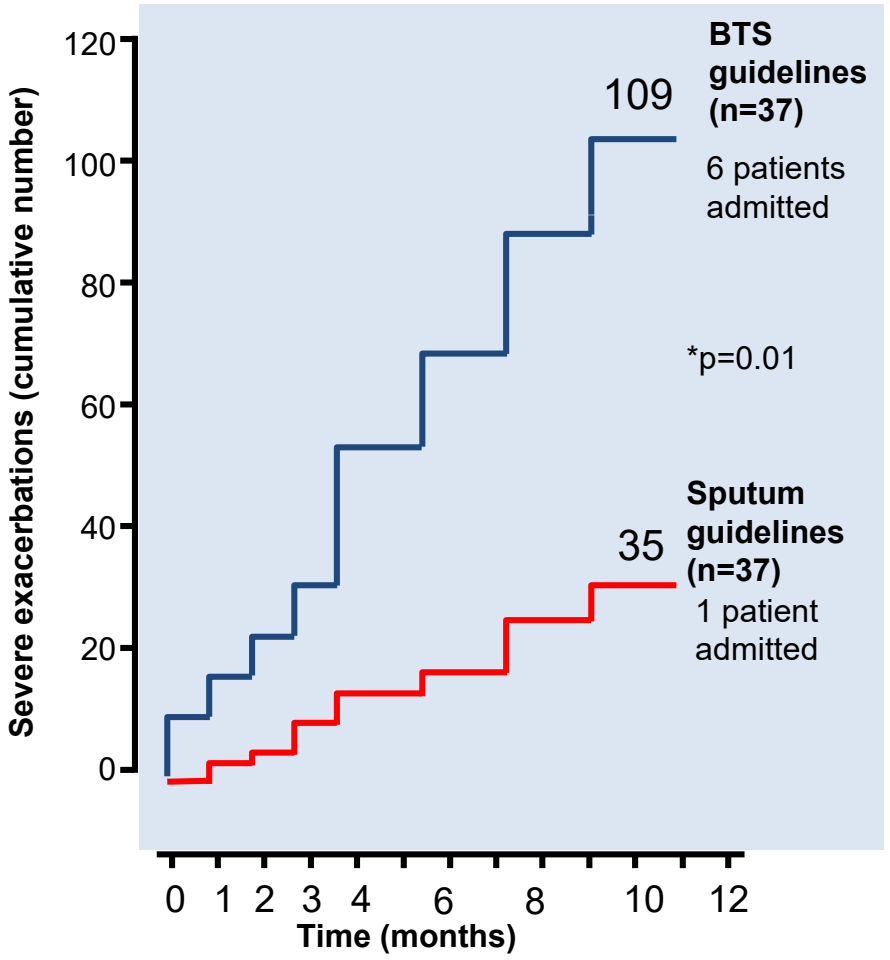
The FACET study



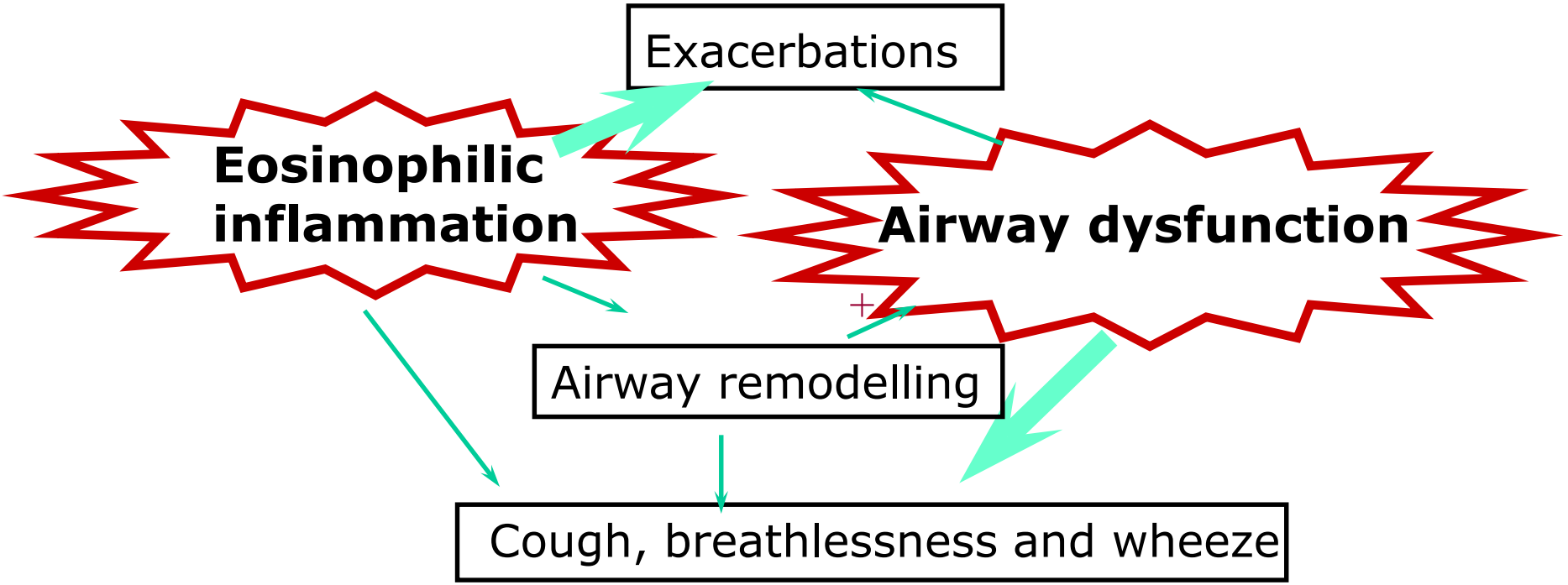
Pauwels et al New Engl J Med 1997;337:1405-1411

Traditional vs inflammation-guided management

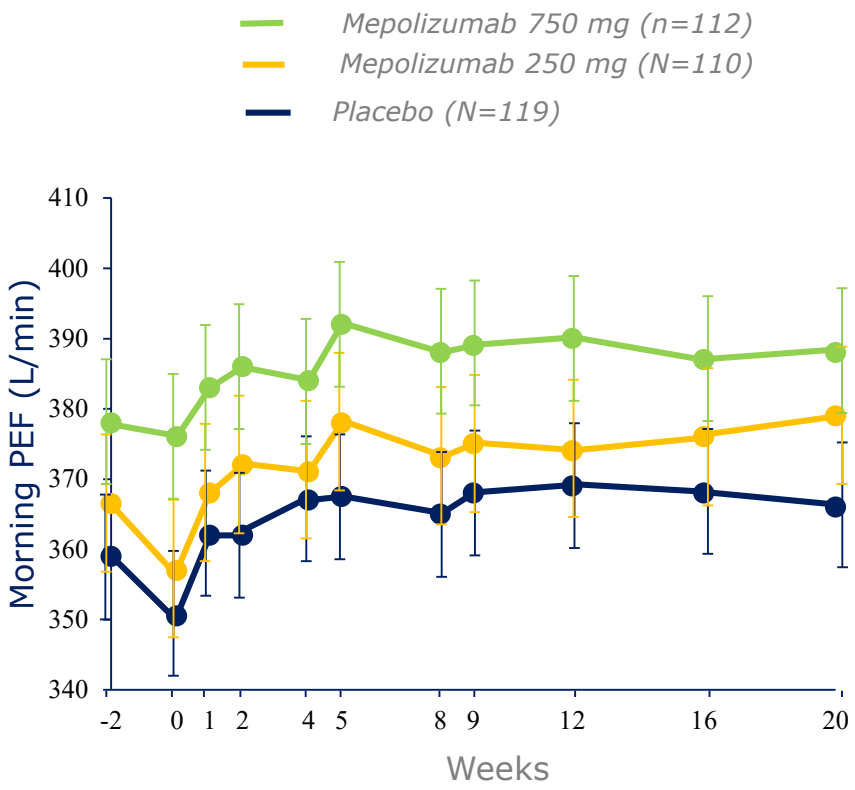


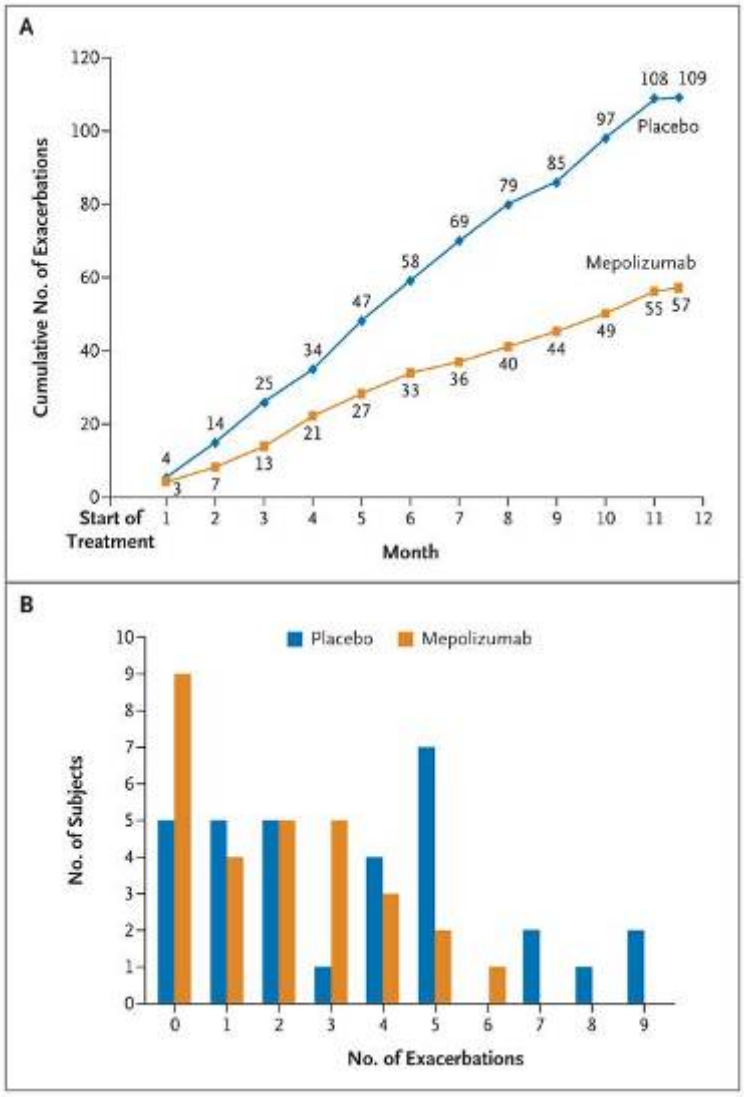


Green et al. Lancet 2002;360:1715-21


Exacerbations
Eosinophilic inflammation
Airway dysfunction
+
Airway remodelling
Cough, breathlessness and wheeze

Mepolizumab (anti-IL-5): effect in 'asthma' and eosinophilic airways disease

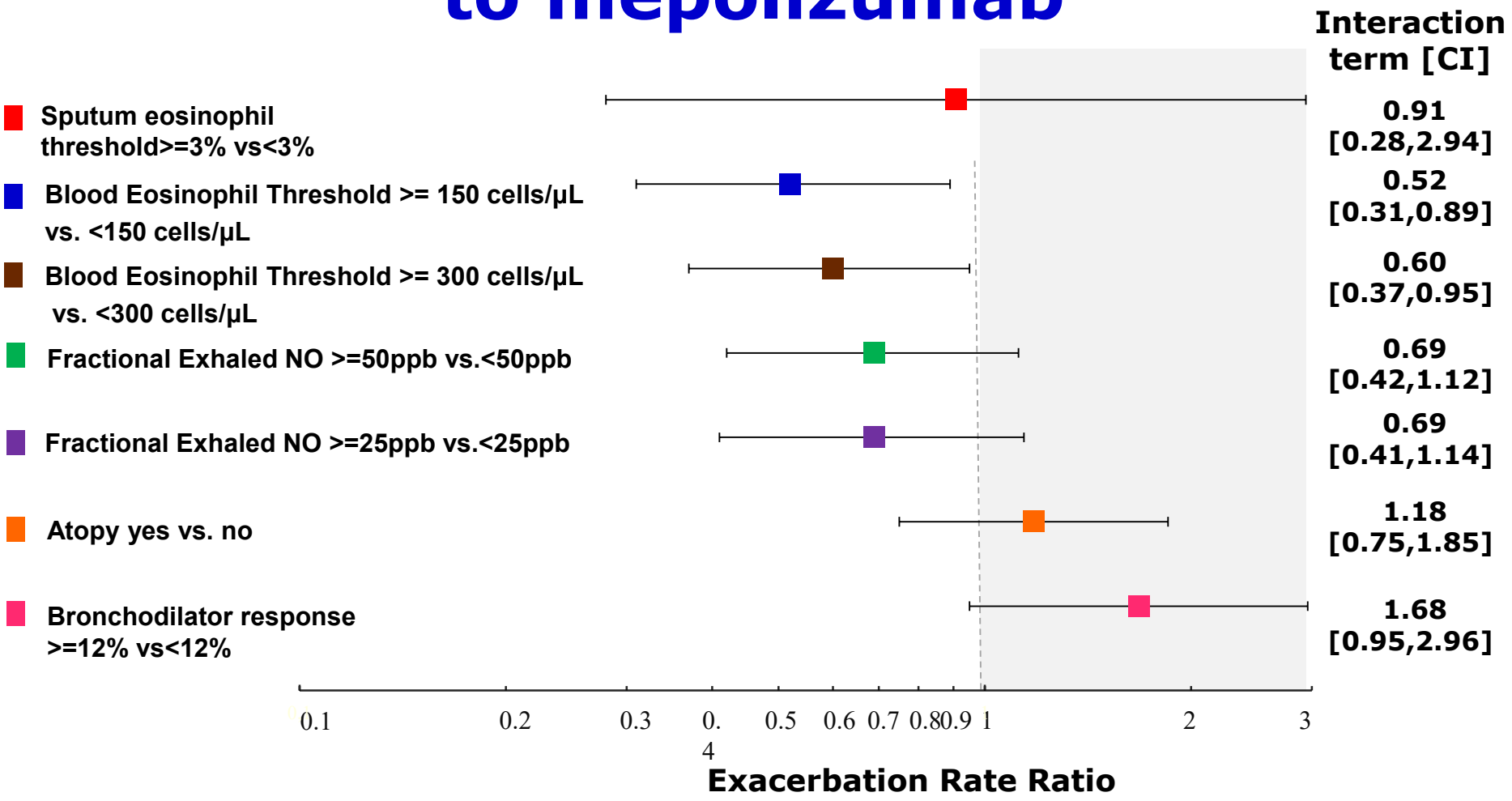




Flood-Page et al. AJRCCM 2007;176:1062-71

Haldar et al. NEJM 2009;360:973-84

DREAM: predictors of response to mepolizumab



- A post hoc analysis of exacerbation reduction ratios compared 7 biomarkers above and below the listed threshold when measured at baseline

Adapted from GSK data on file; DNG# 2016N275692_00GSK, Supplement to Pavord *et al. Lancet*. 2012;380(9842):651-659. GSK data on file: RF/NLA/0153/16

Phenotype-specific clinical trials

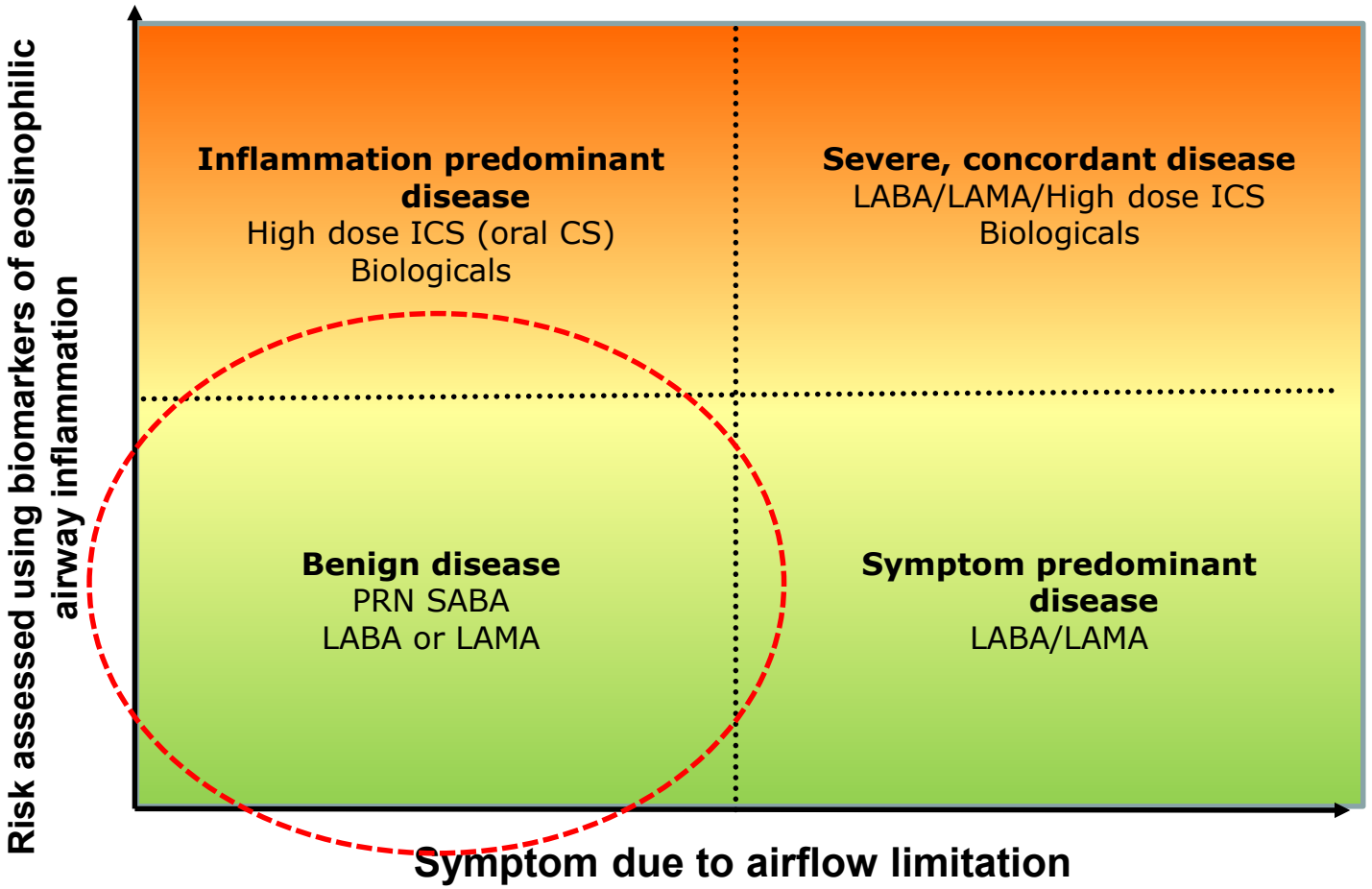
	Mepolizumab*	Tiotropium**
Age	46	53
FEV_1 (% predicted)[#]	78	62
Reversibility (%)	7	13
Exacerbation/pt/yr	3.4	0.66
Sputum eos (%)	6.8	?

[#] Post-bronchodilator

** Haldar et al. NEJM 2009;360:973-84*
*** Kerstjens et al. NEJM 2012;367:1198-207*

Treatable traits: a new approach to airway disease

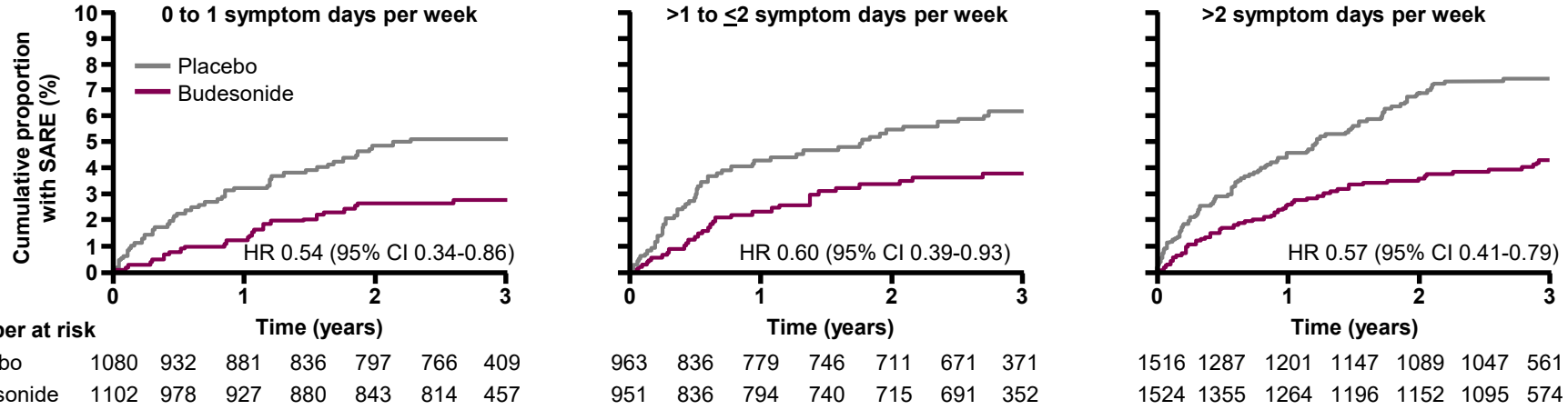
Treatable trait is a measureable aspects of the disease that can be modified with resultant patient benefit



Pavord & Agusti. Eur Respir J 2016;47:1299-303

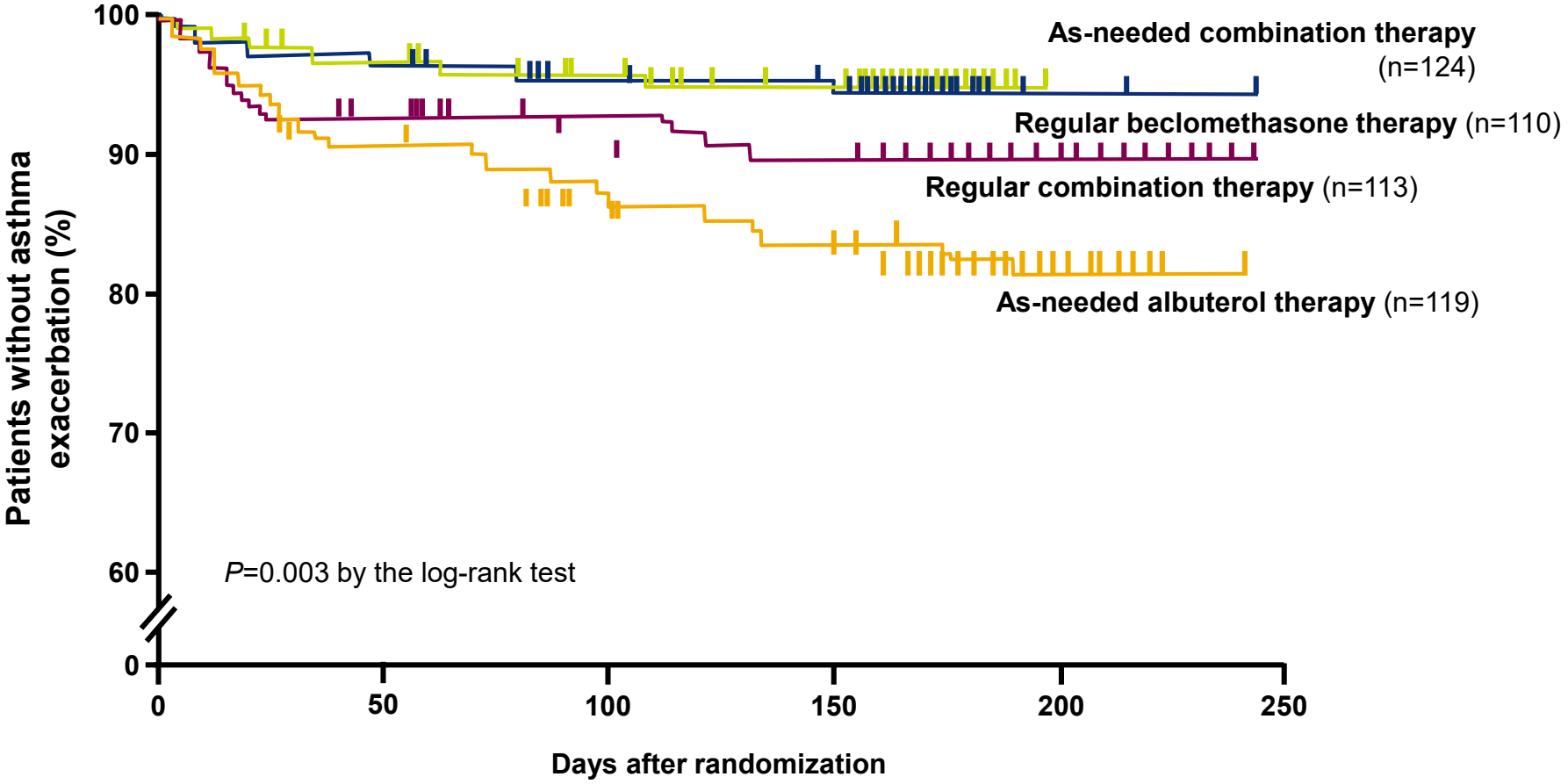
The ‘mild’ episodic asthma paradox

- ‘Mild’ asthma is often episodic asthma in young allergic patients
- Late June, September/October, and mid-winter are high risk times
- Patients are ‘symptom low, risk high’
- They struggle to commit to regular inhaled treatment, although ICS treatment is effective, relatively independent of symptom burden



Reddel et al. Lancet 2017;389:157-66

Maintenance and reliever therapy as an option at steps 1 and 2



Papi A, et al. N Engl J Med 2007;356:2040-2052

Treatable traits: a new approach to management of airway disease

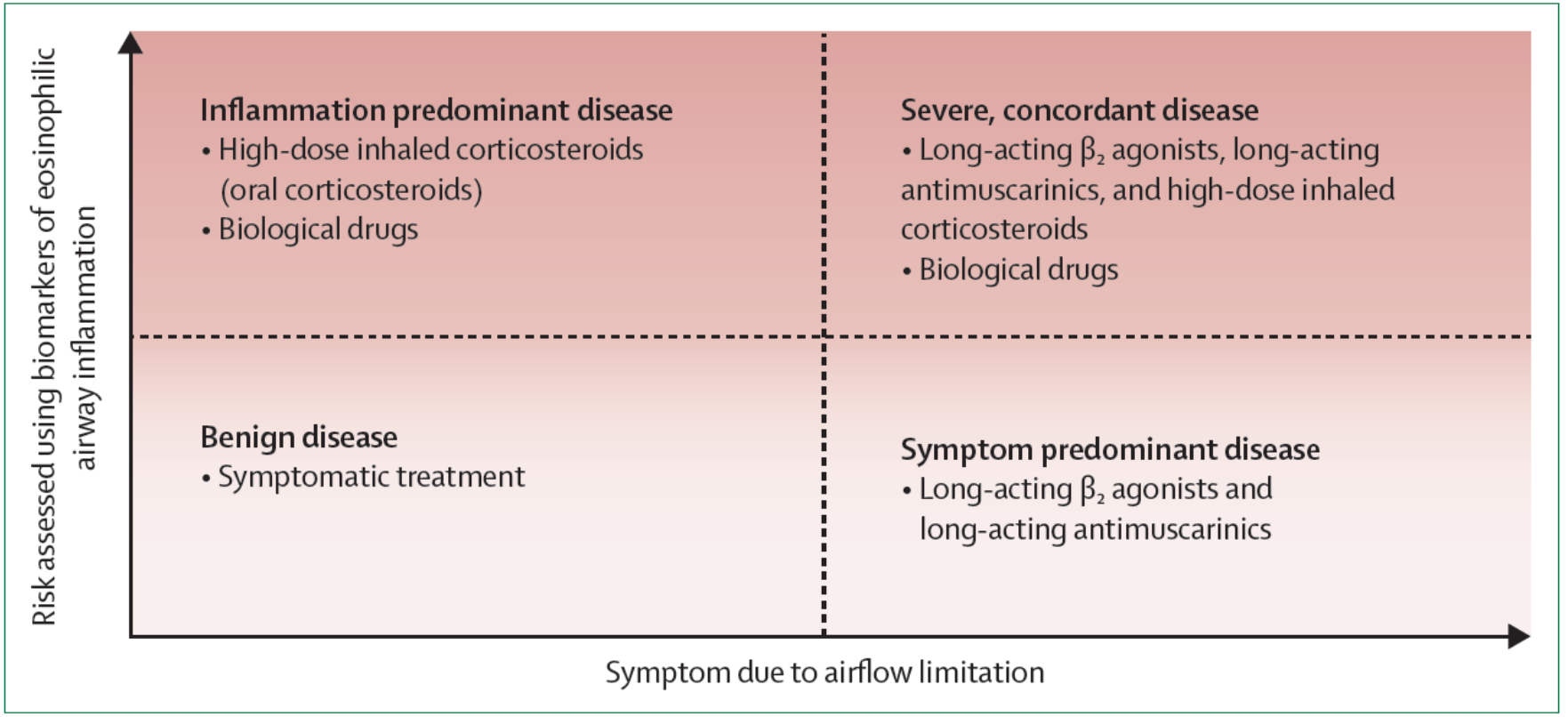


***Figure 7*: Ongoing monitoring of the two dominant treatable traits of airways diseases and precision management**

Combination corticosteroid and rapid-onset β_2 agonist inhaler is the default rescue medication.

Pavord et al. Lancet 2018; 391:350-400

Conclusions

- Key outcomes in asthma have stopped improving despite increasing spending on treatments
- Our current system for classifying airways disease is outmoded and needs replacing
- Our clinical approach needs to move away from categorisation and ‘one size fits all’ management to a precision medicine approach involving analysis and identification of eosinophilic airway inflammation and other treatable traits
- Trait-specific management is already recommended in COPD; it could be offered in asthma with the security of anti-inflammatory reliever therapy

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