FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

VAKGROEP INWENDIGE ZIEKTEN EN PEDIATRIE
ONDERZOEKSGROEP LONGZIEKTEN

ERNSTIG ASTMA EN BIOLOGICALS

Prof dr Guy JOOS, longarts, UZGent - UGent

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UZ GENT

CONFLICT OF INTEREST DISCLOSURE (2018- 21)

Receipt of grants/research supports:
AstraZeneca, Chiesi, GlaxoSmithKline, Novartis

Receipt of honoraria or consultation fees:
AstraZeneca, Bayer, GlaxoSmithKline, Eureca vzw

Participation in a company sponsored speaker bureau:
AstraZeneca, GlaxoSmithKline, Novartis, Lapharcon

ERS Advocacy NCD expert; GINA Advocate; ARIA; EPOS

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ERNSTIG ASTMA EN BIOLOGICALS

1. Moeilijk te controleren astma of ernstig astma ?

2. Onderliggend ziektemechanisme ?

3. Therapeutische mogelijkheden ?

4. Huidige richtlijnen (GINA, severe asthma) ?

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ERS / ATS GUIDELINES ON SEVERE ASTHMA

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

Eur Respir J, 2014

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DEFINITION OF SEVERE ASTHMA (ERS/ATS 2014)

Diagnosis of asthma is confirmed and **comorbidities** addressed

Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic steroids to

* prevent it from becoming uncontrolled, or
* that remains 'uncontrolled' despite this therapy

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DEFINITION OF UNCONTROLLED ASTHMA - AT LEAST ONE OF THE FOLLOWING

Poor symptom control:

ACQ consistently >1.5, ACT < 20

Frequent severe exacerbations:

two or more bursts of systemic corticosteroids in the previous year

Serious exacerbations:

at least one hospitalisation, ICU stay or mechanical ventilation in the previous year

Airflow limitation:

after appropriate bronchodilator withhold, FEV_1 < 80% predicted

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Eur Respir J, 2014

WHY IS ASTHMA NOT CONTROLLED ?

- Problems with compliance
- Problems with inhalation technique
- Environmental factors
  - allergens
  - smoking
- Wrong diagnosis
- Comorbidity(ies)

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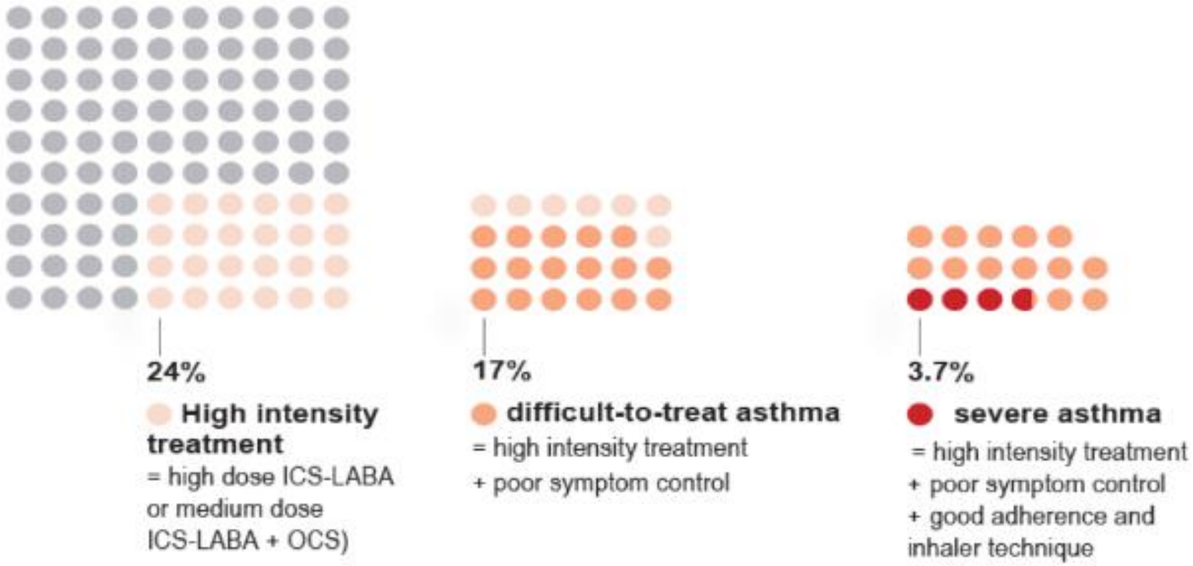
Adherence to medication

“drugs don’t work in patients who don’t take them”

Osterberg and Blaschke, NEJM, 2005

What proportion of adults have severe asthma?



Data from Hekking et al, JACI 2015

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids

WHY IS ASTHMA NOT CONTROLLED ?

- Problems with compliance
- Problems with inhalation technique
- Environmental factors
  - allergens
  - smoking
- Wrong diagnosis
- Comorbidity(ies)

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Strategies to improve adherence in asthma

- Only a few interventions have been studied closely in asthma and found to be effective for improving adherence
  - Shared decision-making
  - Simplifying the medication regimen (once vs twice-daily)
  - Comprehensive asthma education with nurse home visits
  - Inhaler reminders for missed doses
  - Reviewing patients' detailed dispensing records

Comorbidities and associated conditions with severe therapy-resistant asthma

1. Vocal cord dysfunction
2. Dysfunctional breathing
3. Rhinosinusitis
4. Nasal polyps
5. Obstructive sleep apnea
6. Gastroesophageal disease
7. Anxiety
8. Depression
9. Obesity/overweight
10. Corticosteroid side effects: osteoporosis, obesity, diabetes
11. Chronic obstructive pulmonary disease
12. Bronchopulmonary aspergillosis
13. Bronchiectasis
14. Eosinophilic conditions (eosinophilic granulomatosis with angiitis, bronchopulmonary aspergillosis, hypereosinophilic syndrome)

Chung, Semin Respir Crit Care Med 2018

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ERNSTIG ASTMA EN BIOLOGICALS

1. Wat is ernstig astma ?

2. Onderliggend ziektemechanisme ?

3. Therapeutische mogelijkheden ?

4. Huidige richtlijnen (GINA severe asthma) ?

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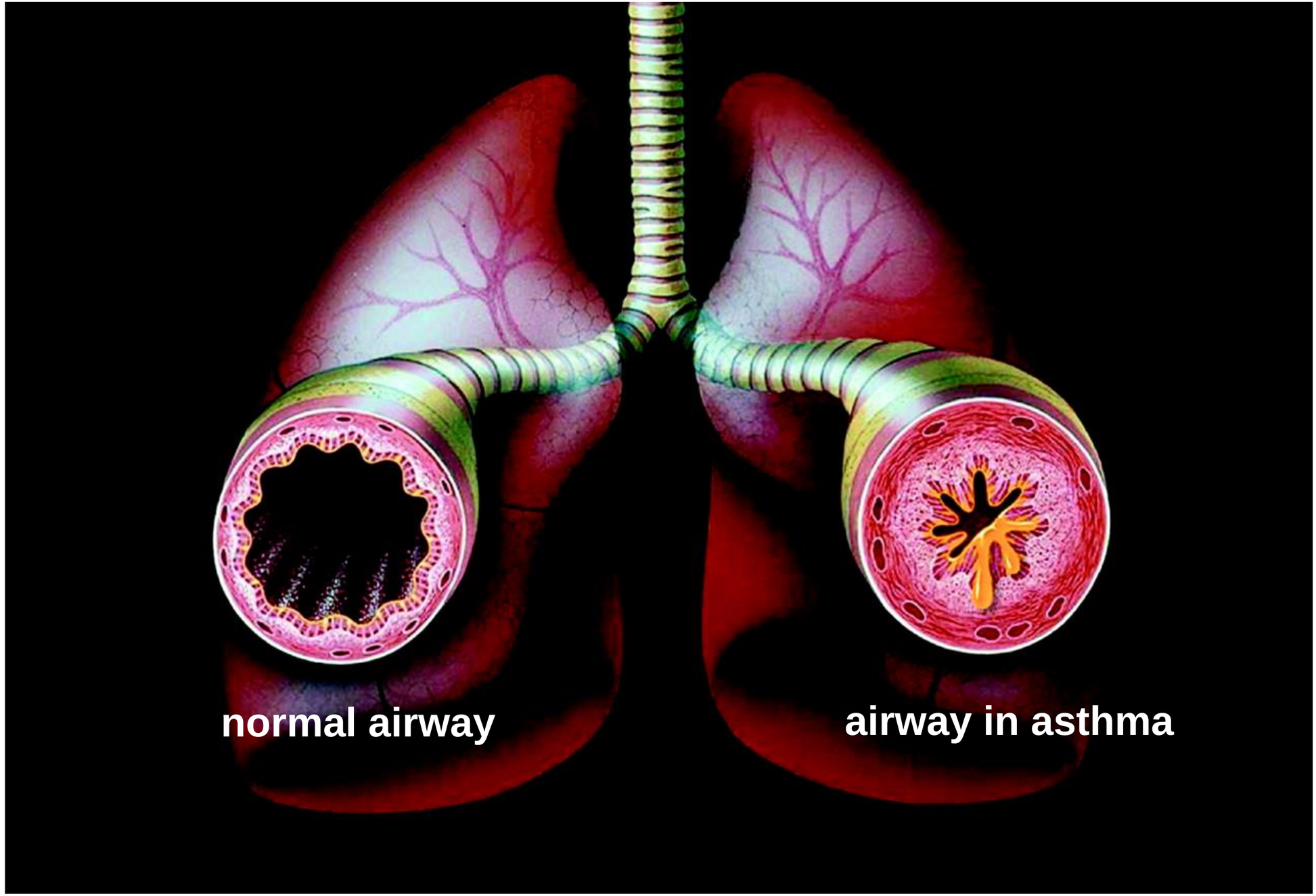

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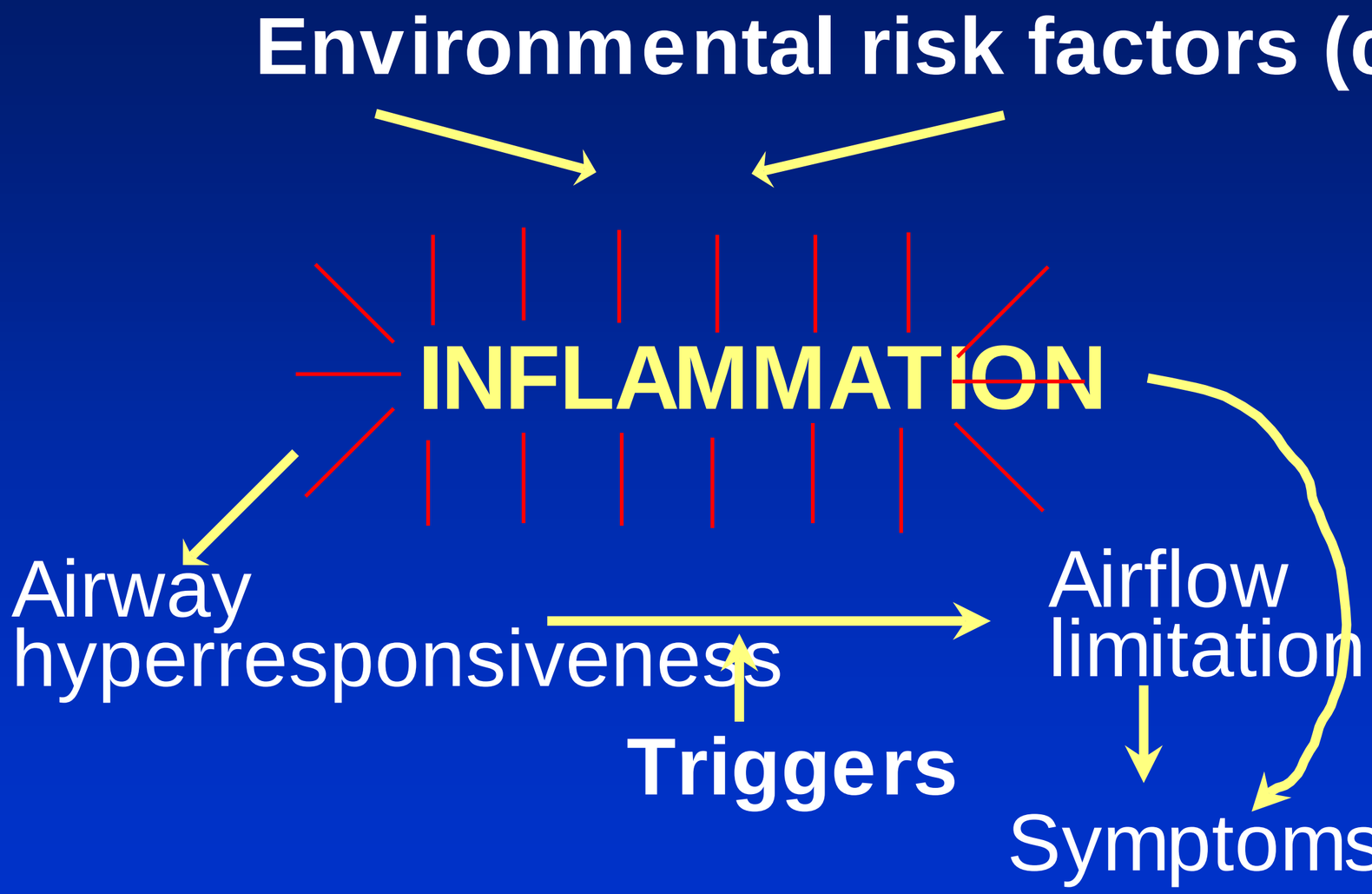
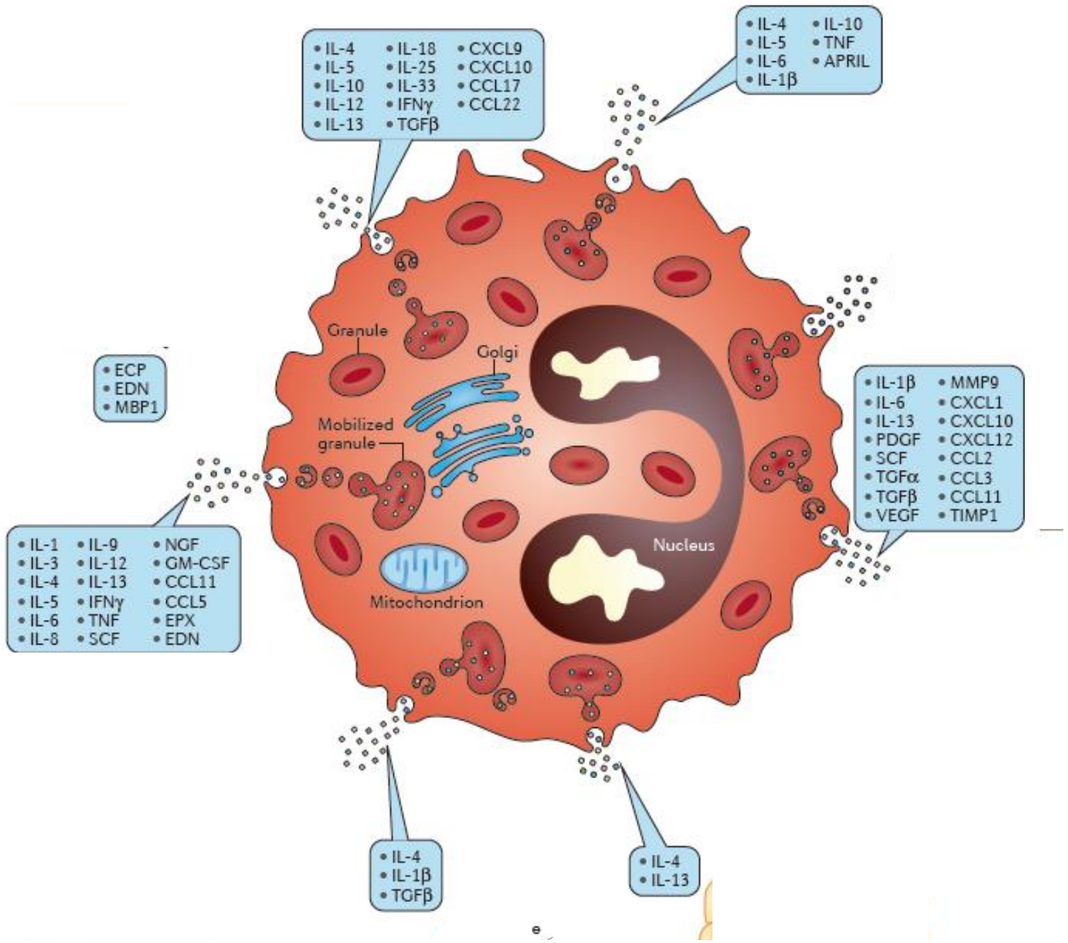
Jeffery, Am J Respir Crit Care Med, 2001, 164, S28-S38

Asthma



GINA 2002

The eosinophil
“the good, the bad, and the ugly”



Weller and Spencer, Nat Rev Immunol 2017

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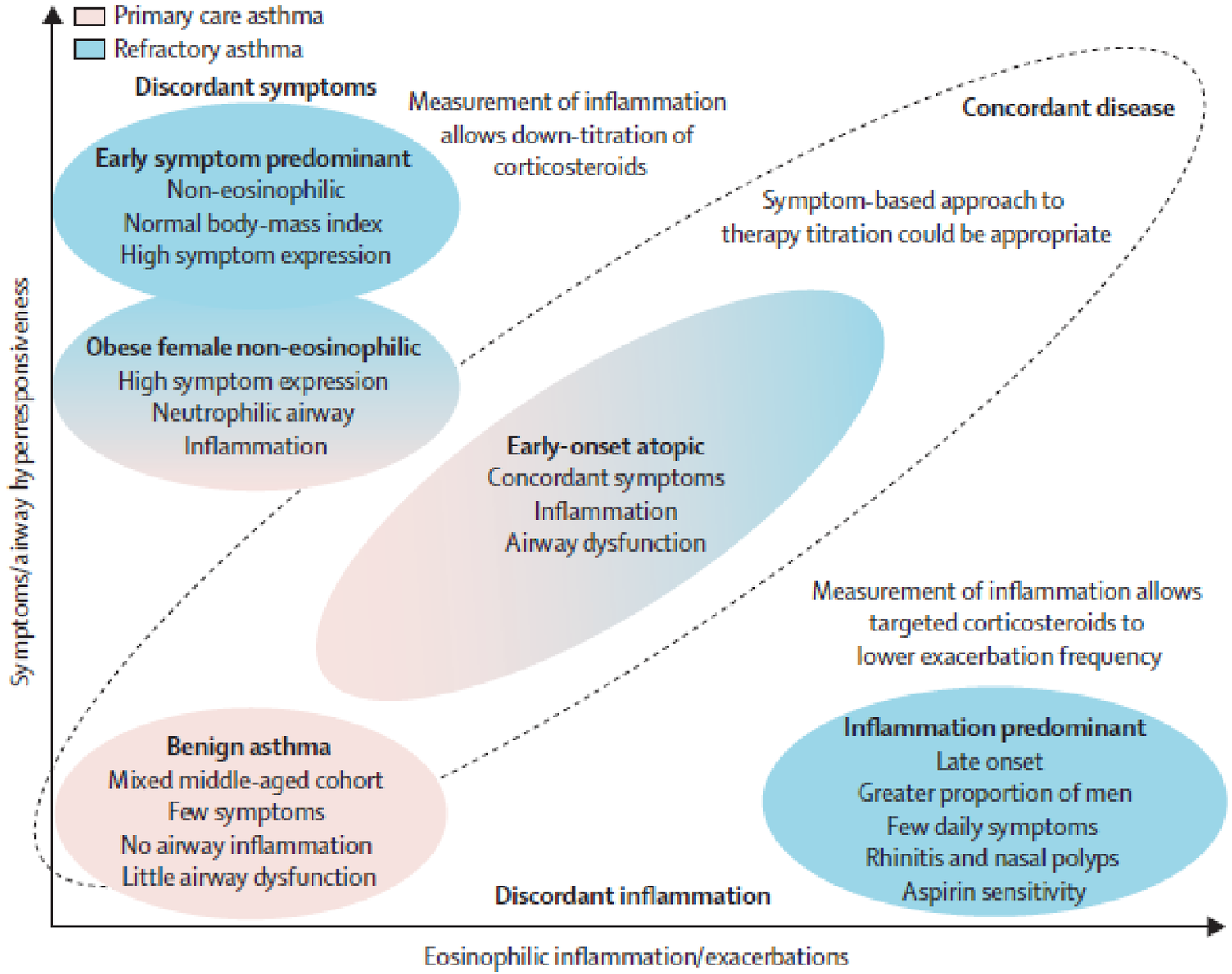
ASTHMA PHENOTYPES IDENTIFIED USING CLUSTER ANALYSIS



Haldar , AJRCCM 2008;
Pavord, Lancet RM 2013

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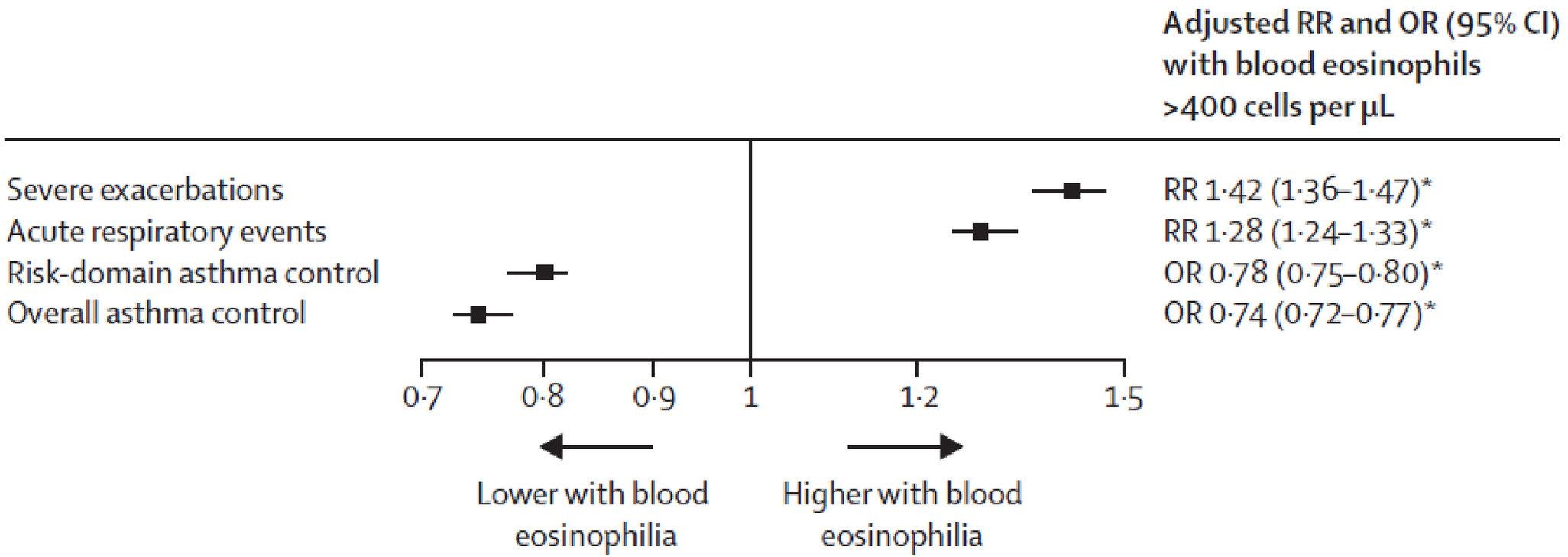
Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study



Price et al, Lancet RM 2015

Respiratory Medicine (2014) 108, 1723–1732

Available online at www.sciencedirect.com

ScienceDirect

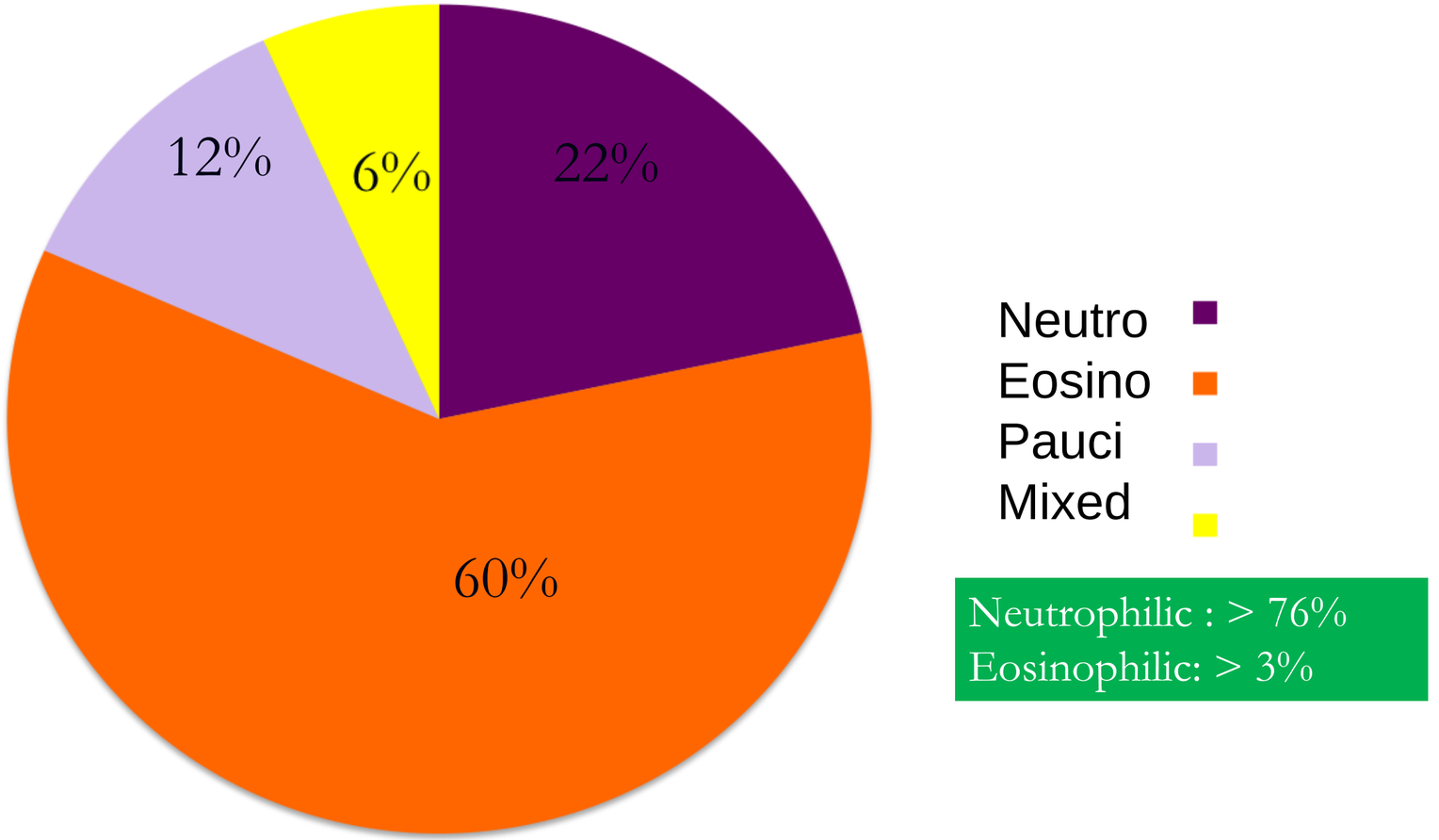
journal homepage: www.elsevier.com/locate/rmed

Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR)

F. Schleich [a,*], G. Brusselle [b], R. Louis [a], O. Vandenplas [c], A. Michils [d], C. Pilette [e], R. Peche [f], M. Manise [a], G. Joos [b]

Sputum cellular phenotypes in severe asthma (N=60)

Success rate = 72% (60/83)



Neutrophilic : > 76%
Eosinophilic: > 3%

Schleich et al., Respir Med 2014

Graff *et al. Respiratory Research* (2020) 21:214
https://doi.org/10.1186/s12931-020-01460-7

Respiratory Research

RESEARCH Open Access

Chronic oral corticosteroids use and persistent eosinophilia in severe asthmatics from the Belgian severe asthma registry

S. Graff[1*], S. Vanwynsberghe[1], G. Brusselle[1], S. Hanon[2], C. Sohy[3], L. J. Dupont[4], R. Peche[5], A. Michils[6], C. Pilette[7], G. Joos[2], R. E. Louis[8] and F. N. Schleich[8]

*"at enrollment, **211 (21%) SA patients** were taking maintenance OCS (median dose: 8 [IQR: 5–10]) mg prednisone equivalent). BEC was high (> 400/mm3) in 44% of the OCS treated population*

***risk factors** for chronic use of OCS in SA were late-onset asthma (i.e. age of onset > 40 yr), frequent exacerbations (i.e. ≥2 exacerbations in the previous year) and non-atopic asthma"*

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ERNSTIG ASTMA EN BIOLOGICALS

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2. Onderliggend ziektemechanisme ?

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4. Huidige richtlijnen (GINA severe asthma) ?

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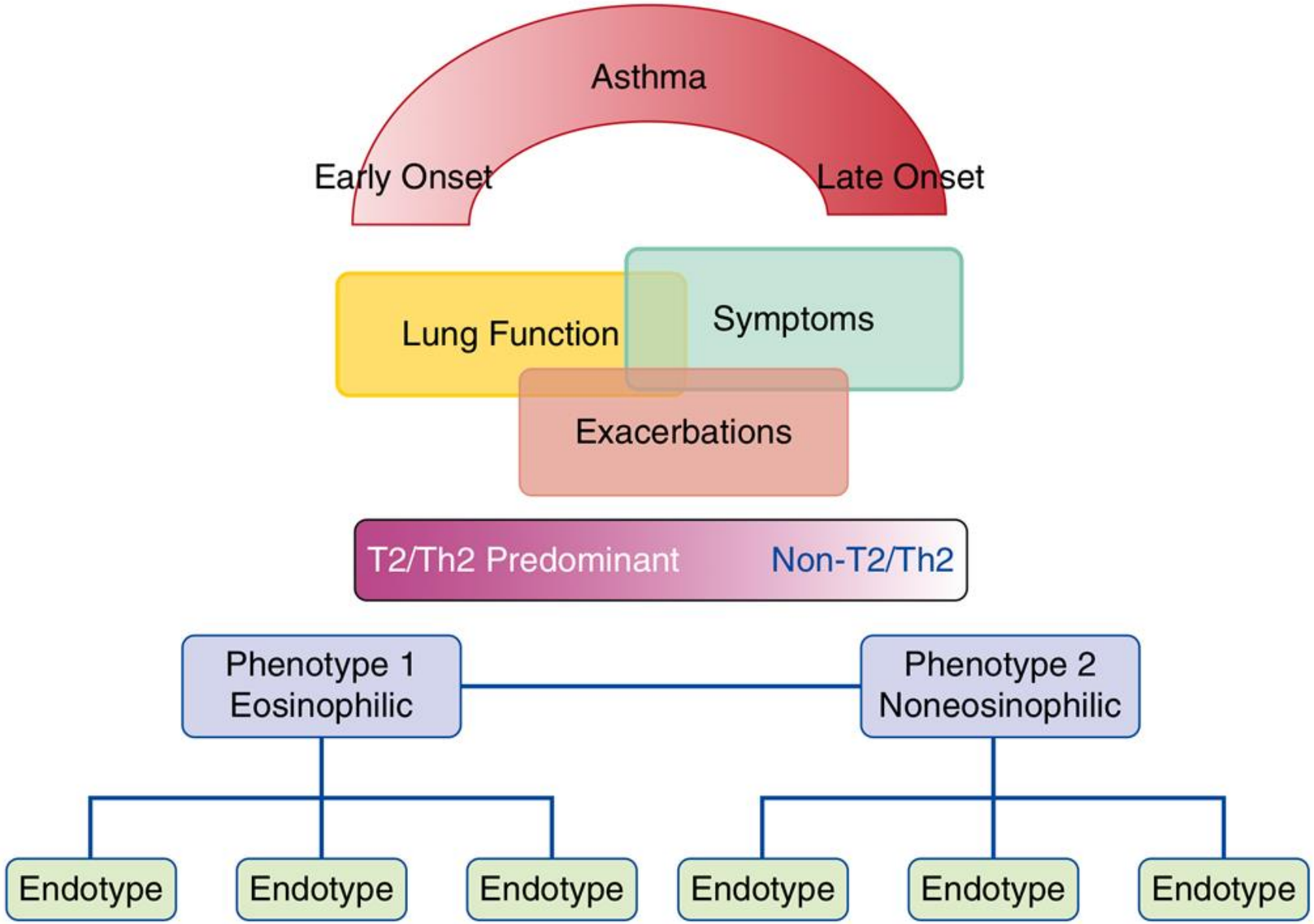
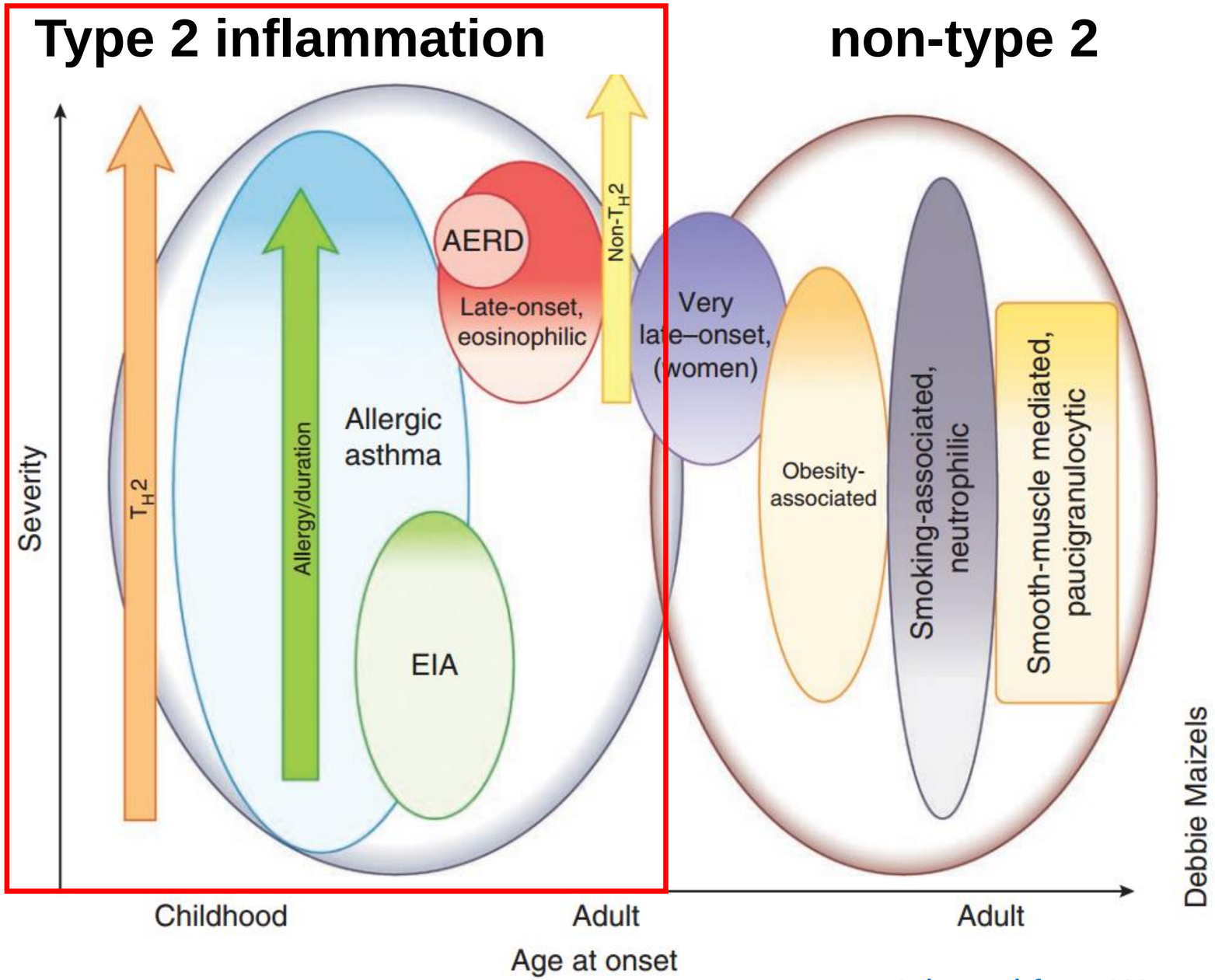


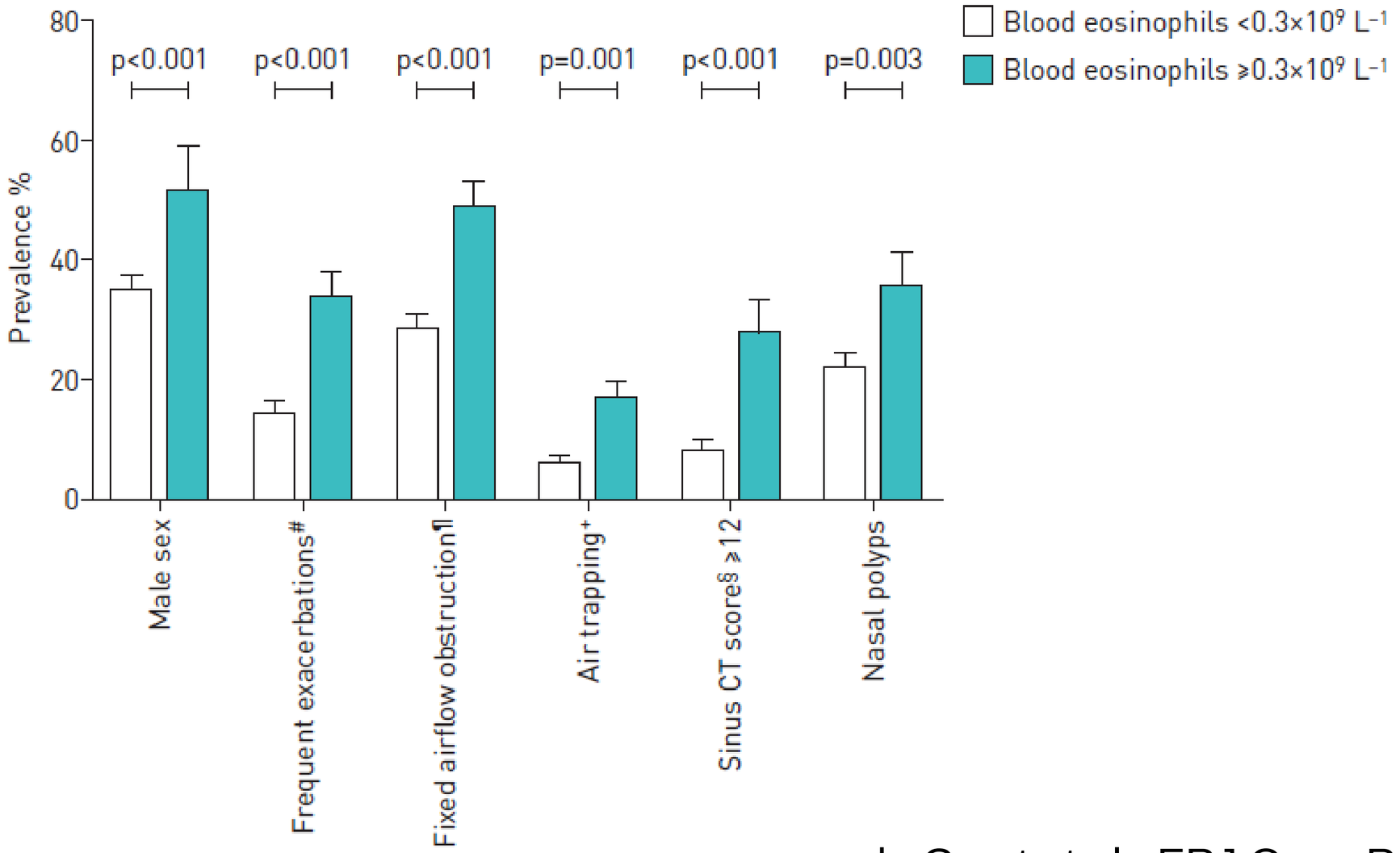
Wenzel, Nat Med 2012; Carr et al., AJRCCM 2018

Asthma is a heterogenous disease



Adapted from Wenzel S. , Nat. Med, 18; 5, 2012

CLINICAL PROFILE OF ADULT-ONSET EOSINOPHILIC ASTHMA



de Groot et al., ERJ Open Res 2016

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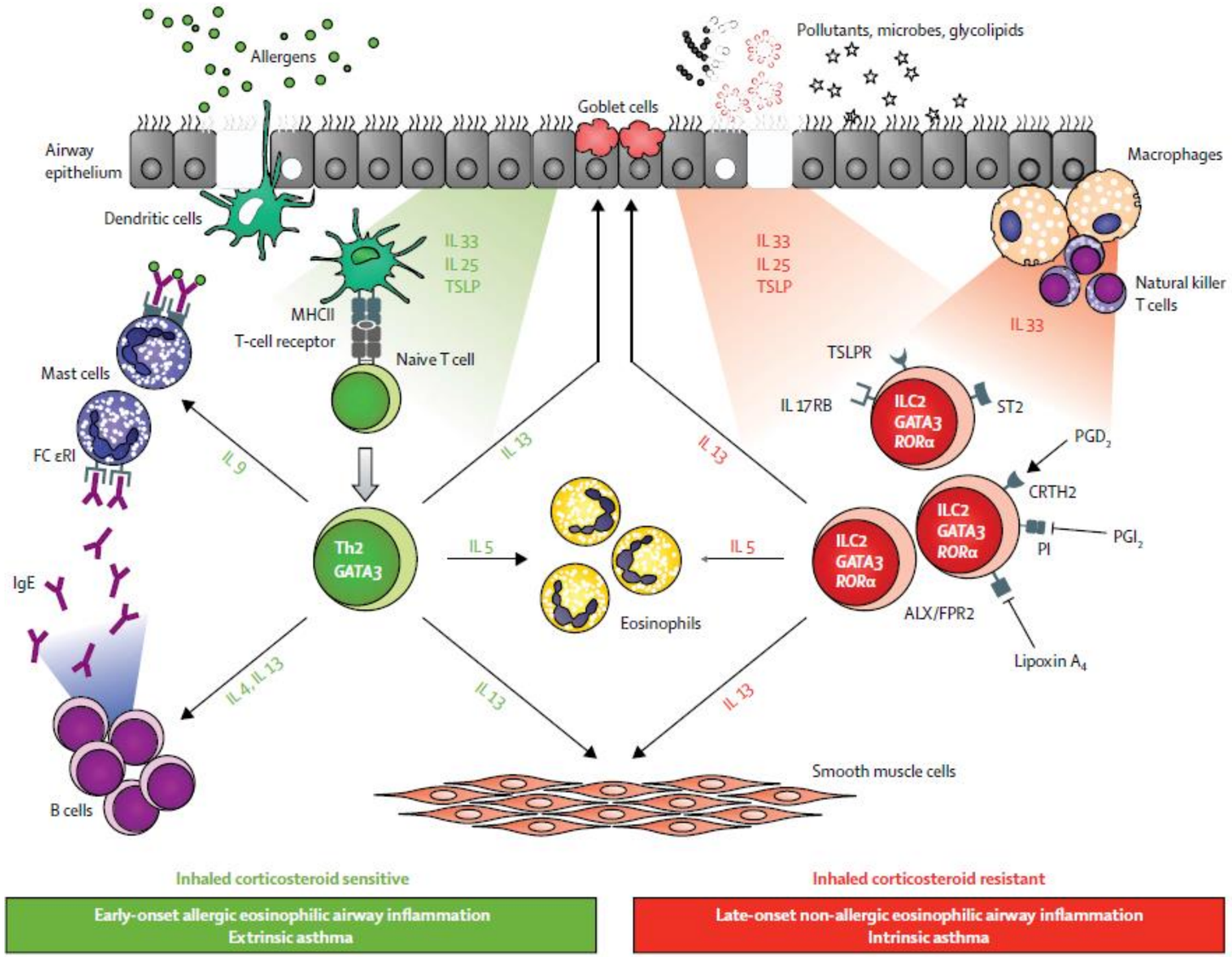
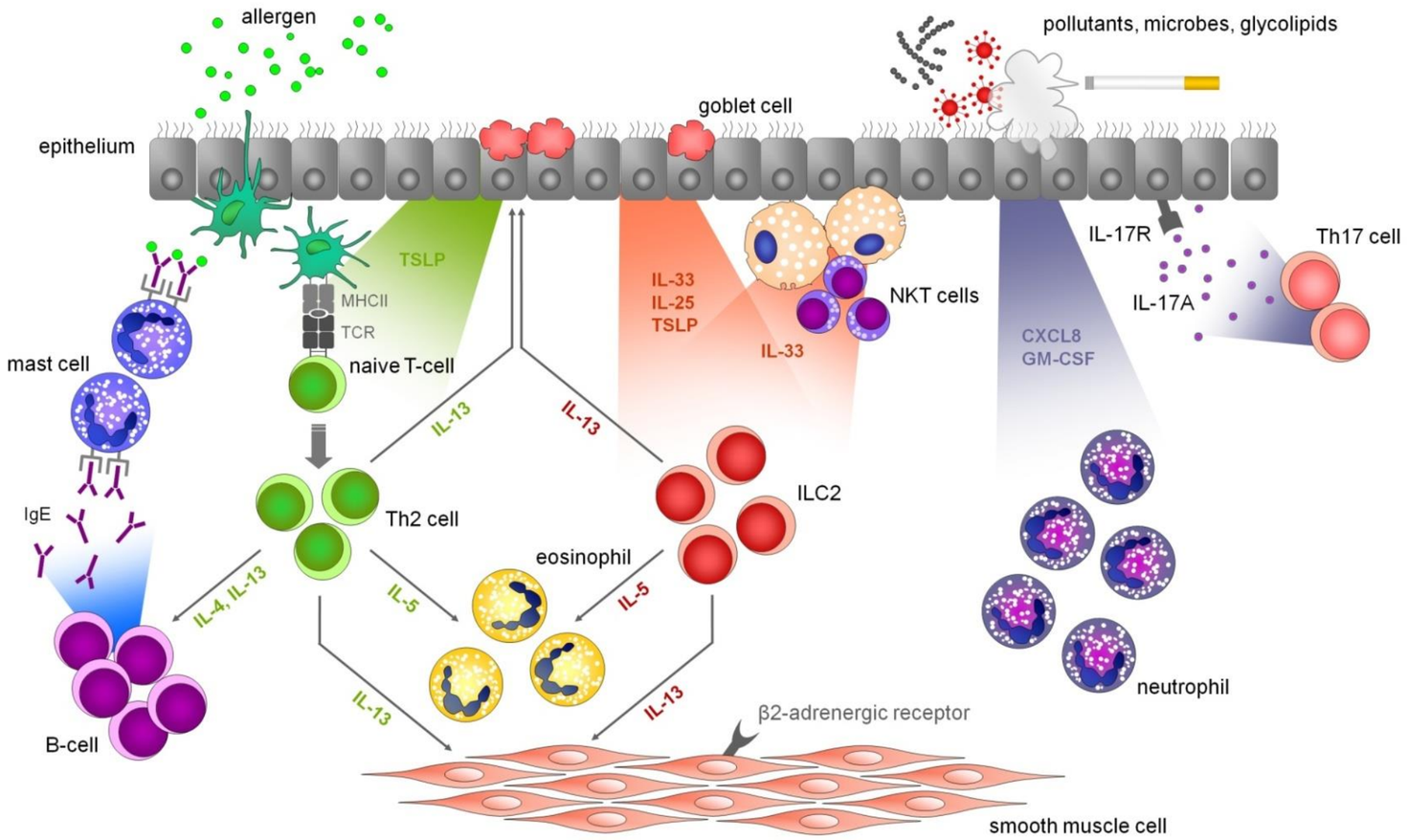
Pathways leading to eosinophilic airway inflammation



Pavord et al., Lancet 2018 (adapted from Brusselle et al., Nat Med 2013)

Targeted therapies in severe asthma



allergic eosinophilic asthma	nonallergic eosinophilic asthma	neutrophilic asthma
ICS ± LABA add-on treatment: • anti-IgE (omalizumab) • anti-IL-13 • anti-IL-4Rα (dupilumab)	ICS ± LABA add-on treatment: • anti-IL-5 (mepolizumab) • anti-IL-13 • anti-IL-4Rα (dupilumab)	ICS ± LABA add-on treatment: • macrolides (azithromycin) • anti-IL-17 • anti-IL-17R (brodalumab)

Brusselle G. et al, Annals of ATS 2014.

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TABLE 1 Type 2 inflammation and phenotypic characteristics of asthma [3–5]

Type 2-high asthma IL-4, IL-5, IL-13	Type 2-low asthma
Blood eosinophilia (⩾150 cells·μL^{-1} [6])	Low blood eosinophil counts (<150 cells·μL^{-1})
Elevated tissue eosinophilia	Sputum neutrophilia (>40% of total cells [6–8])
Elevated serum IgE (surpassing the normal range of 1.5–114 kU·L^{-1}[#] [9, 10])	Obesity associated
Elevated F_{eNO} (>19.5 ppb [11])	Poor response to corticosteroids
Upper airway comorbidities, including AR and CRSsNP/CRSwNP	
Other type 2 comorbidities, including EoE and AD	
Responsive to corticosteroids	

IL: interleukin; Ig: immunoglobulin; F_{eNO}: fraction of exhaled nitric oxide; AR: allergic rhinitis; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; EoE: eosinophilic oesophagitis; AD: atopic dermatitis. [#]: value within the normal range does not exclude atopy [10].

Busse et al., Eur Respir J, 2021

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ADD ON BIOLOGICALS IN SEVERE ASTHMA

➔ anti-IgE (omalizumab)

➔ anti-IL5 (mepolizumab, reslizumab, benralizumab)

➔ anti IL4/13 (dupilumab)

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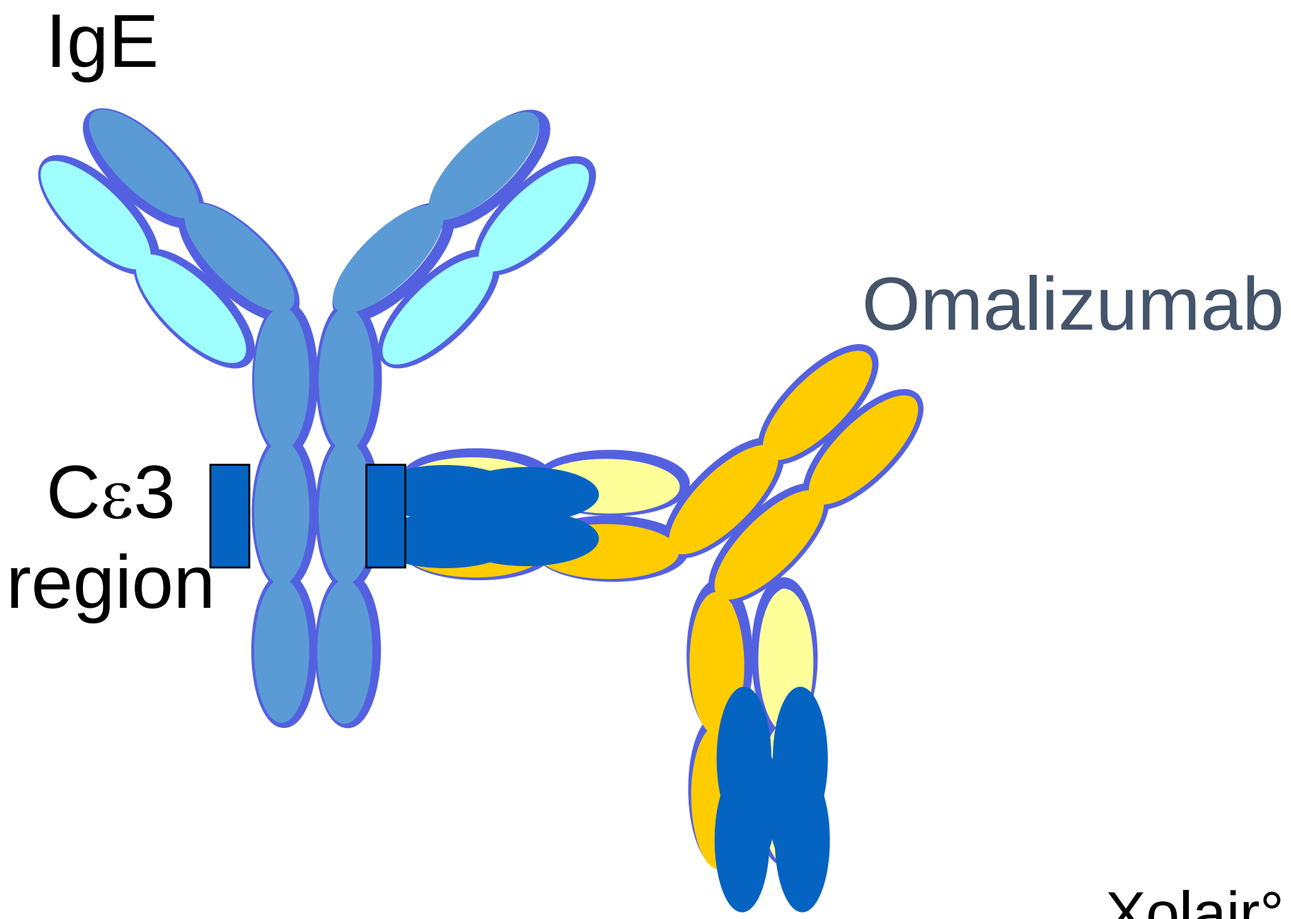
HUMANIZED MONOCLONAL ANTI-IGE ANTIBODY: OMALIZUMAB



Xolair°

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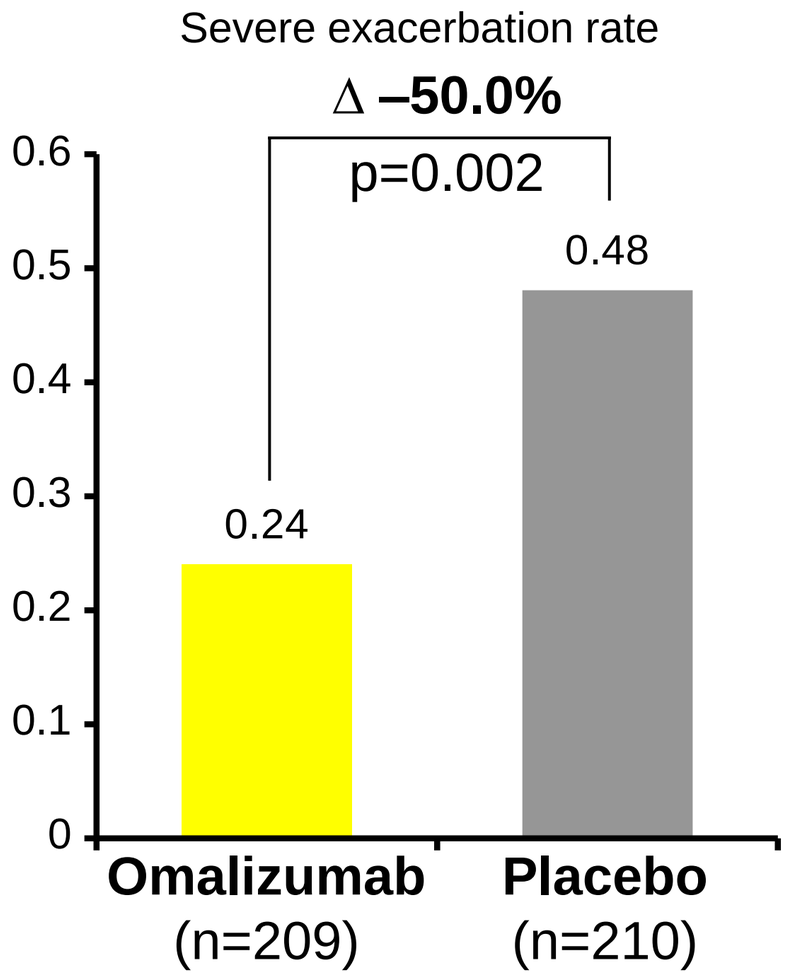
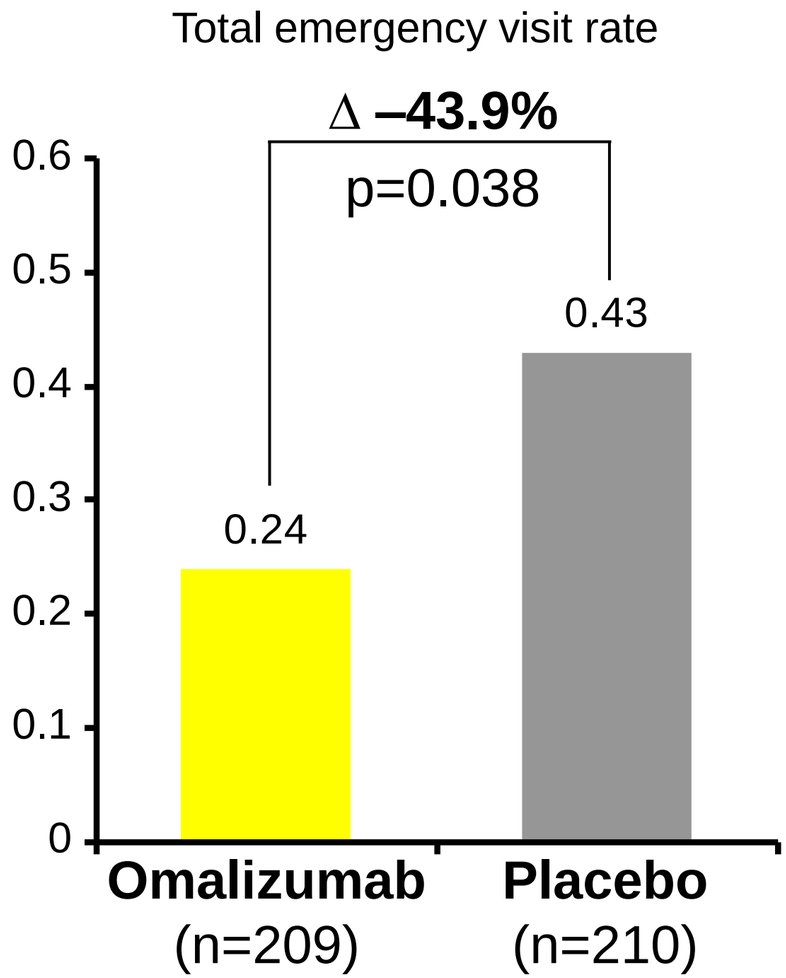
OMALIZUMAB SIGNIFICANTLY REDUCES SEVERE EXACERBATIONS AND EMERGENCY VISITS





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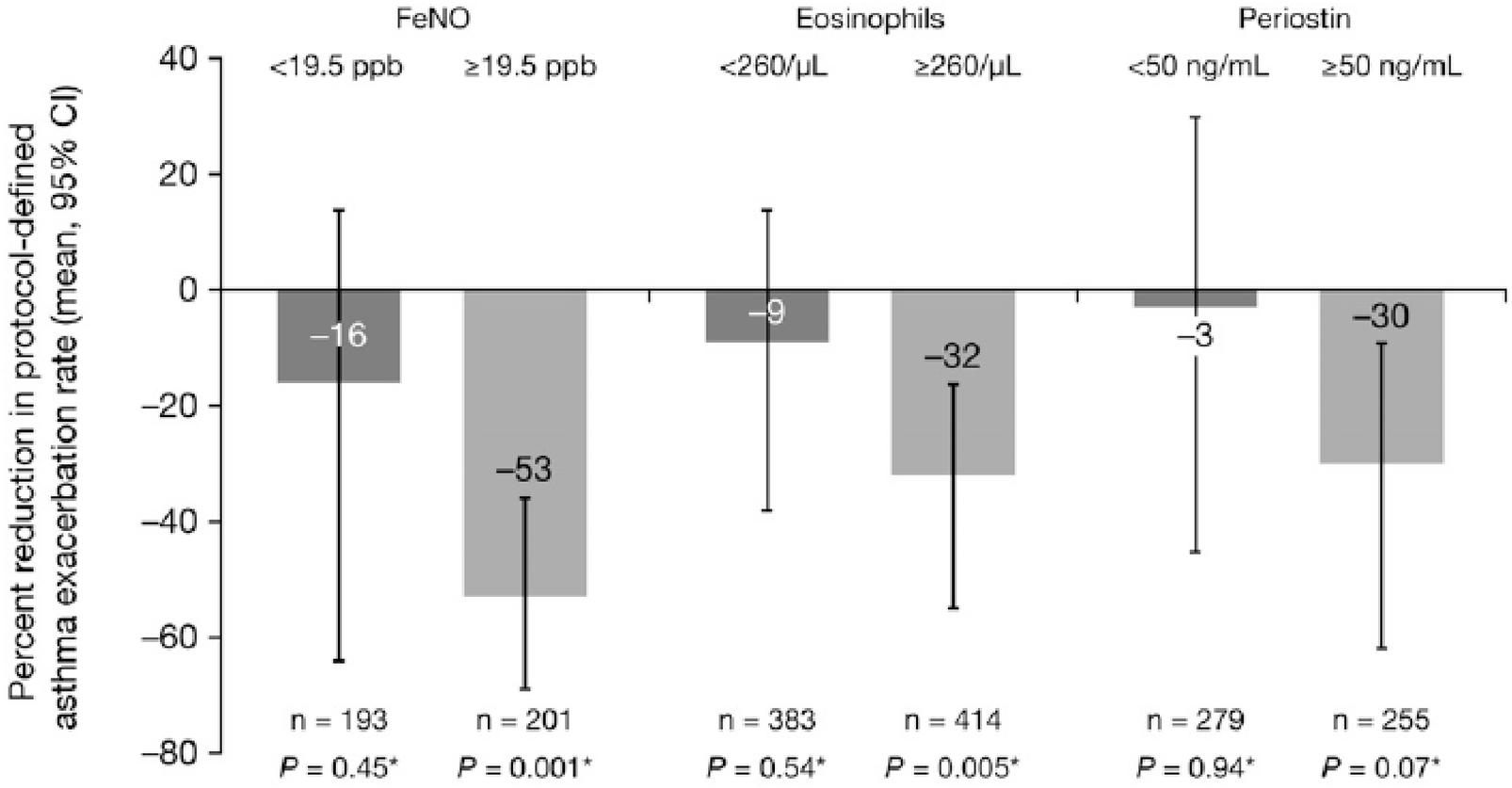
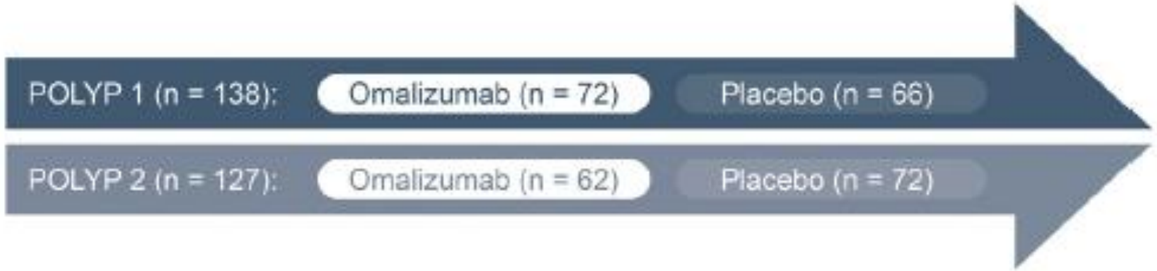
Humbert M, et al. Allergy 2005

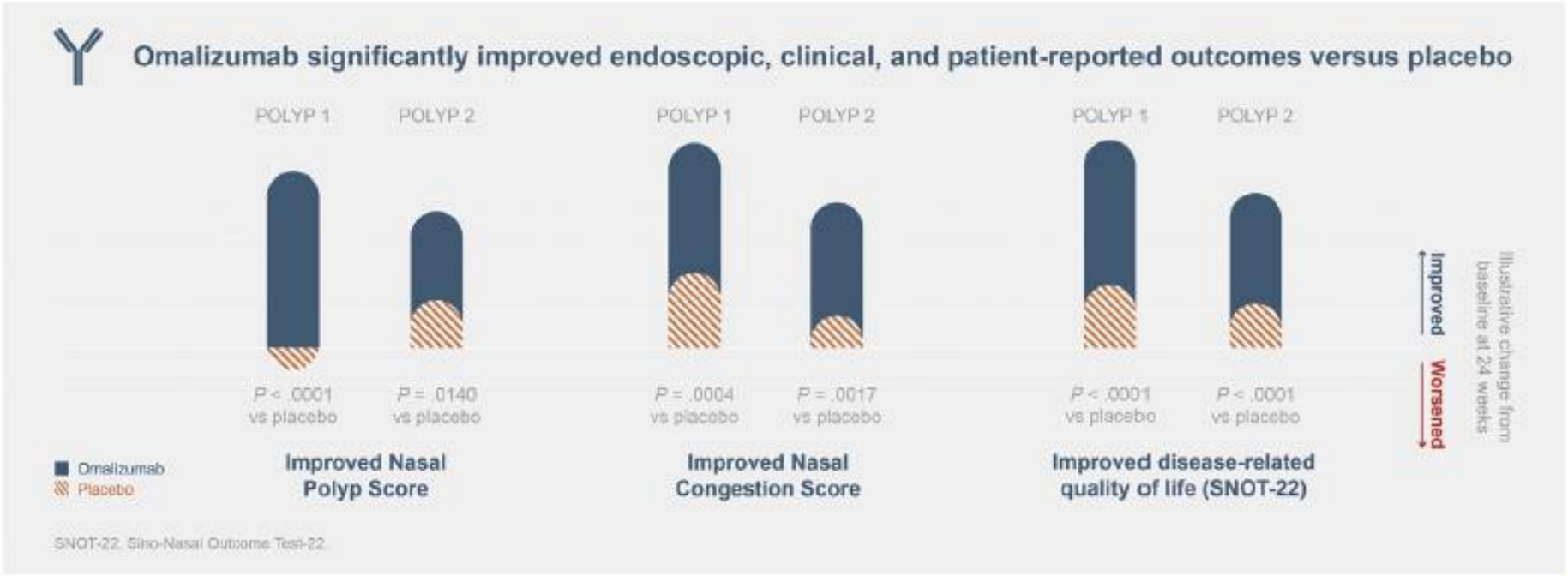
EXPLORING THE EFFECTS OF OMALIZUMAB IN ALLERGIC ASTHMA - AN ANALYSIS OF BIOMARKERS IN THE EXTRA STUDY



Hanania, AJRCCM 2015

Omalizumab in patients with nasal polyposis: 2 replicate phase 3 trials

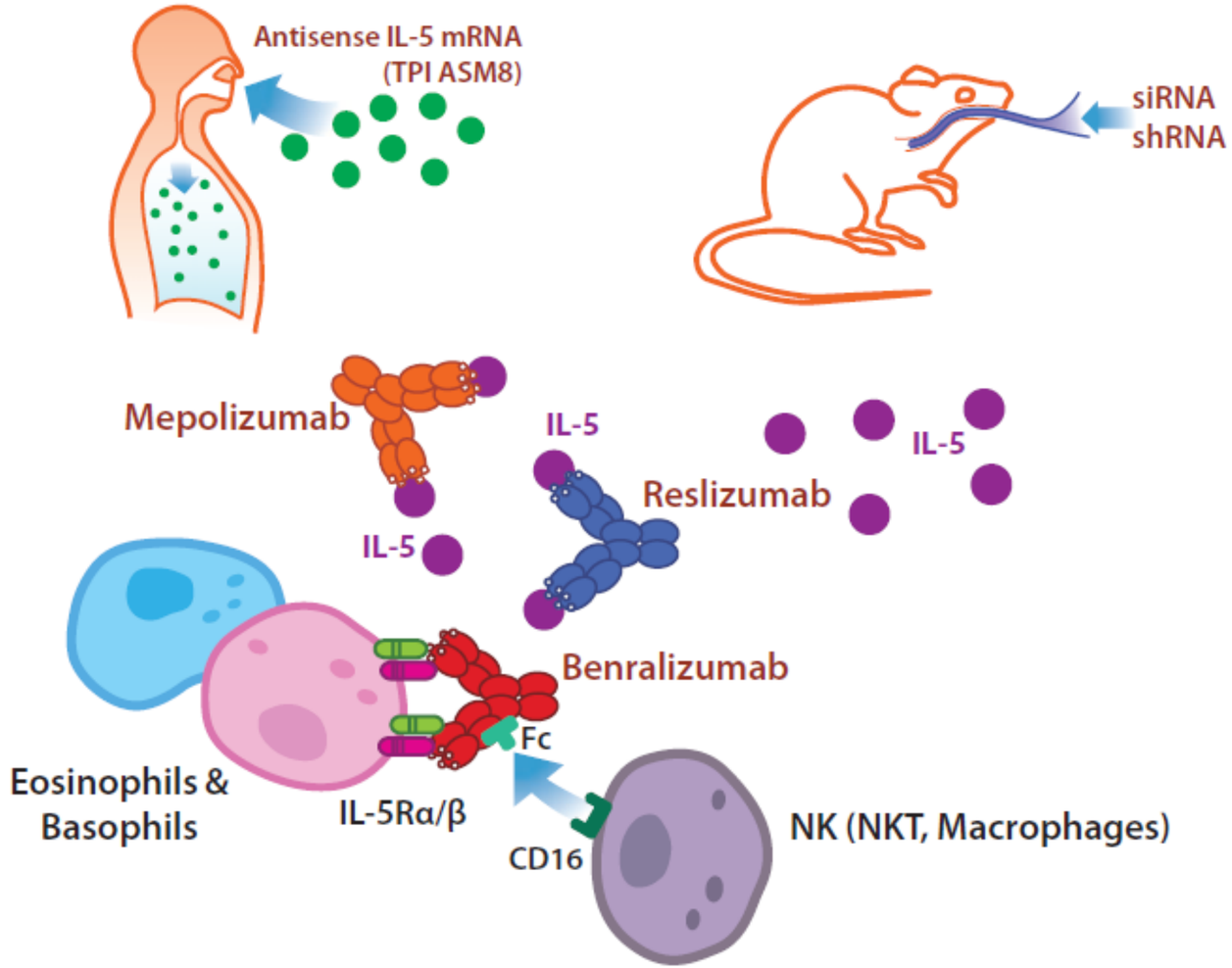




Gevaert et al., J Allergy Clin Immunol 2020

IL-5/IL-5R TARGETED THERAPEUTIC APPROACHES FOR EOSINOPHIL-ASSOCIATED DISEASES

Nucala°



Cinqaero°

Fasenra°

Molfino, Clin Exp Allergy, 2012

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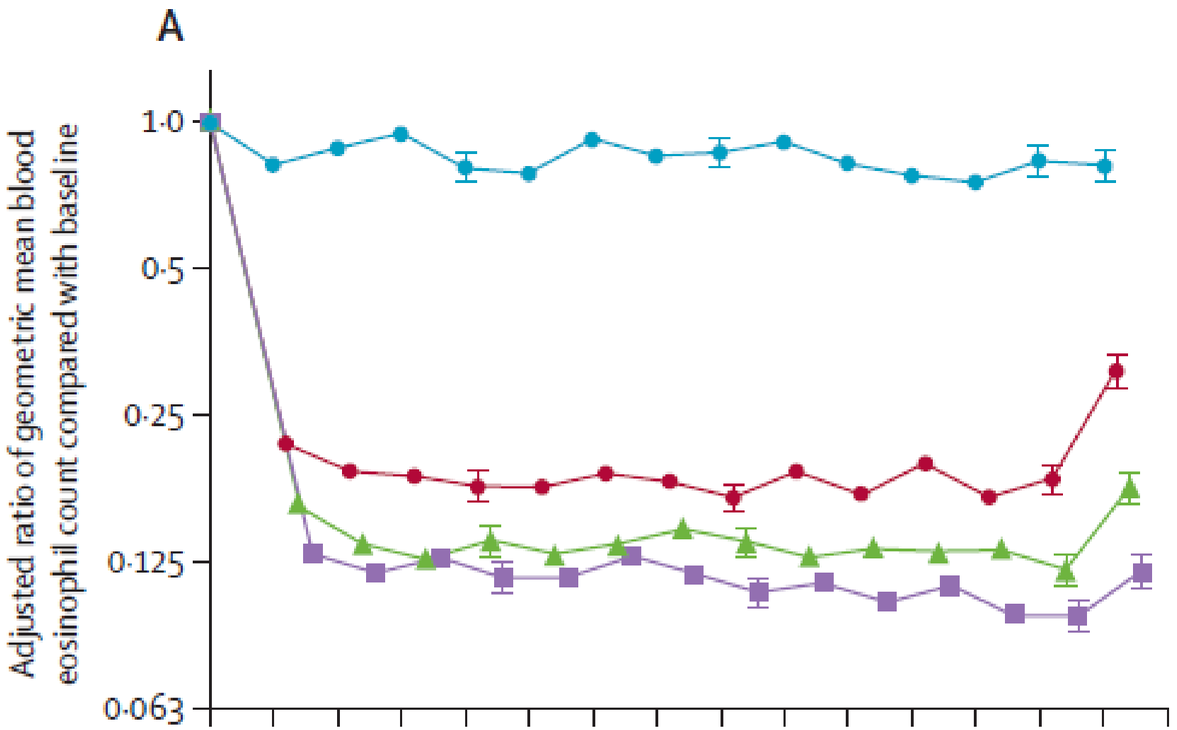
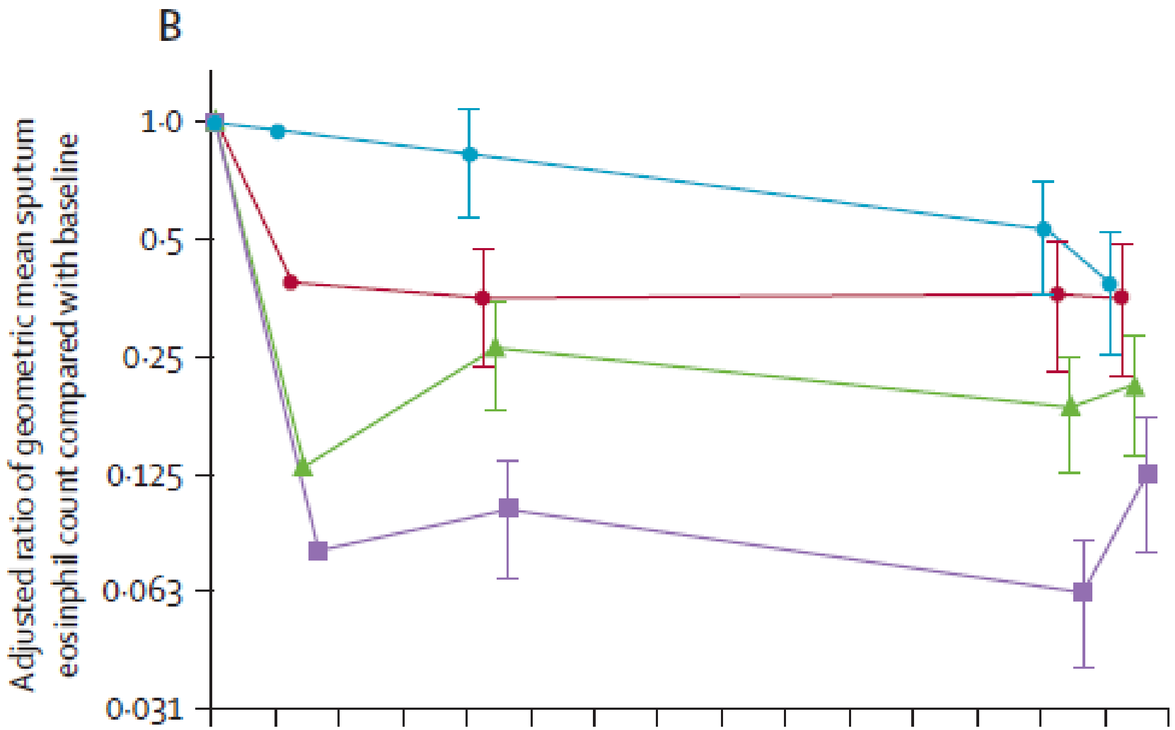
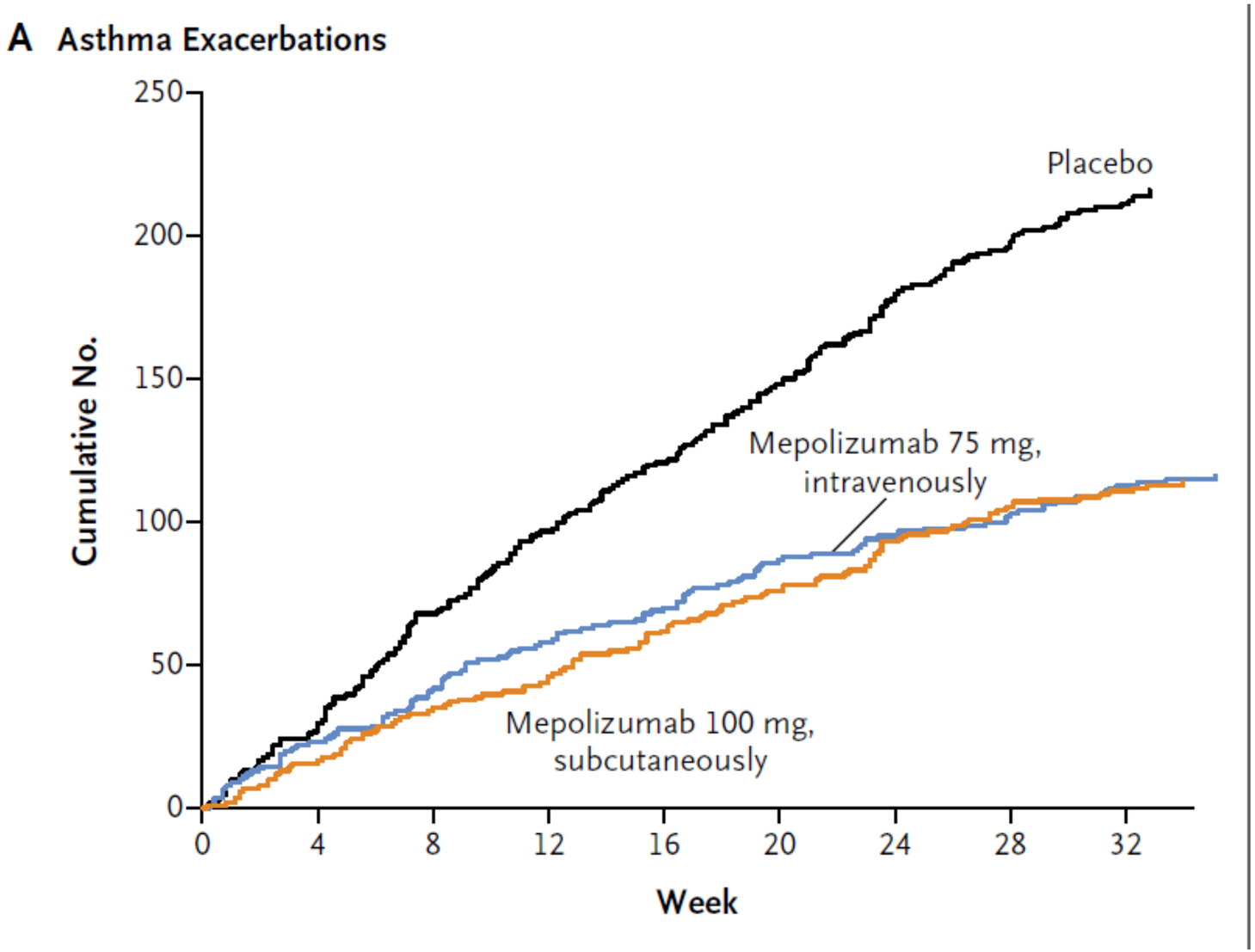
MEPOLIZUMAB IN SEVERE EOSINOPHILIC ASTHMA: BLOOD AND SPUTUM EOSINOPHILIA





Pavord I. et al, Lancet 2012 (DREAM study).

ANTI-IL5 MEPOLIZUMAB REDUCES EXACERBATION RATE IN SEVERE EOSINOPHILIC ASTHMA



Ortega et al., NEJM 2014

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DETERMINANTS OF RESPONSE TO ANTI-IL5

- Eosinophils
- Exacerbations
- Age of onset

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ADD ON BIOLOGICALS IN SEVERE ASTHMA

➔ anti-IgE (omalizumab)

➔ anti-IL5 (mepolizumab, reslizumab, benralizumab)

➔ anti IL4/13 (dupilumab)

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

Dupixent °

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NEJM, 21 may 2018

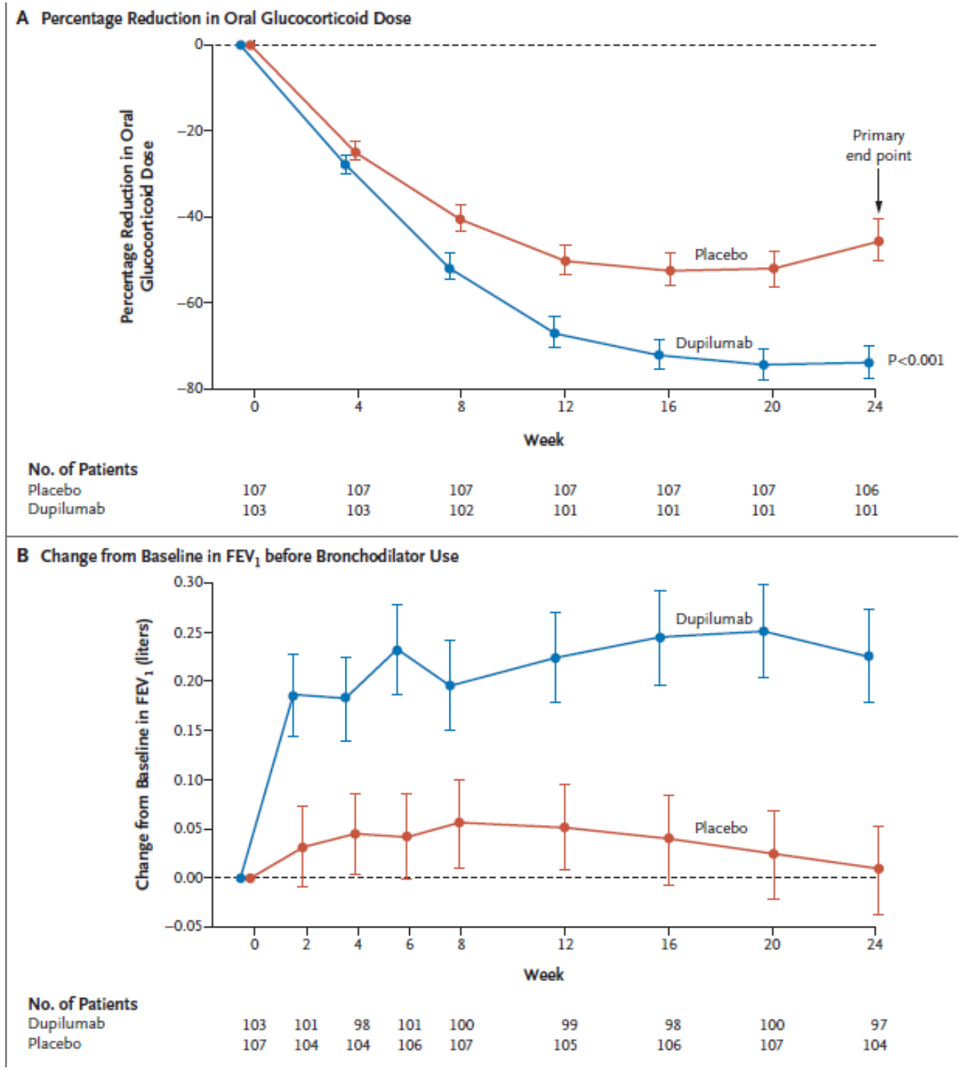
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D., Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma



Rabe et al., NEJM, online 21 may 2018

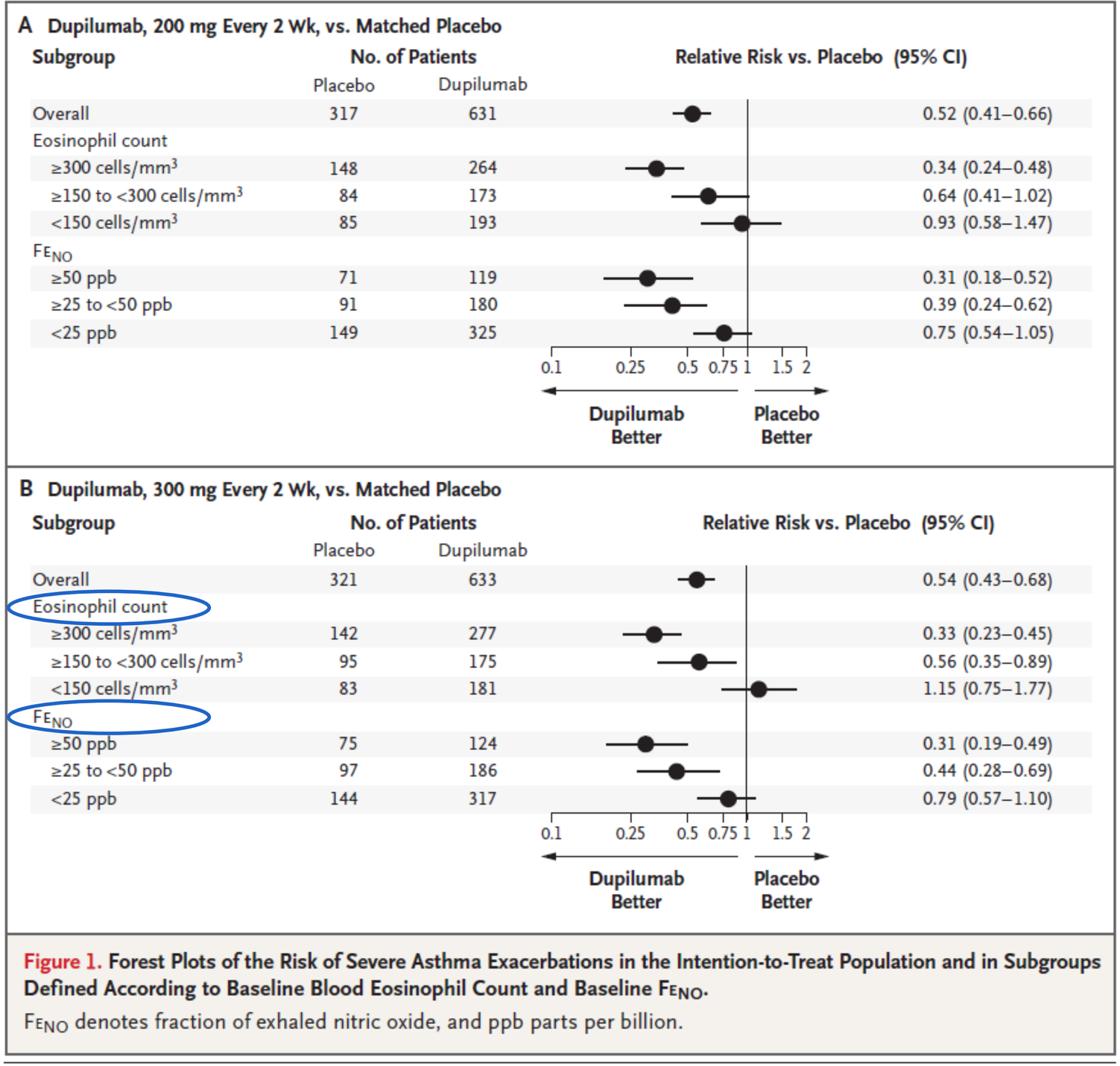


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline F_{ENO}.

F_{ENO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

Castro et al., NEJM 2018

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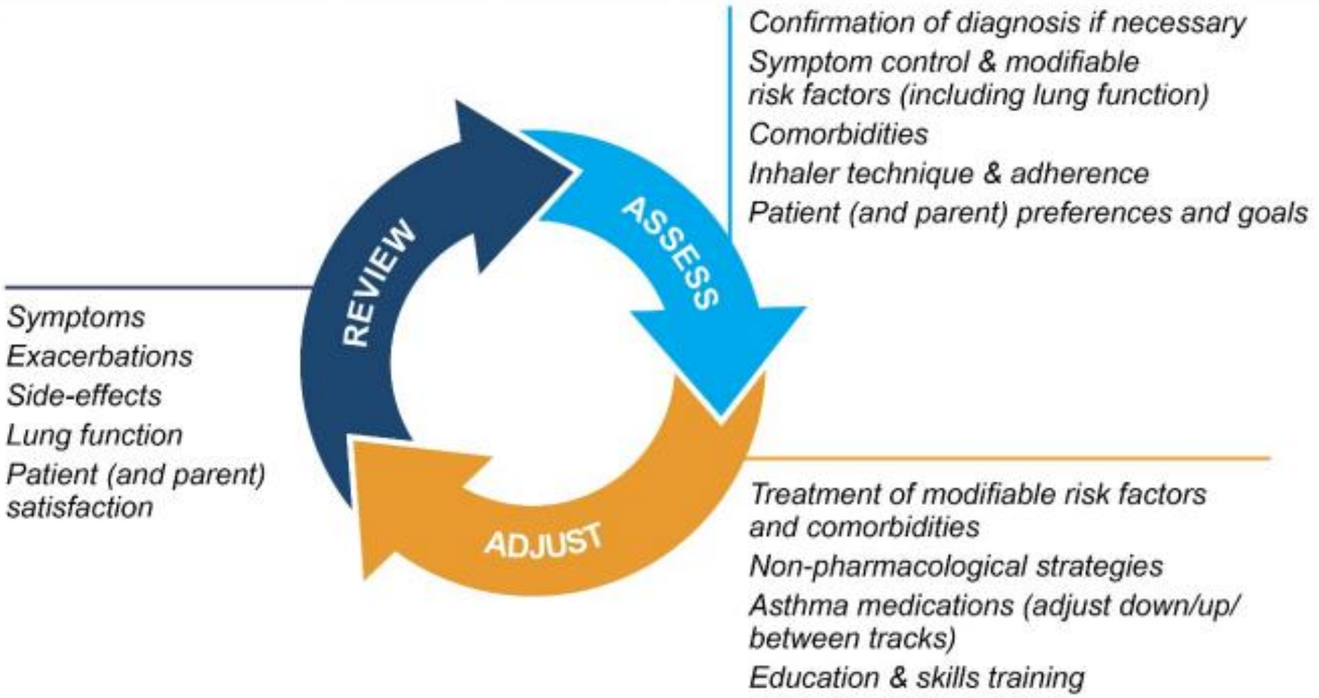
Personalized asthma management



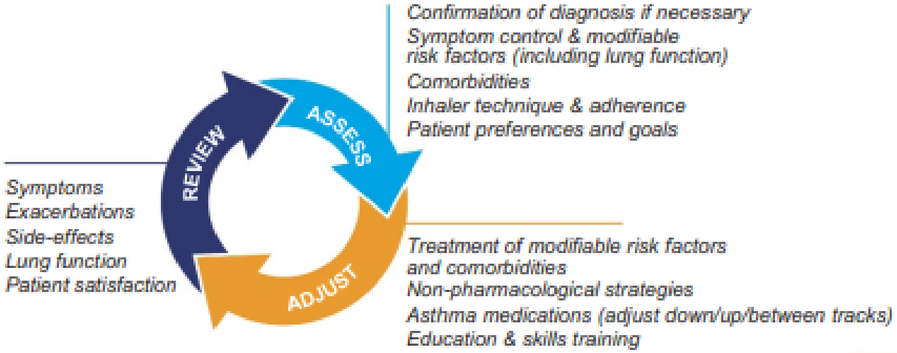
- NOT just about medications, NOT one-size-fits-all

GINA 2021 Box 3-2

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever	**STEPS 1 – 2** As-needed low dose ICS-formoterol		**STEP 3** Low dose maintenance ICS-formoterol	**STEP 4** Medium dose maintenance ICS-formoterol	**STEP 5** Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
	RELIEVER: As-needed low-dose ICS-formoterol				
CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller	**STEP 1** Take ICS whenever SABA taken	**STEP 2** Low dose maintenance ICS	**STEP 3** Low dose maintenance ICS-LABA	**STEP 4** Medium/high dose maintenance ICS-LABA	**STEP 5** Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
	RELIEVER: As-needed short-acting β2-agonist				
Other controller options for either track		*Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

GINA 2021, Box 3-5A

Add-on long-acting muscarinic antagonists (LAMA)

- Step 5 recommendations for add-on LAMA have been expanded to include combination ICS-LABA-LAMA, if asthma is persistently uncontrolled despite ICS-LABA
  - Add-on tiotropium in separate inhaler (ages ≥6 years)
  - Triple combinations (ages ≥ 18 years): beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium
- Lung function:
  - Adding LAMA to medium or high dose ICS-LABA modestly improves lung function (Evidence A) but not symptoms
- Severe exacerbations
  - In some studies, add-on LAMA modestly increased the time to severe exacerbation requiring OCS (Evidence B)
  - For patients with exacerbations, it is important to ensure that the patient receives sufficient ICS, i.e. at least medium dose ICS-LABA, before considering adding a LAMA

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids

TRIPLE THERAPY

Inhaler sensor
Easily attaches to the inhaler[1]

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Add-on azithromycin

- Add-on azithromycin three days a week has been confirmed as an option for consideration after specialist referral
  - Significantly reduces exacerbations in patients taking high dose ICS-LABA
  - Significantly reduces exacerbations in patients with eosinophilic or non-eosinophilic asthma
  - No specific evidence published for azithromycin in patients taking medium dose ICS-LABA *(Hiles et al, ERJ 2019)*
- Before considering add-on azithromycin
  - Check sputum for atypical mycobacteria
  - Check ECG for long QTc (and re-check after a month of treatment)
  - Consider the risk of increasing antimicrobial resistance (population or personal)

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist

Add-on biologic therapy for severe Type 2 asthma

- When assessing eligibility, repeat blood eosinophils if low at first assessment
  - One study found that 65% patients on medium or high dose ICS-LABA shifted their eosinophil category during 12 months' follow-up *(Lugogo et al, Ann Allergy Asthma Immunol 2020)*
- Additional indications for these therapies in Europe and/or USA have been listed
  - Omalizumab: chronic idiopathic urticaria, nasal polyposis
  - Mepolizumab: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (EGPA)
  - Benralizumab: no additional indications at present
  - Dupilumab: chronic rhinosinusitis with nasal polyposis (CRSwNP); atopic dermatitis
- Check local regulatory approvals and eligibility criteria

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** for severe allergic asthma?*

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Choose one if eligible; trial for at least 4 months and assess response

Good asthma response?

yes → Good response to T2-targeted therapy

unclear → Extend trial to 6-12 months

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

no → Little/no response to T2-targeted therapy

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Ernstig astma en biologicals

Astma is een heterogene aandoening

Astma: moeilijk te behandelen *vs* ernstig, refractair astma

Fenotypering is heel belangrijk in de keuze van de behandeling

Voorbeeld van precisiegeneeskunde en gepersonaliseerde geneeskunde
- type 2 inflammatie (eo, IgE, FeNO)
- targeted therapie (cfr biologicals)

Belang van adherentie en inhaler techniek

Nieuwe behandelingen hebben “therapie-resistente” patiënten in responderende patiënten veranderd, en verlost van orale steroïden

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