제44차 대한결핵 및 호흡기학회 Workshop 2017

Respiratory Review of 2017

Asthma

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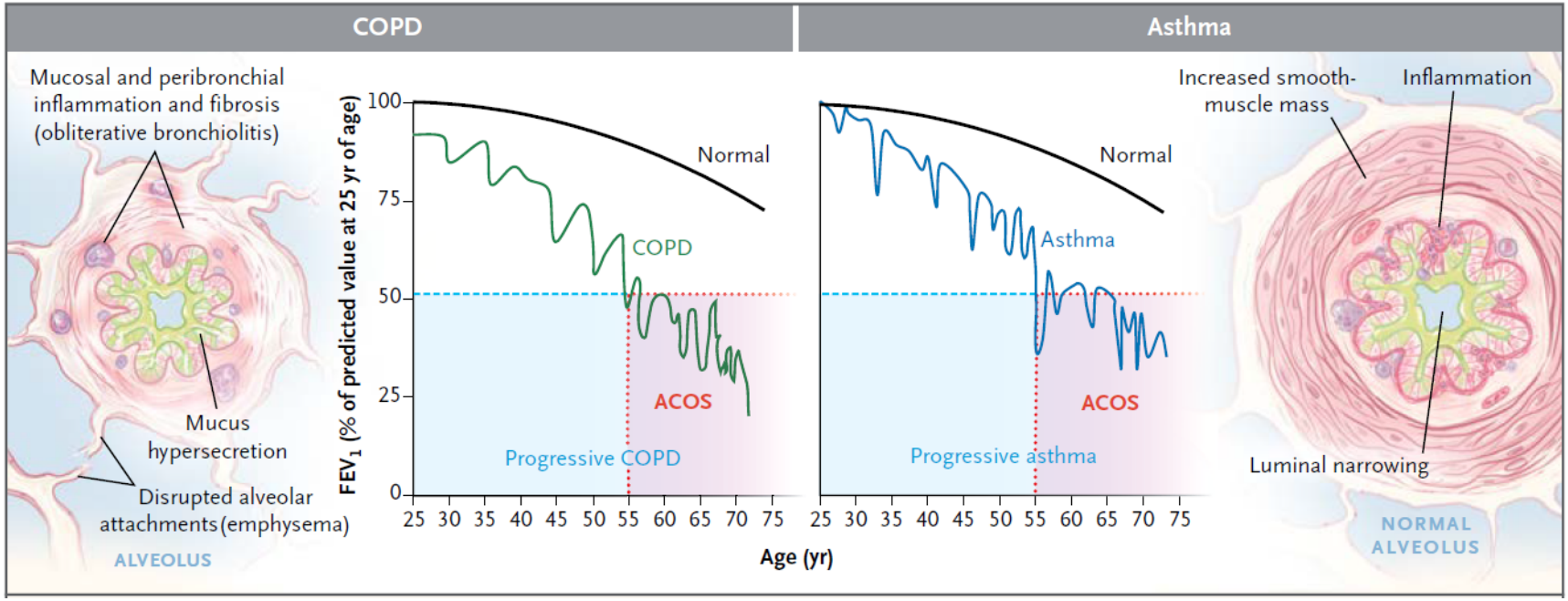
Asthma: Year in Review 2016-2017

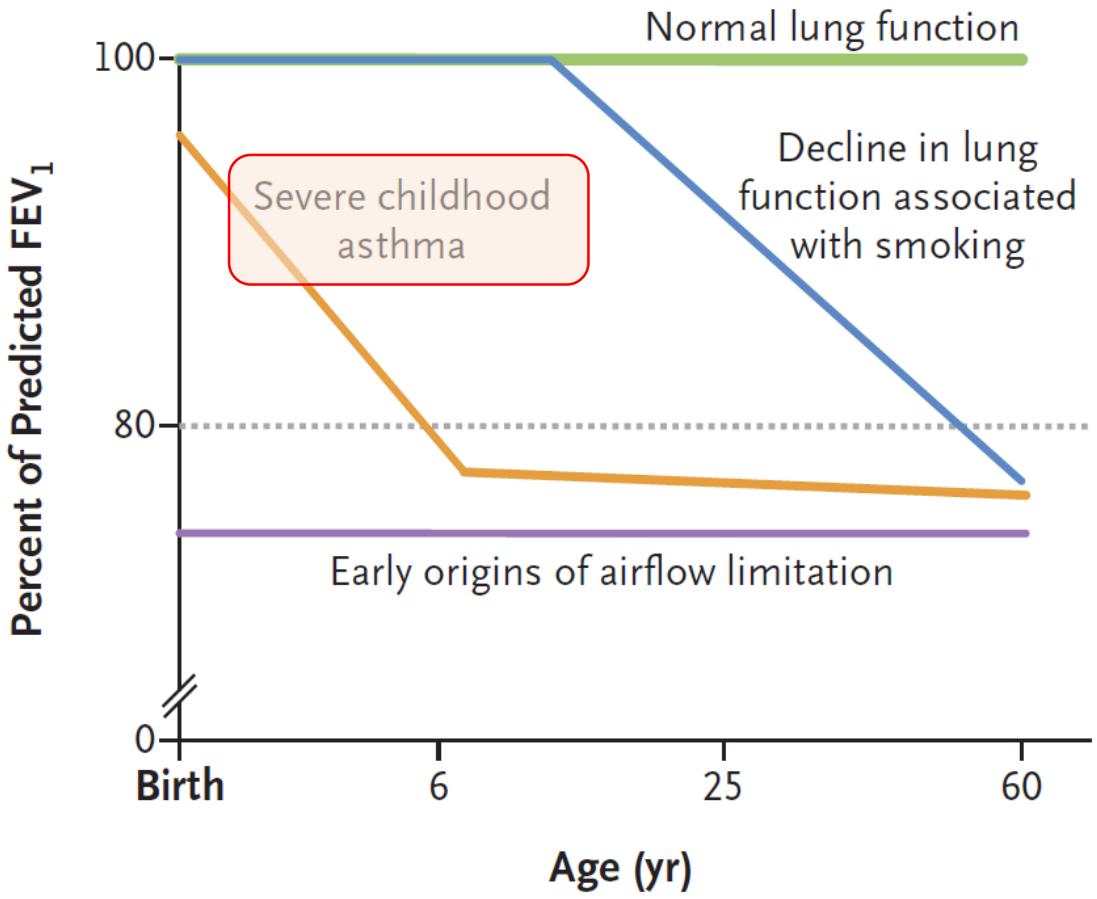
1. Development and Progression
2. Treatment
3. GINA 2017 update

Asthma Progression to ACOS



Postma DS. N Engl J Med 2015; 373:1241-9

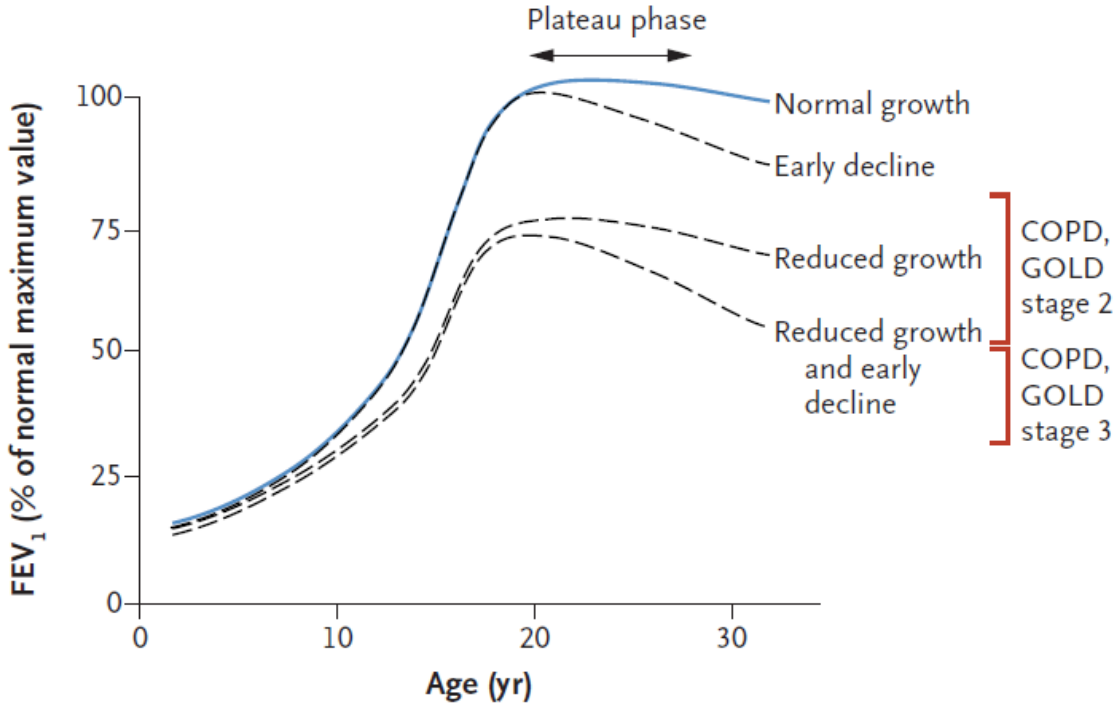
COPD: Different Lung Function Pathway



Martinez FD. N Engl J Med 2016; 375:871-8

Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma

- 684 participants from CAMP childhood asthma cohort
- Spirometry results at 23-30 years old
- Longitudinal Lung-Function Trajectories



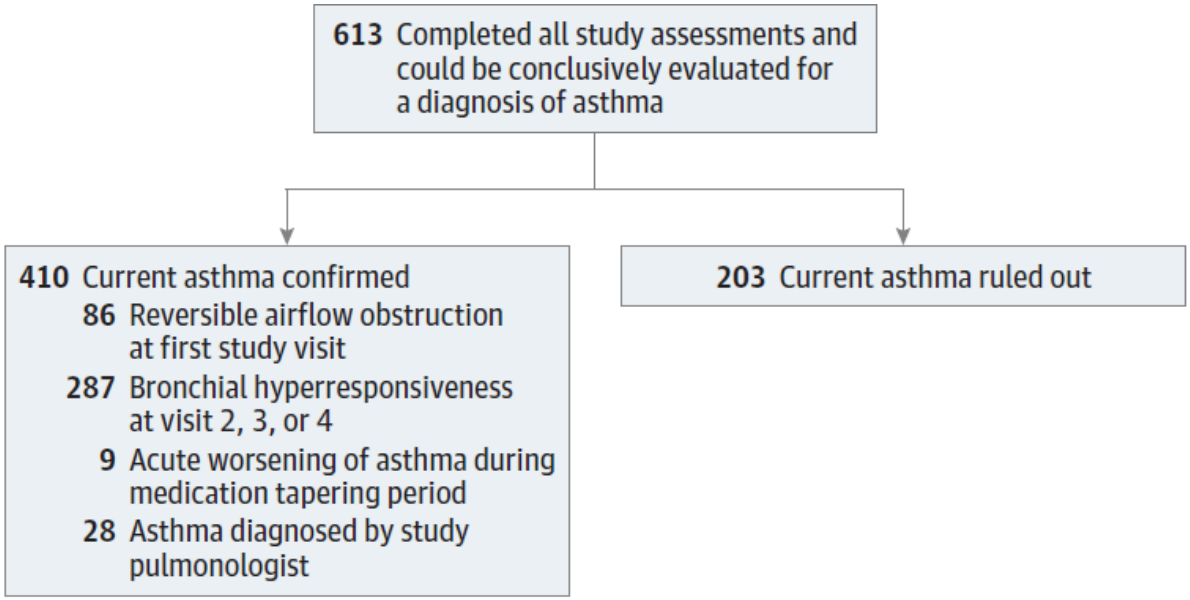
McGeachie MJ et al. N Engl J Med 2016; 374:1842-52

JAMA | Original Investigation

Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

Shawn D. Aaron, MD; Katherine L. Vandemheen, MScN; J. Mark FitzGerald, MD; Martha Ainslie, MD; Samir Gupta, MD; Catherine Lemière, MD; Stephen K. Field, MD; R. Andrew McIvor, MD; Paul Hernandez, MD; Irvin Mayers, MD; Sunita Mulpuru, MD; Gonzalo G. Alvarez, MD; Smita Pakhale, MD; Ranjeeta Mallick, PhD; Louis-Philippe Boulet, MD; for the Canadian Respiratory Research Network

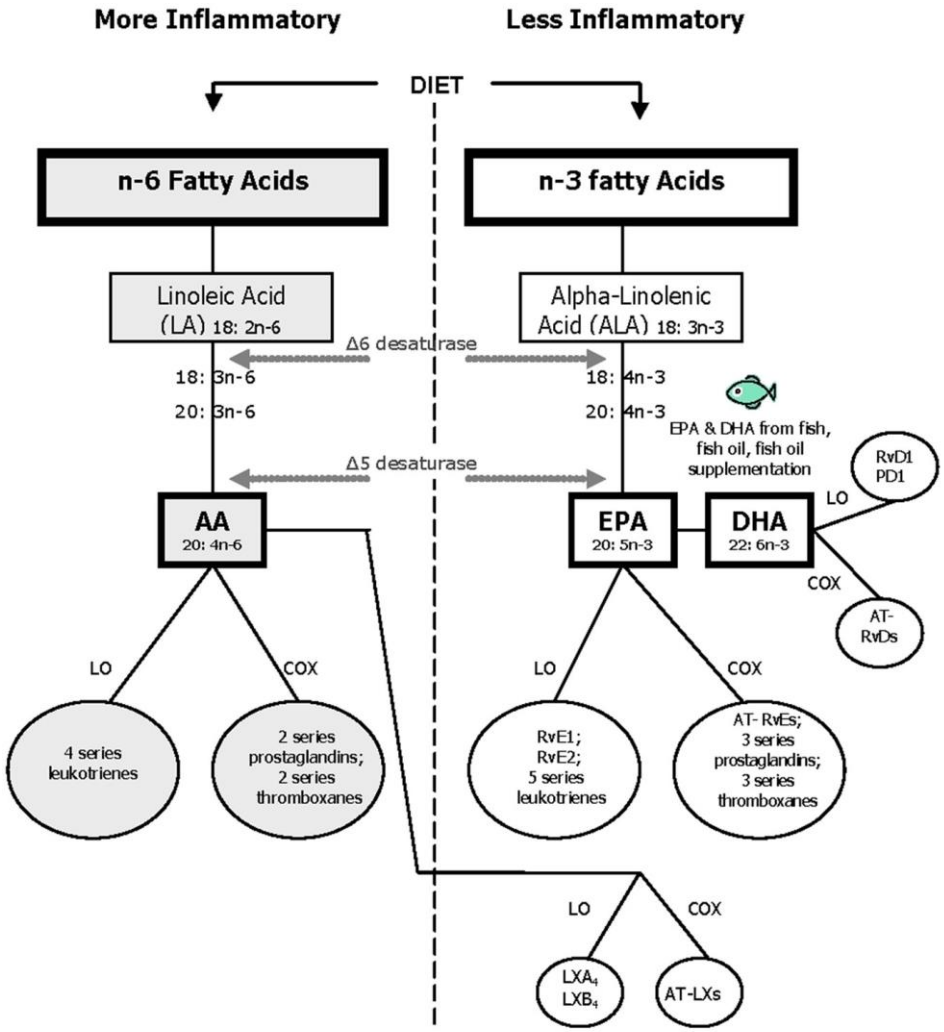
- Spontaneous remission of asthma? Stability of asthma diagnosis?
- Subjects: 701 physician-diagnosed asthma within past 5 years
- Confirmation of asthma by objective testing



Aaron SD et al. JAMA 2017; 317:266-79

천식에 좋은 음식?

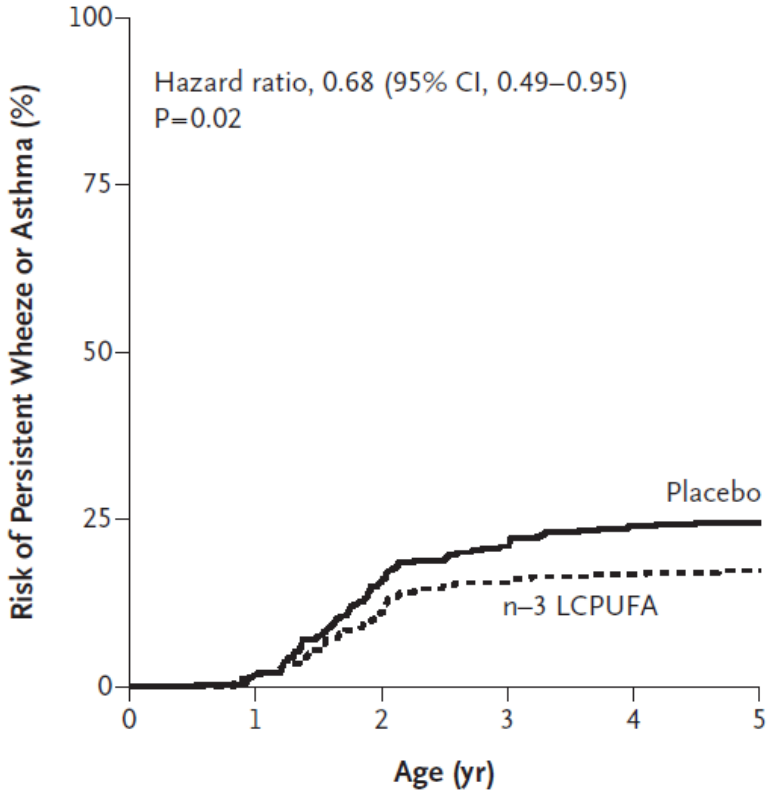
n−3 long-chain polyunsaturated fatty acids (LCPUFAs)



AA = Arachidonic acid; AT = Aspirin-triggered; COX = Cyclooxygenase; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; LO = Lipoxygenase; LX = Lipoxins; PD = DHA-derived protectin; PUFA = Polyunsaturated fatty acids; Rv= Resolvins

n−3 LCPUFA (fish oil) on Prevention of Asthma (1)

- Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$)
- 736 pregnant women at 24 weeks of gestation
- 2.4 g of n−3 LCPUFA (fish oil) or placebo (olive oil)



Bisgaard H et al. N Engl J Med 2016; 375:2530-9

n−3 LCPUFA (fish oil) on Prevention of Asthma (2)

- 533 pregnant women at 3rd trimester in Denmark
- 2.7 g of n−3 LCPUFA (fish oil) or placebo (olive oil)
- 24 years follow up with prescription records

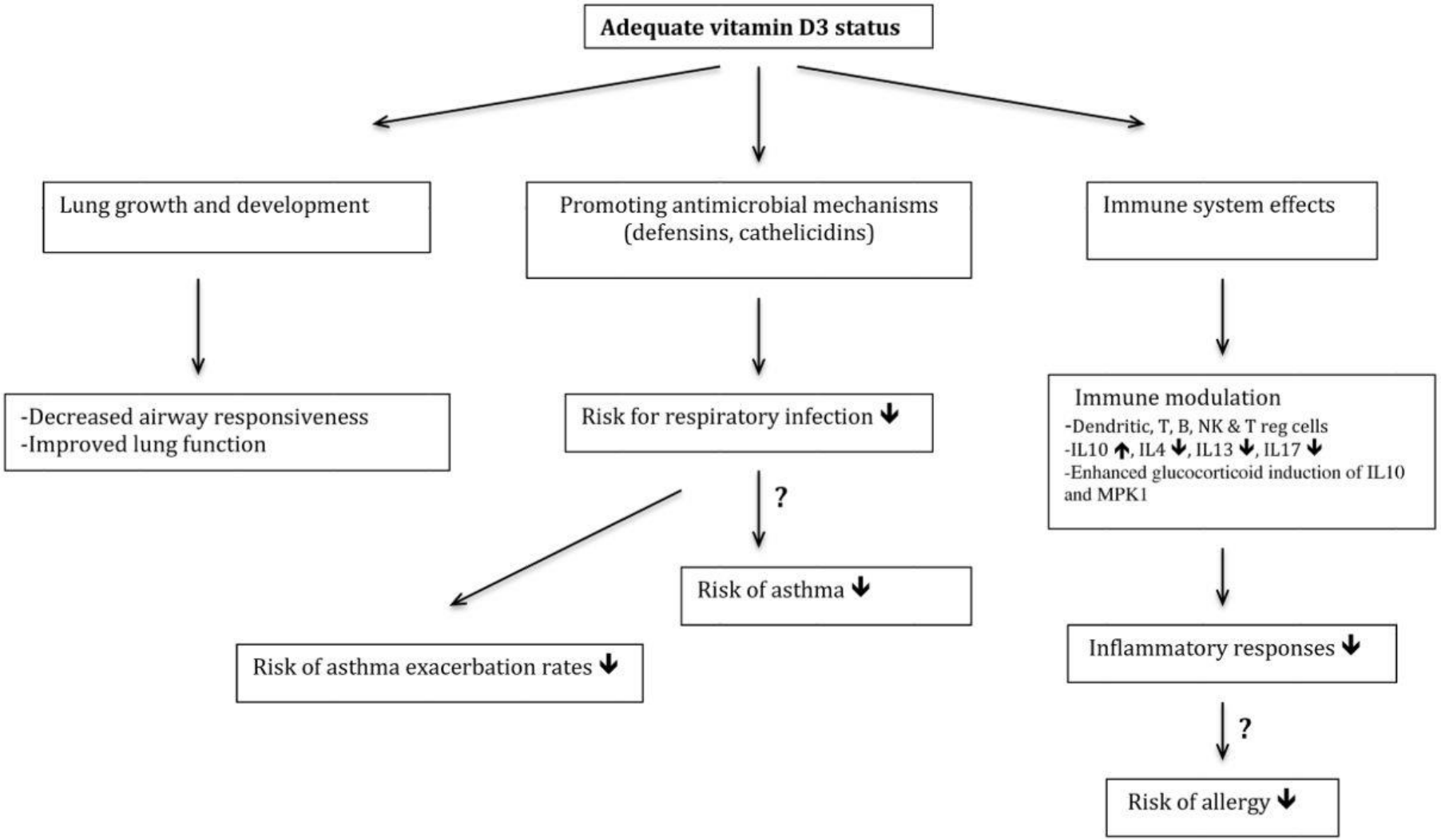
TABLE I. HRs and 95% CIs of register outcomes of asthma and allergic rhinitis up to 24 years of age in the fish oil group relative to the olive oil group

Registry-based outcomes (n = 396)	No. of cases (%)	Crude HRs (95% CI)
Asthma discharge diagnosis		
Fish oil	8 (3)	0.31 (0.13-0.75)
Olive oil	13 (10)	1.00
		$P = .01$
Asthma medication		
Fish oil	31 (12)	0.54 (0.32-0.90)
Olive oil	28 (21)	1.00
		$P = .02$
Allergic rhinitis medication		
Fish oil	57 (22)	0.70 (0.47-1.05)
Olive oil	40 (30)	1.00
		$P = .09$

HRs were calculated by using Cox regression analysis.

Hansen S et al. J Allergy Clin Immunol 2017; 139:104-11

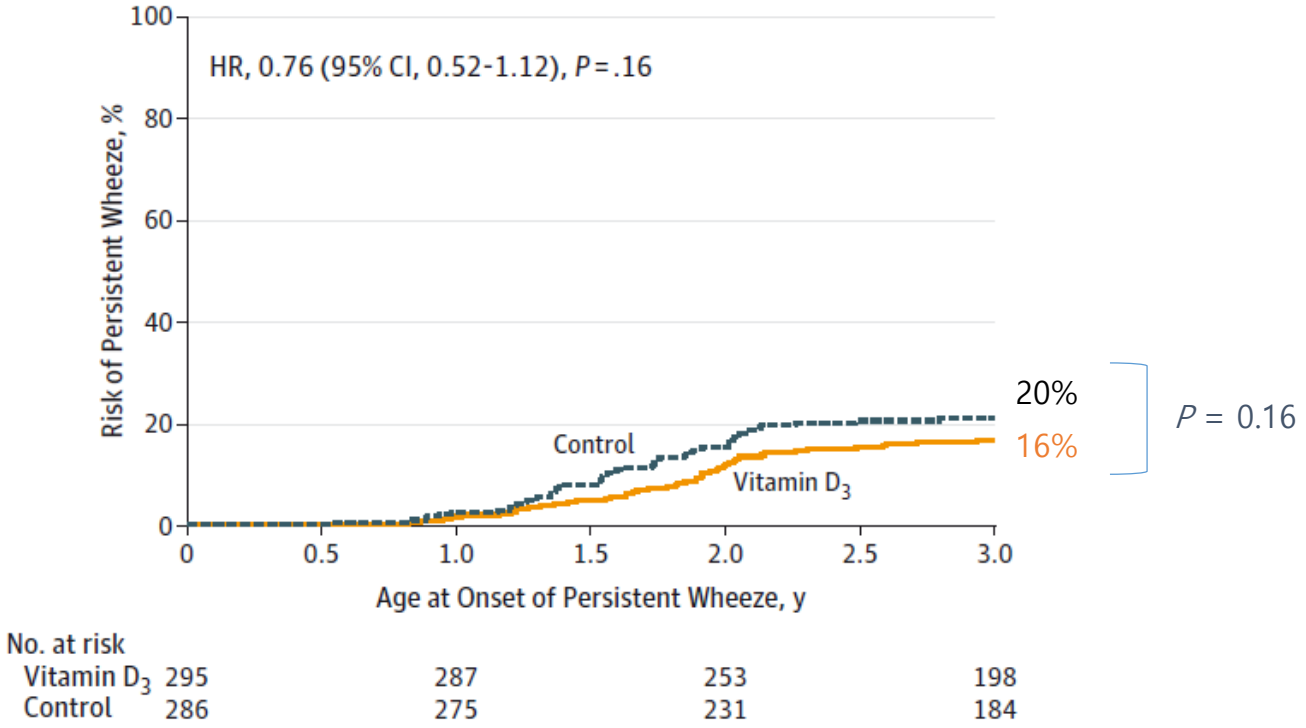
Potential Effects of Vitamin D in Asthma and Allergy



Mirzakhani H et al., Clin Exp Allergy 2015; 45:114-25

Prenatal Vitamin D and Asthma Prevention (1)

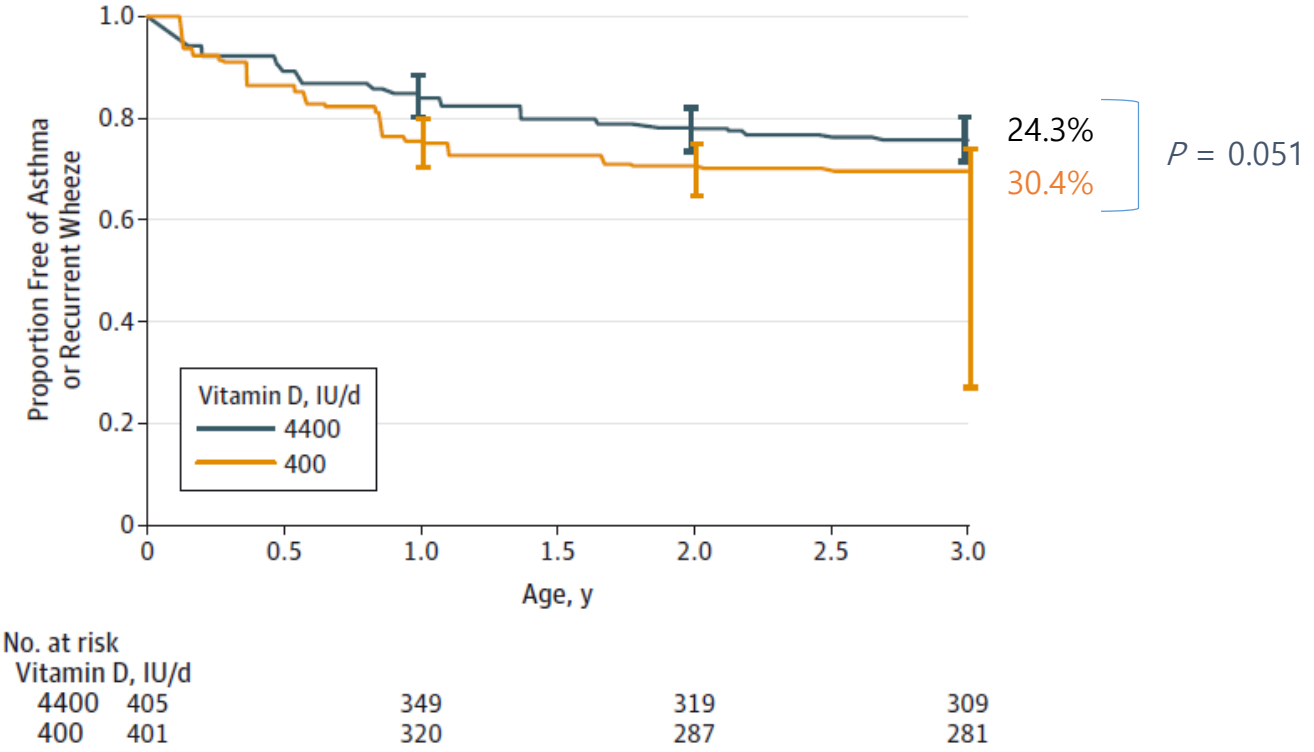
- Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COSPAC_{2010}$)
- 624 women and 581 children followed up to age 3
- Vitamin D3 (2800 IU/d; n = 315) or matching placebo tablets (400 IU/d, n = 308) at 3rd trimester



Chawes BL et al. JAMA 2016; 315:353-61

Prenatal Vitamin D and Asthma Prevention (2)

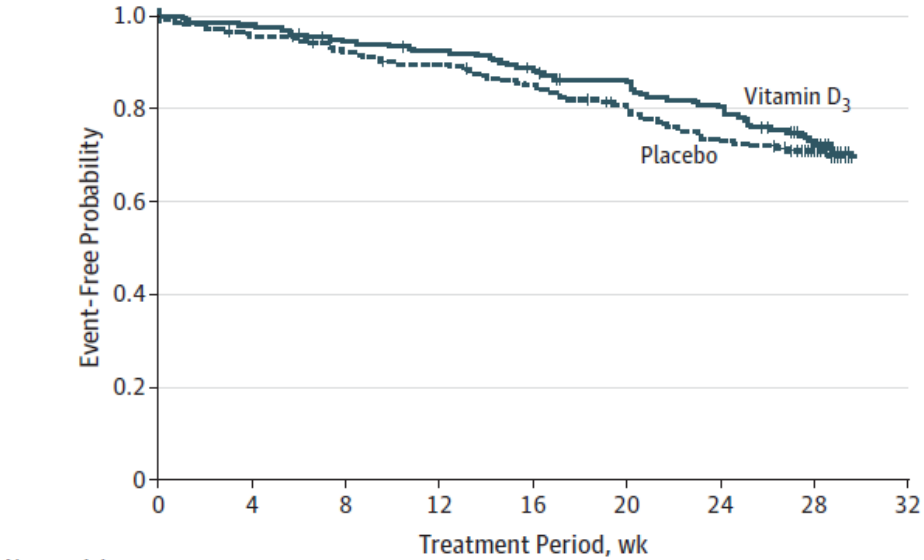
- 881 pregnant women at high risk of having child with asthma in VDAART study in US
- Vitamin D3 (4400 IU/d) or control (400 IU/d)
- Outcome: physician-diagnosed asthma or recurrent wheezing through 3 years of age



Litonjua BL et al. JAMA 2016; 315:362-70

No Effect of Vitamin D on Asthma Exacerbation

- VIDA Randomized Clinical Trial by AsthmaNet
- ICS tapering with oral Vit D3 (100 000 IU once, then 4000 IU/d for 28 weeks) or placebo
- Outcome: time to first asthma treatment failure (lung function, β-agonists, OCS and health care).

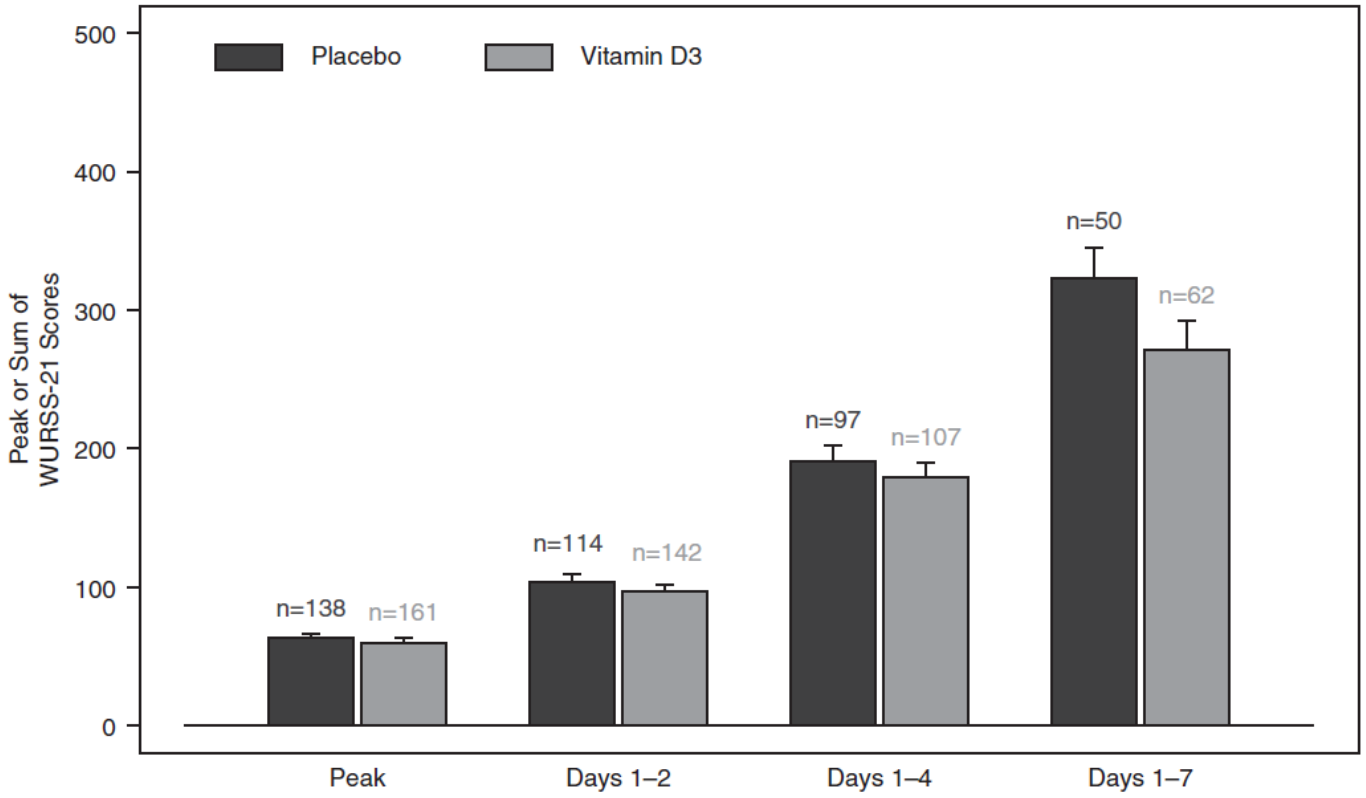


Vertical bars represent censored events. The adjusted hazard ratio for time from randomization to first treatment failure was 0.9 (95% CI, 0.6-1.3) for the vitamin D_3 vs placebo treatment groups (P = .54).

Castro M et al. JAMA 2014; 311:2083-91

No Effect of Vitamin D on Cold in Asthma

- Analysis of VIDA study by AsthmaNet
- Outcome: cold symptom severity (daily scores on the 21-item Wisconsin Upper Respiratory Symptom Survey)



Denlinger LC et al. Am J Respir Crit Care Med 2016; 193:634-41

Severe Asthma: Definition
(International ERS/ATS guideline 2014)

- Asthma requiring GINA step 4-5 medication for the previous year or systemic CS for ≥50% of the previous year to prevent uncontrolled asthma

1. Uncontrolled asthma (one or more)

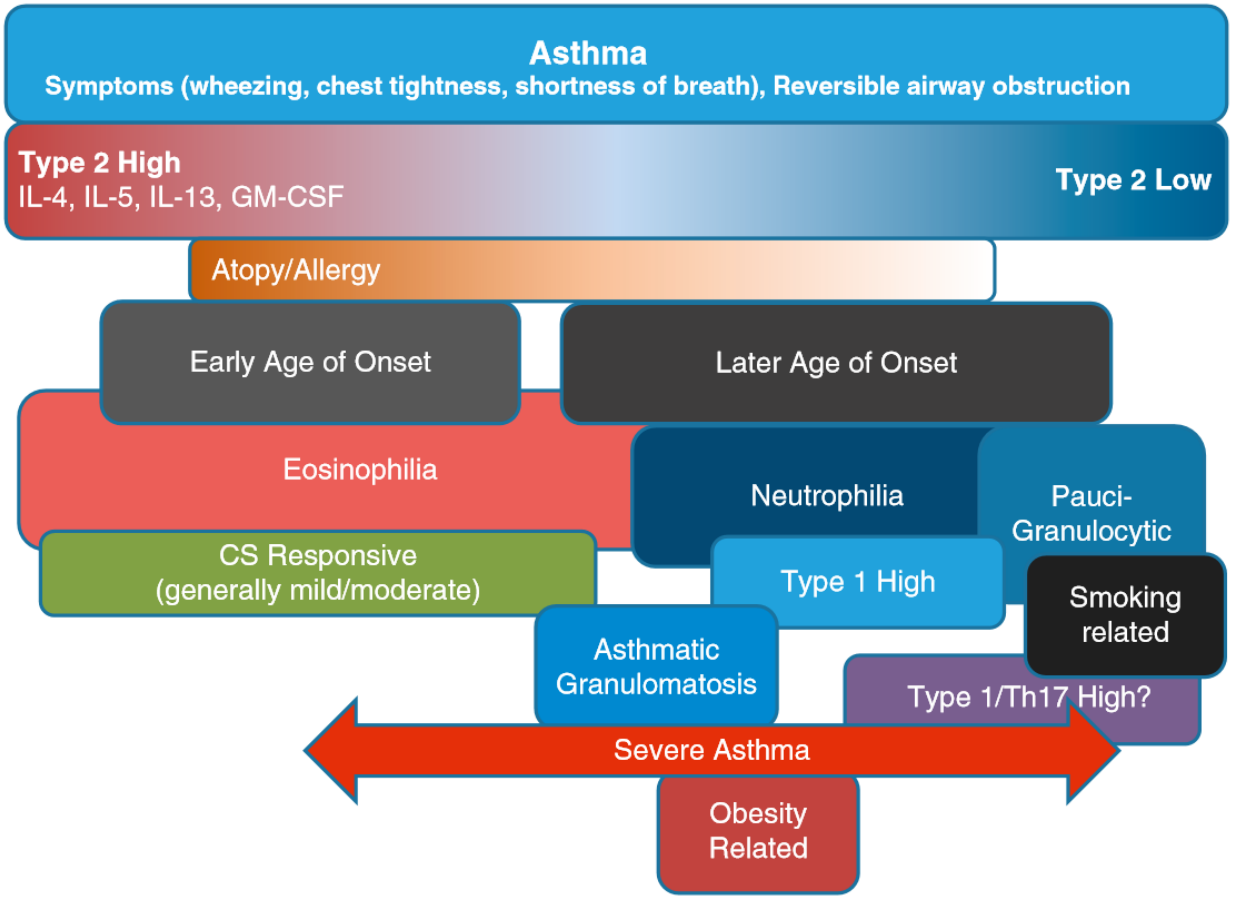
- Poor symptom control: ACT<20
- Frequent severe exacerbation: OCS burst ≥2/yr
- Serious exacerbation: hospitalization ≥1/yr
- Airflow limitation: post-BD FEV1 <80% predicted

2. Controlled asthma

- Worsens on tapering of high ICS or systemic CS

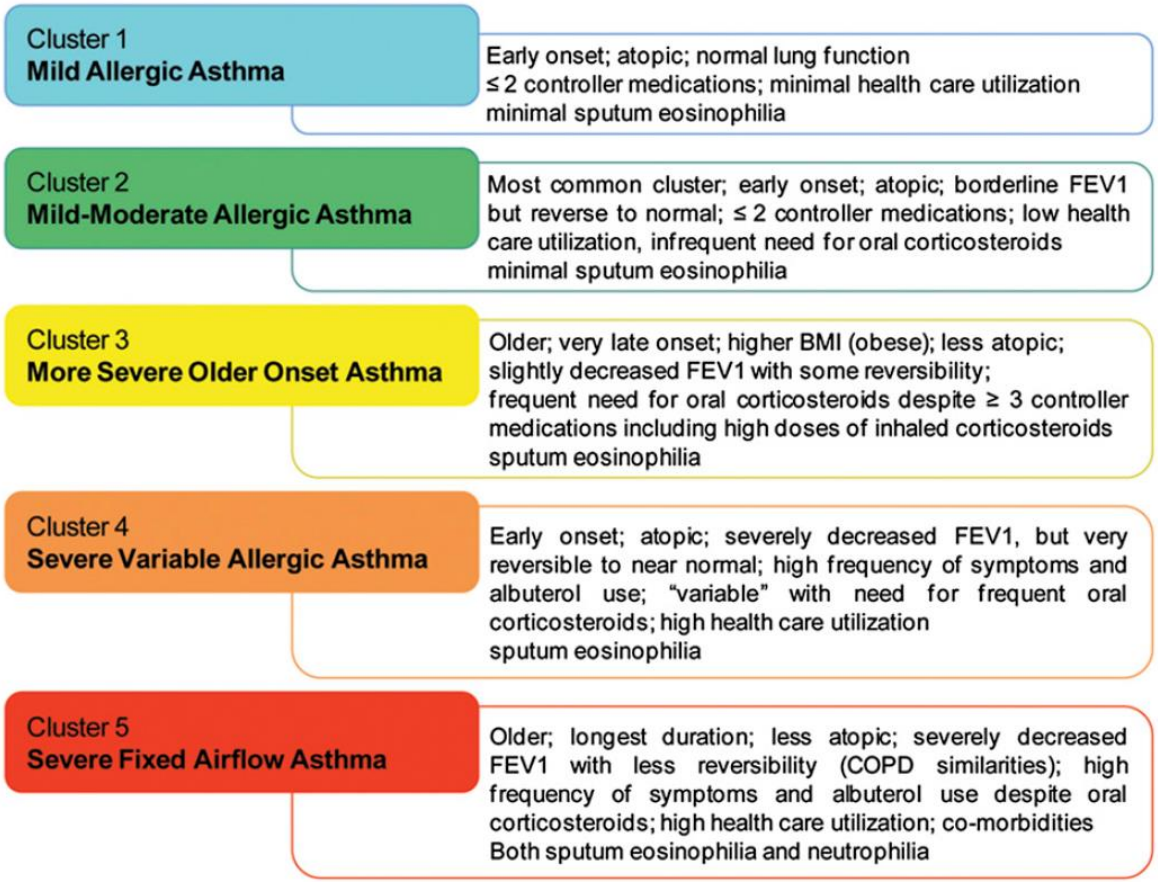
Chung KF et al., Eur Respir J 2014; 43:343-73

Asthma is Heterogeneous, also is Severe Asthma



Gauthier M et al., Am J Respir Crit Care Med 2015; 192:660-8

Cluster Analysis: SARP



Moore WC et al. Am J Respir Crit Care Med 2010;181:315-323

Exacerbation-Prone Asthma (EPA) from SARP

- EPA definition: 3 or more OCS burst in the past year
- Risk factors: Blood eosinophils, BDR, BMI, chronic sinusitis, and GERD

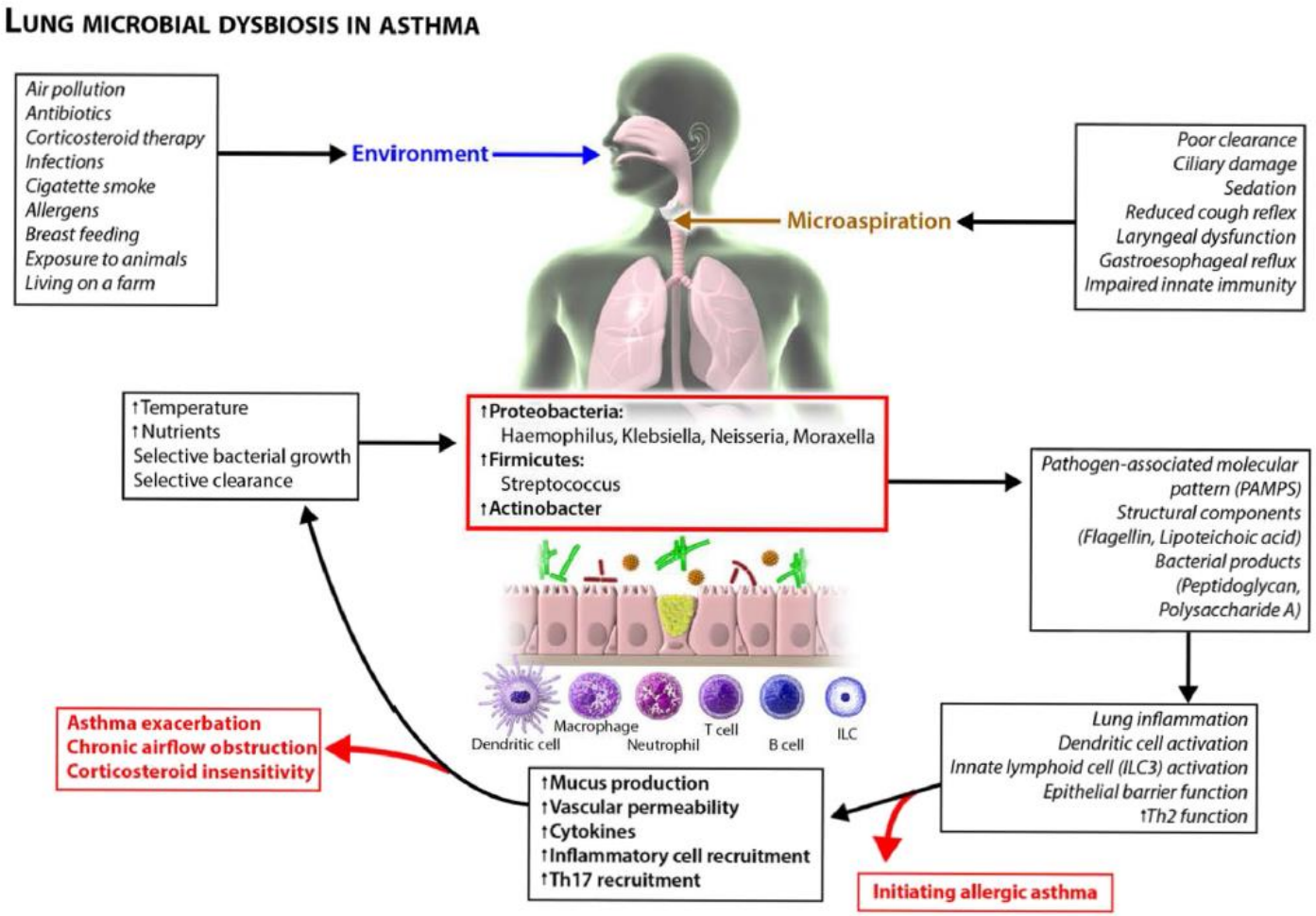
Table 5. Multivariable Negative Binomial Model of Exacerbation Rates

Factor	Annual Rate of Exacerbations		Unit	Rate Ratio	*P* Value
	Factor Present	Factor Absent			
Categorical					
White	2 (1.7–2.5)	1.6 (1.3–2)		1.2 (0.9–1.5)	0.156
Female sex	3.4 (2.4–4.8)	3.3 (2.3–4.7)		1.0 (0.8–1.3)	0.717
Sinusitis	4.4 (3.1–6.3)	2.5 (1.8–3.6)		1.7 (1.4–2.1)	<0.001
GERD	4.2 (3.0–6.0)	2.6 (1.9–3.8)		1.6 (1.3–2.0)	<0.001
Continuous					
Age, yr			10	1 (0.9–1.1)	0.586
Maximum postalbuterol reversibility, % FEV_1 predicted			10	1.2 (1.1–1.4)	<0.001
BMI (adults), kg/m^2			10	1.3 (1.1–1.4)	<0.001
BMI percentile (children <18)			10	1.1 (1.1–1.2)	
IgE, IU/mL (log)			1	0.8 (0.7–1.0)	0.009
Blood eosinophils, cells/μL (log)			1	1.6 (1.2–2.1)	0.004

Definition of abbreviations: BMI = body mass index; GERD = gastroesophageal reflux disease.
Point estimates are shown with the 95% confidence intervals in parentheses. In addition to the factors listed in the table, this model is also adjusted for clinical center and Medication Adherence Report score (not significant).

Denlinger LC et al. Am J Respir Crit Care Med 2017; 195:302-13

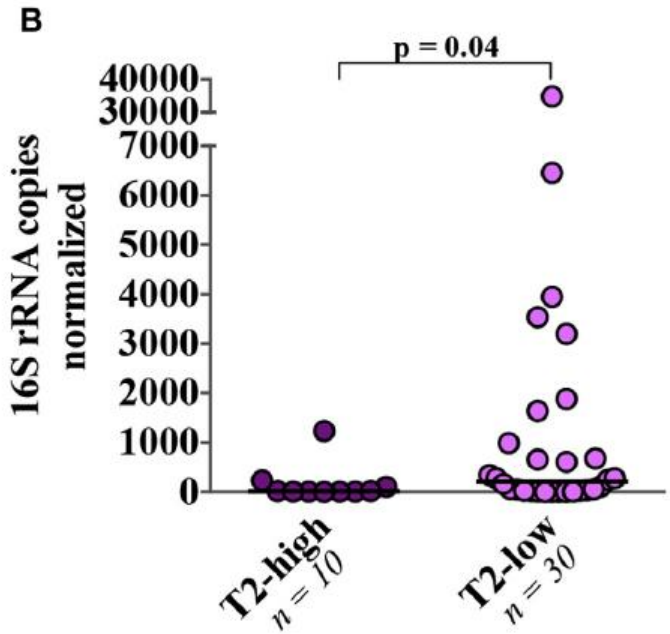
Lung Microbiome: dysbiosis in asthma

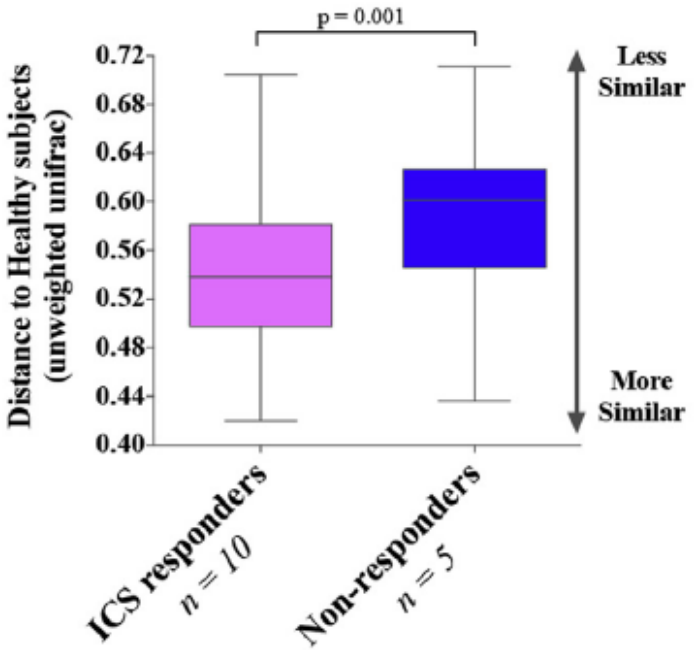


Chung KF. J Allergy Clin Immunol 2017; 139:1071-81

Microbiome in Asthma : association with Th2 type and ICS response

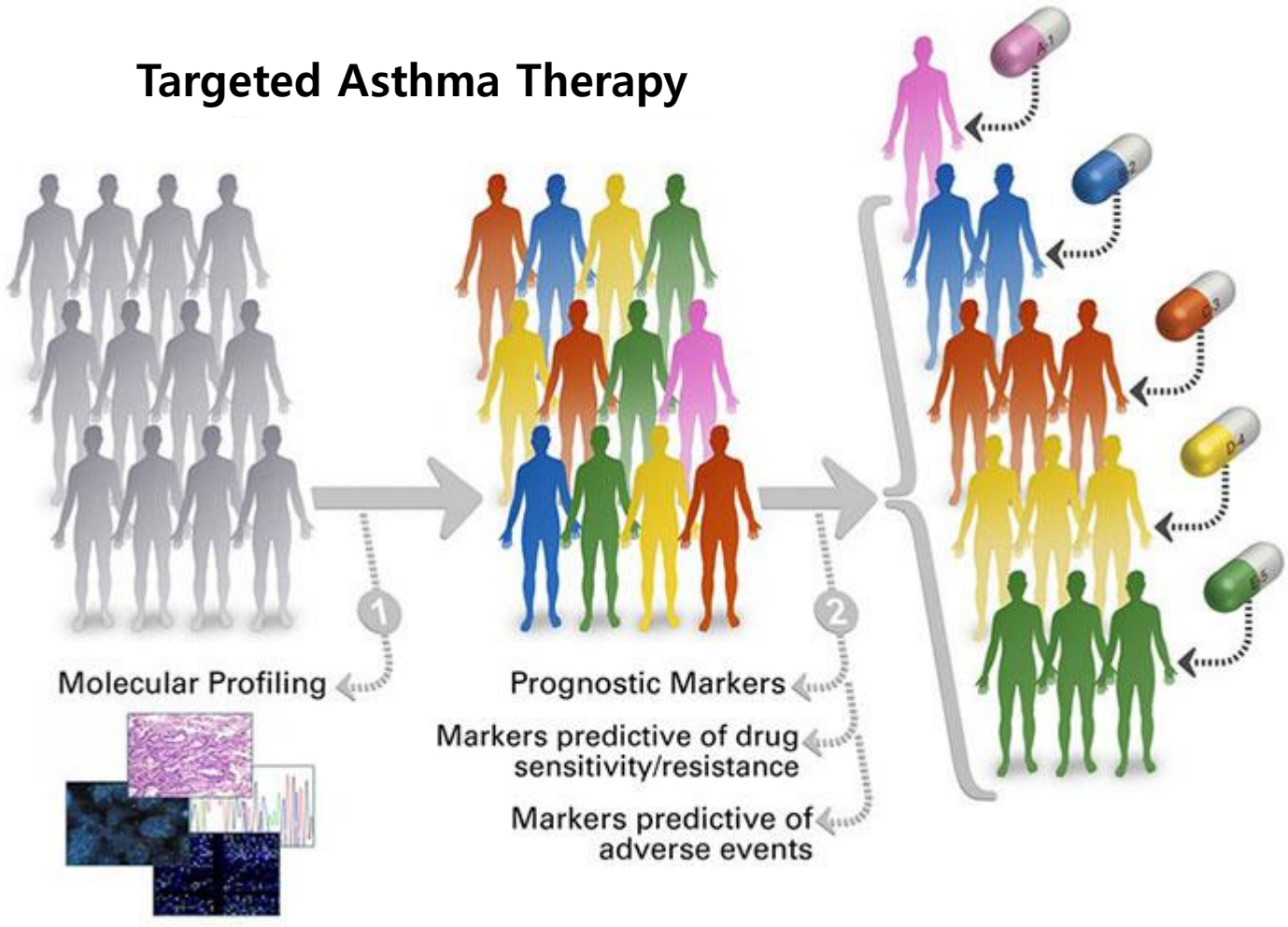
- Bronchial brushing from 40 patients with atopic asthma
- Significantly lower bacterial burden was observed among subjects with T2-high asthma



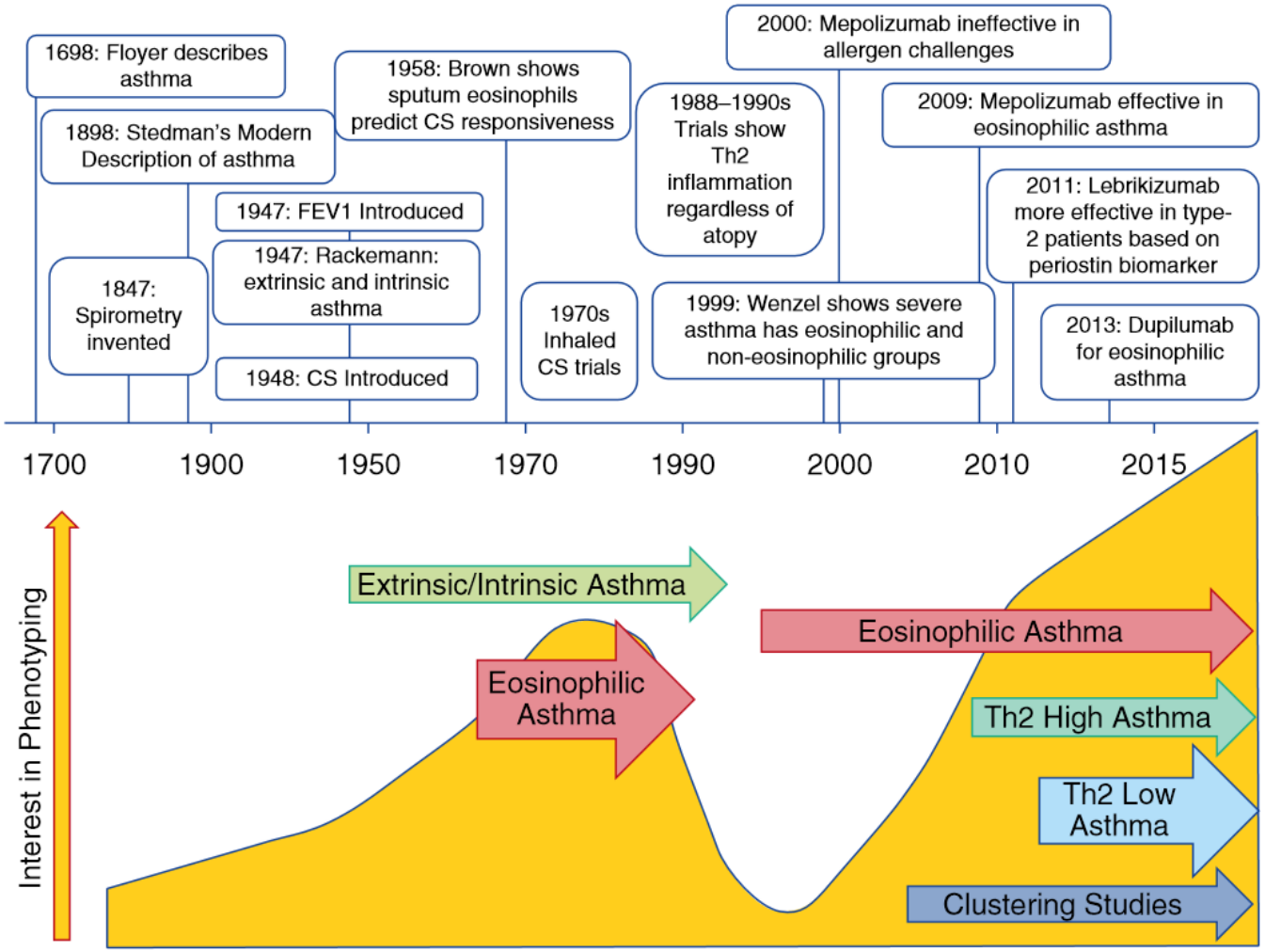


Durack J et al. J Allergy Clin Immunol 2016; 195:302-13

Targeted Therapy (or Precision Medicine)

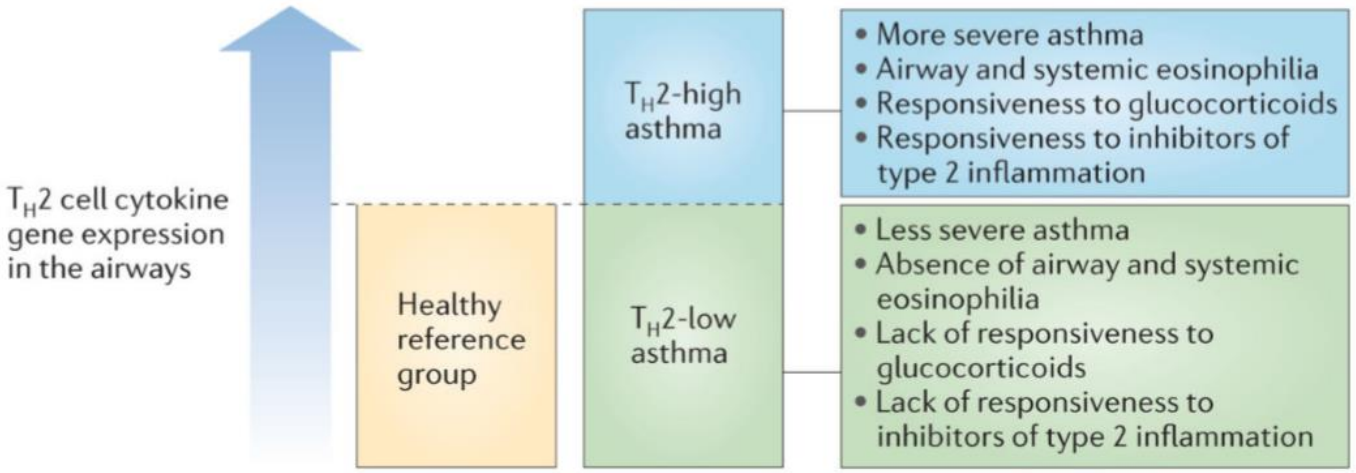


Understanding of Asthma Phenotyping



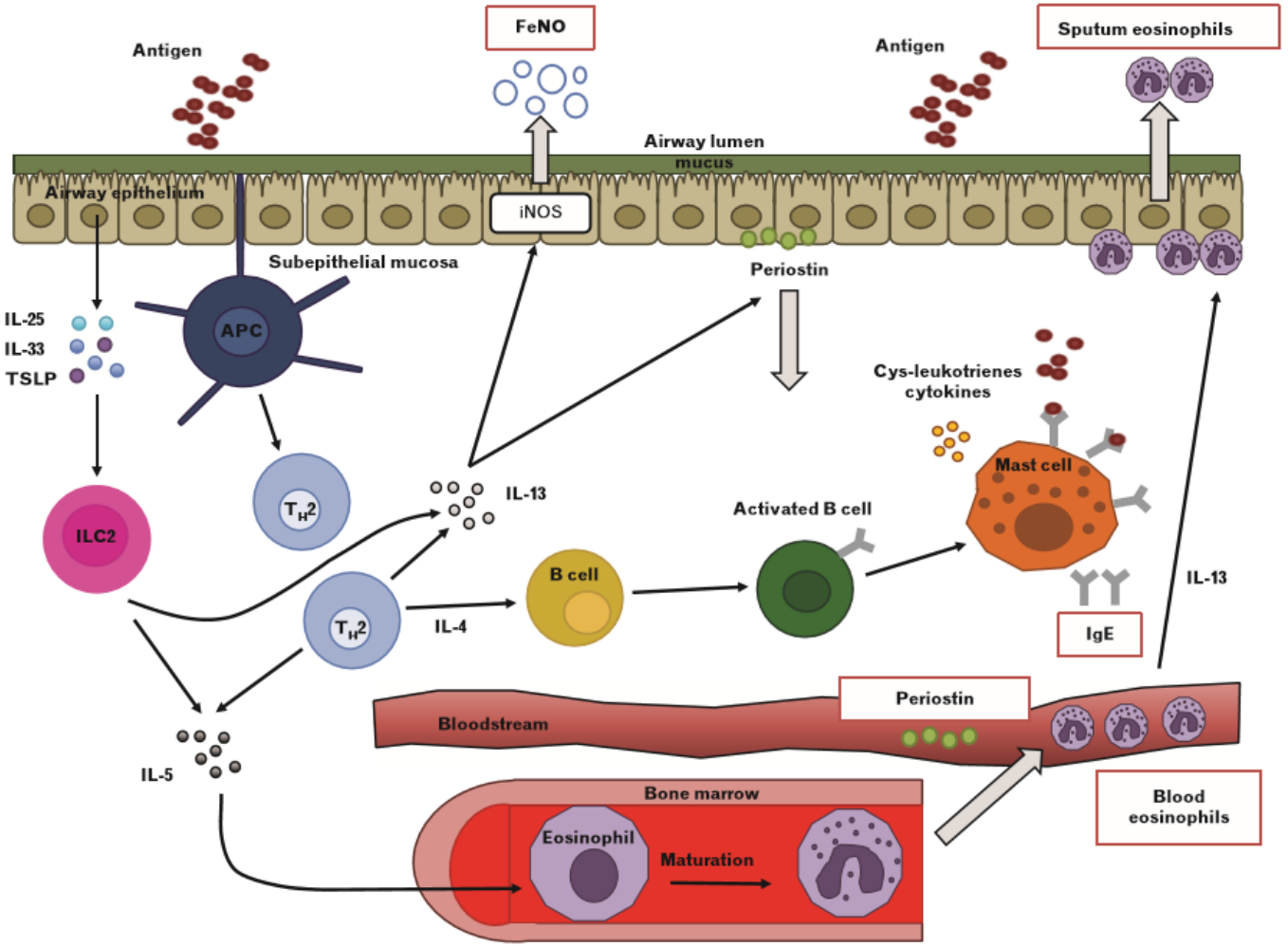
Gauthier M et al., Am J Respir Crit Care Med 2015; 192:660-8

Th2-high and Th2-low asthma



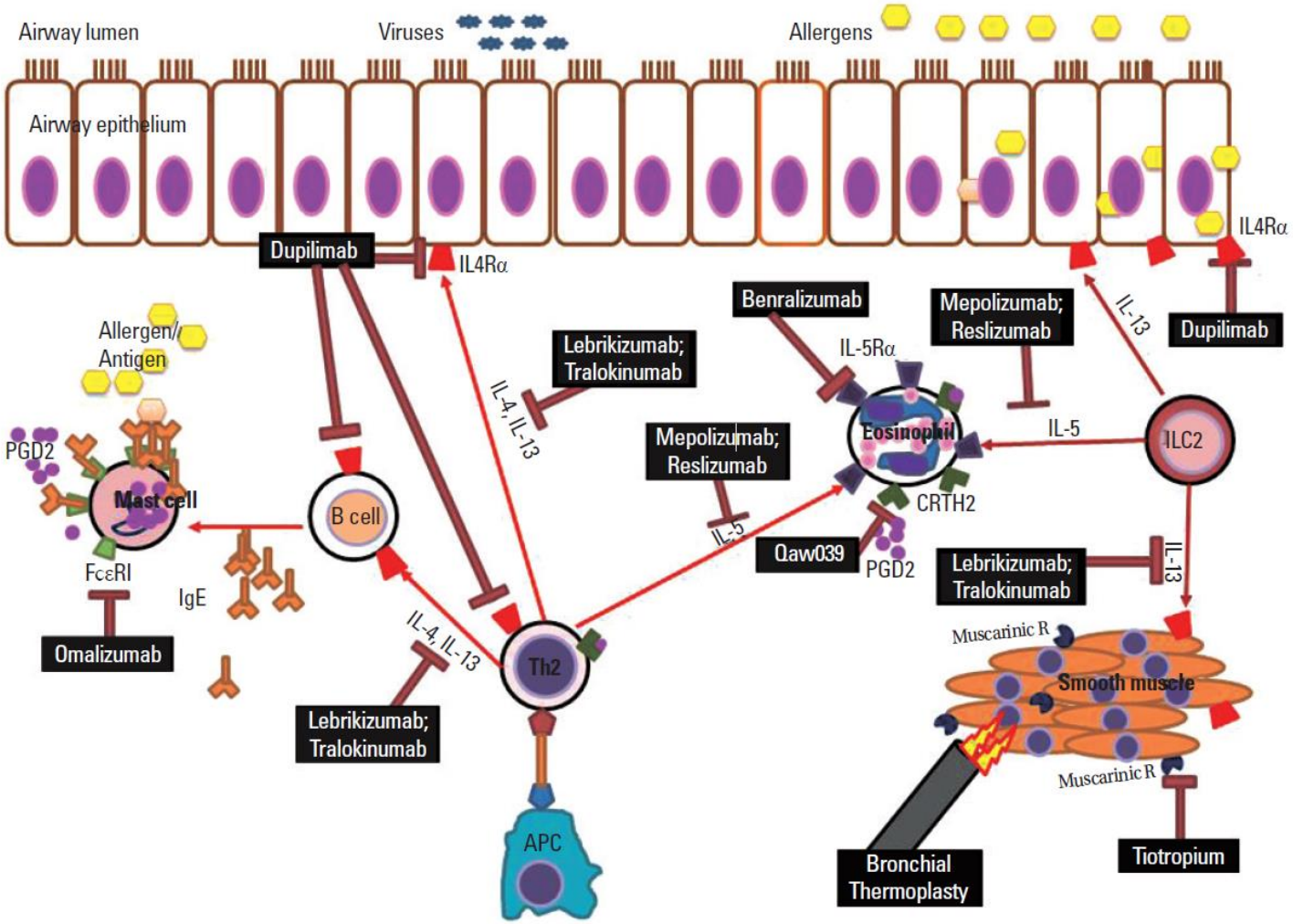
Fahy JV et al. Nat Rev Immunol 2015; 15:57-65

Type 2 Biomarkers



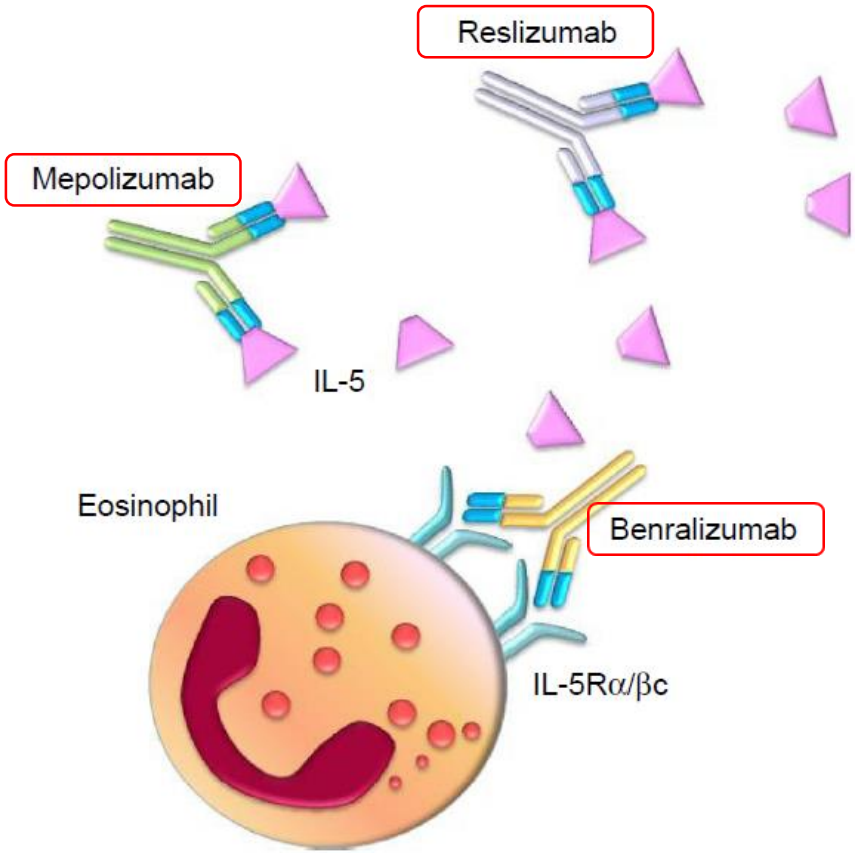
Parulekar AD et al. Curr Opin Pulm Med 2016; 22:59-68

Therapeutic Targets in Severe Asthma



Fajt ML, Wenzel SE. Allergy Asthma Immunol Res 2017; 9:3-14

Anti-IL-5

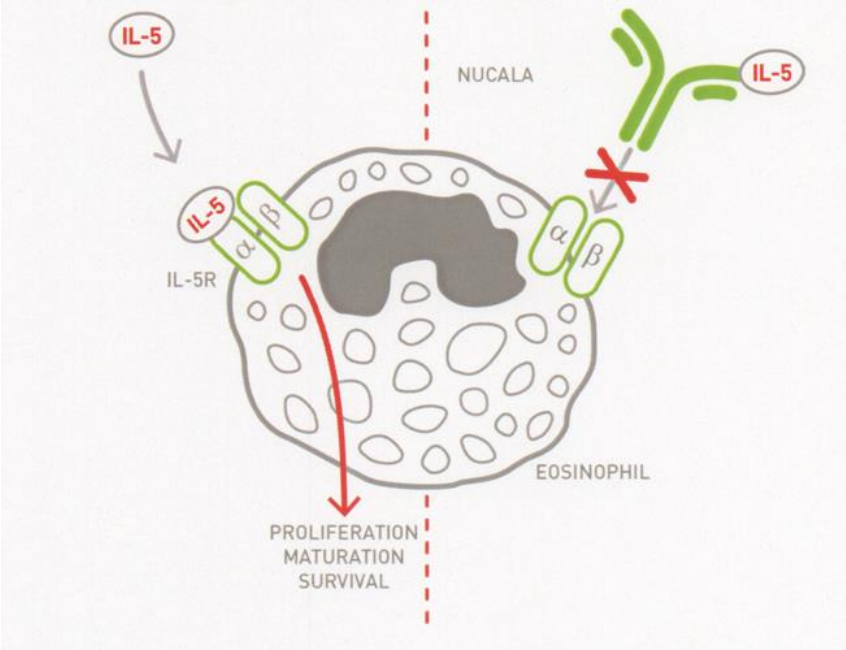


biologic	company	target	route	status
Mepolizumab (Nucala®)	GSK	IL-5	SC	FDA 2015
Reslizumab (Cinquair®)	Teva	IL-5	IV	FDA 2016
Benralizumab	MedImmune AstraZeneka	IL-5R	SC	Phase 3

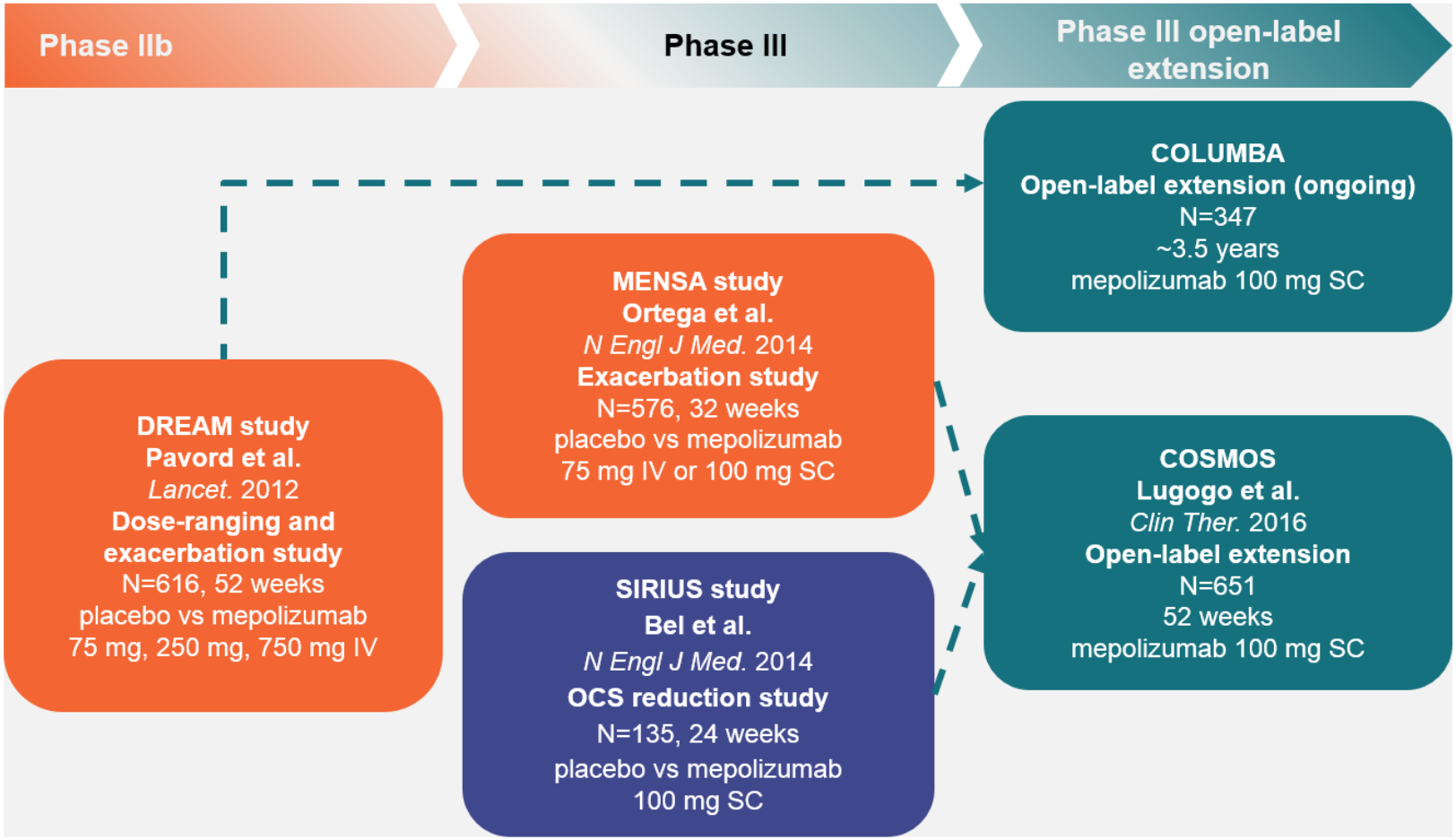
Pelaia G et al. Ther Clin Risk Manag 2016; 12:1075-82

FDA approved Mepolizumab (Nucala®, GSK) in 2015

- add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (≥150 initial or ≥300 in 12 mo)
- 100 mg SC every 4 weeks



Clinical Trials of Mepolizumab in Asthma

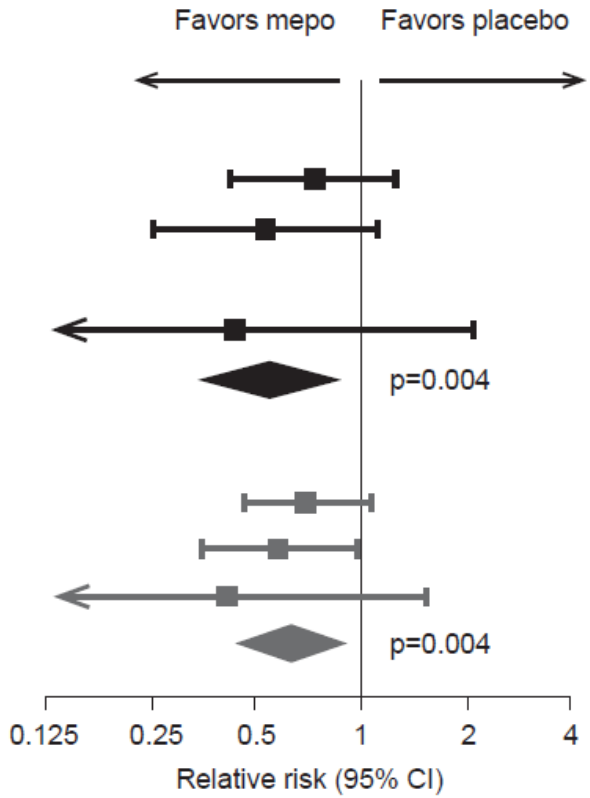


IV, intravenous; OCS, oral corticosteroids; SC, subcutaneous.

Mepolizumab on Hospitalization: Meta-analysis

A

Study	Subjects with event (%) Placebo	Mepo	Relative risk (95% CI)
Patients with ≥1 exacerbation requiring hospitalization*			
DREAM	11.0	8.0	0.73 (0.42, 1.26)
MENSA	6.8	3.6	0.53 (0.26, 1.11)
SIRIUS	10.6	0	0
Haldar 2009	15.6	6.9	0.44 (0.09, 2.10)
Combined	9.5	5.6	0.55 (0.36, 0.83)
Patients with ≥1 exacerbation requiring hospitalization/ER visit†			
DREAM	17.4	12.1	0.70 (0.46, 1.06)
MENSA	12.6	7.3	0.58 (0.35, 0.97)
SIRIUS	10.6	4.3	0.41 (0.11, 1.52)
Combined	14.1	9.5	0.62 (0.45, 0.86)



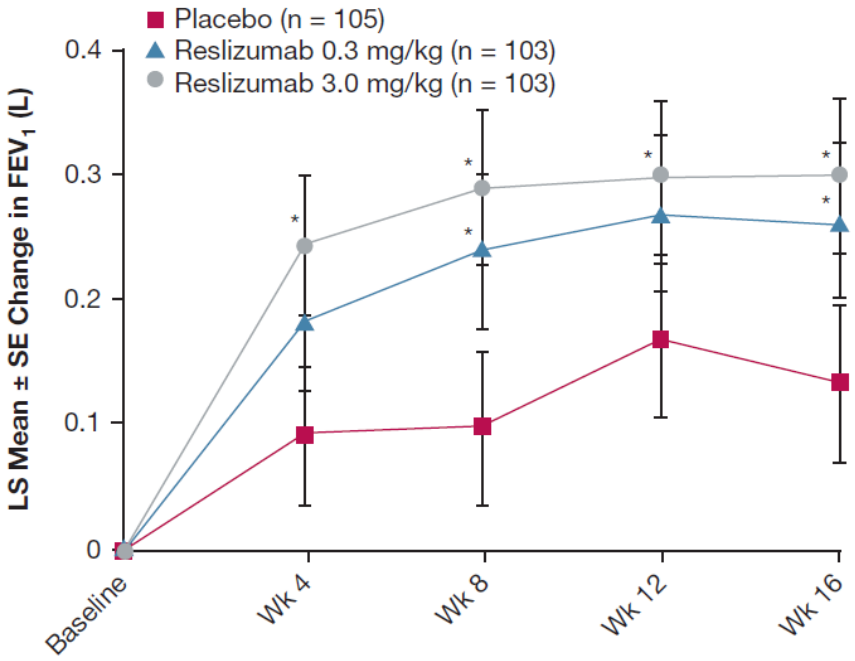
Yancey SW et al. J Allergy Clin Immunol 2016

FDA approved Reslizumab (Cinqair®, Teva) in 2016

- add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype (≥400 PB eosinophils)
- 3 mg/kg IV every 4 weeks

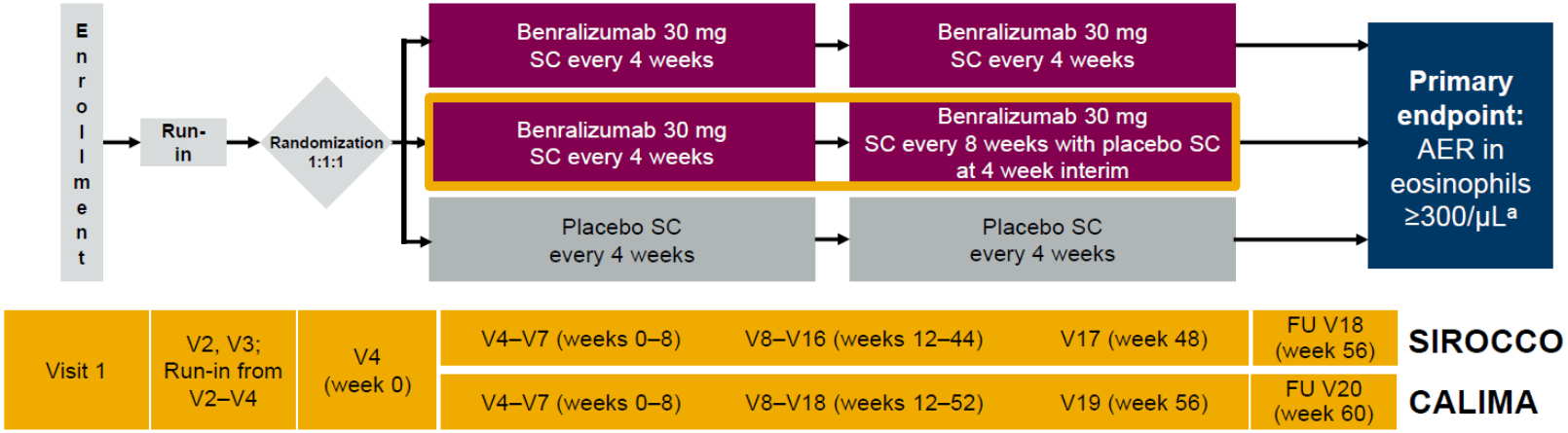
Reslizumab on lung function

- 12 to 75 years with asthma inadequately controlled by at least a medium ICS and with a blood eosinophil count ≥400 cells/mL.
- 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks
- Reslizumab improved lung function, asthma control and symptoms, and quality of life



Bjermer L et al., Chest 2016; 150:789-98

Benralizumab Phase 3: SIROCCO & CALIMA



- 12-75 years with history of 2 or more exacerbations
- Planned 2:1 randomization ratio by eos (≥300/µL vs <300/µL)
- Stratified by ICS dose (high- and medium-dosage ICS, CALIMA only), region, age group, and baseline eosinophils
- Outcome: annual exacerbation rate

Bleecker ER et al. Lancet 2016; 388:2115-27
FitzGerald JM et al. Lancet 2016; 388:2128-41

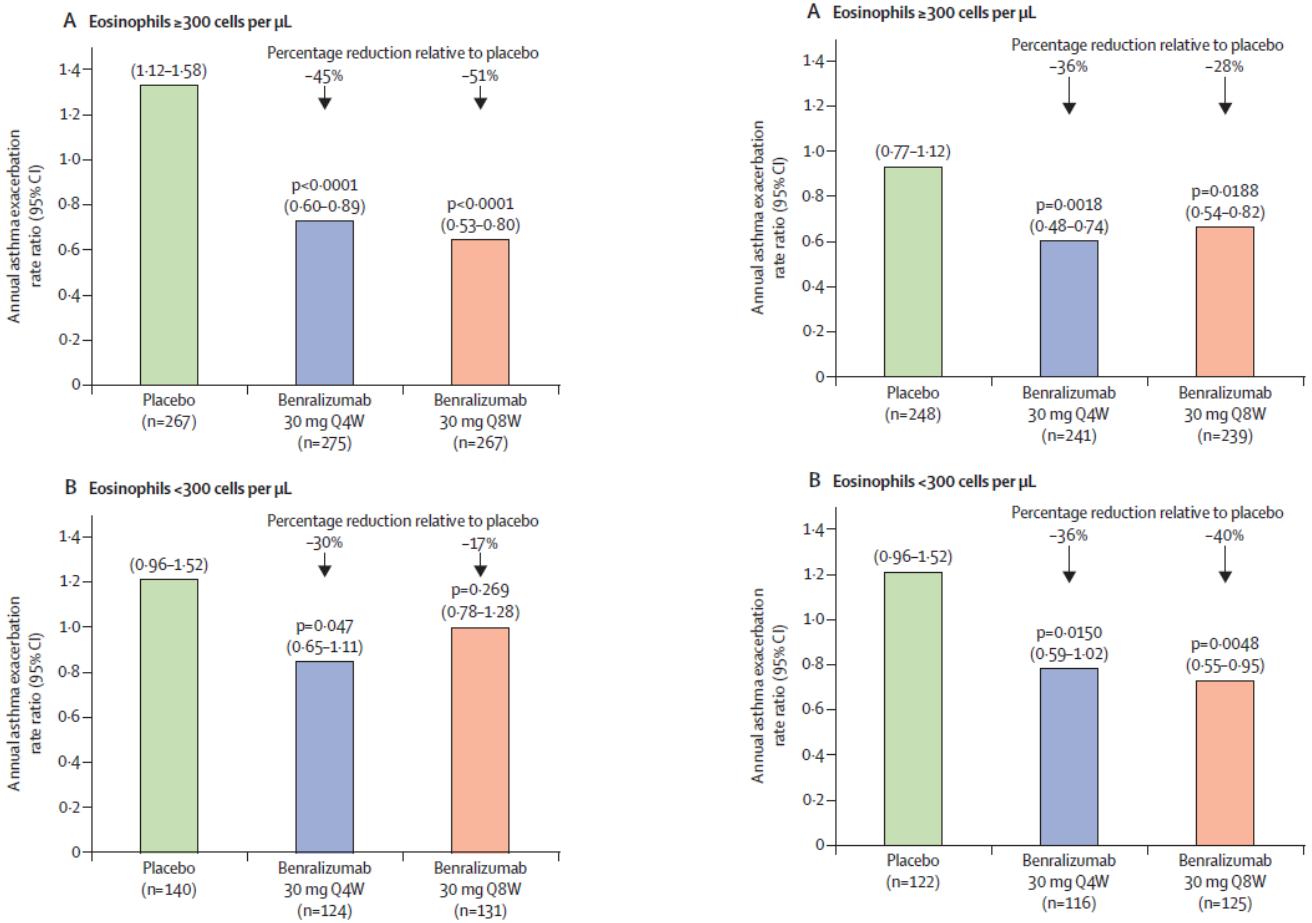
Benralizumab on Exacerbation

SIROCCO

CALIMA

eos ≥300

eos <300



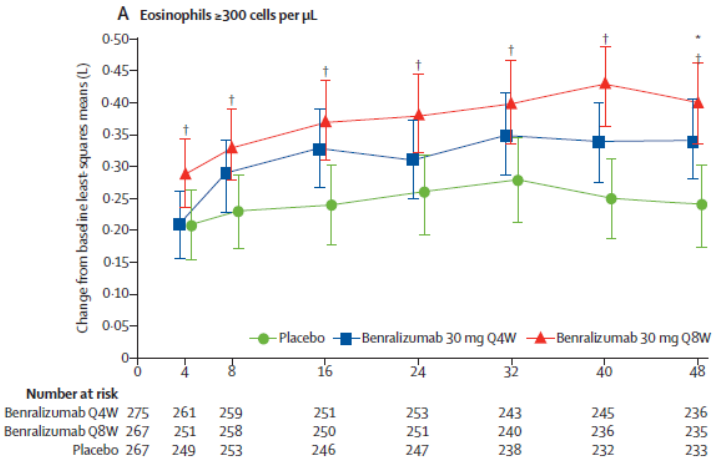
Bleecker ER et al. Lancet 2016; 388:2115-27
FitzGerald JM et al. Lancet 2016; 388:2128-41

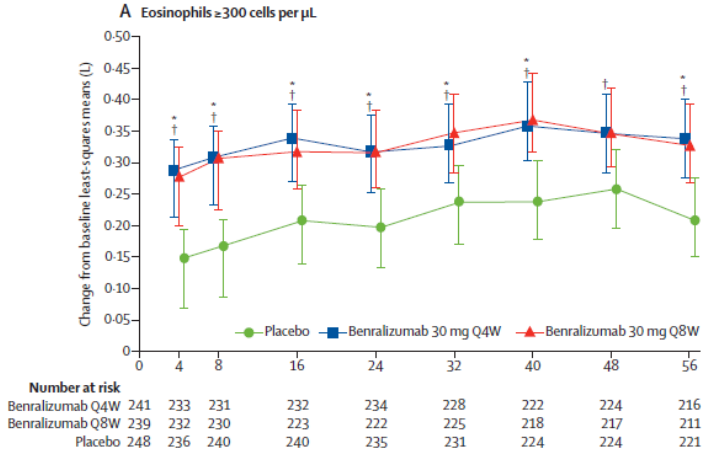
Benralizumab on Lung Function

SIROCCO

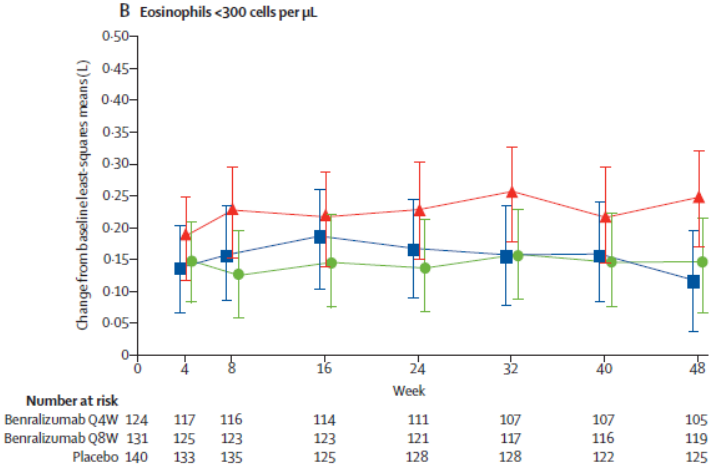
CALIMA

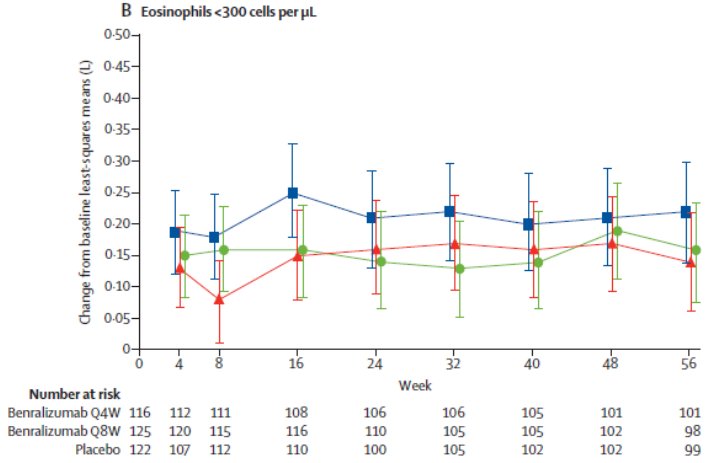
eos ≥300





eos <300





Bleecker ER et al. Lancet 2016; 388:2115-27
FitzGerald JM et al. Lancet 2016; 388:2128-41

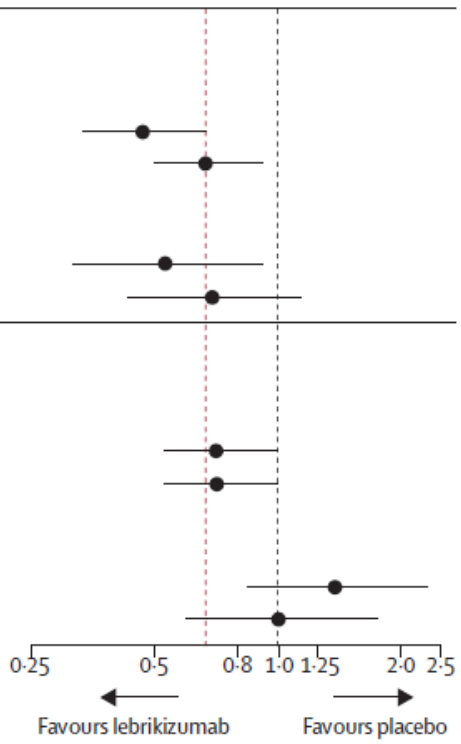
Anti-IL-13

biologic	company	Details	Status
Lebrikizumab	Genentech Roche	IgG4 humanized monoclonal antibody that blocks binding of IL-13 to IL-4Rα	Phase 3
Tralokinumab	MedImmune AstraZeneka	IL-13-neutralising IgG4 monoclonal antibody that blocks the binding of IL-13 to IL-13Rα1 and IL-13Rα2	Phase 3
GSK679586	GSK	blocks the binding of IL-13 to IL-13Rα1	Phase 2

Lebrikizumab Phase 3: LAVOLTA I & II

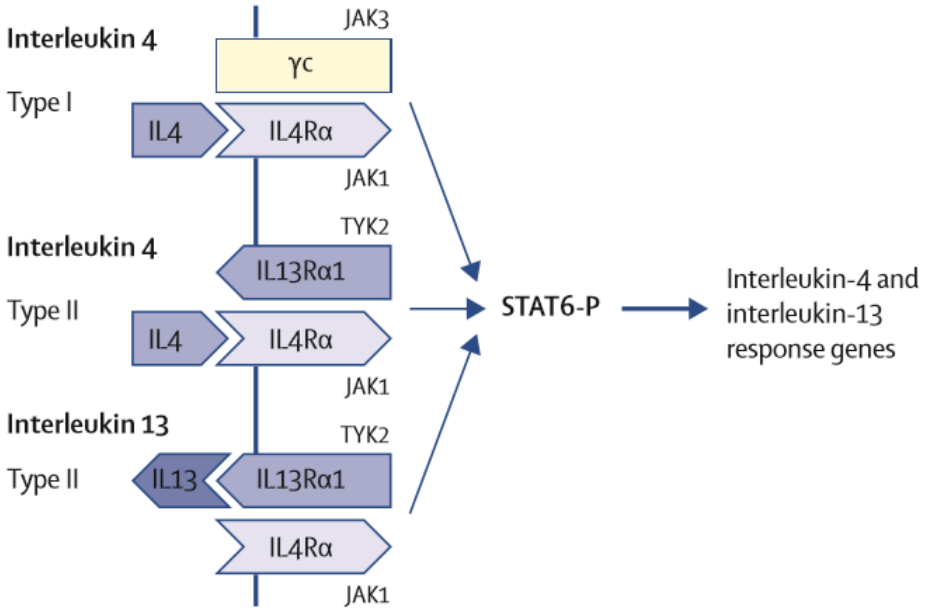
- Lebrikizumab 37·5 mg or 125 mg or placebo SC every 4 weeks for 52 weeks
- biomarker-high (periostin ≥50 ng/mL or blood eosinophils ≥300 cells per µL)
- Outcome: exacerbation rate

	n	Adjusted exacerbation rate (per patient per year)	Rate difference (lebrikizumab–placebo)	Rate reduction (%)	Rate ratio (lebrikizumab *vs* placebo, 95% CI)	p value
LAVOLTA I						
Biomarker high						
Placebo	256	0·94				
Lebrikizumab 37·5 mg	251	0·46	−0·48	51%	0·49 (0·34–0·69)	<0·0001
Lebrikizumab 125 mg	255	0·66	−0·28	30%	0·70 (0·51–0·95)	0·0232
Biomarker low						
Placebo	106	0·60				
Lebrikizumab 37·5 mg	109	0·33	−0·27	45%	0·55 (0·32–0·95)	0·0318
Lebrikizumab 125 mg	104	0·44	−0·17	28%	0·72 (0·44–1·19)	0·2013
LAVOLTA II						
Biomarker high						
Placebo	247	0·72				
Lebrikizumab 37·5 mg	257	0·54	−0·19	26%	0·74 (0·54–1·01)	0·0609
Lebrikizumab 125 mg	251	0·54	−0·19	26%	0·74 (0·54–1·02)	0·0626
Biomarker low						
Placebo	107	0·34				
Lebrikizumab 37·5 mg	99	0·50	0·16	−46%	1·46 (0·87–2·45)	0·1519
Lebrikizumab 125 mg	106	0·36	0·02	−6%	1·06 (0·61–1·83)	0·8346



Hanania NA et al., Lancet Respir Med 2016; 4:781-96

Anti-IL-4Rα

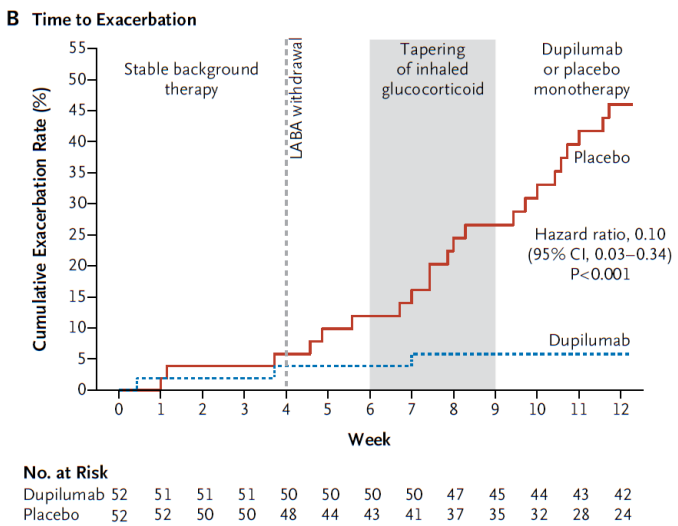


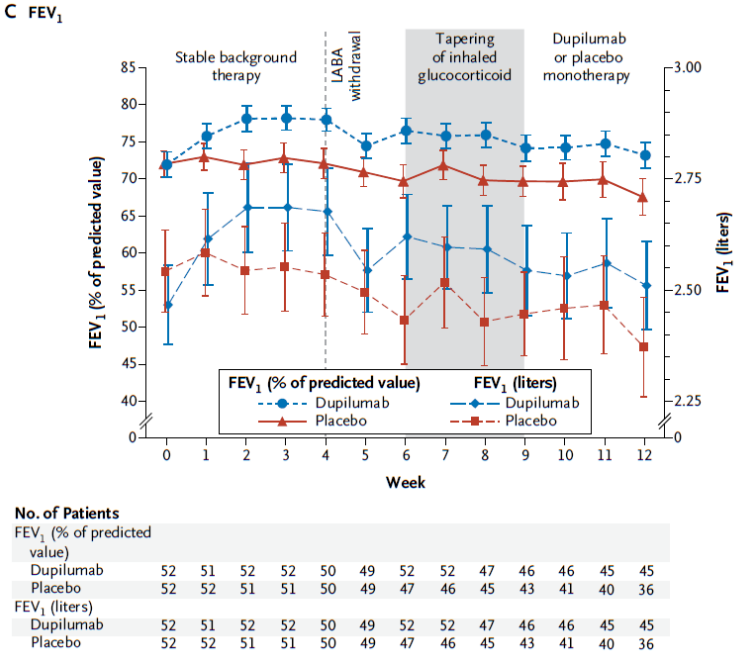
biologic	company	Details	Status
dupilumab	Regeneron Sanofi	human monoclonal antibody that binds to IL-4Rα	Phase 3
Pitrakinra (Aerovant)	Aerovance	mutated form of human interleukin 4 with a high affinity for interleukin 4Rα	Phase 2
AMG317	Amgen	human monoclonal antibody against interleukin 4Rα that blocks both IL-4 and IL-13	Phase 2

Chung KF. Lancet 2015; 386:1086-96

Dupilumab (anti-IL4Rα) in Persistent Asthma with Elevated Eosinophil Levels

- persistent, moderate-to-severe asthma
  - High eosinophils: blood eosinophil ≥300/μl or sputum eosinophil ≥3%
  - Using medium to high-dose ICS/LABA
- dupilumab showed fewer asthma exacerbations with improved lung function when LABAs and ICS were withdrawn





Wenzel S et al. N Engl J Med 2013; 368:2455-66

Dupilumab (anti-IL-4Rα): Phase 2b

- uncontrolled persistent asthma on medium-to-high ICS + LABA
- dupilumab 200 mg or 300 mg or placebo SC every 2 or 4 weeks for 24 weeks

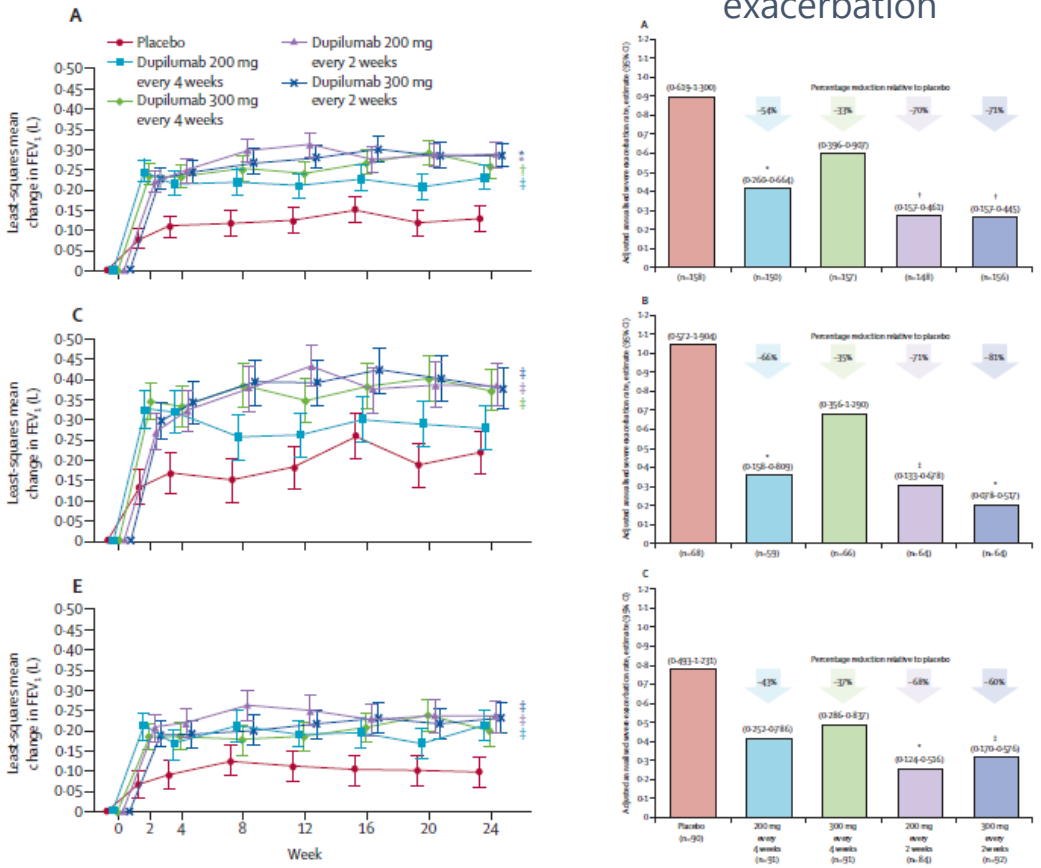
FEV1

Annual rate of exacerbation

all

eos ≥300

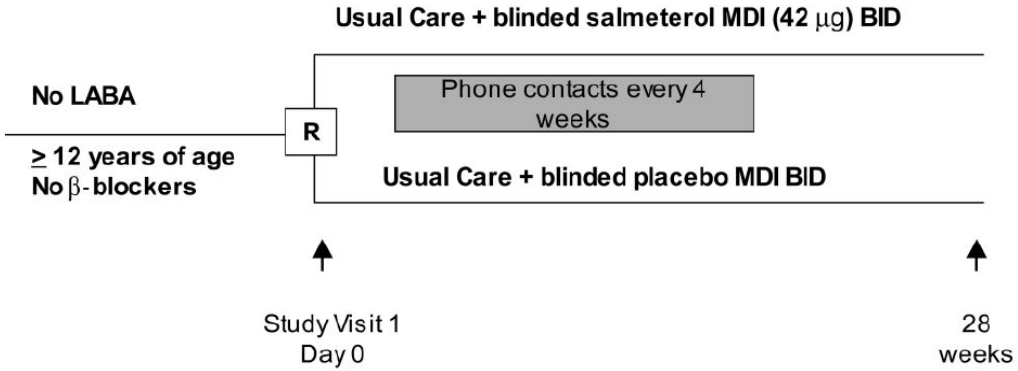
eos <300



Wenzel S et al., Lancet 2016; 388:31-44

Salmeterol Multicenter Asthma Research Trial (SMART)

- Salmeterol Multicenter Asthma Research Trial (SMART)
- Postmarketing surveillance study in US
- 1996-2003 (early termination), age >12



	Serevent MDI (n=13,176)	Placebo (n=13,179)	Relative Risk (95% CI)
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (<1%)	36 (<1%)	1.40 (0.91, 2.14)
Caucasians	29 (<1%)	28 (<1%)	1.05 (0.62, 1.76)
African Americans	20 (<1%)	5 (<1%)	4.10 (1.54, 10.90)
Secondary Endpoint: Asthma-related death			
Total	13 (<1%)	3 (<1%)	4.37 (1.25, 15.34)
Caucasians	6 (<1%)	1 (<1%)	5.82 (0.70, 48.37)
African Americans	7 (<1%)	1 (<1%)	7.26 (0.89, 58.94)

modified from Chest 2006; 129:15-26

FDA: Updated Recommendation on the Use of LABA

1. Use of a **LABA alone** without use of a long-term asthma control medication, such as an inhaled corticosteroid, is **contraindicated** (absolutely advised against) in the treatment of asthma.

2. LABAs should **not be used** in patients whose asthma is **adequately controlled on low or medium dose ICS**.

3. LABAs should **only be used as additional therapy** for patients with asthma who are currently taking but are **not adequately controlled** on a long-term asthma control medication, such as an ICS.

4. Once **asthma control is achieved and maintained,** patients should be assessed at regular intervals and **step down therapy should begin** (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an ICS.

5. **Pediatric and adolescent patients** who require the addition of a LABA to ICS **should use a combination product** containing both an ICS and a LABA, to ensure adherence with both medications.

US FDA Drug Safety Communication. 2 June 2010
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm

Serious Asthma Events with Fluticasone plus Salmeterol vs. Fluticasone Alone

- 26-week, randomized, double-blind, multicenter study (2011-2015)
- 11,679 patients (≥12 years) with history of a severe asthma exacerbation
- Exclusion of history of life-threatening or unstable asthma
- primary safety end point: the first serious asthma-related event (death, endotracheal intubation, and hospitalization)

Table 2. Summary of Safety End Points.*

Safety End Point	Fluticasone–Salmeterol (N=5834)	Fluticasone Alone (N=5845)
Composite safety end point — no. (%)	34 (<1)	33 (<1)
Asthma-related death	0	0
Asthma-related intubation	0	2 (<1)
Asthma-related hospitalization	34 (<1)	33 (<1)
Total no. of asthma-related hospitalizations	36	36
Death from any cause — no. (%)†	3 (<1)	6 (<1)

Stempel DA et al, N Engl J Med 2016; 374:1822-3

Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone

- 26-week, randomized, double-blind, multicenter study (2011-2015)
- 11,693 patients (≥12 years) from 25 countries one to four asthma exacerbations in the previous year
- Patients with a history of life- threatening asthma were excluded.
- primary end point: the first serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization)

Table 2. Patients with Serious Asthma-Related Events.*

End Point or Event	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg+4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg+4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
	number (percent)					
Composite end point	6 (0.4)	8 (0.5)	37 (0.9)	32 (0.8)	43 (0.7)	40 (0.7)
Asthma-related hospitalization	6 (0.4)	8 (0.5)	36 (0.9)	32 (0.8)	42 (0.7)	40 (0.7)
Asthma-related intubation	0	0	1 (<0.1)	0	1 (<0.1)	0
Asthma-related death	0	0	2 (<0.1)	0	2 (<0.1)	0

Peters SP et al, N Engl J Med 2016; 375:850-60

Immunotherapy (GINA 2017)

- Allergen-specific immunotherapy may be an option

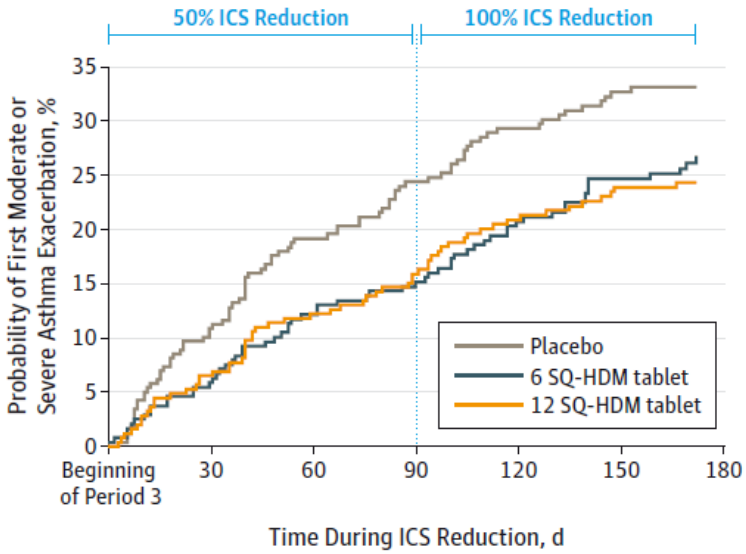
  if allergy plays a prominent role.

- 2 major approaches
  - Subcutaneous immunotherapy (SCIT)
  - Sublingual immunotherapy (SLIT)

HDM Sublingual Immunotherapy (SLIT)

- 834 HDM sensitized asthma ($FEV_1 \geq 70\%$, not well controlled by ICS) and allergic rhinitis in 109 European sites
- ICS reduced during the last 6 months

Figure 2. Probability of Having the First Moderate or Severe Asthma Exacerbation in the Full Analysis Set



No. at risk							
Placebo	257	228	200	188	171	163	109
6 SQ-HDM tablet	237	224	207	201	187	171	122
12 SQ-HDM tablet	248	228	214	207	189	180	121

Virchow JC et al., JAMA 2016; 315:1715-25

SLIT: Practice Parameter 2017

Practice Parameter

Sublingual immunotherapy
A focused allergen immunotherapy practice parameter update

Matthew Greenhawt, MD, MBA, MSc; John Oppenheimer, MD; Michael Nelson, MD, PhD; Hal Nelson, MD; Richard Lockey, MD; Phil Lieberman, MD; Anna Nowak-Wegrzyn, MD; Anju Peters, MD; Charlotte Collins, JD; David I. Bernstein, MD; Joann Blessing-Moore, MD; David Khan, MD; David Lang, MD; Richard A. Nicklas, MD; Jay M. Portnoy, MD; Christopher R. Randolph, MD; Diane E. Schuller, MD; Sheldon L. Spector, MD; Stephen A. Tilles, MD; Dana Wallace, MD

SLIT in Asthma

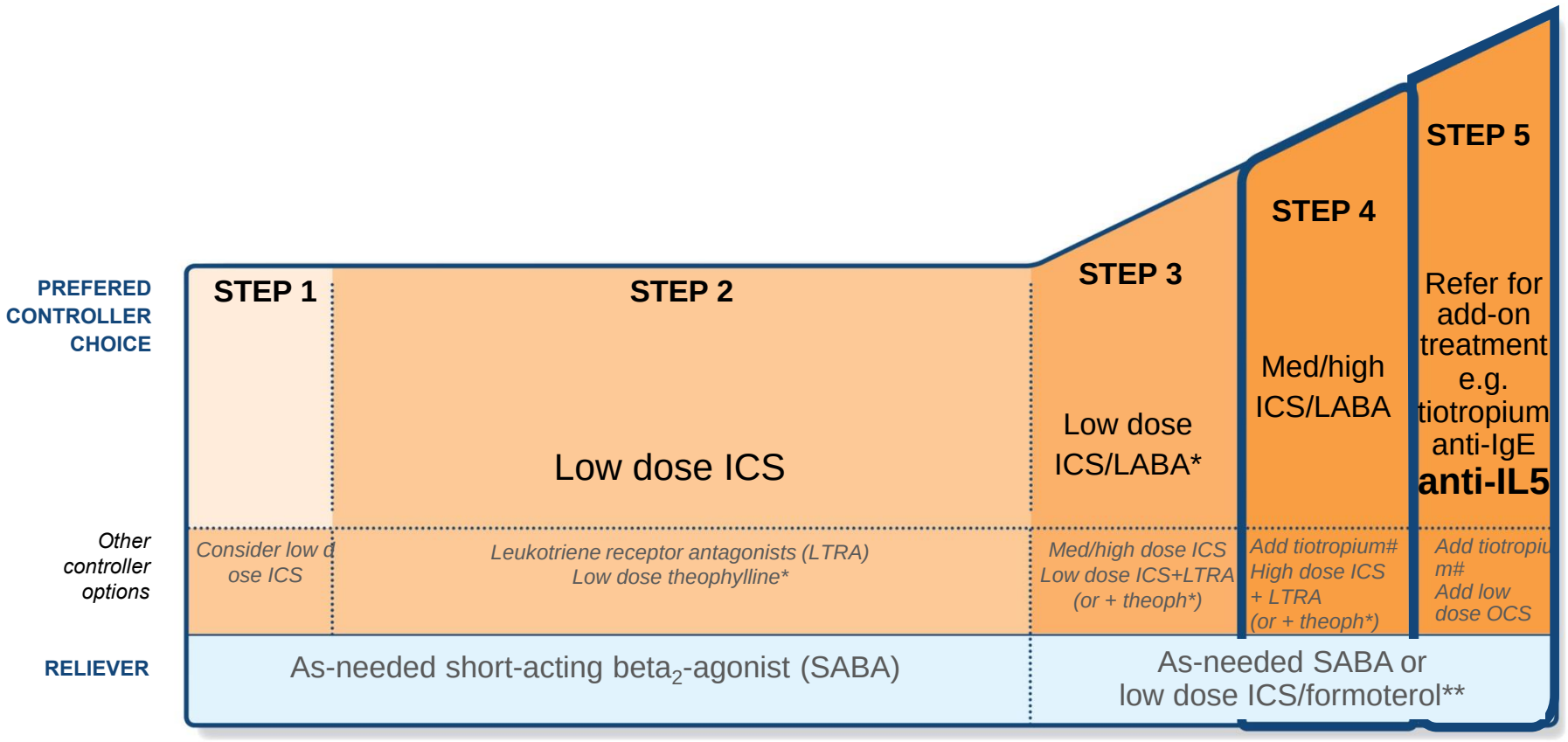
- SLIT is currently not approved for patients with severe, unstable, or uncontrolled asthma.
- Patients with controlled mild to moderate asthma may be given SLIT when the patient and physician have determined that the benefits of treatment outweigh the potential risks.

Ann Allergy Asthma Immunol 2017; 118:276-82

GINA 2017: "ACO" is preferred to ACOS

- The **word 'syndrome' has been removed** from the previous term 'asthma-COPD overlap syndrome (ACOS)' because:
  - This term was being commonly used in the respiratory community as if it was a single disease ('the asthma-COPD overlap syndrome')
  - There are two medically-accepted definitions of 'syndrome'
- The descriptive term **asthma-COPD overlap (ACO)** **is useful** to maintain awareness by clinicians, researchers and regulators of the needs of these patients, since most guidelines and clinical trials are about asthma alone or COPD alone.

GINA 2017: anti-IL-5 in step 5



The Global Initiative for Asthma 2017, www.ginasthma.org

GINA 2017: SLIT for HDM-sensitive asthma

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is 70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT: sublingual immunotherapy

GINA 2017: Monitoring of Asthma

- Spirometry
  - should be assessed at diagnosis or start of treatment
  - after 3–6 months of controller treatment to assess the patient's personal best FEV_1
  - periodically thereafter: at least every 1-2 years, more frequently in higher risk
- FeNO
  - not helpful in ruling in or ruling out asthma
  - cannot be recommended for deciding against treatment with ICS
  - High FeNO is independent predictor of exacerbations in allergic patients