천식의 치료, 예방, 환자교육

이정규

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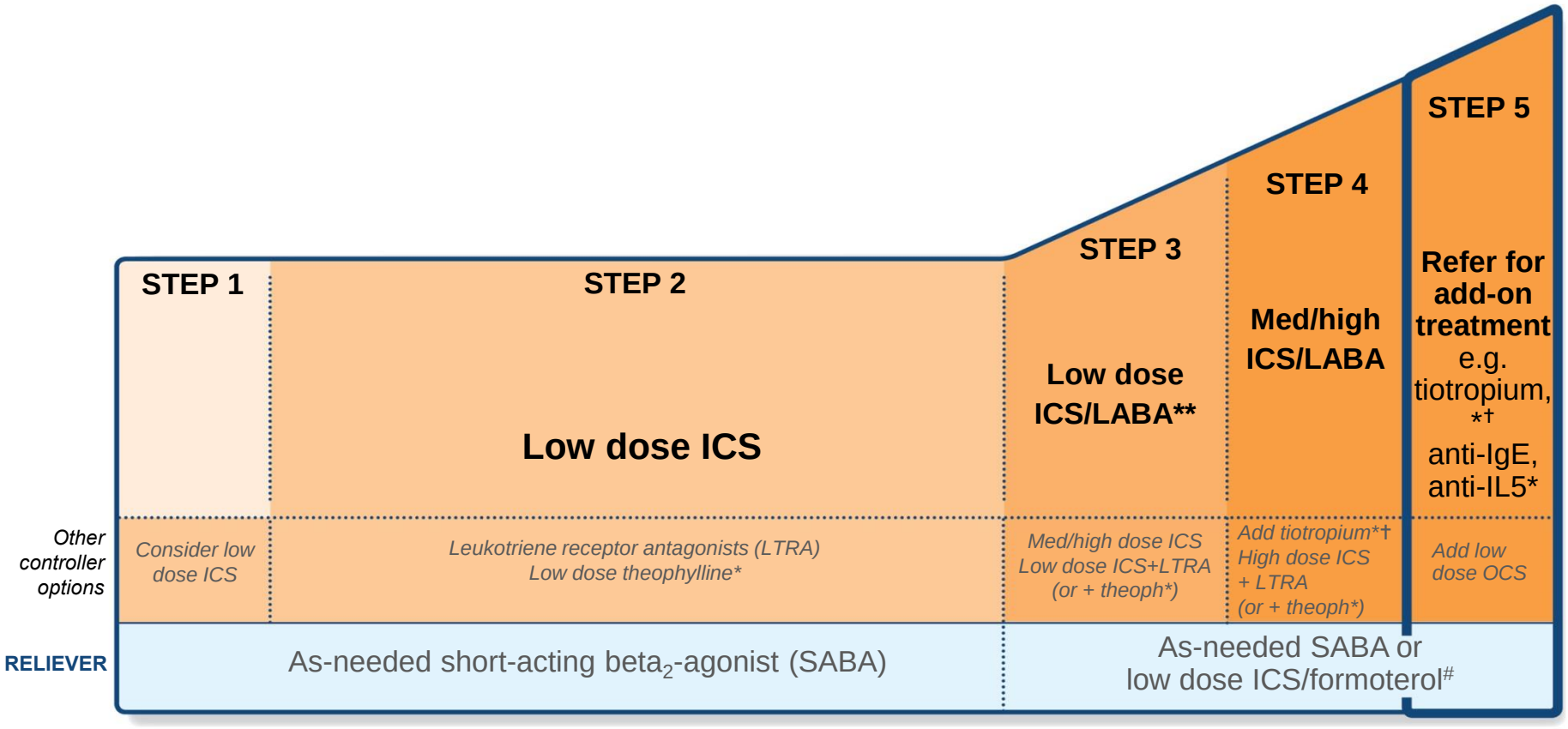
Stepwise approach to asthma treatment



* Not for children <12 years
** For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
# For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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Indication of initial controller

- Asthma symptoms or need for SABA ≥ 2/month (Evidence A)
- Asthma symptoms or need for SABA, 2/week ~ 2/month, or patient wakes due to asthma ≥ 1/month (Evidence B)
- Infrequent asthma symptoms, but the patient has ≥ 1 risk factors for exacerbations (e.g. low lung function, or exacerbation requiring OCS in the last year, or has ever been in intensive care for asthma) (Evidence D)

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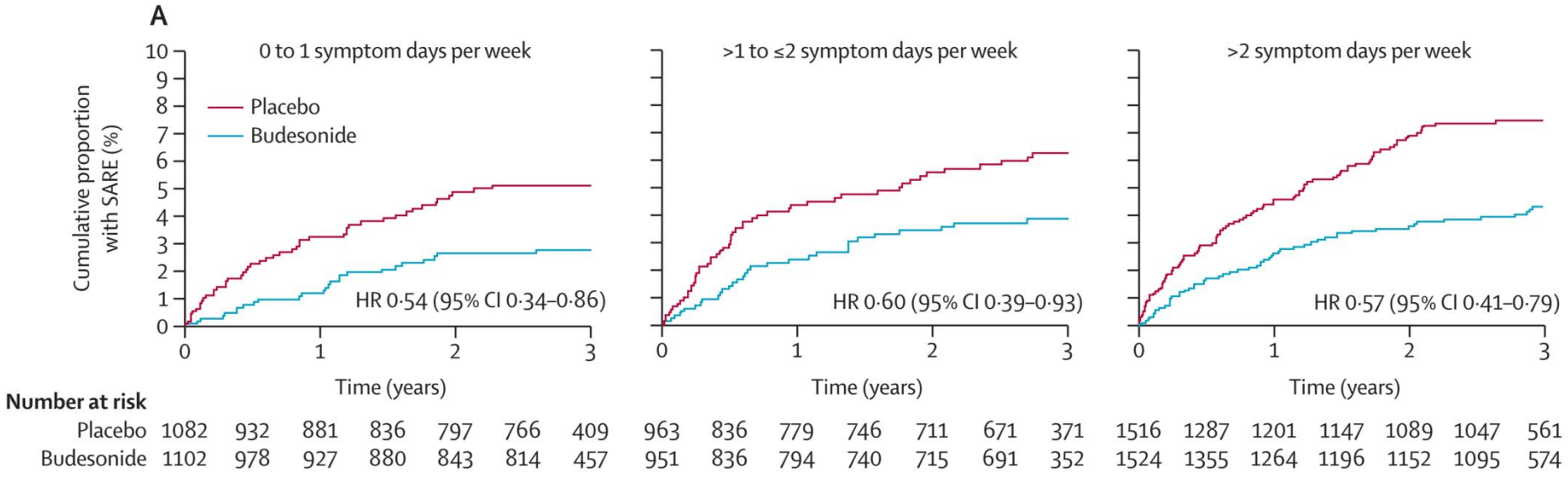
ICS start for mild asthma: START

- Validation of the previous symptom-based cutoff for starting ICS
- 7138 patients with mild asthma, age 4-66 yrs
- Once daily budesonide (400 µg, or 200 µg if aged <11 yrs) vs placebo, 1:1, for 3 yrs

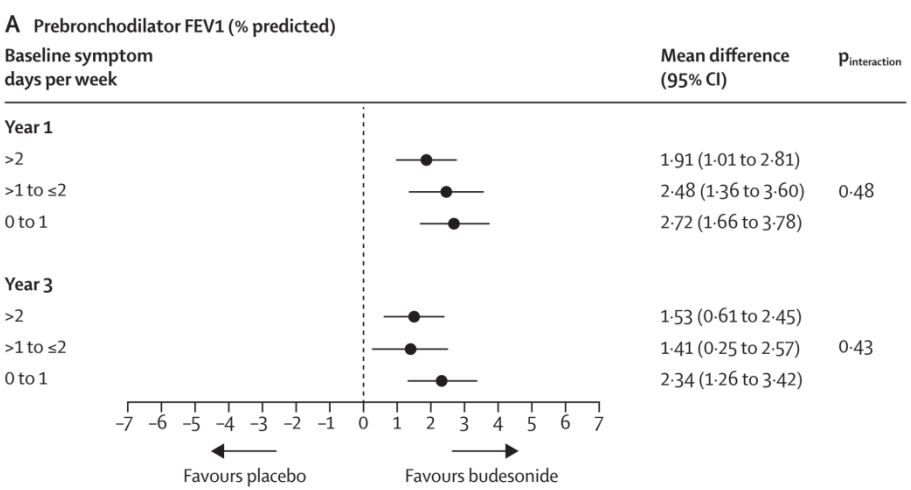


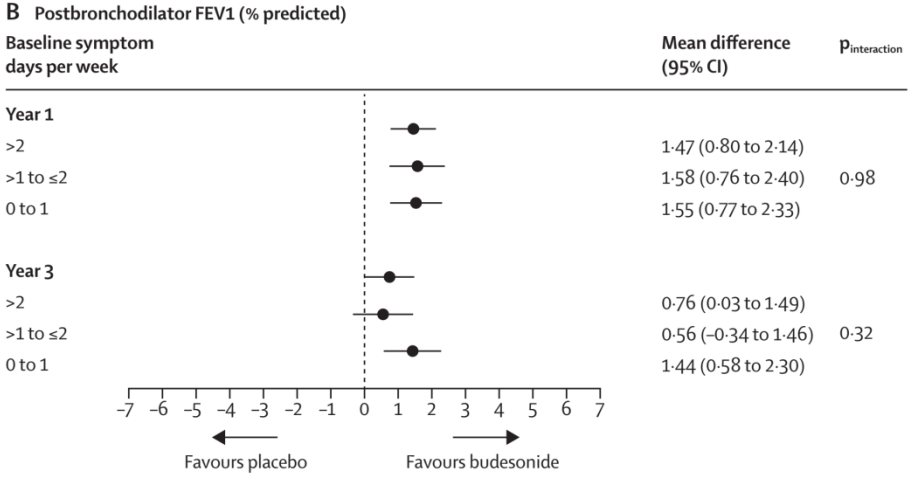
* SARE : Severe asthma-related events (hospital admission, emergency treatment, or death

Reddel HK, et al. Lancet 2017;389(10065):157-166.

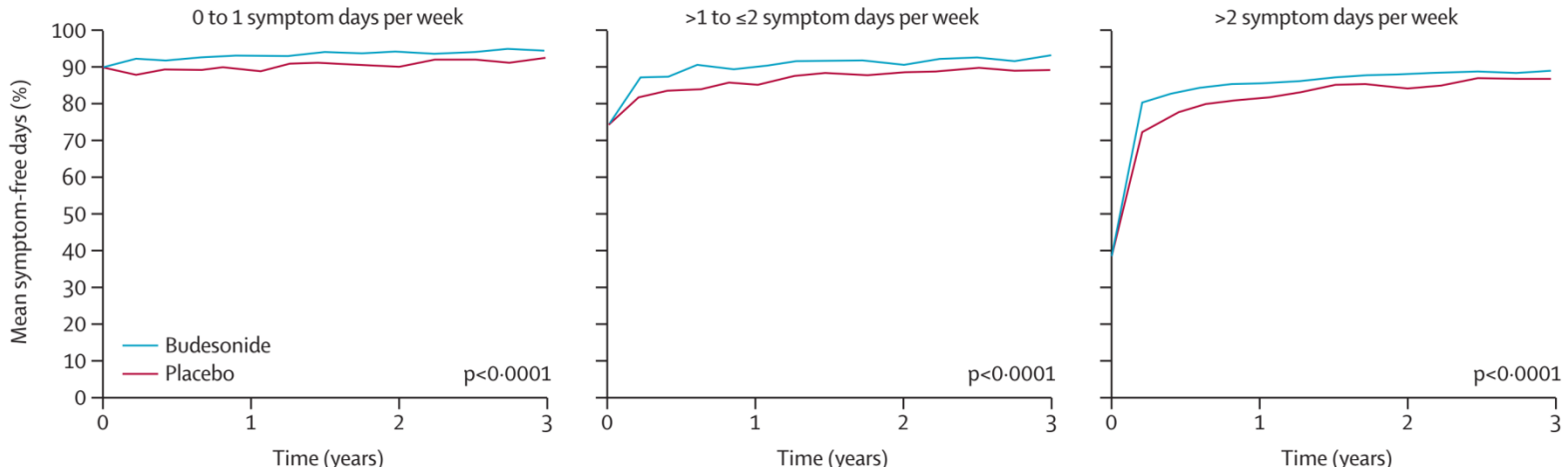
ICS start for mild asthma: START

- Lung function





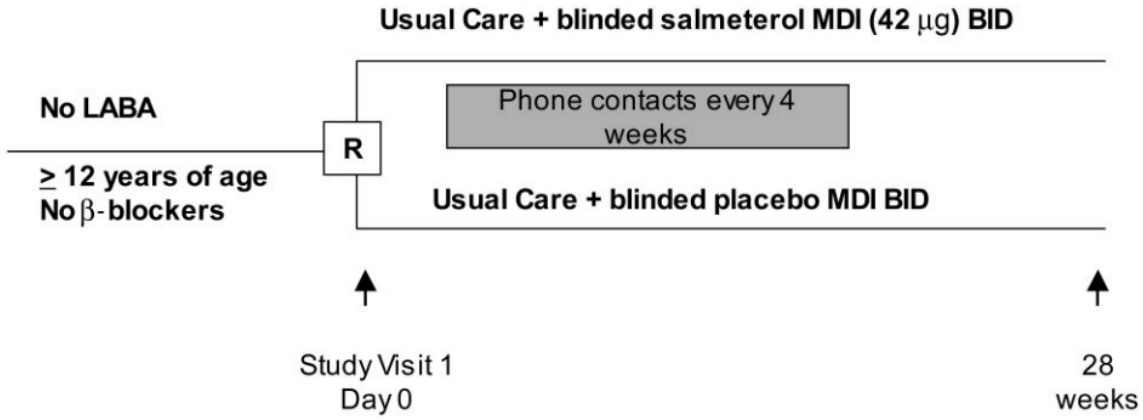
- Symptom-free days



Reddel HK, et al. Lancet 2017;389(10065):157-166.

Concern for safety of LABA

- Salmeterol Multicenter Asthma Research Trial (SMART)
- 26,355 patients with asthma, >12yrs old
- Salmeterol xinafoate vs placebo added to usual care, 28 wk



Asthma-related death	Salmeterol (n=13,176)	Placebo (n=13,179)	RR (95% CI)	Excess deaths expressed per 10,000 patiens (95% CI)
All patients	13	3	4.37 (1.25-15.33)	8 (3-13)
Caucasians	6	1	5.82 (0.70-48.37)	6 (1-10)
African Americans	7	1	7.26 (0.89-58.94)	27 (8-46)

Nelson HS, et al. Chest 2006;129:15-26.

FDA new safety requirement for LABA

- Meta-analysis of 110 studies, evaluating the use of LABAs in 60,954 patients with asthma
- Composite endpoint : severe exacerbation of asthma symptoms (asthma-related death, intubation, hospitalization)

Population	LABA (n=30,148)	Placebo (n=30,806)	Risk difference estimate per 1,000 treated patients (95% CI)
All patients	381	304	2.80 (1.11-4.49)
Age 12-17 yrs	48	30	5.57 (0.21-10.92)
Age 4-11 yrs	61	39	14.83 (3.24-26.43)

FDA Drug Safety Communication 2010 Feb

FDA updated recommendations for LABA

The new recommendations in the updated labels state:
✓ 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.
✓ LABAs **should not be used** in patients whose asthma **is adequately controlled** on low or medium dose inhaled corticosteroids.
✓ 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 inhaled corticosteroid.
✓ 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 inhaled corticosteroid.
✓ **Pediatric and adolescent patients** who require the addition of a LABA to an inhaled corticosteroid **should use a combination product** containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

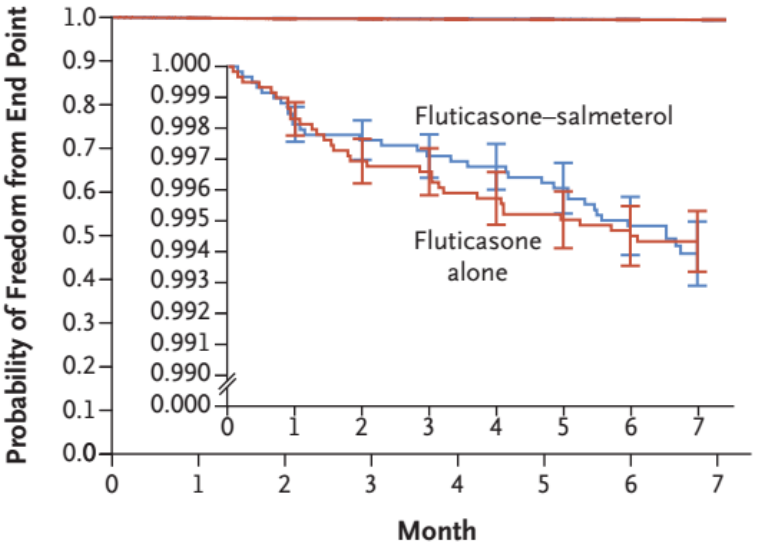
FDA Drug Safety Communication 2010 June

Serious asthma events with Fluticasone plus Salmeterol versus Fluticasone alone

- 11,679 patients with persistent asthma, age ≥ 12 yrs
  - ➢ History of a severe asthma exacerbation in the year
- Multicenter, randomized, double-blind trial, 26wks (2011-2015)
- Primary safety end point : the first serious asthma-related event (death, endotracheal intubation, or 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;374:1822-30.

Serious asthma events with Budesonide plus Formoterol versus Budesonide alone

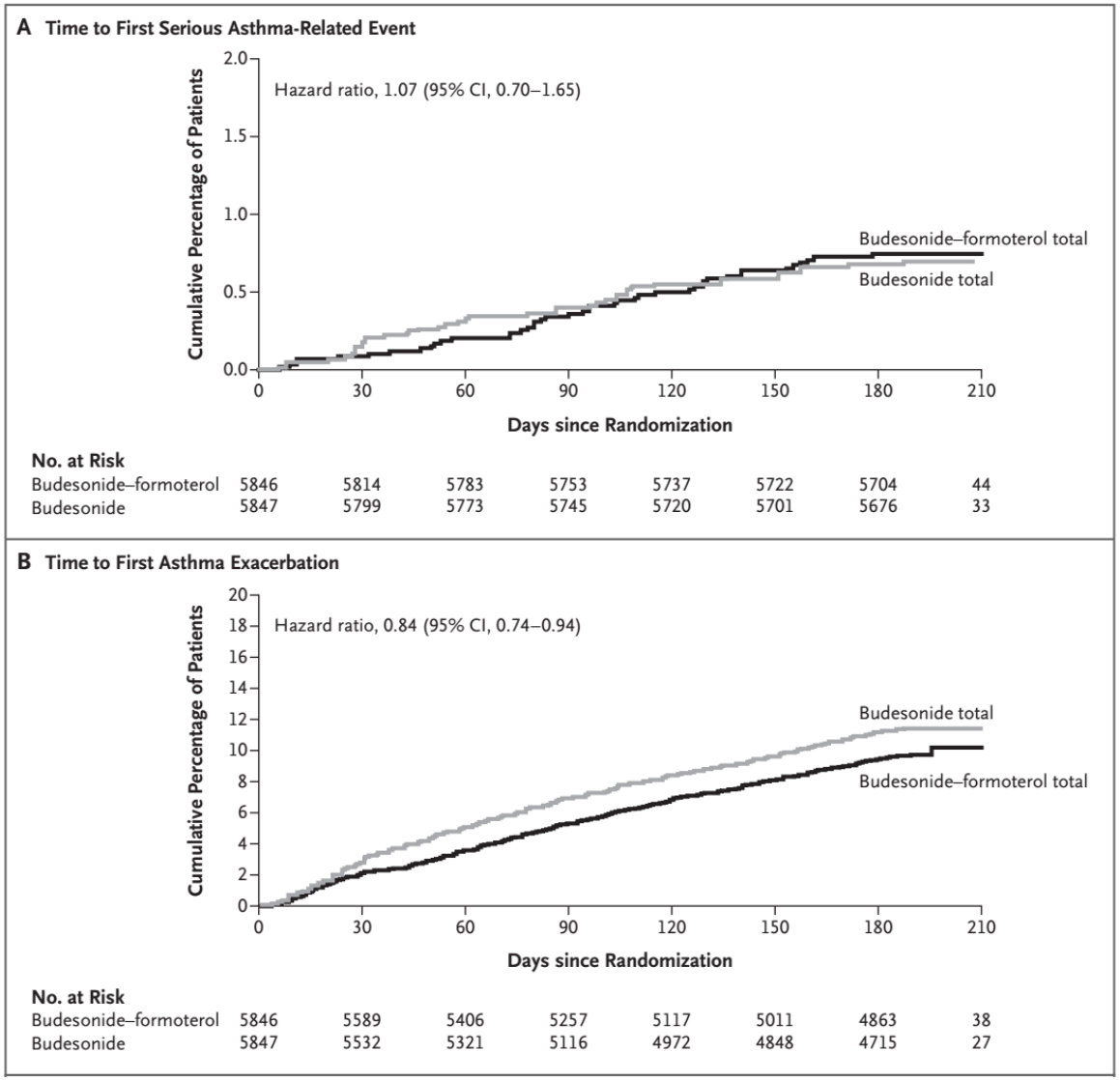
- 11,693 patients with persistent asthma, age ≥ 12 yrs
  - ➢ History of one to four asthma exacerbations in the previous year
- Multicenter, randomized, double-blind trial, 26wks
- Primary end point : the first serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization)

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.

Serious asthma events with Budesonide plus Formoterol versus Budesonide alone



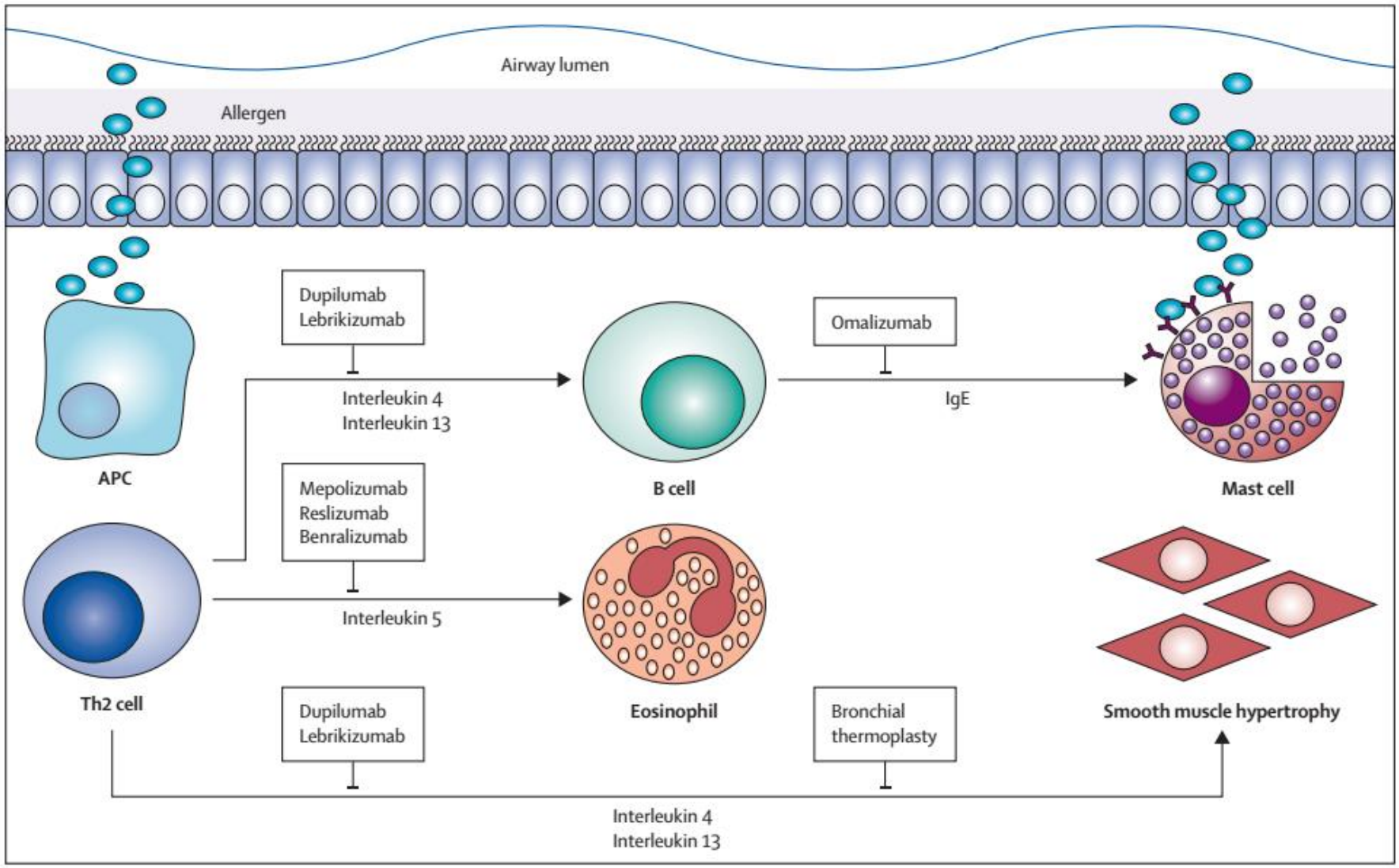
Peters SP, et al. N Engl J Med 2016;375:850-60.

Step 5: Higher level care and/or add-on treatment

- Preferred option is referral for specialist investigation and consideration of add-on treatment
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on **tiotropium**
    - for patients ≥12 years with history of exacerbations
  - Add-on **anti-IgE** (**omalizumab**)
    - for patients with severe allergic asthma
  - Add-on **anti-IL5** (**mepolizumab** (SC) or **reslizumab** (IV))
    - for severe eosinophilic asthma (≥12 yrs)

GINA 2017.

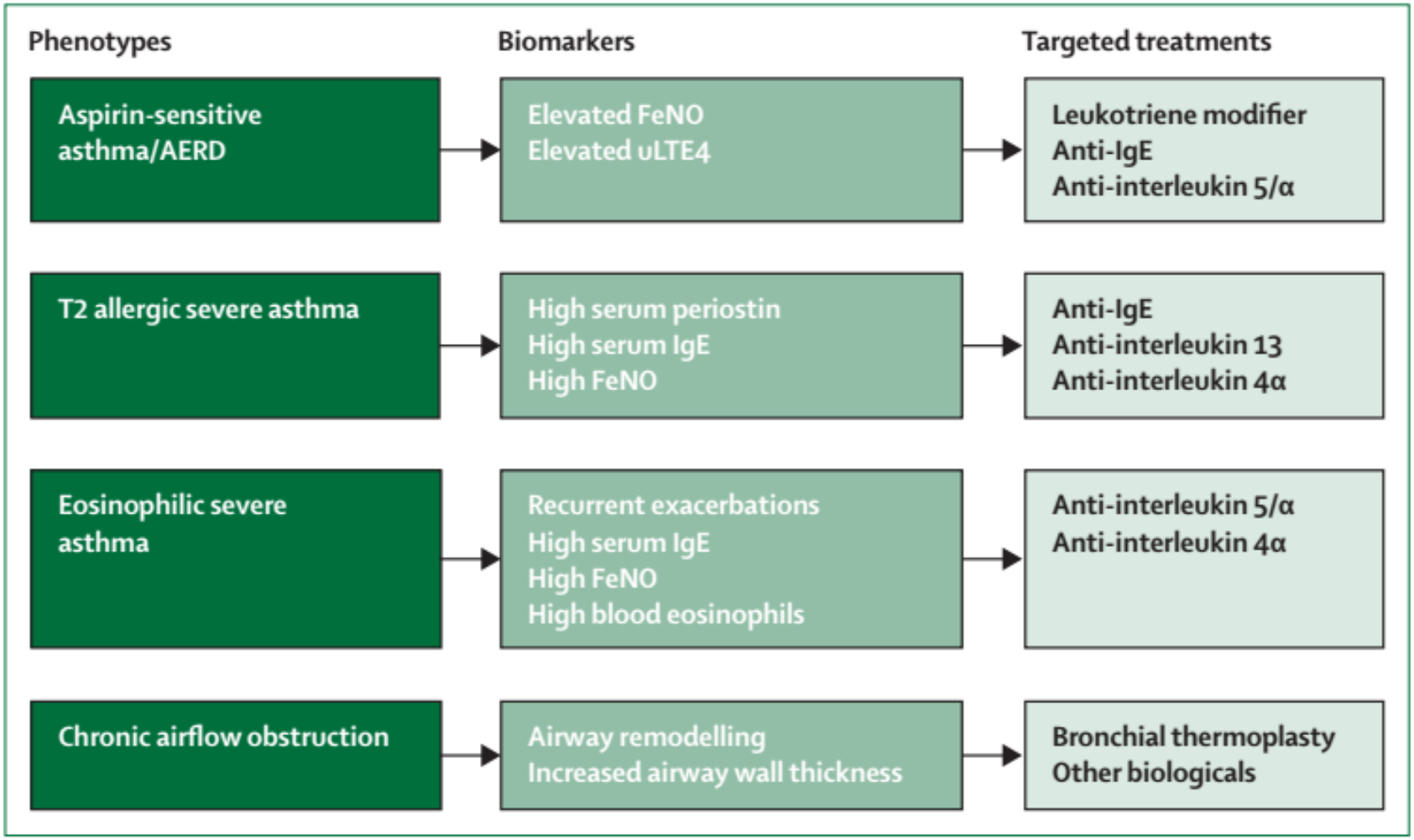
Targeted treatments for severe asthma



Trevedi A, et al. Lancet Respir Med 2016;4:585-92.

Targeted treatments for severe asthma

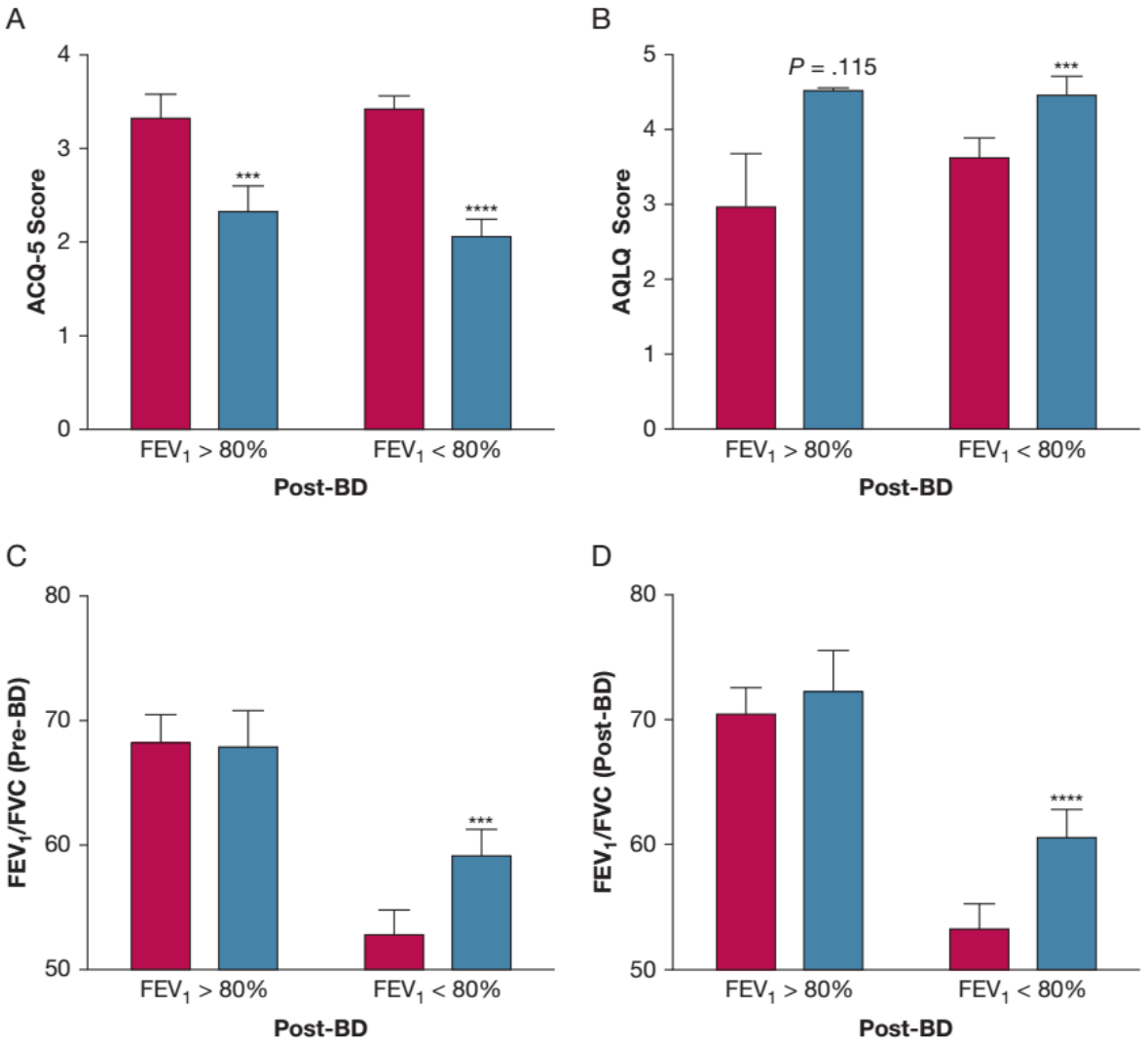
- Based on phenotypes with associated with biomarkers



Trevedi A, et al. Lancet Respir Med 2016;4:585-92.

Omalizumab in asthma-COPD overlap

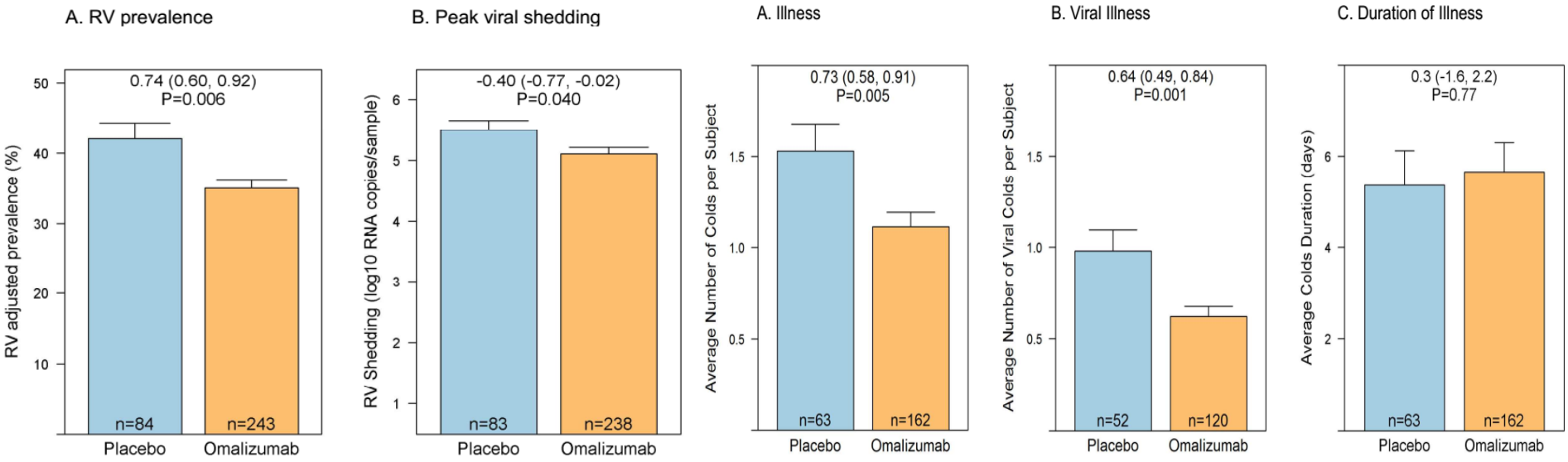
- Data from the Australian Xolair Registry
- Asthma-COPD overlap vs. asthma alone
- 6 months of omalizumab treatment



Matby S, et al. Chest 2017;151(1):78-89.

Omalizumab on rhinovirus infections

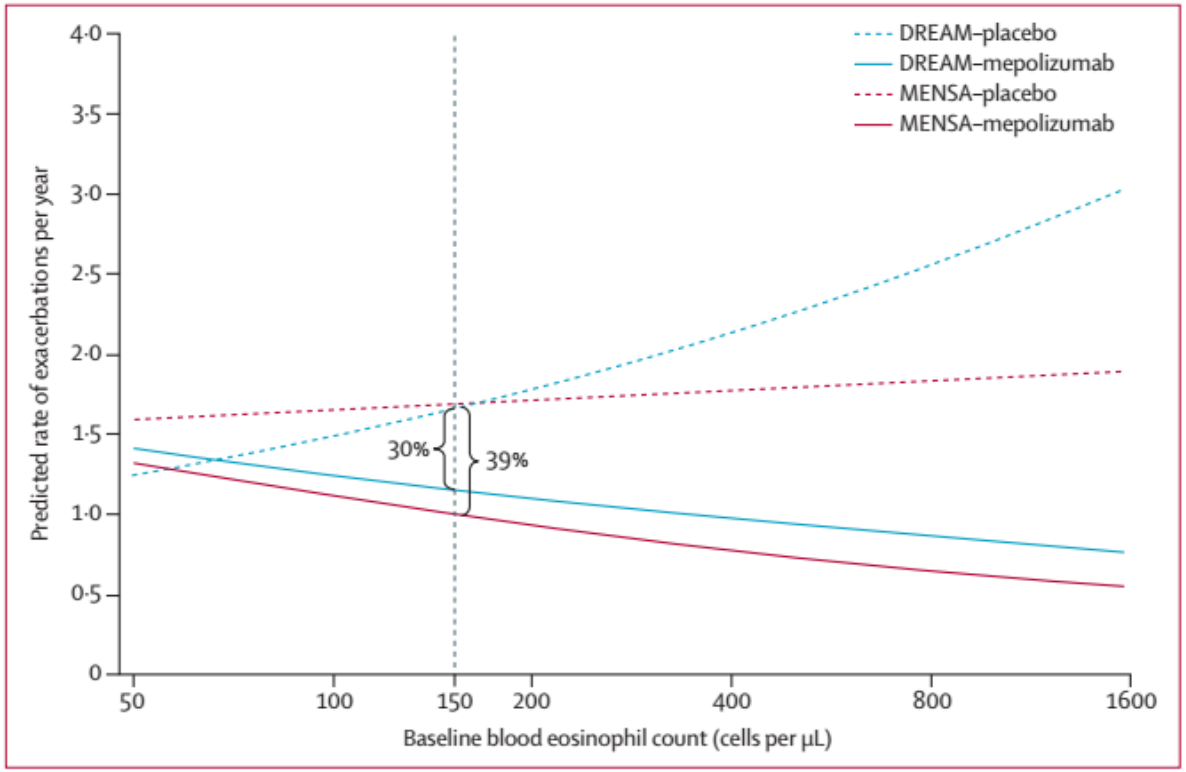
- Based on PROSE study
- Children with allergic asthma (6-17 years, n=478) from low-income census tracts in 8 US cities
- Guideline-based asthma care (n=89) vs add-on omalizumab(n=259) : omalizumab or placebo every 2 or 4 wk SQ
- Over a 90-day period during the fall seasons of 2012 or 2013



Esqiovel A, et al. Am J Respir Crit Care Med 2017 (In Press)

Mepolizumab in eosinophilic asthma

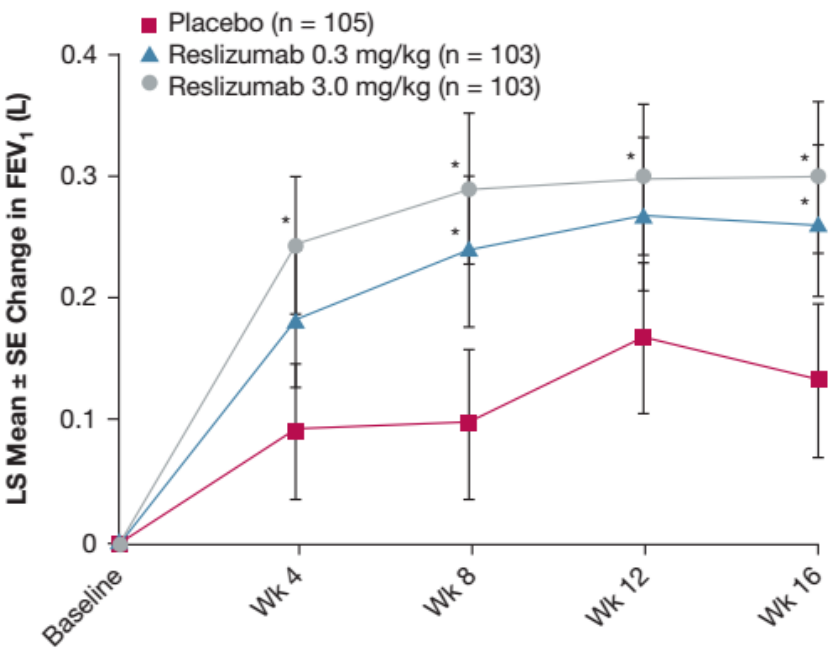
- 2 RCT, 32wk, 2009-2014 : DREAM, MENSA
- Age ≥ 12 yrs, severe eosinophilic asthma
- Mepolizumab vs placebo, 4wk interval, add-on therapy
- Primary outcome : Annualised rate of exacerbations in patients stratified by baseline eosinophil thresholds

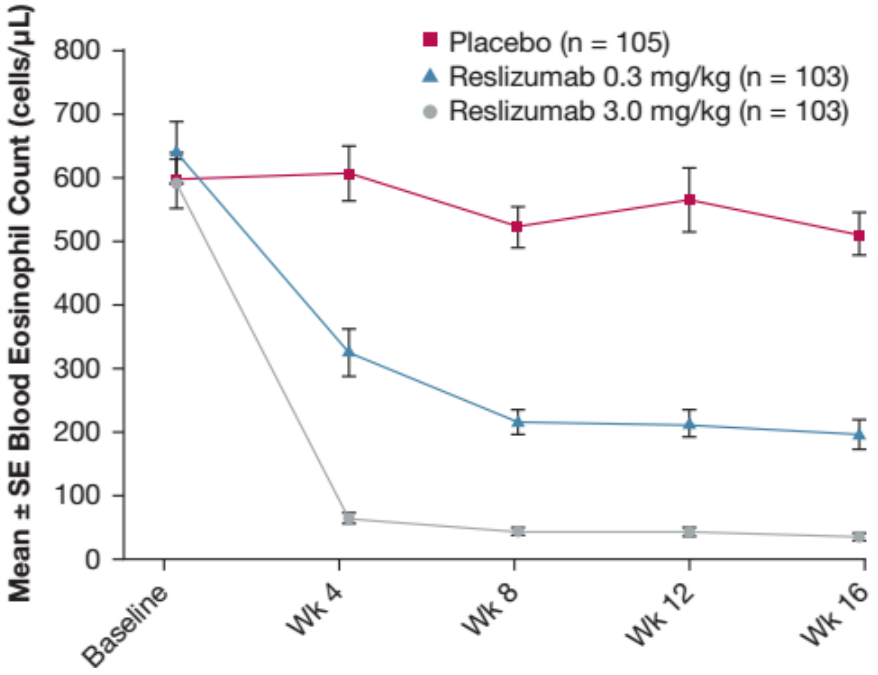


Ortega HG, et al. Lancet Respir Med 2016;4:549-56.

Reslizumab in eosinophilic asthma

- Asthma inadequately controlled by at least a medium-dose ICS, blood eosinophil count ≥ 400 cells/mL, age 12-75 yrs
- Phase 3 RCT, resilizumab vs placebo, every 4 wks for 16 wks
- Improvement of lung function, asthma control/symptoms, QOL





Bjermer L, et al. Chest 2016;150(4):789-798.

Benralizumab: anti-IL-5 receptor antibody

- Age 12–75 yrs, physician-based diagnosis of asthma for at least 1 year, at least 2 exacerbations while on high-dose ICS/LABA in the previous year

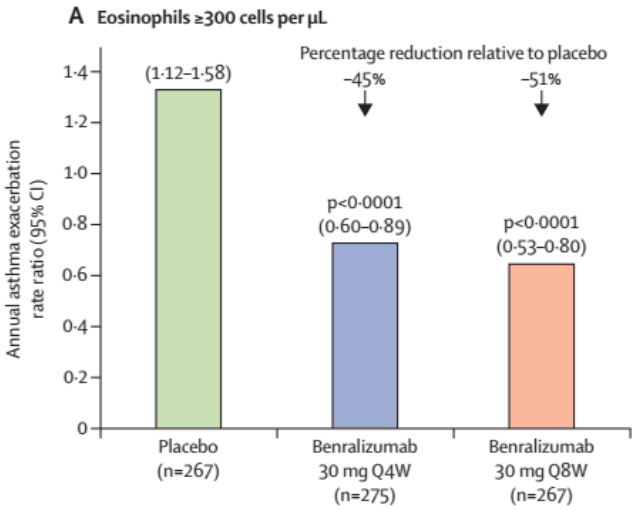
- Benralizumab 40mg every 4 wk or 8 wk (1st 3 doses every 4wk) vs. placebo, add-on therapy
- Stratified 2:1 according to blood eosinophil counts
  - ≥ 300 cell/μL vs < 300 cells/μL

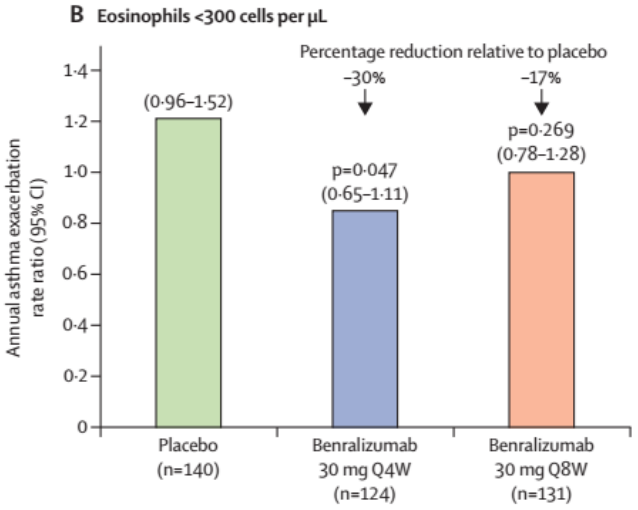
- 48 wks in SIROCCO study, 56 wks in CALIMA study
- Primary endpoint : annual exacerbation rate ratio

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

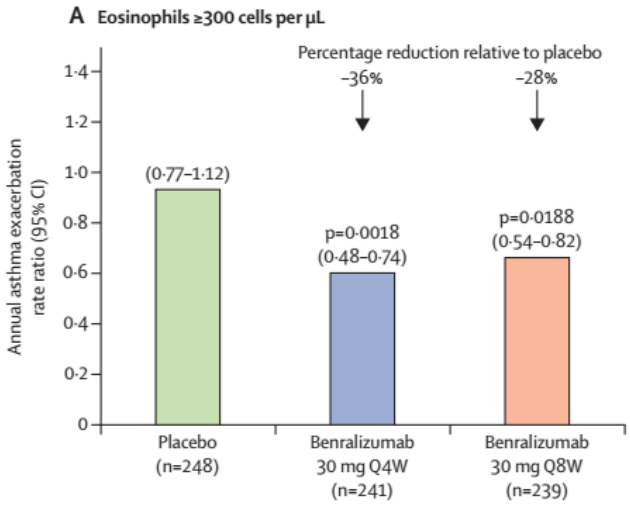
Benralizumab: anti-IL-5 receptor antibody

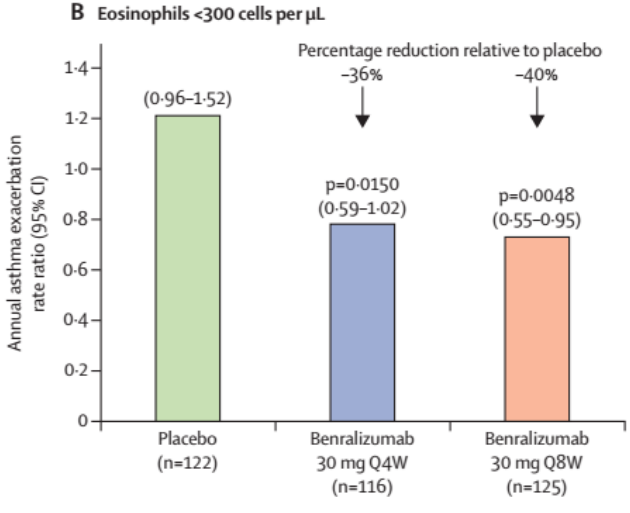
➢ SIROCCO





➢ CALIMA

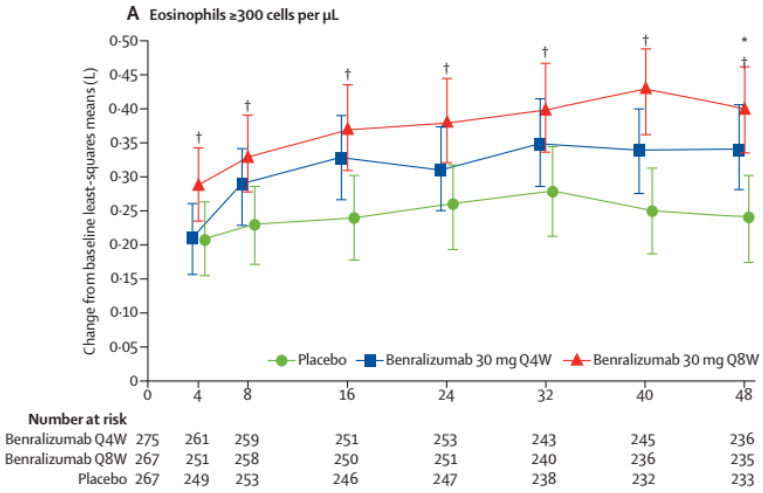


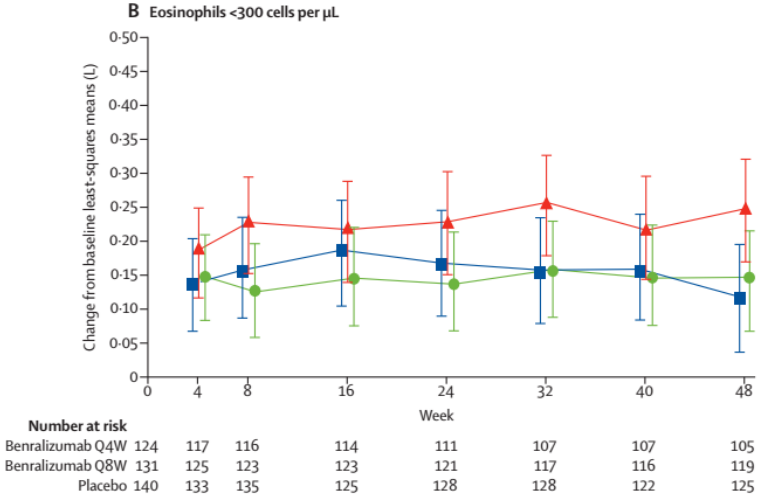


Bleecker ER, et al. Lancet 2016;388:2115-27.
FitzGerald JM, et al. Lancet 2016;388;2128-41.

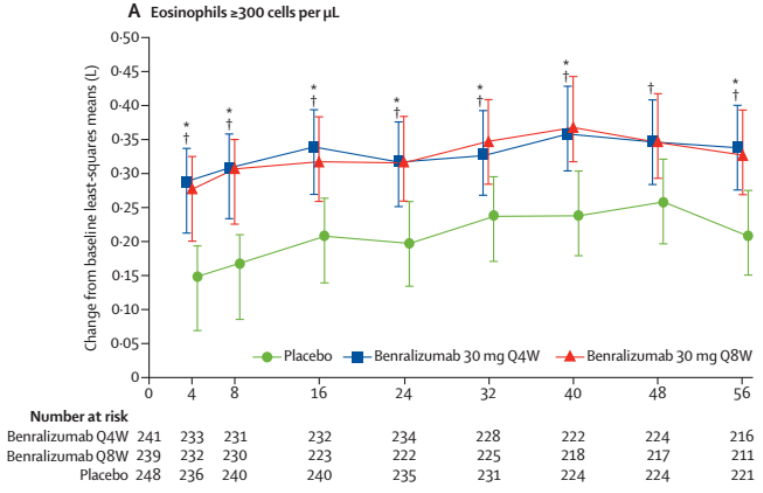
Benralizumab: anti-IL-5 receptor antibody

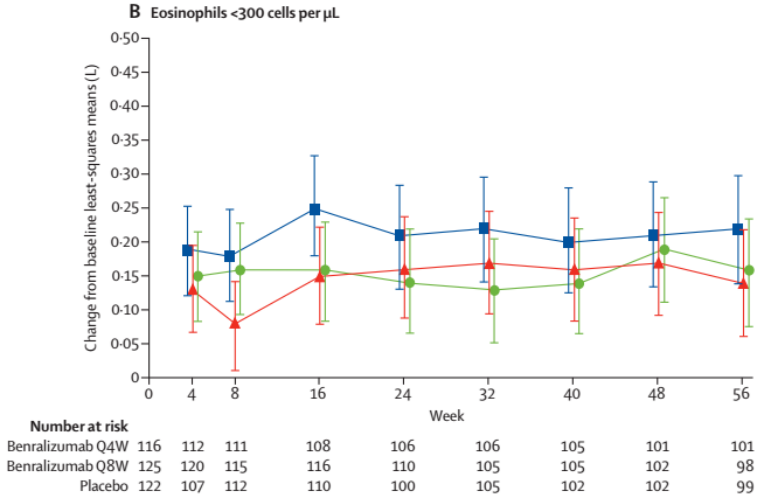
➢ SIROCCO





➢ CALIMA

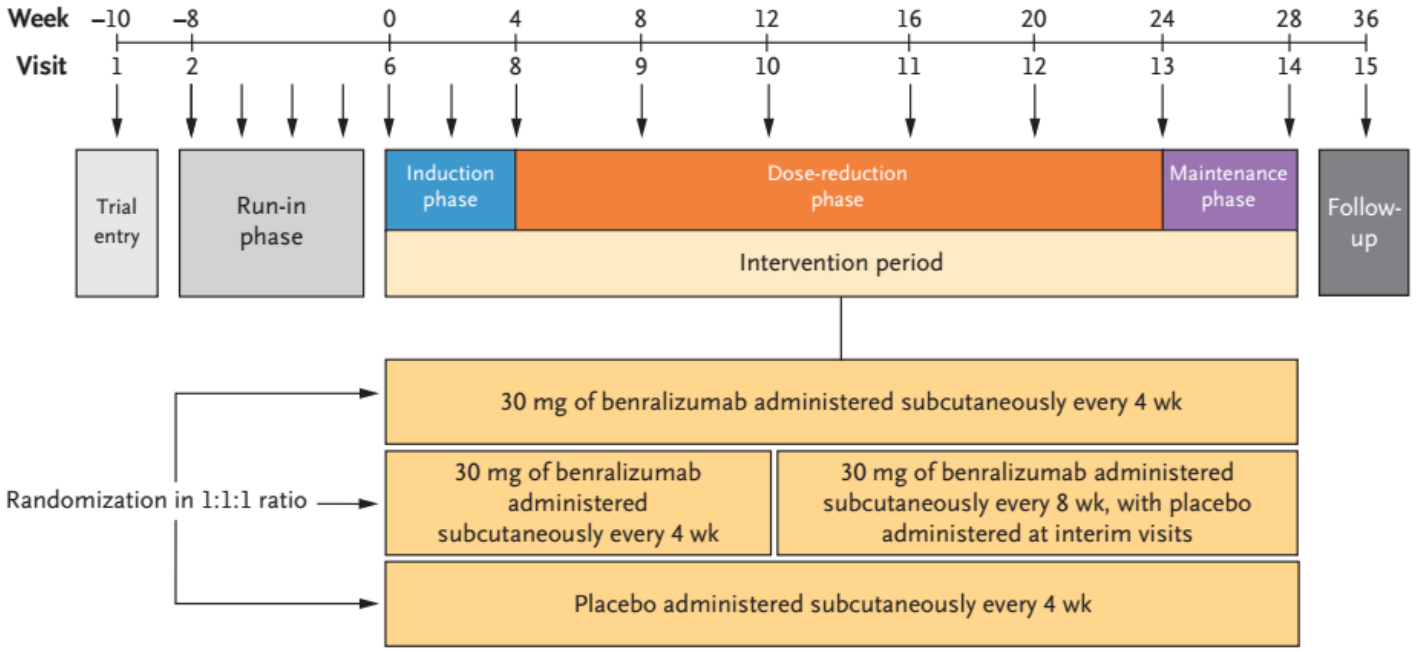




Bleecker ER, et al. Lancet 2016;388:2115-27.
FitzGerald JM, et al. Lancet 2016;388;2128-41.

Benralizumab : steroid-sparing effect

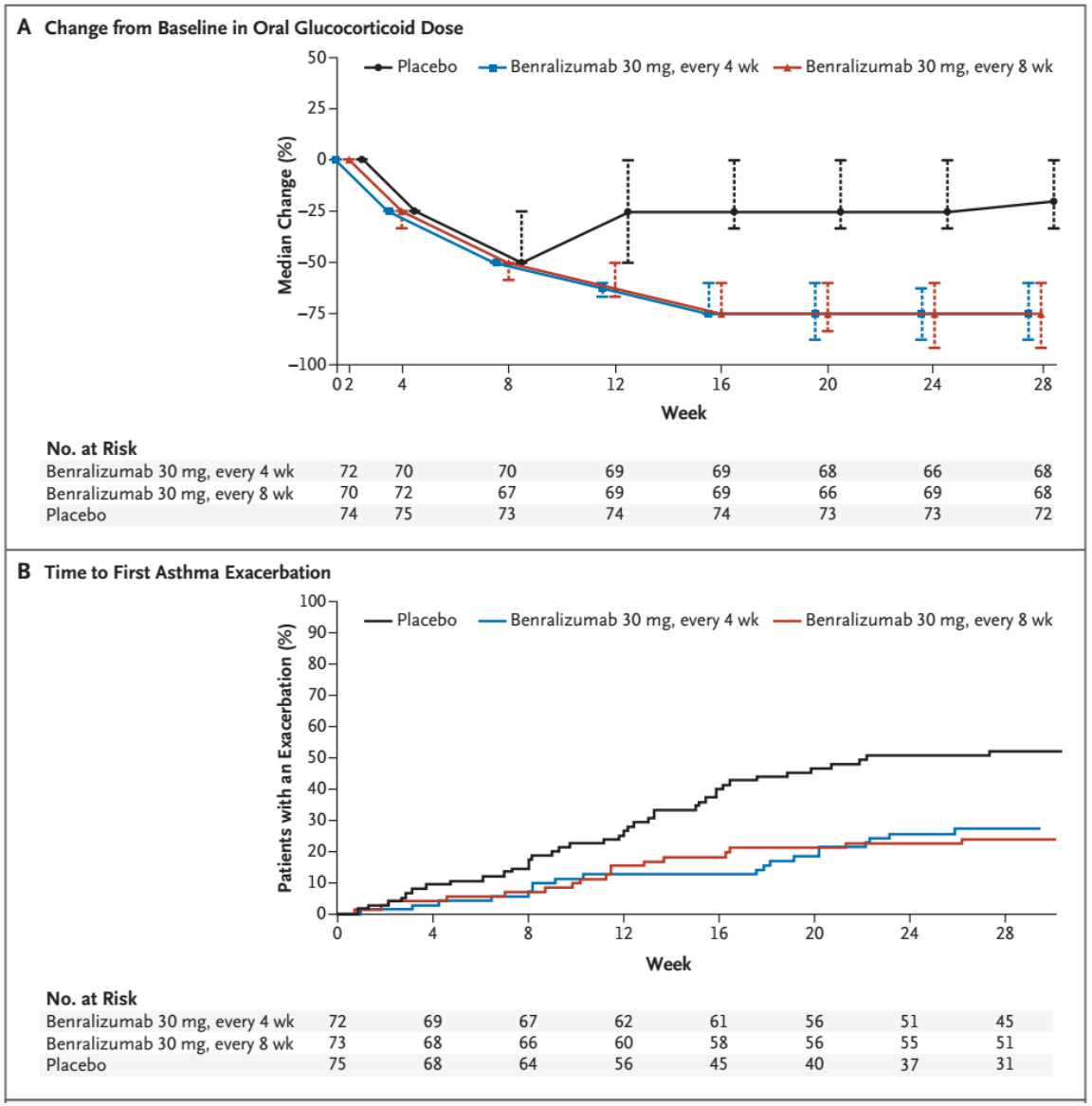
- 369 patients with severe asthma, with continuous oral glucocorticoids for 6 months or more before enrollment
- Benralizumab 30mg SC every 4 wk or 8 wk (1st 3 dose every 4 wk) vs placebo, on the reduction in the oral glucocorticoid dose while asthma control was maintained
- Primary end point : Percentage change in the oral glucocorticoid dose from baseline to 28 wk



Nair P, et al. N Engl J Med 2017;376:2448-2458.

Benralizumab : steroid-sparing effect

- Change from baseline in oral glucocorticoid dose
- Time to first asthma exacerbation

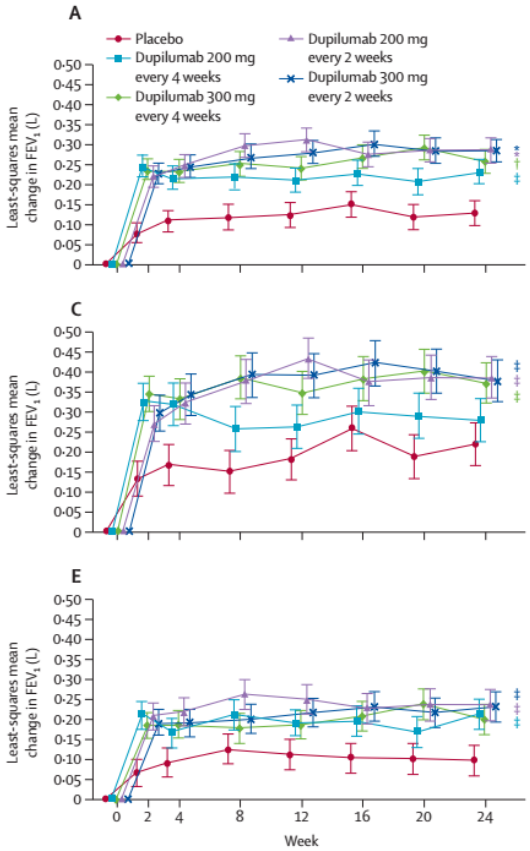


Nair P, et al. N Engl J Med 2017;376:2448-2458.

Dupilumab: anti-IL-4Rα antibody

- Phase 2b dose-ranging RCT
- Adults (aged ≥18 yr) with asthma, with medium-to-high-dose ICS/LABA, history of exacerbation in the previous year
- Dupilumab 200 or 300mg SC every 2wk or 4wks vs. placebo
- Primary outcome : FEV1 change from baseline at 12 wk

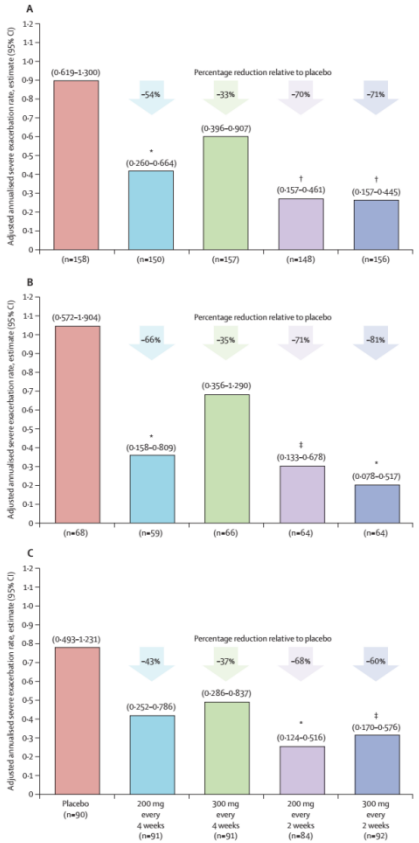
➢ FEV1



Overall

Blood eosinophil ≥ 300μL

Blood eosinophil < 300μL



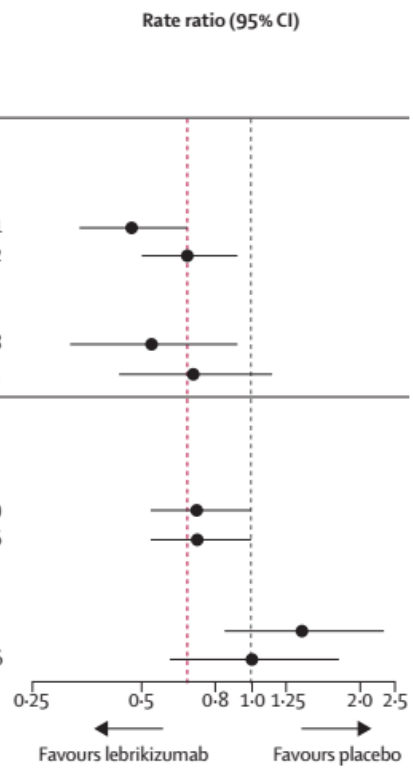
➢ Annualized severe exacerbation event rates

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

Lebrikuzumab: anti-IL-13 antibody

- LAVOTA I (n=1,081) and II (n=1,067) study
- Adults patients with uncontrolled asthma, pre-bronchodilator FEV1 40-80%
- Lebrikizumab 37.5mg vs 125mg vs placebo
- Primary outcome : exacerbation rate, over 52 wks in higher-biomarker patients (periostin ≥ 50 ng/mL, blood eosinophil ≥ 300/µL)

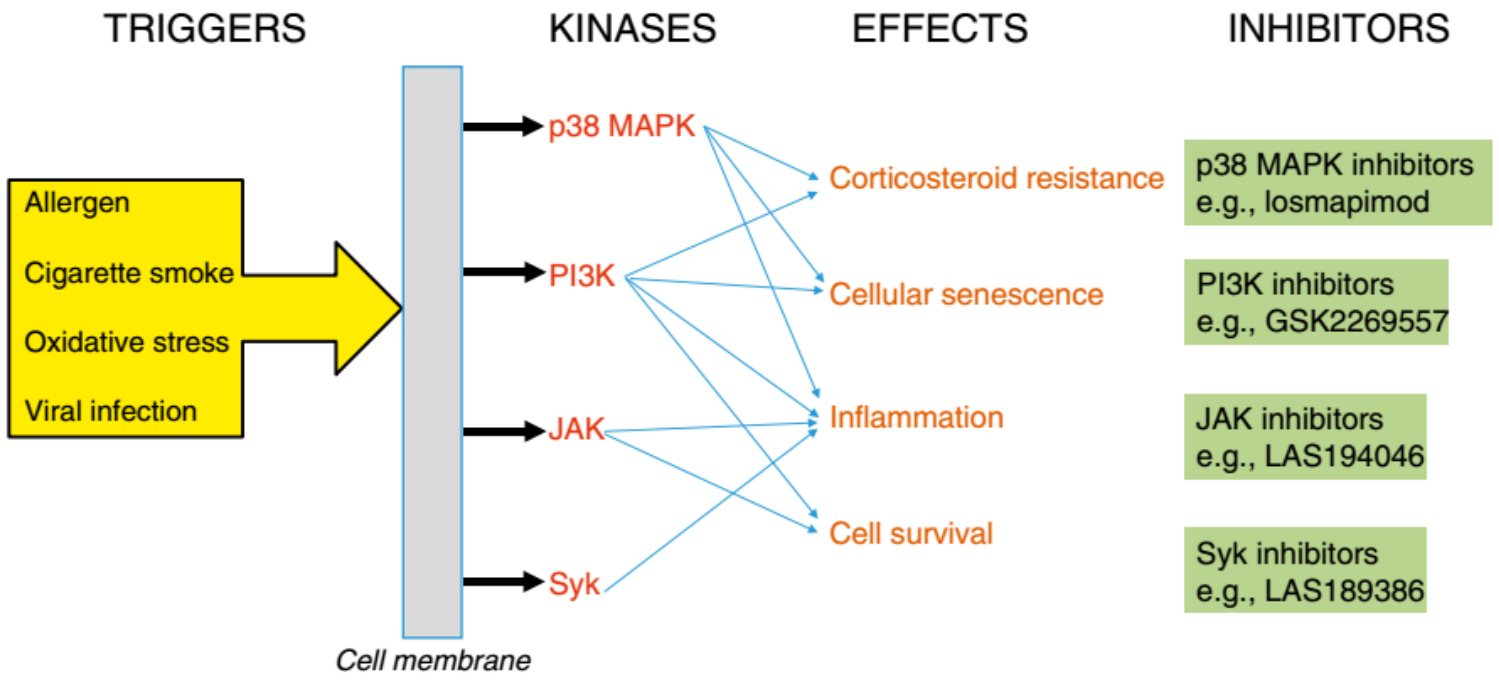
	n	Adjusted exacerbation rate (per patient per year)	Rate difference (lebrikizumab–placebo)	Rate reduction (%)	Rate ratio (lebrikizumab *vs* placebo, 95% CI)	p value
LAVOLTA I						
Biomarker high						
Placebo	256	0·94				
Lebrikizumab 37·5 mg	251	0·46	−0·48	51%	0·49 (0·34–0·69)	<0·0001
Lebrikizumab 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(10):781-96.

Kinase inhibitor in air way disease

- Several classes of kinase are activated in airway diseases as a result of several triggers
- Lead to multiple downstream effects, especially inflammation, corticosteroid resistance, cellular senescence, cell survival/proliferation

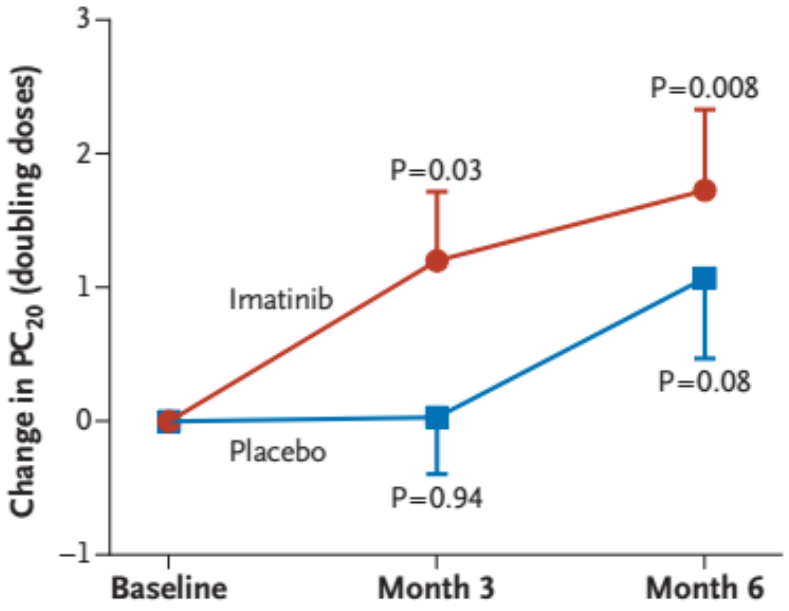


Gross NJ, et al. Am J Respir Crit Care Med 2017;195(2):159-166.

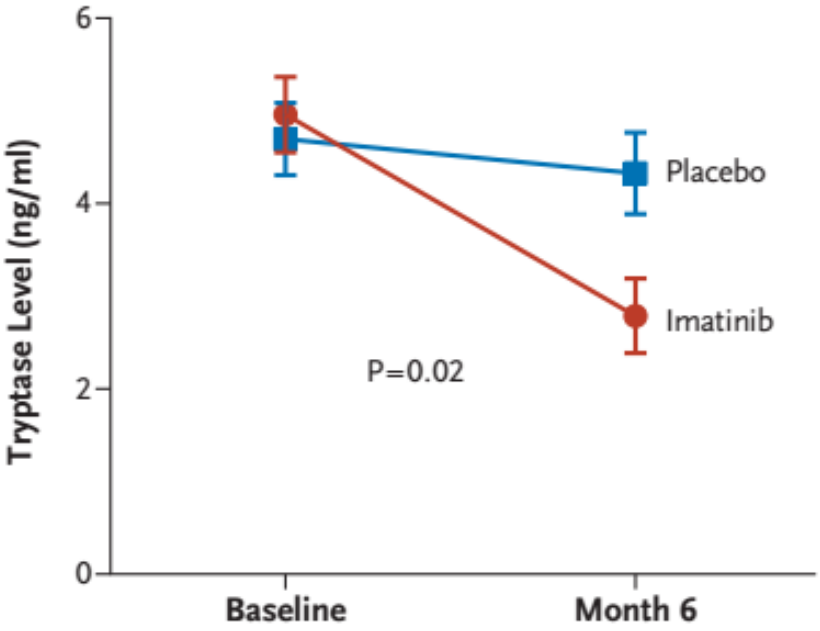
Imatinib : KIT inhibitor

- 62 patients with poorly controlled severe asthma despite receiving maximal medical therapy, age 18-65 yrs
- Imatinib (po; 200mg qd, 2wks → 400mg qd) vs. placebo, 24wk
- Primary outcome : change in airway hyperresponsiveness (PC_{20})

➢ **Change in airway methacholine reactivity**



➢ **Total tryptase levels in serum**



Cahill KN, et al. N Engl J Med 2017;376:1911-20.

Stepwise management : additional components

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.

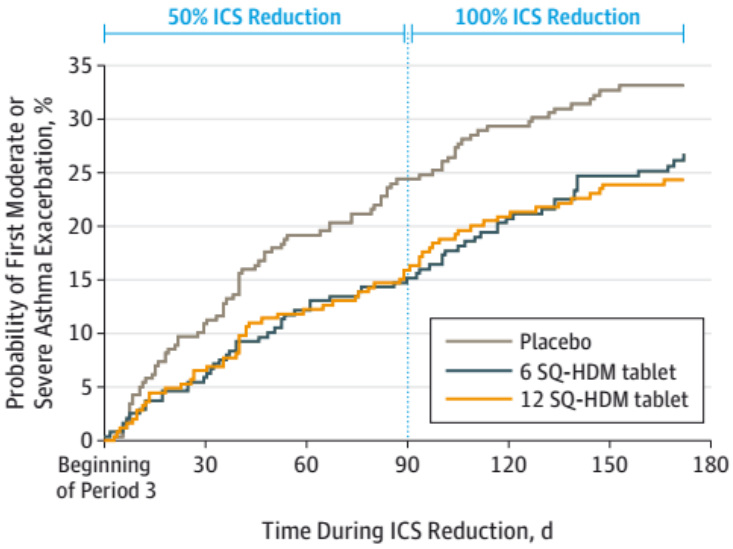
SLIT: sublingual immunotherapy

GINA 2017.

HDM sublingual immunotherapy

- 834 adults with HDM allergy-related asthma (FEV1≥70%, not well controlled by ICS or combination products) and with HDM allergy-related rhinitis
- ICS reduced during the last 6 months

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

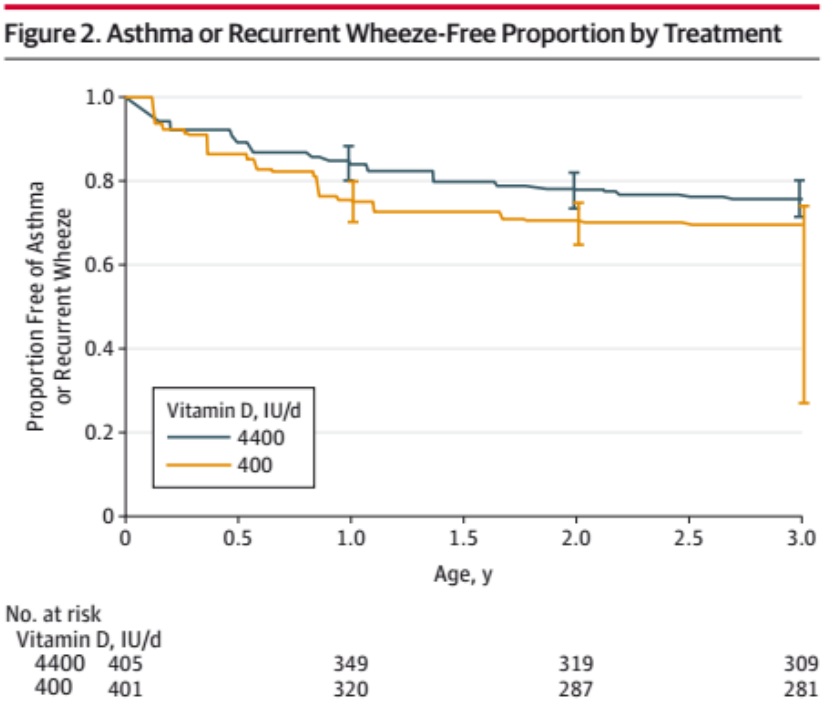


No. at risk							
Placebo	257	228	200	188	171	163	109
6 SQ-HDM tablet	237	224	207	201	187	171	122
12 SQ-HDM tablet	248	228	214	207	189	180	121

Virchow JC, et al. JAMA 2016;315(16):1715-25.

Prenatal supplementation of Vitamin D

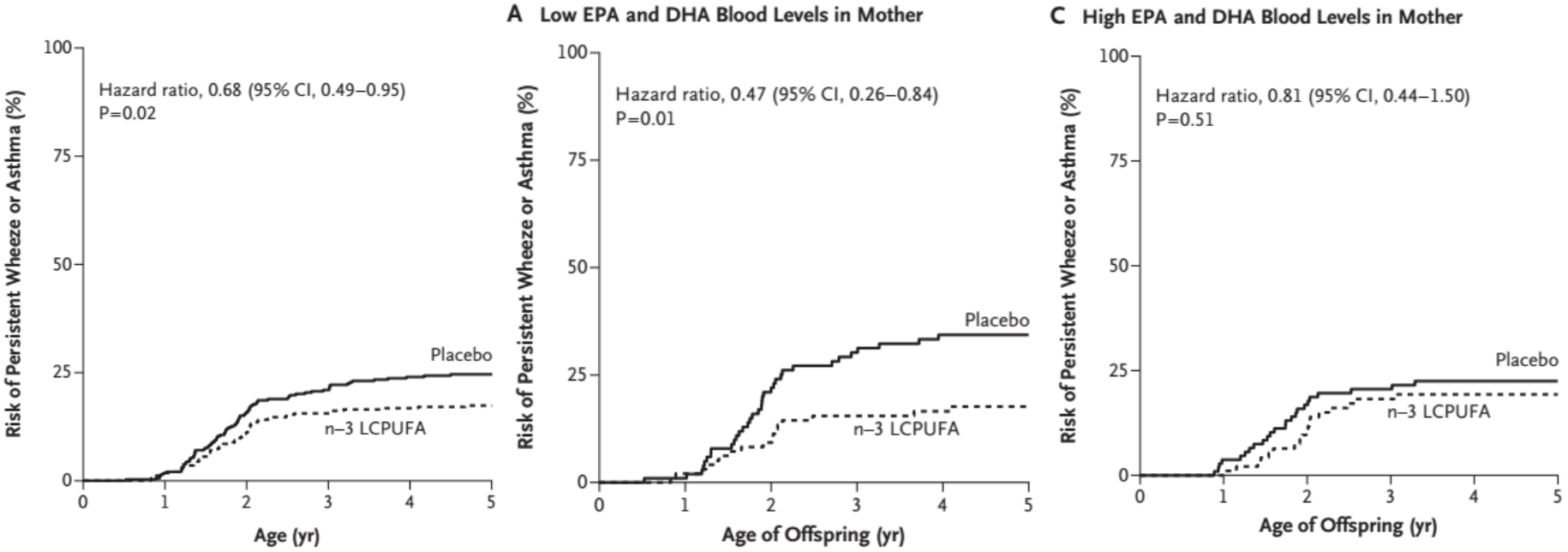
- Vitamin D Antenatal Asthma Reduction Trial (VDAART study)
- 881 pregnant women, age 18-39, high risk of having children with asthma
- Randomization at 10-18 wks' gestation
- Vitamin D (4400 IU) vs placebo (400IU)
- Primary outcome : physician-diagnosed asthma or recurrent wheezing through 3 years of age



Litonjua AA, et al. JAMA 2016;315(4):362-70.

Fish oil-derived fatty acids in pregnancy

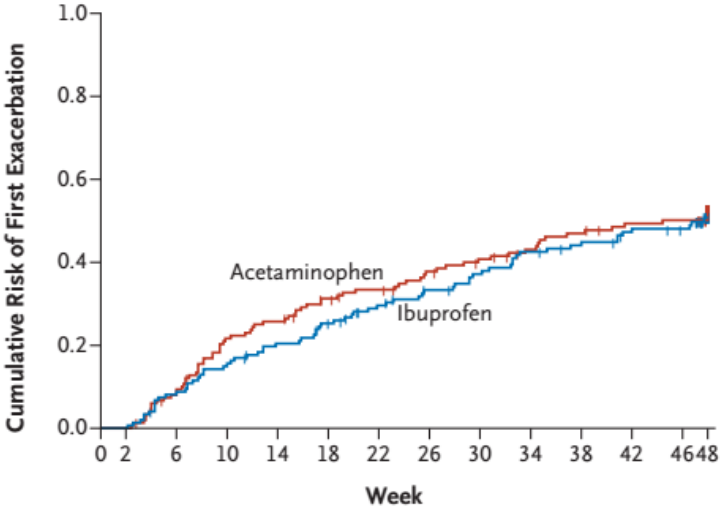
- Based on results of observational studies about association between deficiency of n-3 LCPUFA during pregnancy and increased risk of asthma and wheezing in offspring
- 736 pregnant women, randomization at 24 wks' gestation
- n-3 LCPUFA (fish oil) 2.4g vs placebo (olive oil) per day
- Primary outcome: persistent wheeze and asthma



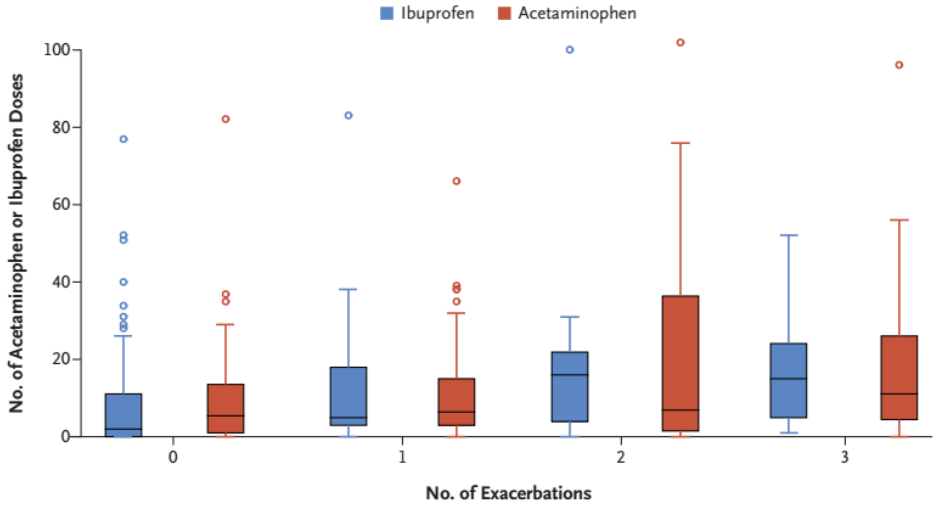
Bisqaard H, et al. N Engl J Med 2016;375(26):2530-9.

Acetaminophen and asthma exacerbation

- Based on results of studies about association between frequent acetaminophen use and asthma-related complications among children
- 300 children (age 12-59 months), mild persistent asthma
- Acetaminophen vs ibuprofen when needed for the alleviation of fever or pain over the course of 48 wks
- Primary outcome: asthma exacerbation requiring systemic steroid



No. at Risk												
Acetaminophen	150	136	115	109	98	93	85	79	73	68	63	62
Ibuprofen	148	135	125	115	107	96	88	82	75	71	65	62



No. of Patients	78	76	34	42	21	16	15	16
Median No. of Doses (IQR)	2.0 (0–11.0)	5.5 (1.0–13.5)	5.0 (3.0–18.0)	6.5 (3.0–15.0)	16.0 (4.0–22.0)	7.0 (1.5–36.5)	15.0 (5.0–24.0)	11.0 (4.5–26.0)
Nonparametric P Value	0.08		0.80		0.53		0.72	

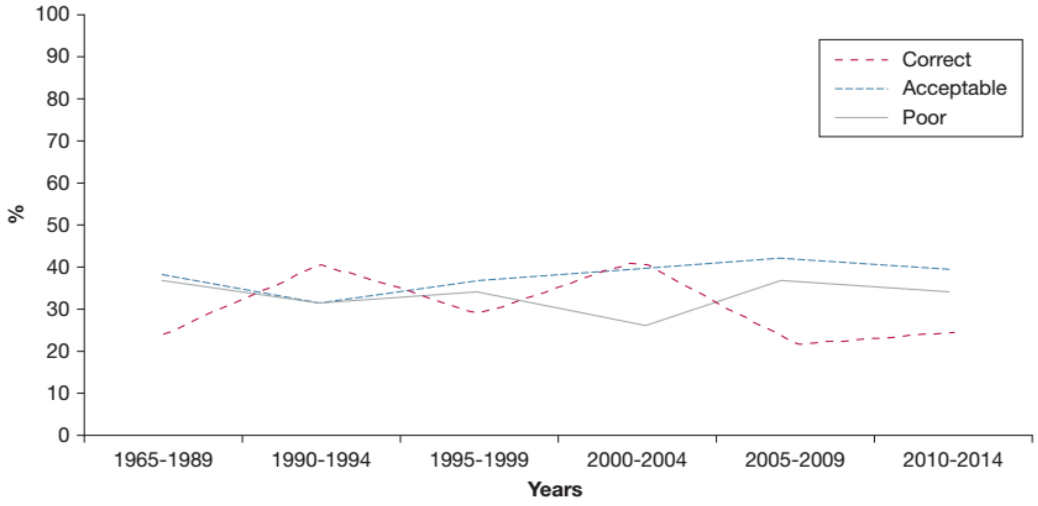
Sheehan WJ, et al. N Engl J Med 2016;375(7):619-30.

Errors in inhaler use : systematic review

- 144 articles reporting direct observation of inhaler technique by trained personnel, 1975-2014

TABLE 5] Frequencies of Errors in Studies Reporting Data for All Steps

Step	Percentage	95% CI
MDI and BAMDI (n = 56 groups)		
Preparation	22	18-26
Full expiration	42	38-46
Coordination (inspire and actuate)	34	29-39
Slow deep inspiration	41	37-44
Breath-hold	41	38-45
DPI (n = 52 groups)		
Preparation	25	21-30
Full expiration	45	40-51
Lips on mouthpiece	8	6-11
Brisk, accelerated deep inspiration	16	13-20
Breath-hold	35	31-39



- CONCLUSIONS: Incorrect inhaler technique is unacceptably frequent and has not improved over the past 40 years, pointing to an urgent need for new approaches to education and drug delivery.

Sanchis J, et al. Chest 2016;150(2);394-406.

Thank You for Your Attention