Asthma
Respiratory review of 2022

순천향의대 호흡기내과

나주옥

Contents

01 **Guidelines:** GINA 2021 update and COVID in asthma

02 **Risk factor and diagnosis of asthma**

03 **Treatment**: Single inhaler triple therapy / Biologics

04 **Take home messages**

The GINA 2021 treatment figure for adults and adolescents

- For clarity, the GINA treatment figure now shows two ‘tracks’

- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred approach**
  - Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and similar lung function
  - ICS-formoterol should not be used as the reliever in patients prescribed a different ICS-LABA for their controller therapy

- **Track 2, with SABA as the reliever, is an alternative approach**
  - Use this if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current controller therapy
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment

ICS: inhaled corticosteroids; SABA: short-acting beta$_2$-agonist

Personalized asthma management
Assess, Adjust, Review for individual patient needs

Symptoms Exacerbations
Side-effects Lung function
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

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	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	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

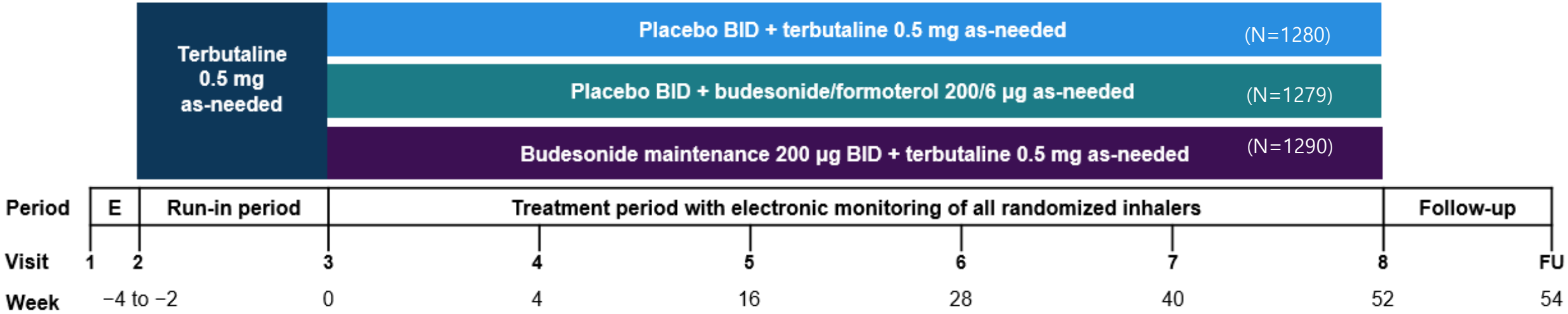
STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

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*

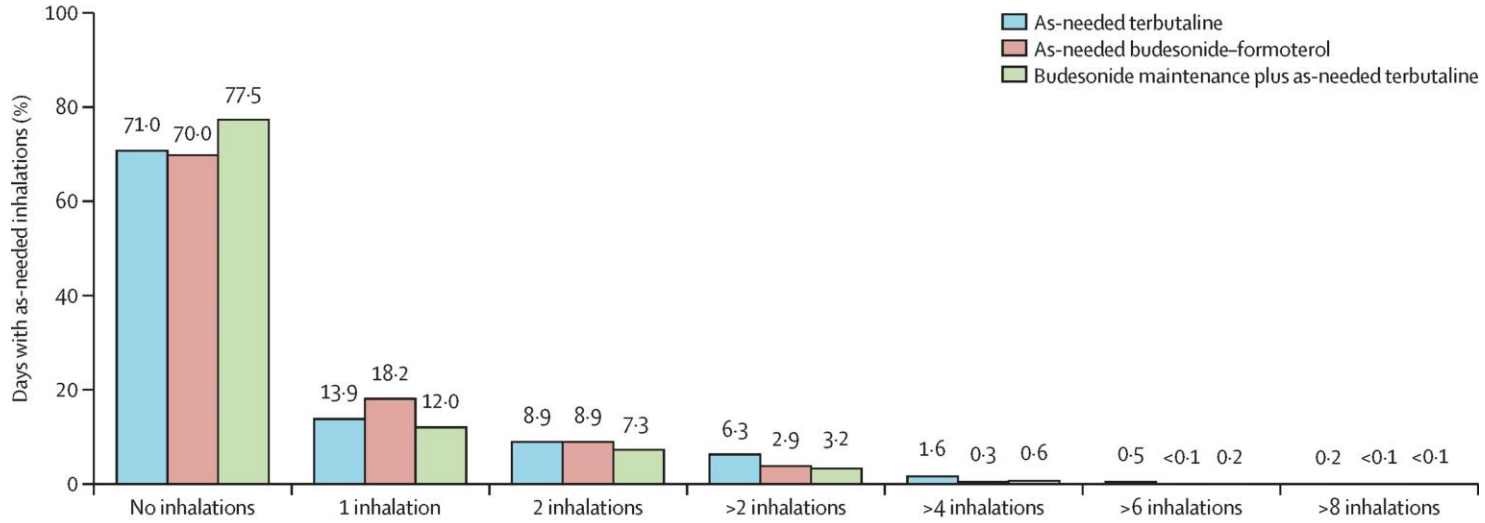
Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study

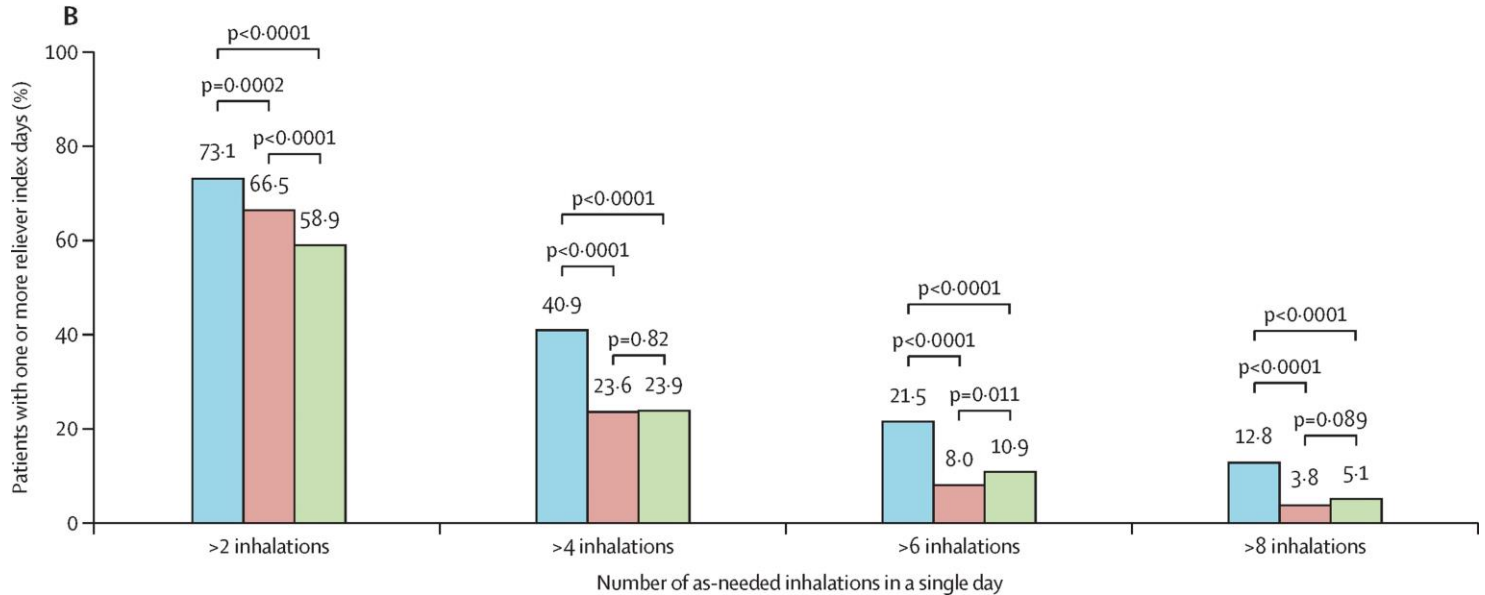
- short-term risk of severe exacerbations after a single day with various levels of reliever use.
- frequency of reliever use and the risk of a severe exacerbation in the 21 days after first use of more than two, four, six, or eight reliever inhalations in 24 h.



O'Byrne PM, et al. Lancet Respir Med 2021;9:149-58.

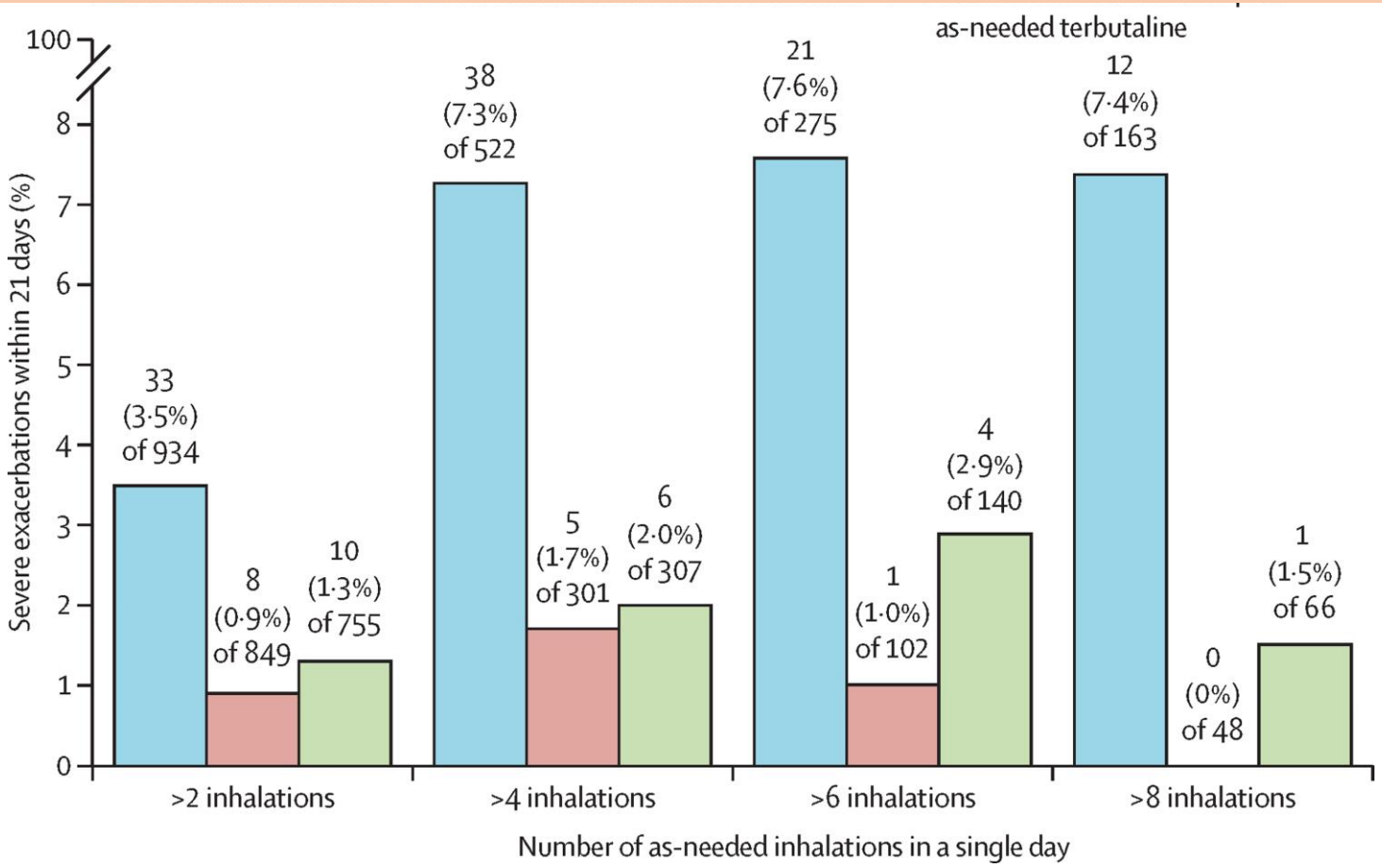
Significantly fewer patients in both the as-needed budesonide–formoterol and budesonide maintenance groups ever used more than two, four, six, or eight inhalations of reliever in a single day than did in the as-needed terbutaline group





O'Byrne PM, et al. Lancet Respir Med 2021;9:149-58.

As-needed terbutaline group, the risk of a severe exacerbation increased after the first reliever index day of more than four, six, or eight inhalations compared with the first day of more than two inhalations



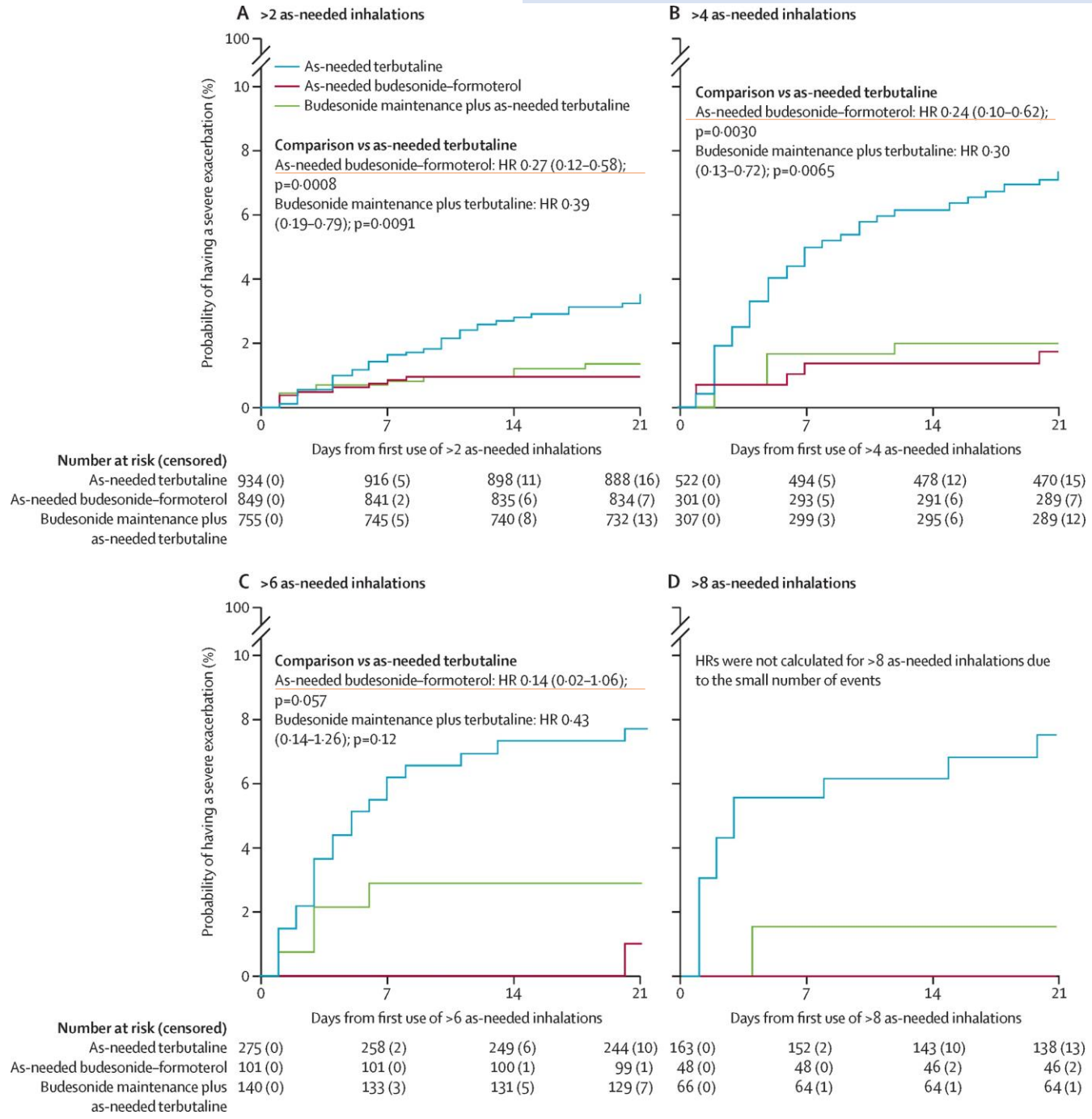
Proportion of patients with a severe exacerbation within 21 days after the first day with more than two, four, six, or eight as-needed inhalations

O'Byrne PM, et al. Lancet Respir Med 2021;9:149-58.

Probability of a severe exacerbation during the 21 days after the first day with more than two (A), more than four (B), more than six (C), and more than eight (D) as-needed inhalations

Conclusion

Use of an anti-inflammatory reliever might reduce the risk of short-term severe exacerbations by the timely provision of increased doses of as-needed inhaled corticosteroids and formoterol when symptoms occur



O'Byrne PM, et al. Lancet Respir Med 2021;9:149-58.

Asthma severity – severe asthma

- To avoid confusion, the definition of severe asthma has been reworded without reference to GINA steps

- Severe asthma definition

Asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA or that requires high dose ICS-LABA to prevent it from becoming uncontrolled

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

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
  - 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

Add-on azithromycin

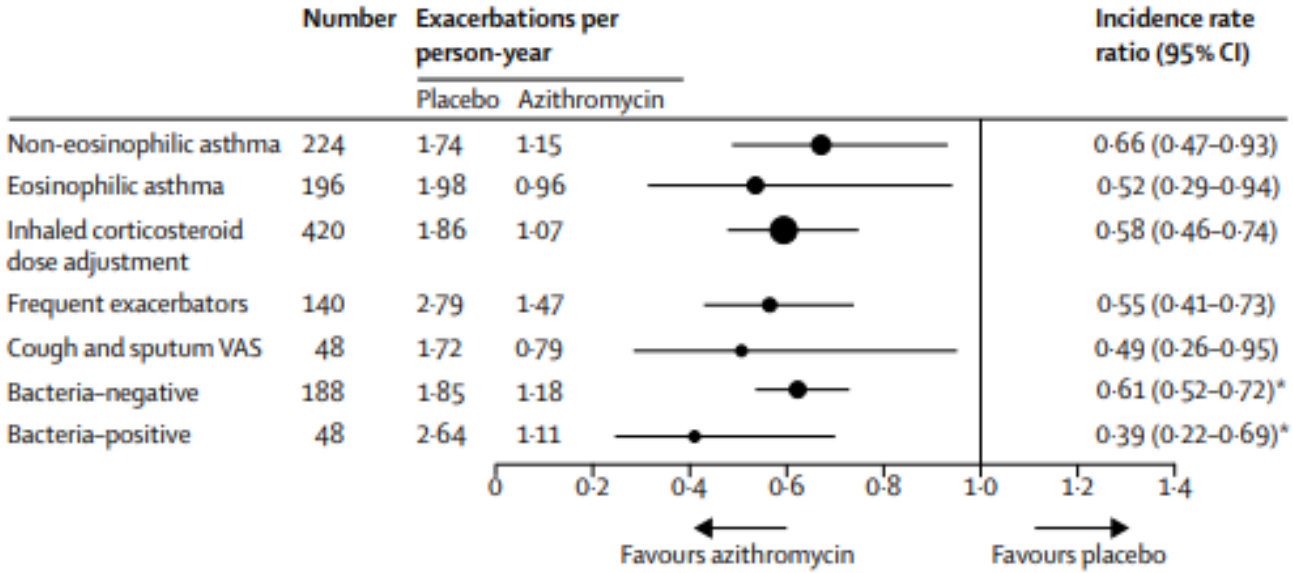
- Add-on azithromycin three days a week has been confirmed as an option for consideration after specialist referral
  - Significantly reduces exacerbations in patients taking high dose ICS-LABA
  - Significantly reduces exacerbations in patients with eosinophilic or non-eosinophilic asthma
  - No specific 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)

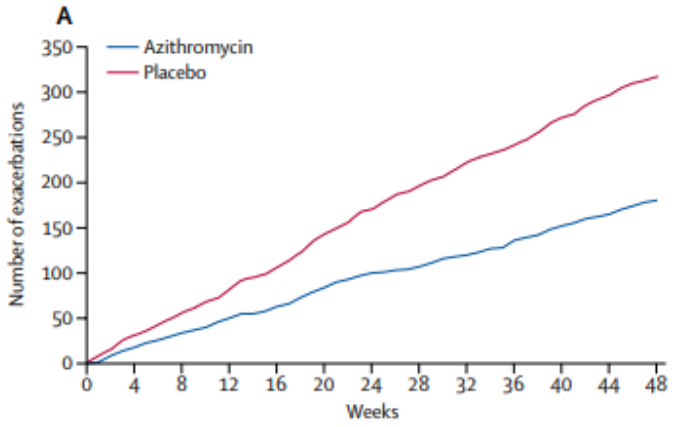
ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist

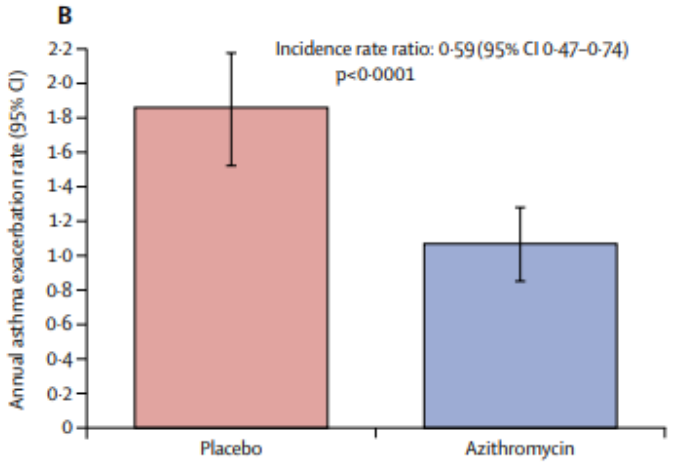
Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

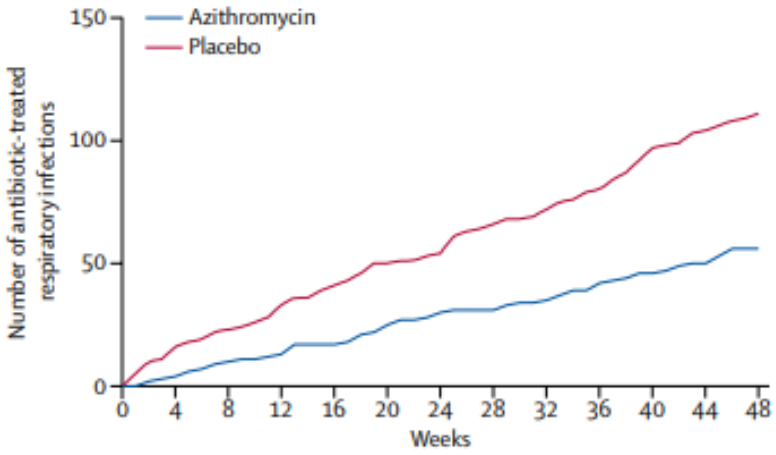
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

- June 12, 2009- Jan 31, 2015,
- 420 patients (213 in the azithromycin vs 207 in the placebo)









Lancet 2017; 390: 659–68

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

ORIGINAL ARTICLE | Full Access

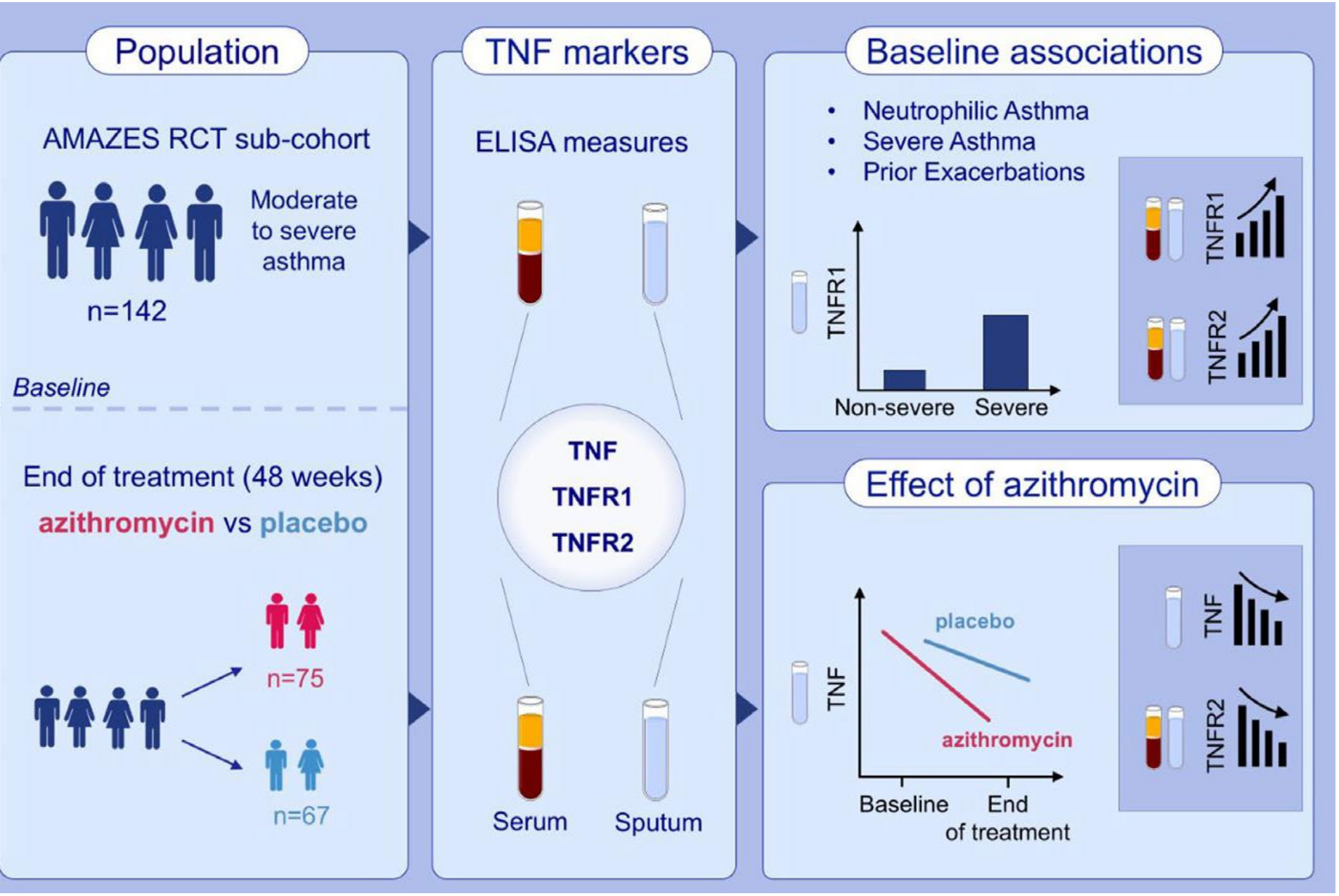
Sputum TNF markers are increased in neutrophilic and severe asthma and are reduced by azithromycin treatment

Natalie M. Niessen, Peter G. Gibson, Katherine J. Baines, Daniel Barker, Ian A. Yang, John W. Upham, Paul N. Reynolds, Sandra Hodge, Alan L. James, Christine Jenkins, Matthew J. Peters ... See all authors

First published: 11 February 2021 | https://doi.org/10.1111/all.14768 | Citations: 7

- To determine the inflammatory and clinical associations of soluble TNF signalling proteins (TNF receptors [TNFR] 1 and 2, TNF) in sputum and serum, and to test the effect of 48 weeks of azithromycin vs placebo on TNF markers.

- Sputum supernatant and serum TNFR1, TNFR2 (n = 142; 75 azithromycin-treated, 67 placebo-treated) and TNF (n = 48; 22 azithromycin-treated, 26 placebo-treated)



- Baseline sputum TNFR1&2 증가 in neutrophilic asthma
- Baseline serum TNFR1 증가 in severe asthma
- Sputum & serum TNFR2 증가 in prior exacerbators

COVID-19 and asthma

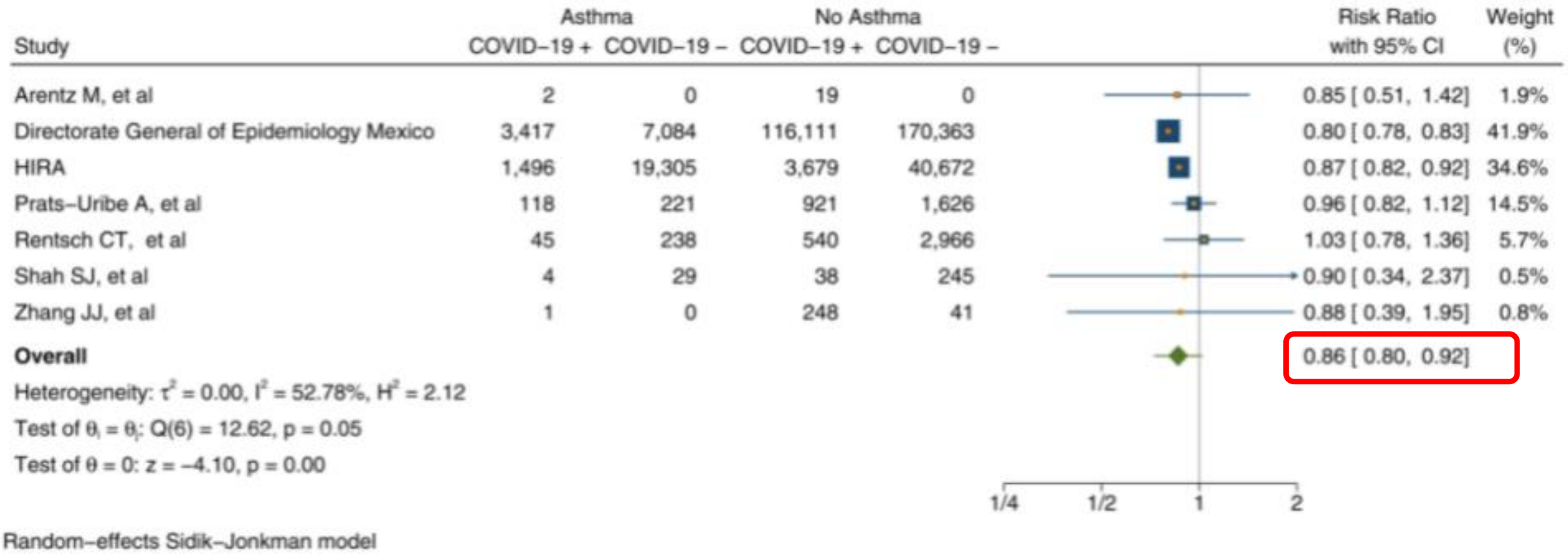
- Are people with asthma at increased risk of COVID-19, or severe COVID-19?
  - People with asthma do not appear to be at increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe COVID-19 in people with well-controlled, mild-to-moderate asthma
- Are people with asthma at increased risk of COVID-19-related death?
  - Overall, people with well-controlled asthma are not at increased risk of COVID-19-related death *(Williamson, Nature 2020; Liu et al JACI IP 2021)*
  - However, the risk of COVID-19 death was increased in people who had recently needed oral corticosteroids (OCS) for their asthma *(Williamson, Nature 2020)* and in hospitalized patients with severe asthma *(Bloom, Lancet Respir Med 2021)*.
- What are the implications for asthma management?
  - It is important to continue good asthma management (as described in the GINA report), with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimise the need for OCS
- Have there been more asthma exacerbations during the pandemic?
  - No. In 2020, many countries saw a *reduction* in asthma exacerbations and influenza-related illness. The reasons are not precisely known, but may be due to handwashing, masks and social/physical distancing that reduced the incidence of other respiratory infections, including influenza

COVID-19 and asthma - medications

- Advise patients to continue taking their prescribed asthma medications, particularly inhaled corticosteroids (ICS)
  - For patients with severe asthma, continue biologic therapy or oral corticosteroids if prescribed
- Are ICS protective in COVID-19?
  - In one study of hospitalized patients aged ≥50 years with COVID-19, ICS use in those with asthma was associated with lower mortality than in patients without an underlying respiratory condition *(Bloom, Lancet RM 2021)*
- Make sure that all patients have a written asthma action plan, advising them to:
  - Increase controller and reliever medication when asthma worsens (see GINA report Box 4-2)
  - Take a short course of OCS when appropriate for severe asthma exacerbations
- Avoid nebulizers where possible, to reduce the risk of spreading virus
  - Pressurized metered dose inhaler via a spacer is preferred except for life-threatening exacerbations
  - Add a mouthpiece or mask to the spacer if required

Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: Systematic review and meta-analysis

The pooled analysis of 6 studies (*n* = 369 405) showed a Risk Ratio Reduction (RRR) in acquiring COVID-19 of 14% for people with asthma compared to those without asthma



JOURNAL OF ASTHMA 2021, AHEAD-OF-PRINT, 1-14 . ttps://doi.org/10.1080/02770903.2021.1888116

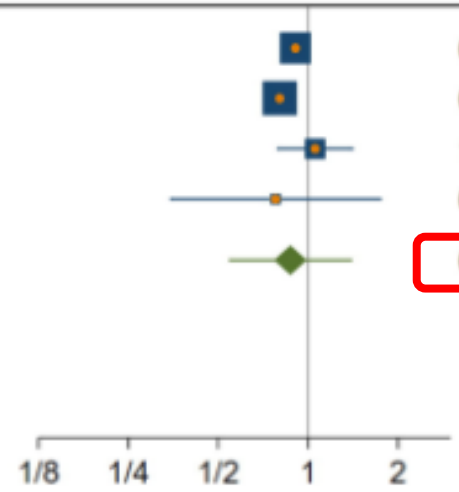
Significant RRR in hospitalization from COVID-19 of 13% for people with asthma compared to no asthma : ICU, MV –No difference between asthma vs no asthma

Study	Asthma		No Asthma		Risk Ratio with 95% CI	Weight (%)
	Hospitalized	Non hospitalized	Hospitalized	Non hospitalized		
Argenziano MG, et al	88	25	762	125	0.91 [0.82, 1.00]	37.9%
Directorate General of Epidemiology Mexico	917	2,500	38,822	77,289	0.80 [0.76, 0.85]	46.2%
Rentsch CT, et al	24	21	273	267	1.05 [0.79, 1.40]	13.6%
Wei XS, et al	1	0	13	0	0.78 [0.35, 1.74]	2.2%
Overall					0.87 [0.77, 0.99]	

Heterogeneity: $\tau^2 = 0.01$, $I^2 = 62.76\%$, $H^2 = 2.69$

Test of $\theta_i = \theta_j$: Q(3) = 6.99, p = 0.07

Test of $\theta = 0$: z = -2.18, p = 0.03



Random-effects Sidik-Jonkman model

JOURNAL OF ASTHMA2021, AHEAD-OF-PRINT, 1-14 . ttps://doi.org/10.1080/02770903.2021.1888116

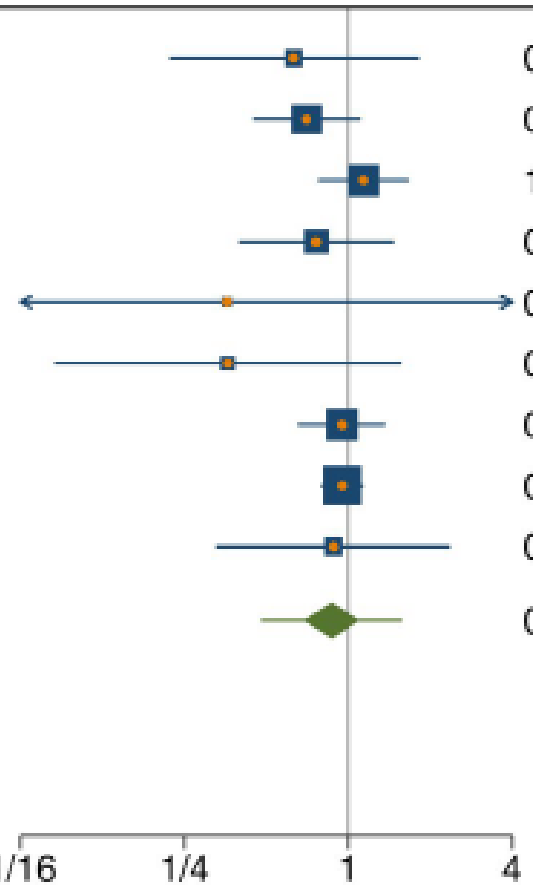
Risk of death against recovered from COVID-19 among those with asthma compared to no asthma – no difference

Study	Asthma Deaths	Asthma Recovery	No Asthma Deaths	No Asthma Recovery	Risk Ratio with 95% CI	Weight (%)
Auld SC, et al	3	13	49	116	0.63 [0.22, 1.80]	4.48
Borobia AM, et al	17	98	443	1,668	0.70 [0.45, 1.10]	14.98
Carr E, et al	21	44	138	349	1.14 [0.78, 1.67]	17.53
Grasselli G, et al	5	6	304	206	0.76 [0.40, 1.46]	9.44
Jacobs JP, et al	0	1	10	4	0.36 [0.03, 4.03]	0.95
Mahdavinia M, et al	2	239	16	678	0.36 [0.08, 1.55]	2.47
Paranjpe I, et al	23	61	287	707	0.95 [0.66, 1.36]	18.26
Sapey E, et al	116	323	495	1,283	0.95 [0.80, 1.13]	26.90
Tomlins J, et al	4	17	16	58	0.88 [0.33, 2.35]	4.99
Overall					0.87 [0.68, 1.10]	

Heterogeneity: $\tau^2 = 0.05$, $I^2 = 45.38\%$, $H^2 = 1.83$

Test of $\theta_i = \theta_j$: $Q(8) = 5.74$, $p = 0.68$

Test of $\theta = 0$: $z = -1.15$, $p = 0.25$



Random–effects Sidik–Jonkman model

JOURNAL OF ASTHMA2021, AHEAD-OF-PRINT, 1-14 . ttps://doi.org/10.1080/02770903.2021.1888116

- This risk reduction which include the observation that people with T2-high asthma have down regulated angiotensin-converting-enzyme-2 (ACE-2) receptors that may reduce their risk of infection with COVID
- Inhaled corticosteroid (ICS) therapy, the main treatment modality in asthmatics is associated with lower ACE-2 (one of the binding sites for SARS-CoV-2) expression
- The use of ICS may be a contributing factor in reducing the risk of acquiring COVID-19 as well as the risk of severe illness warranting hospitalization.
- Systemic corticosteroids are also given to treat acute exacerbations of asthma, it is possible that this is one mechanism

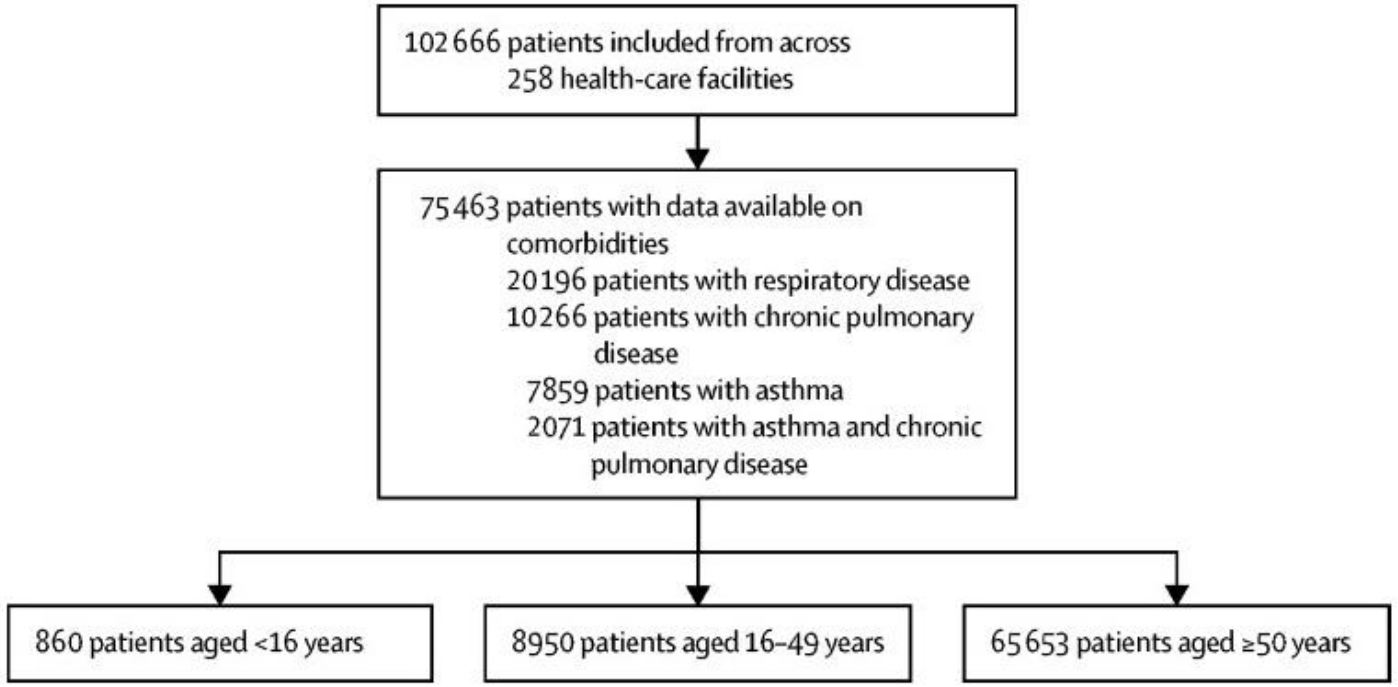
Conclusion

The prevalence of people with asthma among COVID-19 patients is similar to the global prevalence of asthma. The overall findings suggest that people with asthma have a lower risk than those without asthma for acquiring COVID-19 and have similar clinical outcomes.

JOURNAL OF ASTHMA2021, AHEAD-OF-PRINT, 1-14 . ttps://doi.org/10.1080/02770903.2021.1888116

Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK

Chloe I Bloom*, Thomas M Drake*, Annemarie B Docherty, Brian J Lipworth, Sebastian L Johnston, Jonathan S Nguyen-Van-Tam, Gail Carson, Jake Dunning, Ewen M Harrison, J Kenneth Baillie, Malcolm G Semple, Paul Cullinan†, Peter J M Openshaw†, on behalf of the ISARIC investigators‡

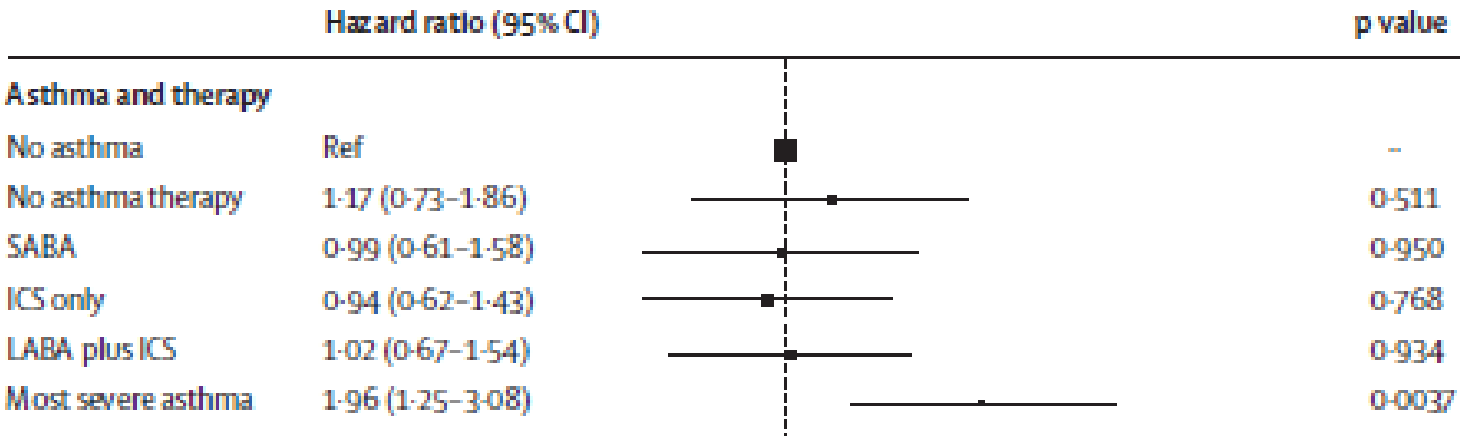


- Patients admitted to hospital with COVID-19 across England, Scotland, and Wales between Jan 17 and Aug 3, 2020
- Patients with asthma, chronic pulmonary disease or both
- Severe asthma : ICS + LABA + another maintenance asthma medication

Chloe Bloom et al. Lancet Respir Med. 2021 Jul;9(7):699-711

Association between asthma and death from COVID-19

- Severe asthma had a significant increase in mortality (adjusted hazard ratio 1·96 aged 16-49, 1.24 aged 50 years older) compared to those with no asthma

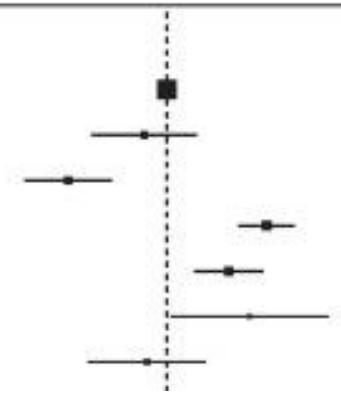


	Critical care		Invasive mechanical ventilation		Non-invasive ventilation		Oxygen	
	Adjusted OR* (95% CI)	p value	Adjusted OR* (95% CI)	p value	Adjusted OR* (95% CI)	p value	Adjusted OR* (95% CI)	p value
Patients aged 16–49 years								
No asthma	Ref	--	Ref	--	Ref	--	Ref	--
Asthma	1·20 (1·05–1·37)	0·0080	1·17 (1·00–1·38)	0·053	1·36 (1·18–1·57)	<0·0001	1·33 (1·17–1·50)	<0·0001
Patients aged ≥50 years								
No respiratory condition	Ref	--	Ref	--	Ref	--	Ref	--
Asthma	1·17 (1·08–1·27)	<0·0001	1·07 (0·97–1·18)	0·207	1·18 (1·09–1·28)	<0·0001	1·08 (1·02–1·15)	0·012

Lancet Respir Med. 2021 Jul;9(7):699-711

Association of ICS use with respiratory condition and in-hospital mortality in patients aged 50 years and older

	Hazard ratio (95% CI)	p value
Respiratory disease		
No respiratory disease; no inhaled steroids	Ref	..
Asthma only; no inhaled ICS	0·97 (0·89–1·05)	0·391
Asthma only; on inhaled ICS	0·86 (0·80–0·92)	<0·0001
Chronic pulmonary disease only; no inhaled ICS	1·16 (1·12–1·22)	<0·0001
Chronic pulmonary disease on inhaled ICS	1·10 (1·04–1·16)	<0·0001
Asthma and chronic pulmonary disease; no inhaled ICS	1·13 (1·01–1·28)	0·041
Asthma and chronic pulmonary disease on inhaled ICS	0·97 (0·89–1·06)	0·506



- Among patients aged 50 years and older, those with chronic pulmonary disease had a significantly increased mortality risk, regardless of inhaled corticosteroid use, compared to patients without an underlying respiratory condition

- In patients aged 50 years and older, ICS use within 2 weeks of hospital admission was associated with decreased mortality in those with asthma, compared to those without an underlying respiratory condition (adjusted HR 0·86 [95% CI 0·80–0·92]).

Lancet Respir Med. 2021 Jul;9(7):699-711

Conclusions

- Patients with chronic pulmonary disease had a high level of mortality, with a prevalence of 40% for in-hospital death.
- Of patients with asthma, only those with severe asthma had increased mortality compared to those without an underlying respiratory condition.
- Patients with asthma (aged ≥50 years) had a lower mortality risk if they had used ICS within 2 weeks of admission.
- The role of ICS in COVID-19 remains unclear, but ICS protect against exacerbations of respiratory disease and might therefore protect against severe COVID-19.

Lancet Respir Med. 2021 Jul;9(7):699-711

Contents

01 **Guidelines:** GINA 2021 update and COVID in asthma

02 **Risk factor and diagnosis of asthma**

03 **Treatment**: Single inhaler triple therapy / Biologics

04 **Take home messages**

CHEST®
Volume 160, Issue 1, July 2021, Pages 45-52

Asthma: Original Research

Hormone Replacement Therapy and Development of New Asthma

Erik Soeren Halvard Hansen MD [a], Kristian Aasbjerg PhD [c], Amalie Lykkemark Moeller MSPH [d], Elisabeth Juul Gade PhD [e], Christian Torp-Pedersen DMSci [d], Vibeke Backer DMSci [a, b]

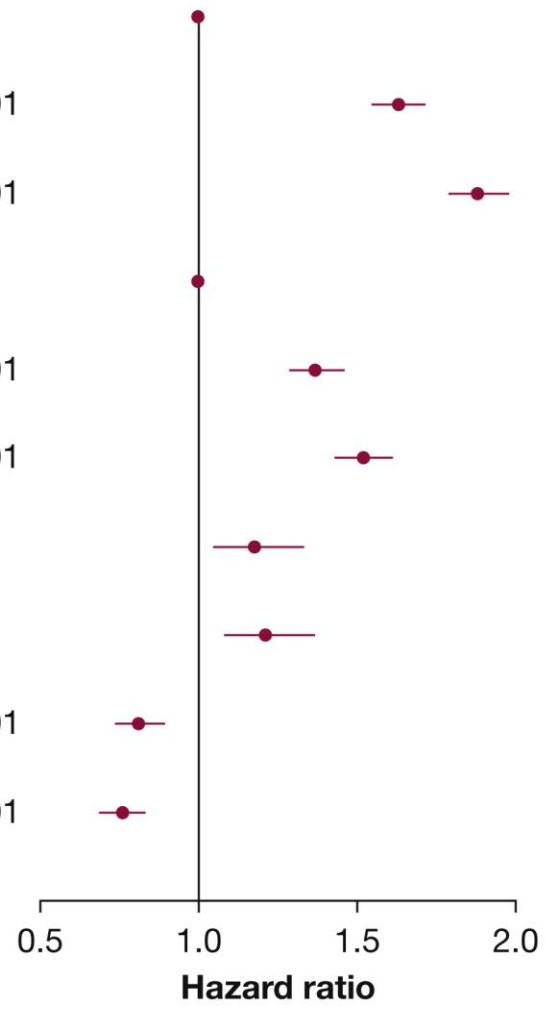
STUDY DESIGN

- Nested case-control study using Danish registers from June 1, 1995 to December 31, 2018
- Included all women aged 40 to 65 years with a new diagnosis of asthma
- Matched by age with 10 healthy control women using incidence density matching

34,533	345,116
women **with** asthma	women **without** asthma

In multivariable analysis, active hormone replacement therapy associated with new asthma development

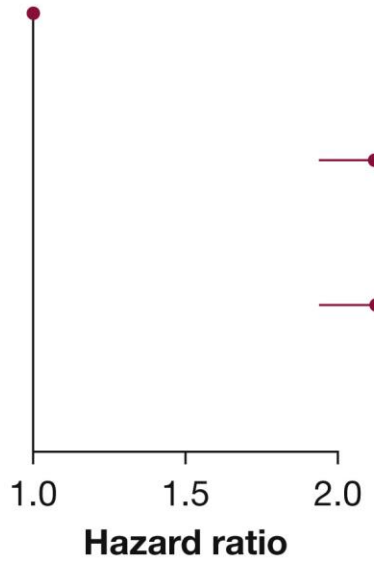
	Exposure	N	*P* value	Estimate (CI_{95})
HRT of all types present at index date	No HRT	364,615	1.00	Ref
	HRT, adjusted	15,034	< .001	1.63 (1.55-1.71)
	Unadjusted	15,034	< .001	1.88 (1.79-1.98)
Subtypes of HRT present at index date	No HRT	364,615	1.00	Ref
	Estrogen monotherapy, adjusted	7,392	< .001	1.37 (1.29-1.46)
	Unadjusted	7,392	< .001	1.52 (1.43-1.61)
	Estrogen and progesterone combination therapy, adjusted	6,380	.006	1.18 (1.05-1.33)
	Unadjusted	6,380	.001	1.21 (1.08-1.36)
	Progesterone monotherapy, adjusted	1,262	< .001	0.81 (0.74-0.89)
	Unadjusted	1,262	< .001	0.76 (0.69-0.83)



al. CHEST **160**(1): 45-52.

Hazard ratio of termination of asthma when terminating or continuing treatment with HRT

Action	N	*P* value	Estimate (CI_{95})
No recent termination of HRT	467,017	1.00	Ref
Recent termination of HRT, adjusted	3,346	< .001	2.12 (1.94-2.33)
Unadjusted	3,346	< .001	2.13 (1.94-2.33)



Conclusion

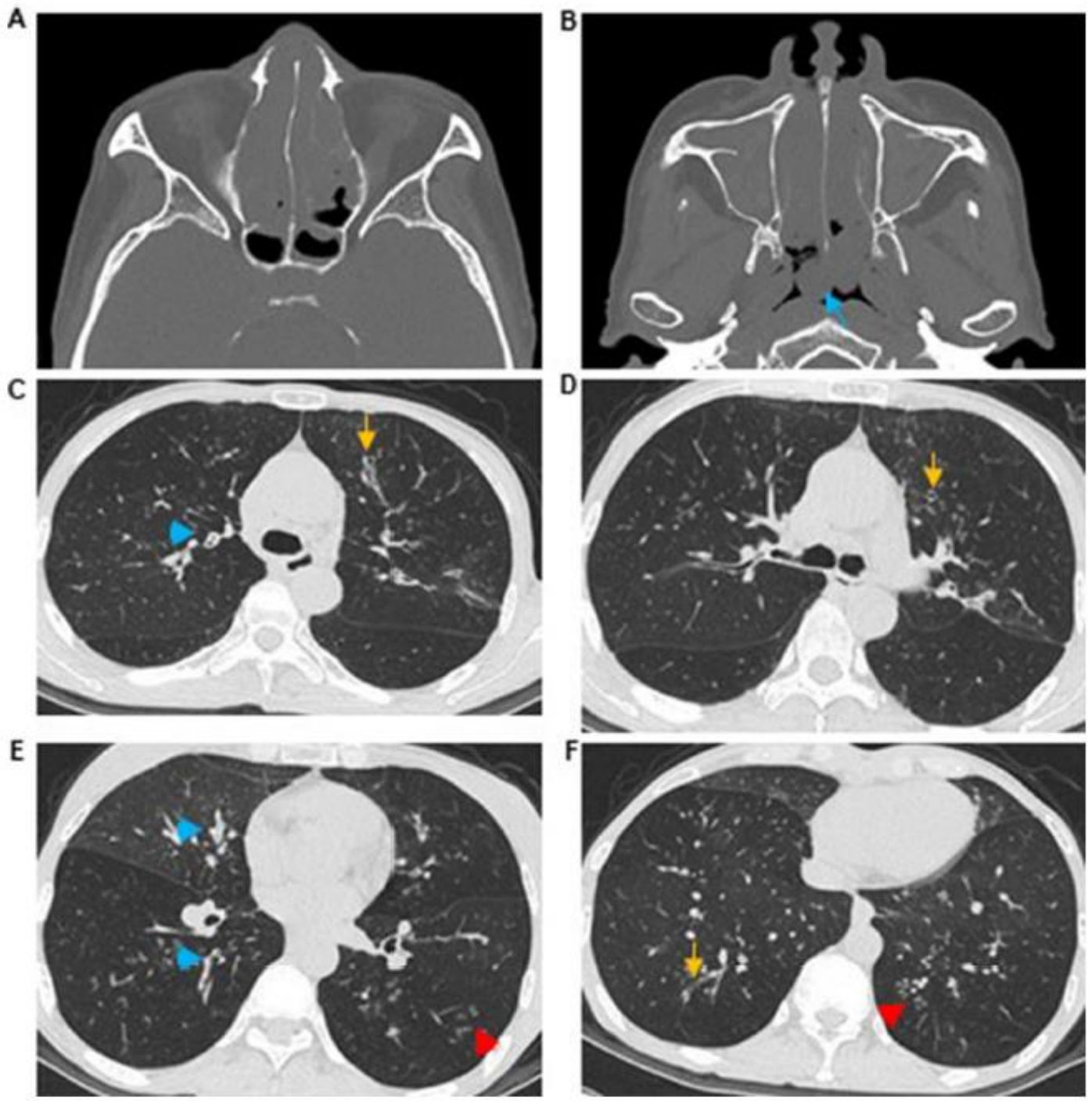
HRT seems to play a role in the development of asthma in mature women. Clinicians prescribing HRT and women receiving HRT should be aware that new airway symptoms can develop, and discontinuation of HRT should be considered.

Hansen, E. S. H., et al. CHEST **160**(1): 45-52.

Prevalence and clinical implications of bronchiectasis in patients with overlapping asthma and chronic rhinosinusitis : a single-center prospective study

- The purpose of the study was to explore the presence and characteristics of bronchiectasis in patients with overlapping asthma and Asthma-chronic rhinosinusitis (CRS)
- Prospective study with consecutive asthma-CRS patients.
- Seventy-two (40.91%) of 176 asthma-CRS patients were diagnosed with bronchiectasis

Sheng *et al. BMC Pulm Med (2021) 21:211*
https://doi.org/10.1186/s12890-021-01575-7



- A 55-year-old female suffered from asthma for 30 years and CRS for 20 years and experienced one severe exacerbation of asthma in the last 12 months.
- A, B Paranasal sinus CT imaging revealing CRS involving the whole sinuses with the existence of nasal polyps (blue arrow).
- C–F Lung windows of HRCT depicting extensive bronchiectasis (yellow arrow), with thickened bronchial walls (blue arrowhead) and the presence of a tree-in-bud pattern (red arrowhead)

Sheng *et al. BMC Pulm Med (2021) 21:211*

Comparison of characteristics of asthma- CRS patients with bronchiectasis versus nonbronchiectasis

Variables	Nonbronchiectasis group (n = 104)	Bronchiectasis group (n = 72)	*P* Value
Male sex, n (%)	51 (49.04)	38 (52.78)	0.626
Age, y	53.28 ± 14.66 (50.43–56.13)	54.81 ± 13.71 (51.58–58.03)	0.487
BMI, kg/m^2	24.87 ± 3.61 (24.17–25.57)	24.12 ± 4.37 (23.09–25.14)	0.213
Positive smoking status[a], n (%)	31 (29.81)	24 (33.33)	0.620
Smoking index[b], pack-years	10.00 (8.00,14.00)	8.00 (6.25,13.50)	0.113
Duration of asthma, y	5.50 (1,12.75)	8.00 (2.00, 20.00)	0.171
NPs, n (%)	35 (33.65)	40 (55.56)	0.004
Prior sinus surgery, n (%)	16 (15.38)	18 (25.00)	0.112
Allergic rhinitis, n (%)	63 (60.58)	49 (68.06)	0.311
Atopic dermatitis, n (%)	11 (10.58)	3 (4.17)	0.122
Gastroesophageal reflux disease, n (%)	9 (8.65)	5 (6.94)	0.680
ICS dose (fluticasone equivalent), μg/d	320.00 (160.00, 320.00)	285.00 (160.00, 320.00)	0.713
Severe asthma, n (%)	11 (10.58)	15 (20.83)	0.059
≥ 1 severe exacerbation of asthma in the last 12 months, n (%)	**23 (22.12)**	**31 (43.06)**	**0.003**
≥ 1 pneumonia in the last 12 months, n (%)	27 (25.96)	24 (33.33)	0.289
Peripheral blood eosinophil counts, × 10^9/L	**0.32 (0.15, 0.58)**	**0.44 (0.23, 0.90)**	**0.022**
FeNO, ppb	**32.00 (18.00, 61.75)**	**44.00 (23.00,74.75)**	**0.056**
Total IgE, IU/mL	**135.50 (48.10, 285.50)**	**232.00 (56.75,525.25)**	**0.044**
Atopy, n (%)	57 (54.81)	34 (47.22)	0.322
Postbronchodilator FEV_1% predicted, %	**83.09 ± 16.47 (79.89–86.30)**	**73.32 ± 22.94 (67.93–78.71)**	**0.006**
LM scores	9.00 (6.00, 15.75)	11.50 (7.25, 18.00)	0.044
Smith scores of bronchiectasis		7.56 ± 3.46 (6.75–8.37)	
Bhalla scores of bronchiectasis		3.97 ± 1.50 (3.62–4.32)	

Logistic regression analyses for bronchiectasis

Variables	Bronchiectasis: logistic regression		
	OR	*95% CI*	*P* value
Nasal polyp	2.79	1.43 to 5.46	0.003
≥ 1 severe exacerbation of asthma in the last 12 months	2.14	1.02 to 4.51	0.045
Peripheral blood eosinophil counts	2.60	1.19 to 5.67	0.016
Postbronchodilator FEV_1% predicted	0.98	0.96 to 1.00	0.039

Sheng *et al. BMC Pulm Med (2021) 21:211*

Differential diagnostic values of postbronchodilator FEV_1% predicted, peripheral blood eosinophil counts and combined model in detecting bronchiectasis in asthma-CRS overlap patients

Items	Cutoff value	Sensitivity (%)	Specificity (%)	Youden index
postbronchodilator FEV1% predicted, %	71.40	51.39	79.81	0.31
peripheral blood eosinophil counts, × 10^9/L	0.60	41.67	77.88	0.20
combined model	0.33	72.22	70.19	0.42

Conclusions

- Bronchiectasis commonly overlaps in asthma-CRS patients. The coexistence of bronchiectasis predicts a more severe disease subset in terms of asthma and CRS.
- We suggest that asthma-CRS patients with NPs, severe airflow obstruction, eosinophilic inflammation, and poor asthma control should receive HRCT for the early diagnosis of bronchiectasis.

Sheng *et al. BMC Pulm Med (2021) 21:211*

Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis

- Phase 3 LIBERTY ASTHMA QUEST study (Dupilumab Efficacy/Safety)
- 620 patients with moderate-to-severe asthma
- Uncontrolled asthma : ICS +up to two controllers

  one or more exacerbations in the previous year

  FEV1 percent predicted 40–80%

  FEV1 reversibility of 12% or higher and 200 Ml

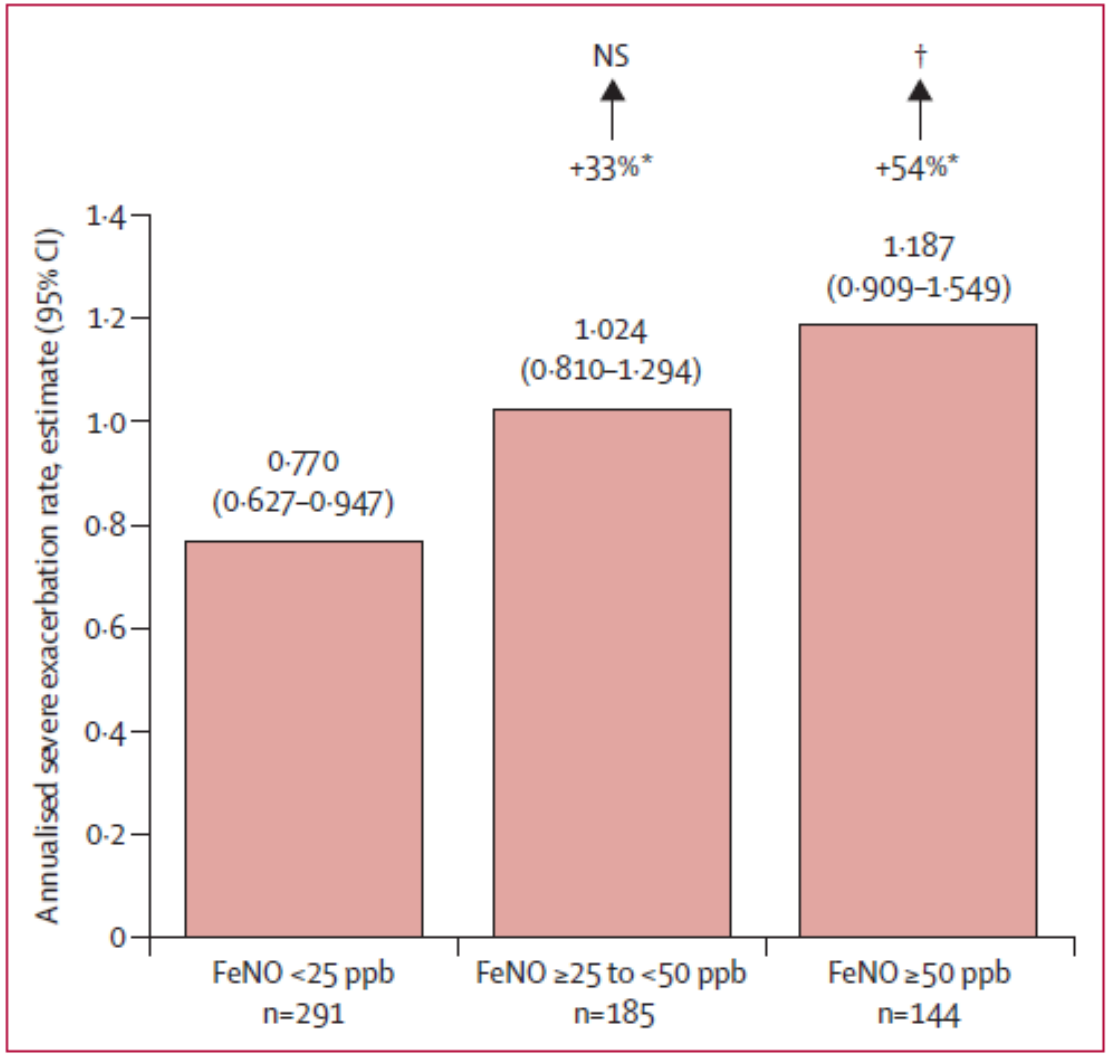
  Asthma Control Questionnaire (ACQ-5) score of 1·5 or higher

William W Busse.Lancet Respir Med 2021; 9: 1165–73

FeNO was a risk factor for annualised severe exacerbation when analysed independently from type 2 biomarkers

Baseline FeNO ≥25 to <50 ppb
: 1·33-times greater annualised severe exacerbation rate than patients with baseline FeNO of less than 25 ppb

FeNO of 50 ppb or higher
: 1·54-times greater annualised severe exacerbation rate than patients with baseline FeNO of less than 25 ppb



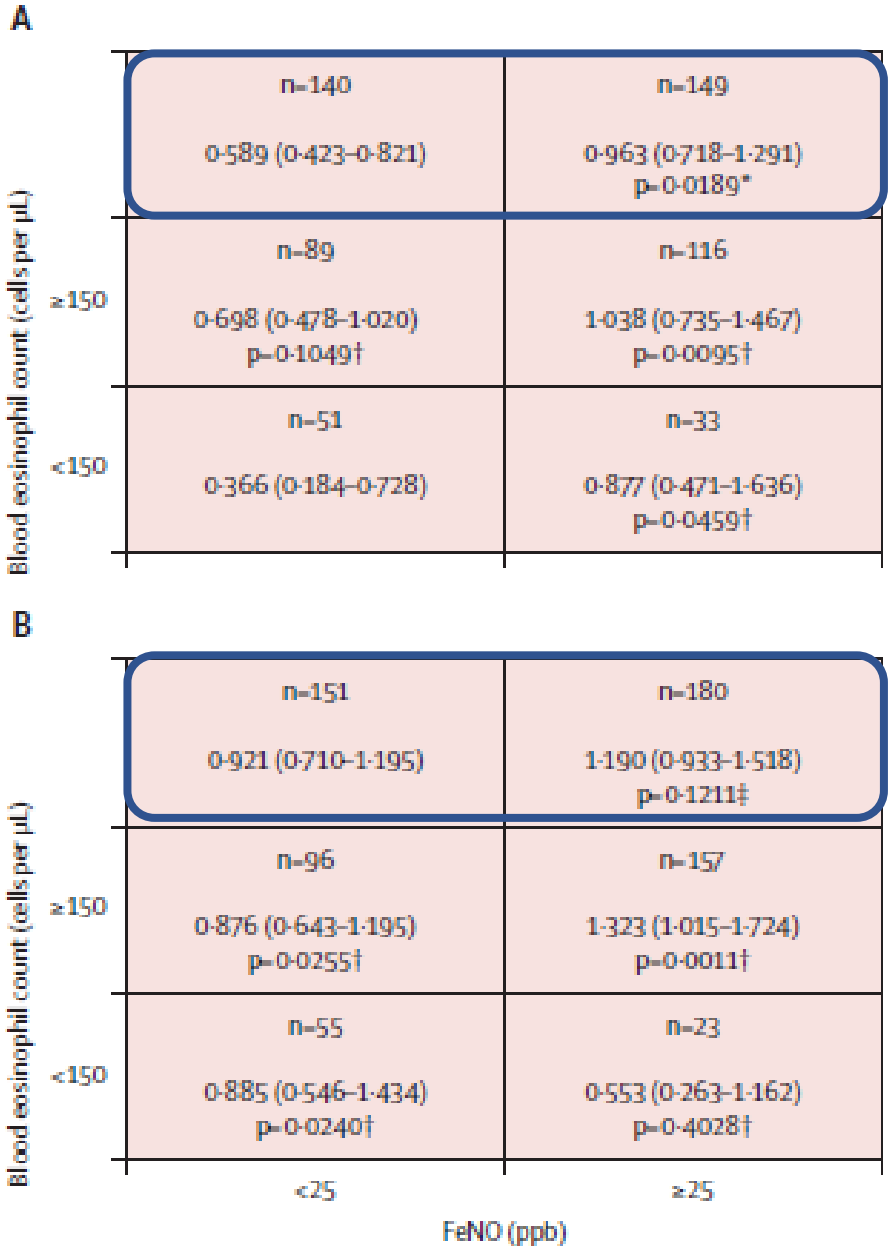
William W Busse.Lancet Respir Med 2021; 9: 1165–73

The risk of future severe exacerbations in the 52-week
Baseline FeNO in combination with elevated baseline blood eosinophil count compared with FeNO of less than 25 ppb and blood eosinophil count of less than 150 cells per µL.

- FeNO of ≥25 to <50 ppb & eosinophil count of ≥150 to <300 cells per µL (RR 2·05)
- FeNO of ≥25 to <50 ppb & eosinophil count of 300 cells per µL or higher (RR 2·22)
- FeNO of 50 ppb or higher & eosinophil count of 300 cells per µL or higher (RR 3·19)

William W Busse.Lancet Respir Med 2021; 9: 1165–73

Fig) Baseline FeNO level and estimated annualised severe exacerbation rate (95% CI) over the following 52 weeks in placebo-treated patients further stratified by blood eosinophil count and one (A) or two or more (B) prior severe exacerbations



- The highest rate of future severe exacerbations
  : in patients with FeNO of 25 ppb or higher,
  a blood eosinophil count of 150 cells per µL or higher,
  and two or more prior exacerbations.

William W Busse.Lancet Respir Med 2021; 9: 1165–73

- Patients with baseline FeNO of 25 ppb or higher, a blood eosinophil count of 150 cells per µL or higher, and two or more prior exacerbations (n=157) had an exacerbation rate 3·62-times higher than patients with FeNO of less than 25 ppb, a blood eosinophil count of less than 150 cells per µL, and one prior exacerbation (n=116; 3·62 [1·67–7·81]; p=0·0011).

- In uncontrolled, moderate-to-severe asthma, higher baseline FeNO levels were associated with greater risk of severe asthma exacerbations, particularly in combination with elevated eosinophil count and prior exacerbations, supporting the added value of FeNO as a prognostic biomarker. Further research is needed to confirm FeNO as an independent predictor for asthma exacerbations.

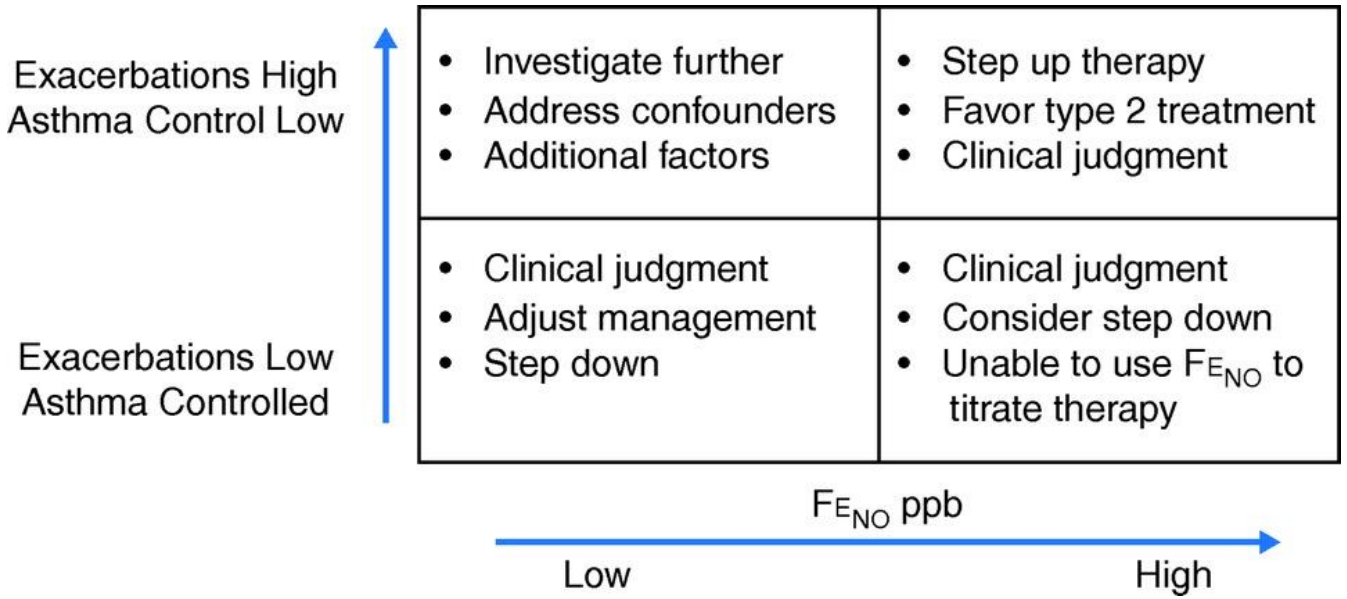
William W Busse.Lancet Respir Med 2021; 9: 1165–73

AMERICAN THORACIC SOCIETY DOCUMENTS

Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma

An Official American Thoracic Society Clinical Practice Guideline

Sumita B. Khatri, Jonathan M. Iaccarino, Amisha Barochia, Israa Soghier, Praveen Akuthota, Anna Brady, Ronina A. Covar, Jason S. Debley, Zuzana Diamant, Anne M. Fitzpatrick, David A. Kaminsky, Nicholas J. Kenyon, Sandhya Khurana, Brian J. Lipworth, Kevin McCarthy, Michael Peters, Loretta G. Que, Kristie R. Ross, Elena K. Schneider-Futschik, Christine A. Sorkness, and Teal S. Hallstrand; on behalf of the American Thoracic Society Assembly on Allergy, Immunology, and Inflammation



Conditional recommendation for the use of FENO testing in addition to usual care in patients with asthma in whom treatment is being considered

Am J Respir Crit Care Med. Nov 15, 2021. Vol 204, Iss 10, pp e97–e109,

Contents

01 **Guidelines:** GINA 2021 update and COVID in asthma

02 **Risk factor and diagnosis of asthma**

03 **Treatment:** Single inhaler triple therapy / Biologics

04 **Take home messages**

Received: 11 March 2021 | Accepted: 20 July 2021

DOI: 10.1111/all.15076

Allergy WILEY

REVIEW

Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications

Alvar Agusti[1] | Leonardo Fabbri[2] | Lies Lahousse[3] | Dave Singh[4] | Alberto Papi[5]

4 | CONCLUSIONS

Single-inhaler triple therapy offers a novel safe and effective therapeutic option for patients with asthma uncontrolled on medium- to high-dose ICS/LABA. In clinical practice, however, several important patient-related factors, including compliance, need to be considered carefully, and the optimum place for these treatments within existing treatment guidelines needs to be properly established.

Study name[ref]	FEV_1 improvement for SITT versus ICS/LABA	Reduction of moderate-severe exacerbation for SITT versus ICS/LABA
TRIMARAN[10] BDP/FF/GLY versus BDP/FF	57 mL (95% CI 15–99; $p = .0080$) for medium dose	15% (RR 0.85, 95% CI 0.73–0.99; $p = .033$) for medium dose
TRIGGER[10] BDP/FF/GLY versus BDP/FF BDP/FF/GLY versus BDP/FF+TIO	73 mL (95% CI 26–120; $p = .0025$) for high dose −45 mL [95% CI −103 to 13; $p = .13$) for high dose	12% (RR 0.88, 95% CI 0.75–1.03; $p = .11$) for high dose 7% (RR1·07, 95% CI 0·88–1·30; $p = .50$) for high dose
IRIDIUM[15] MF/IND/GLY versus MF/IND MF/IND/GLY versus FP/SLM	• 76 mL ($p < .001$) for medium dose • 65 mL ($p < .001$) for high dose • 99 mL ($p < .001$) for medium dose • 119 mL ($p < .001$) for high dose	• 13% (RR 0.87, 95% CI 0.71–1.06; $p = .17$) for medium dose • 15% (RR 0.85, 95% CI 0.68–1.04; $p = .12$) for high dose • 19% r (RR 0.81, 95% CI 0.66–0.99; $p = .041$) for medium dose • 36% (RR 0.64, 95% CI 0.52–0.78; $p < .001$) for high dose
ARGON[17] MF/IND/GLY versus FP/SLM+TIO	High-dose and medium-dose MF/IND/GLY were non-inferior to high-dose FP/SLM+TIO for AQLQ (least square mean treatment difference: 0.073 and −0.038, respectively; both $p < .001$). High-dose MF/IND/GLY improved trough FEV_1 at Weeks 8 (Δ: 67 mL; $p = .007$), 16 (Δ: 66 mL; $p = .007$) and 24 (Δ: 96 mL; $p < .001$) versus high-dose FP/SLM+TIO. Medium-dose MF/IND/GLY medium-dose versus high-dose FP/SLM+TIO at Weeks 8 (Δ: 3 mL; $p = .892$), 16 (Δ: −2 mL; $p = .945$) and 24 (Δ: 9 mL; $p = .713$).	Medium-dose MF/IND/GLY versus FP/SLM high dose+TIO • 4% increase (RR 1.04, 95% CI 0.77, 1.39; $p = .798$) High-dose MF/IND/GLY versus FP/SLM high dose+TIO • 12% reduction (RR 0.88, 95% CI 0.65, 1.19; $p = .414$)
CAPTAIN[18] F/UMEC/VI 100/62.5/25 versus F/VI 100/25 F/UMEC/VI 200/62.5/25 versus F/VI 200/25	110 mL (66, 153; $p < .001$) for medium dose 92 mL (49, 135; $p < .001$) for high dose Adding UMEC 31.25 µg to F/VI produced similar improvements.	No statistically significant difference F/UMEC 62.5 µg/VI versus F/VI (pooled analysis)

Single inhaler triple therapy vs ICS/LABA

- FEV1 improvement
- Reduction moderate to severe exacerbation

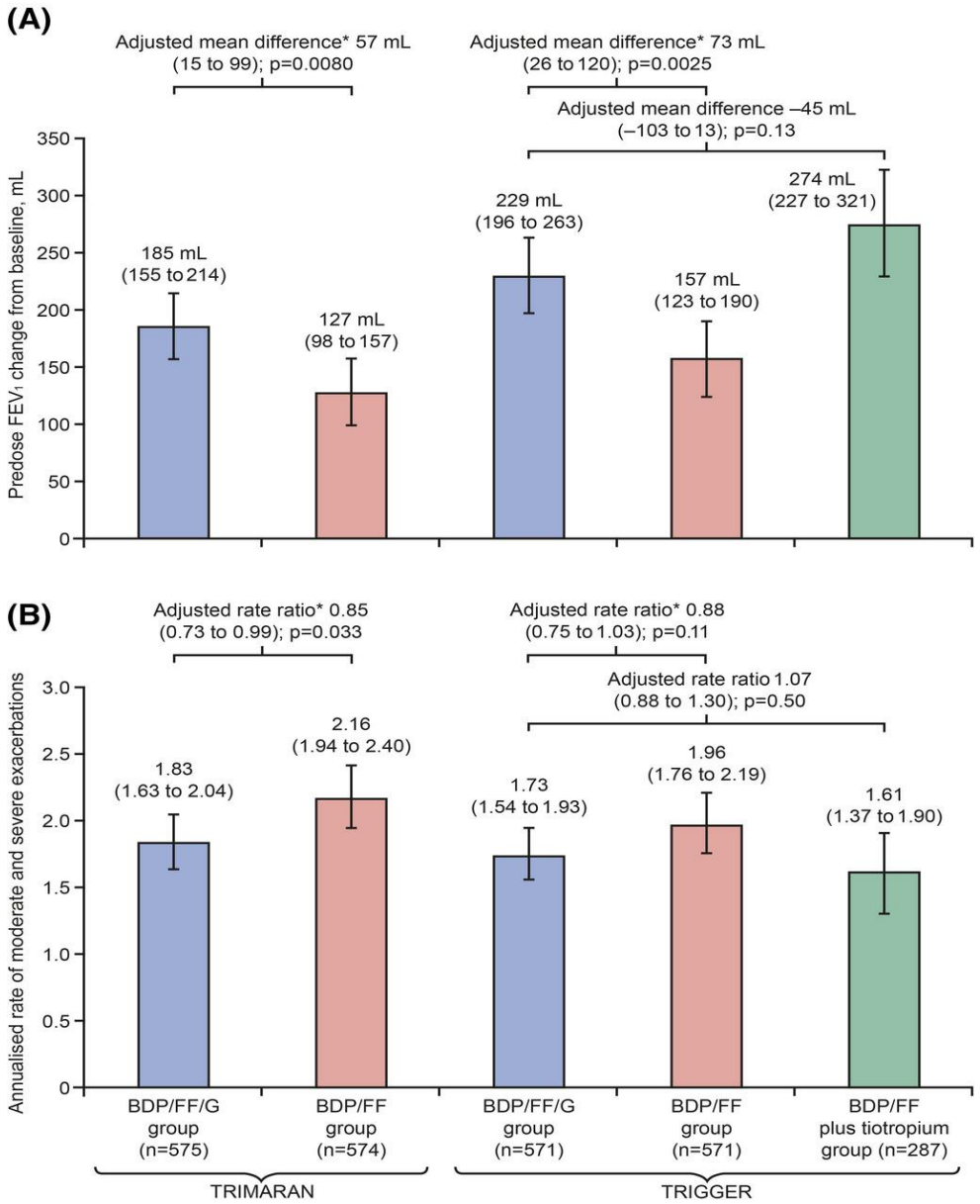
Single inhaler triple therapy vs ICS/LABA/LAMA

- FEV1 improvement
- Reduction moderate to severe exacerbation
- Non-inferior to high dose FP/SLM+TIO in AQLQ

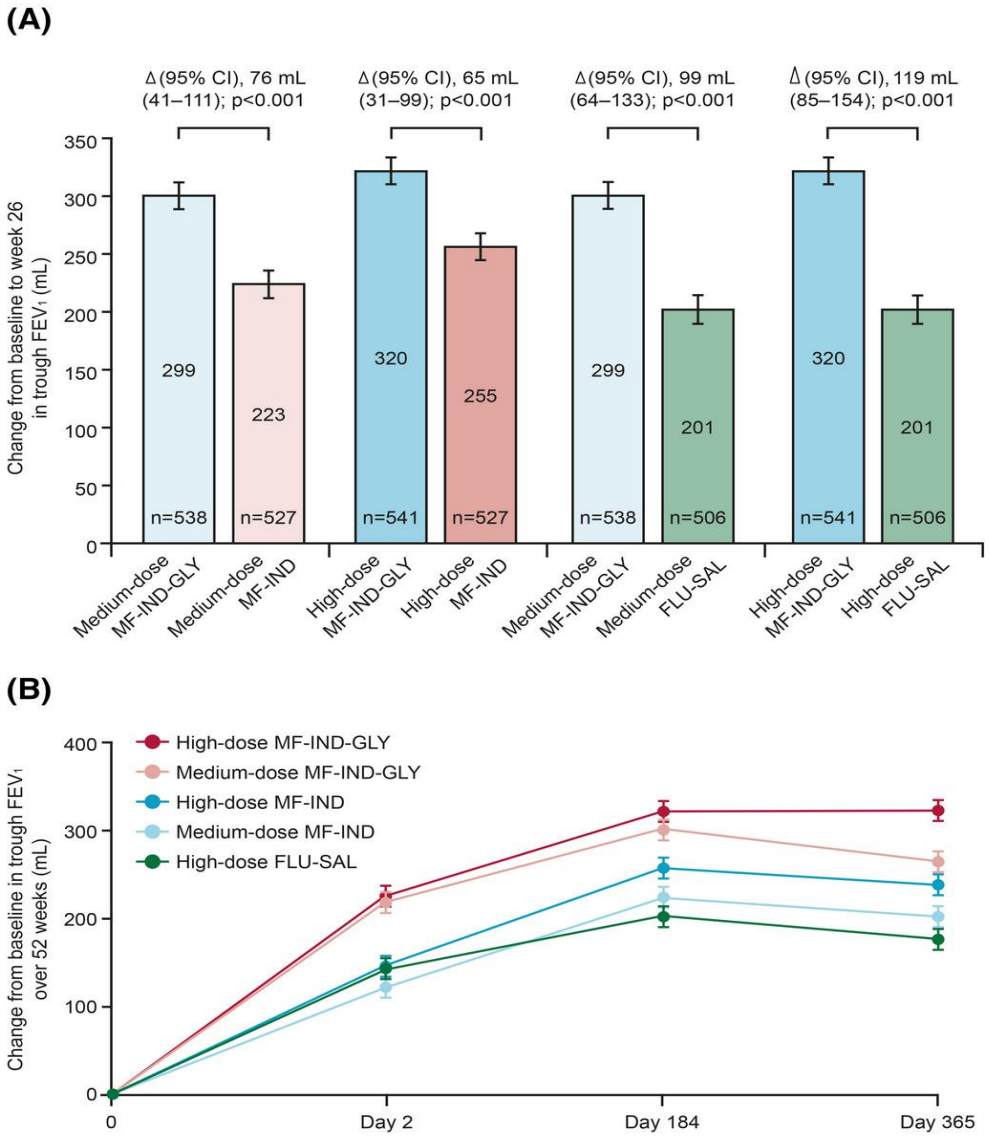
Allergy, First published: 03 September 2021, DOI: (10.1111/all.15076)

Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications

TRIMARAN & TRIGGER

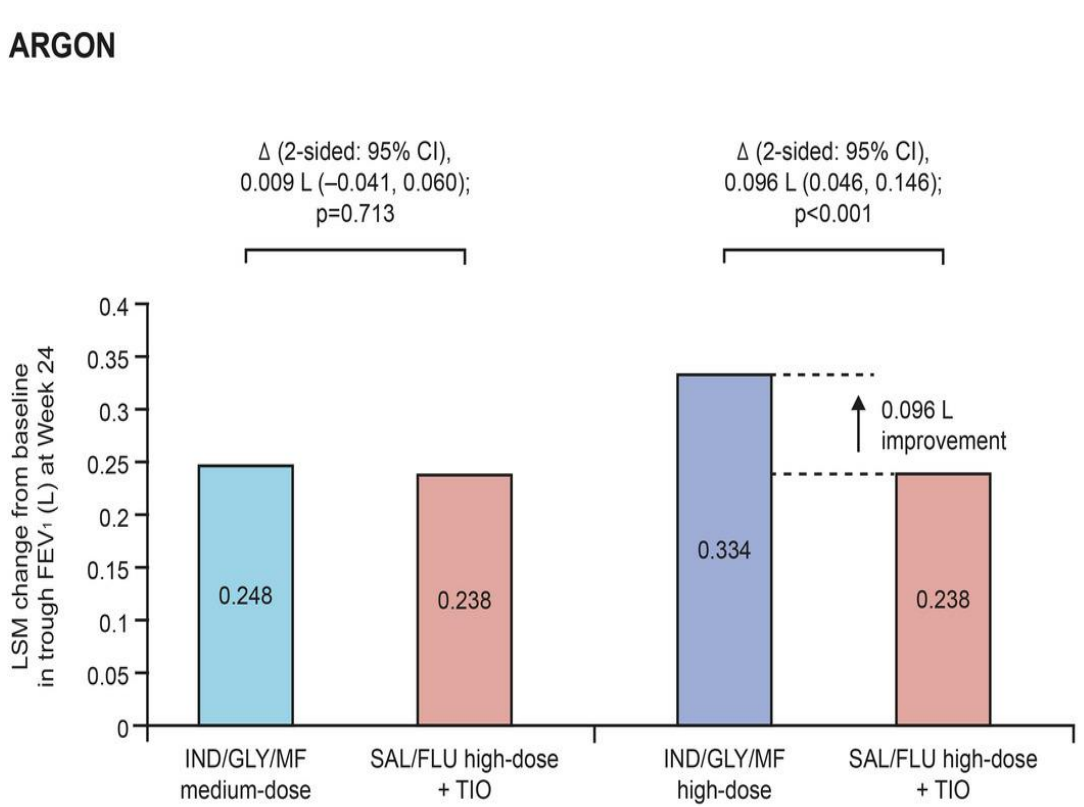


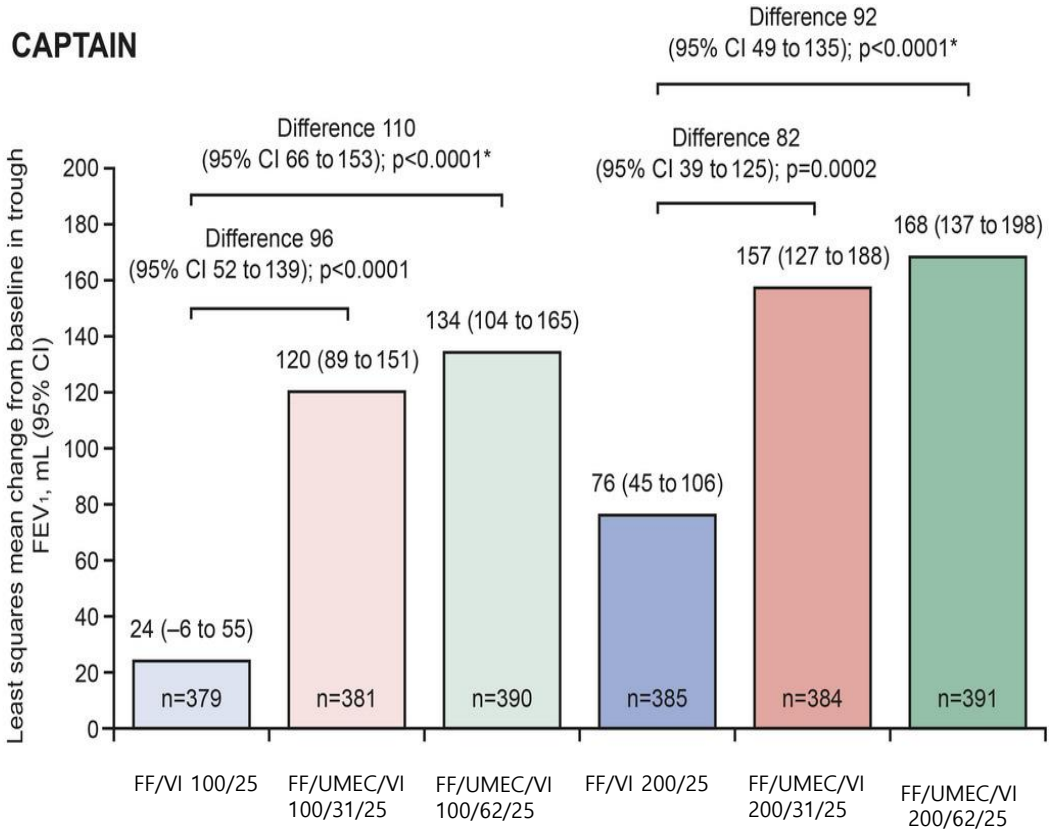
IRIDIUM



Allergy, First published: 03 September 2021, DOI: (10.1111/all.15076)

Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications





Allergy, First published: 03 September 2021, DOI: (10.1111/all.15076)

Recommendations for positioning of SITT in asthma management

(1) Patients with uncontrolled asthma despite medium-dose ICS/ LABA, adherence should be evaluated, and medium ICS dose in a SITT should be considered particularly for exacerbation prevention in subjects with low T2 markers as an alternative to high-dose ICS+LABA

(2) Patients with uncontrolled asthma despite high-dose ICS/LABA, we propose to evaluate adherence and consider high ICS dose SITT before using oral corticosteroids or a biologic, particularly if there is persistent airflow limitation and/or history of severe exacerbations, or certainly in patients not eligible for biologic treatment

(3) Patients who are well-controlled on high-dose ICS/LABA or high ICS dose SITT but at risk for or experiencing ICS-related side effects, we suggest to consider a medium ICS dose in SITT.

Allergy, First published: 03 September 2021, DOI: (10.1111/all.15076)

Biologic Therapies for Severe Asthma

Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study

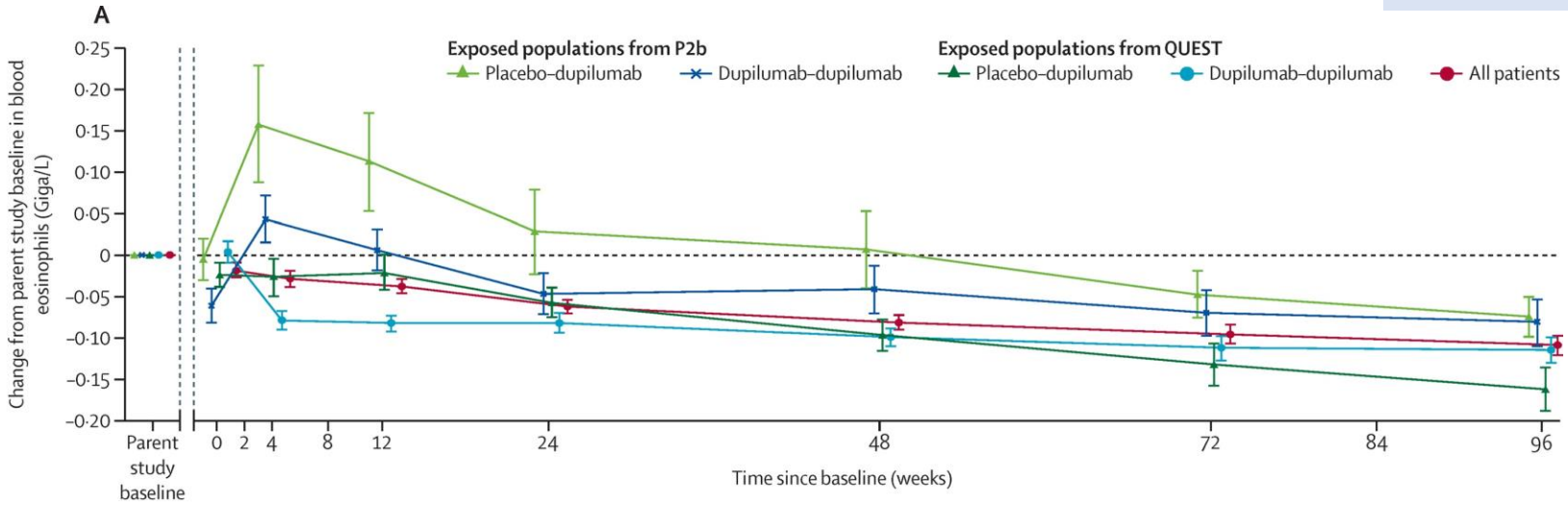
Objective : evaluate the long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma, as data for extended treatment with dupilumab beyond 1 year

Method : dupilumab 300 mg every 2 weeks up to 96 weeks (aged 12–84 years) with moderate-to-severe or oral-corticosteroid-dependent severe asthma who had completed a previous dupilumab asthma study

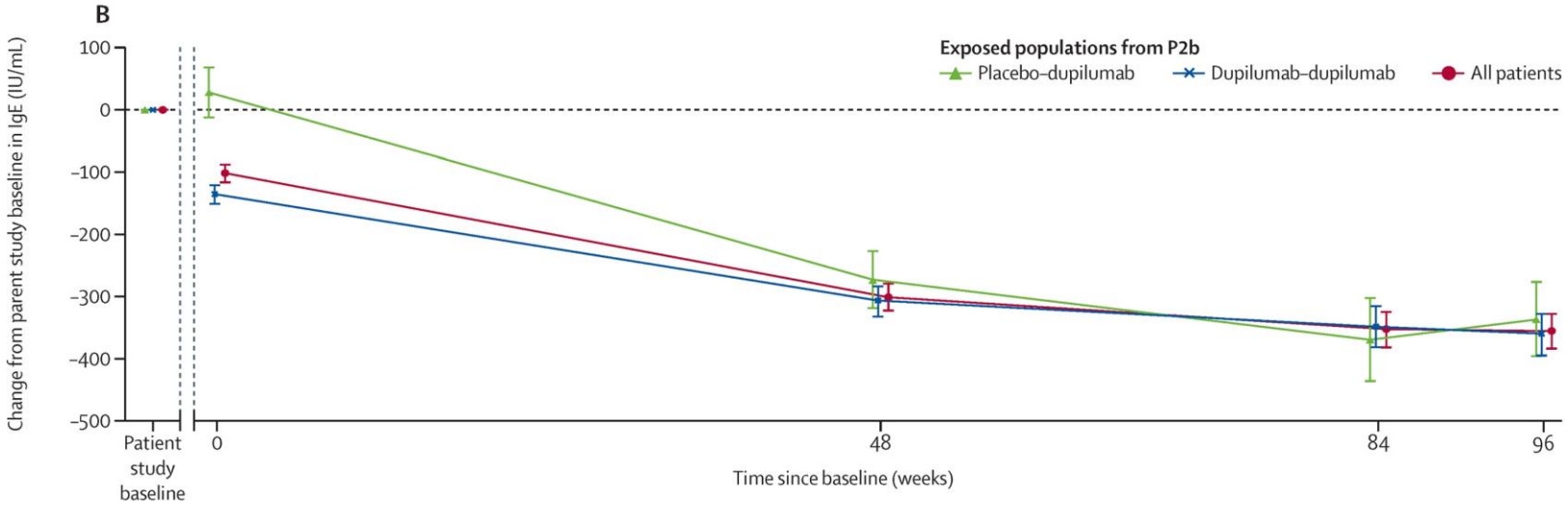
Primary endpoint : any treatment-emergent adverse event - similar to those observed in the parent studies

Secondary endpoints : annualised exacerbation rate (AER), change from parent study baseline in pre-bronchodilator $FEV_{1,}$ five-item asthma control questionnaire (ACQ-5), the asthma quality of life questionnaire (AQLQ), type 2 biomarkers (blood eosinophils and serum total IgE), and anti-drug antibodies (ADAs)

Wechsler, M. E. Lancet Respir Med 2022 Jan 10(1): 11-25

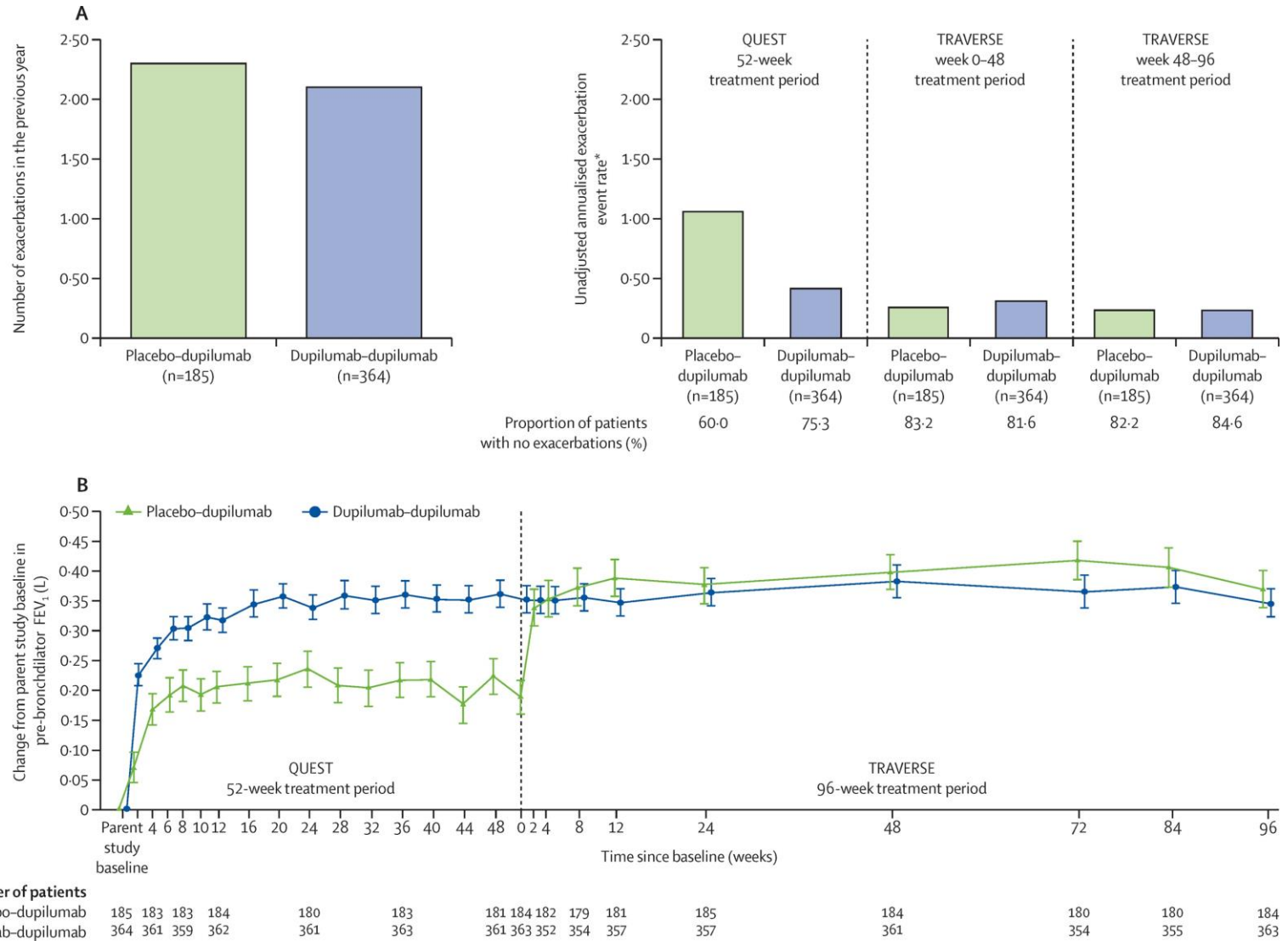


Number of patients								
P2b placebo–dupilumab	111	109	103	110	110	103	106	102
P2b dupilumab–dupilumab	421	408	404	419	408	386	382	381
QUEST, placebo–dupilumab	516	500	493	500	496	474	220	218
QUEST, dupilumab–dupilumab	1012	962	974	982	979	935	450	435
All patients	2060	1979	1974	2011	1993	1898	1158	1136



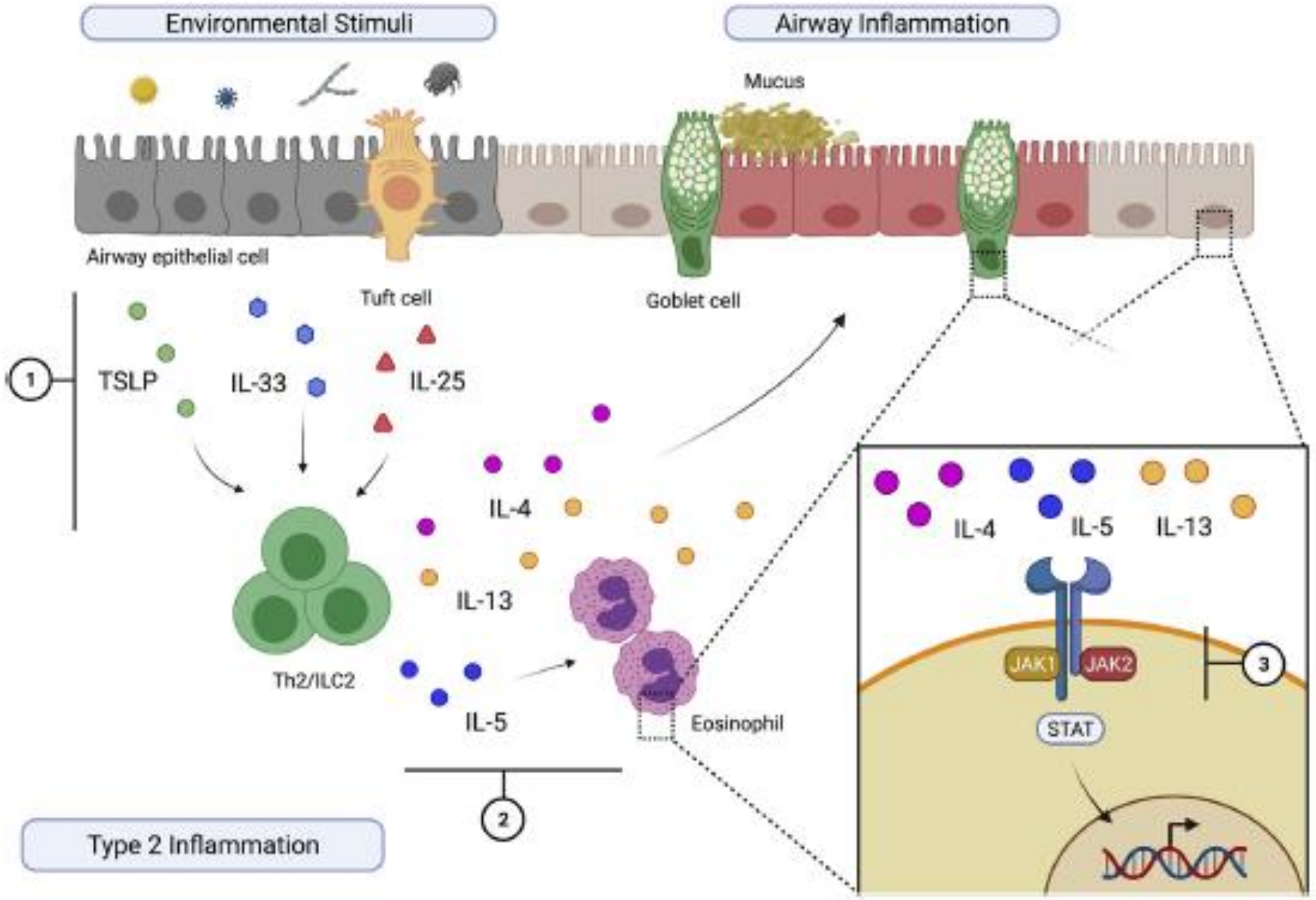
Number of patients					
P2b placebo–dupilumab	110	110	110	110	110
P2b dupilumab–dupilumab	421	421	421	421	421
All patients	531	531	531	531	531

long-term dupilumab 300 mg every 2 weeks is well tolerated and can provide sustained improvements in clinical efficacy up to 148 weeks in adult and adolescent patients with moderate-to-severe asthma



Wechsler, M. E. Lancet Respir Med 2022 Jan 10(1): 11-25

Alarmin-molecules produced by damaged tissue that activate inflammation

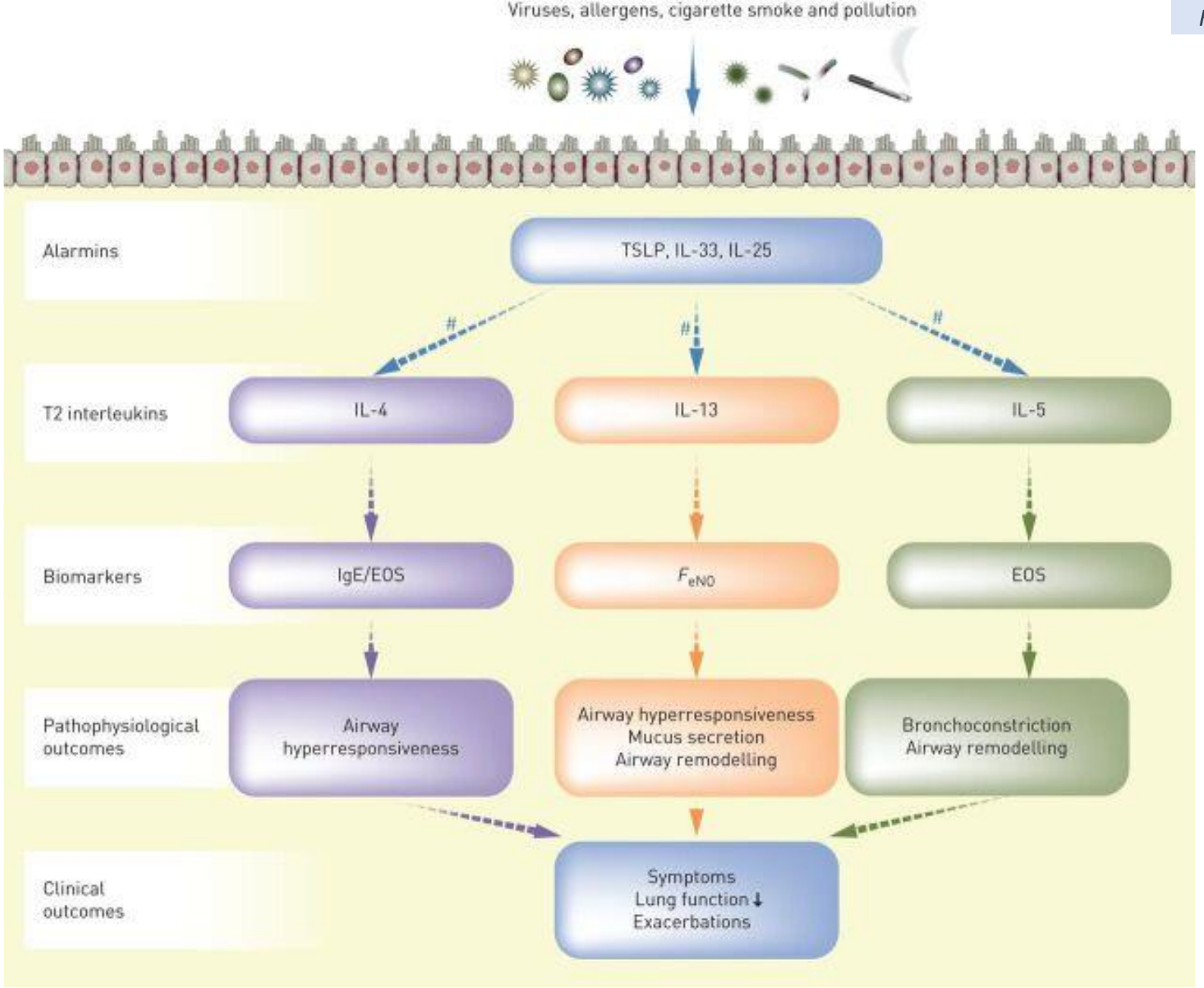


- The epithelium has been shown to mediate complex inflammatory processes in response to these allergic and non-allergic triggers, including the release of a trio of epithelial cytokines, known as “alarmins”

- Thymic stromal lymphopoietin (TSLP), IL-33 and IL-25

- Strong potential therapeutic targets with type2- high and type2-low asthma

J Allergy Clin Immunol 2021;148:719-21.



- The central, upstream role of alarmins makes them attractive potential therapeutic targets

- Blocking alarmins, however, has the potential to inhibit airway hyperresponsiveness and remodelling and produce sustained reductions in disease activity

Eur Respir J. 2020 Nov; 56(5): 2000260.

Editorial

Emerging targeted therapeutics underscore immunologic heterogeneity of asthma

Masato Tamari, MD, PhD, Anna M. Trier, BA, and Brian S. Kim, MD, MTR *St Louis, Mo*

There are limited treatment options for T2-low patients, as they exhibit weaker clinical responses to inhaled corticosteroids and there are no approved treatments specifically targeting this population.

ZENYATTA –astegolimab : a mAb directed against the IL-33 receptor (ST2) in severe asthma-phase 2b

NAVIGATOR-tezepelumab : a mAb against the alarmin thymic stromal lymphopoietin(TSLP)-phase 3

J Allergy Clin Immunol 2021;148:719-21.

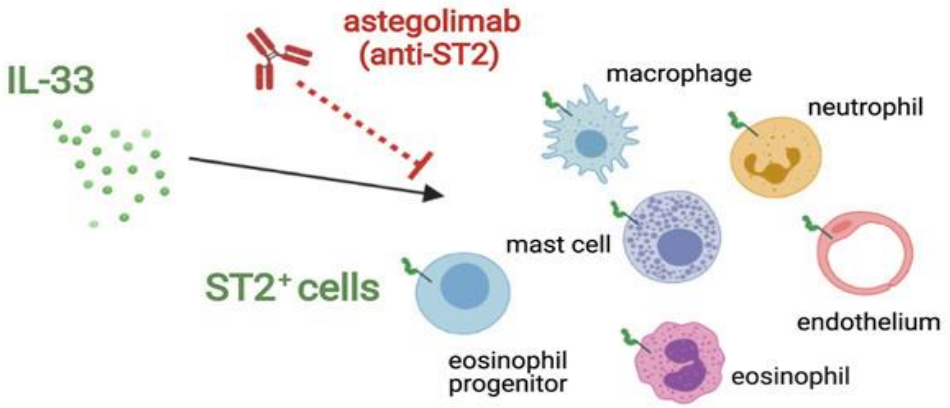
Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

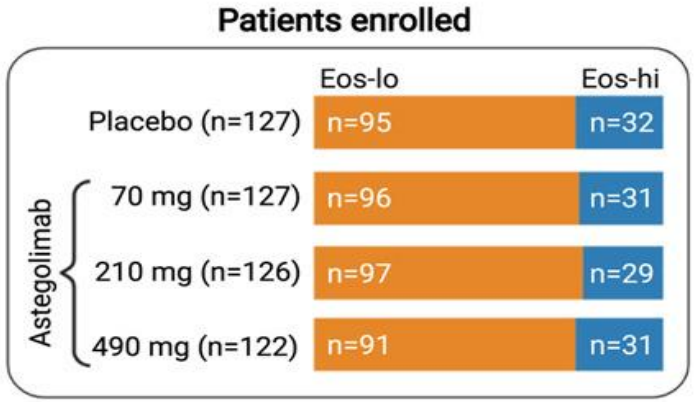
Steven G. Kelsen, MD, Ioana O. Agache, MD, PhD, Weily Soong, MD, Elliot Israel, MD, Geoffrey L., Christopher E. Brightling, FMedSci, PhD

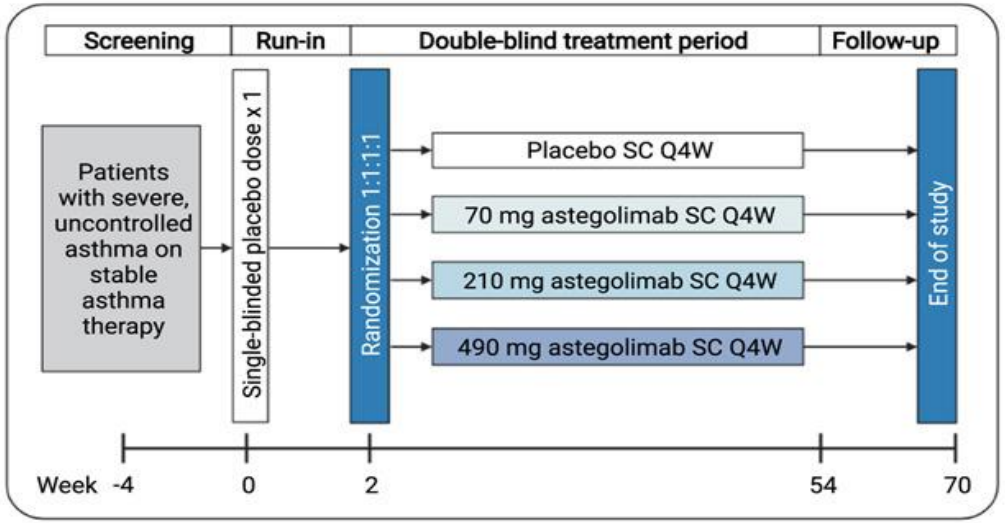
Journal of Allergy and Clinical Immunology
Volume 148 Issue 3 Pages 790-798 (September 2021)

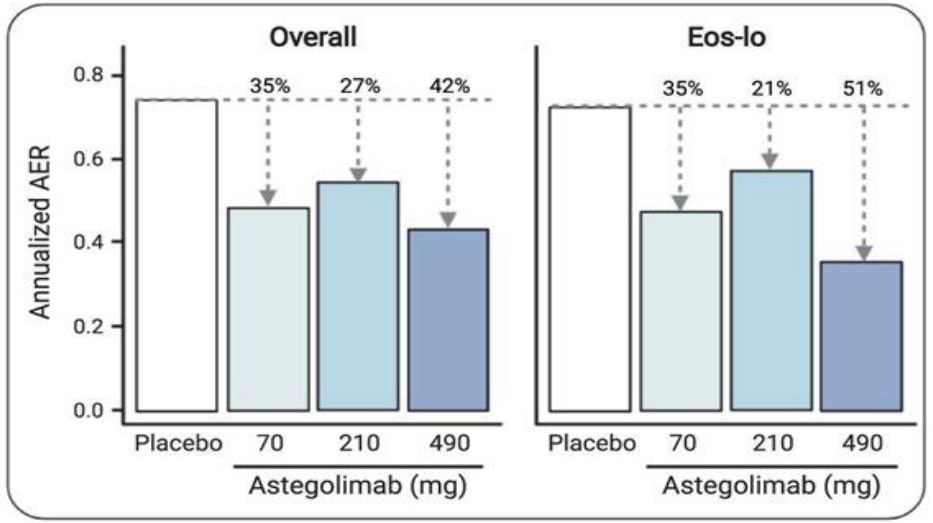
Astegolimab is a human IgG_2 mAb that blocks IL-33 signaling by targeting ST2, the IL-33 receptor. Because cell types involved in both T2-high and T2-low asthma express ST2

Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma, including patients with low eosinophils





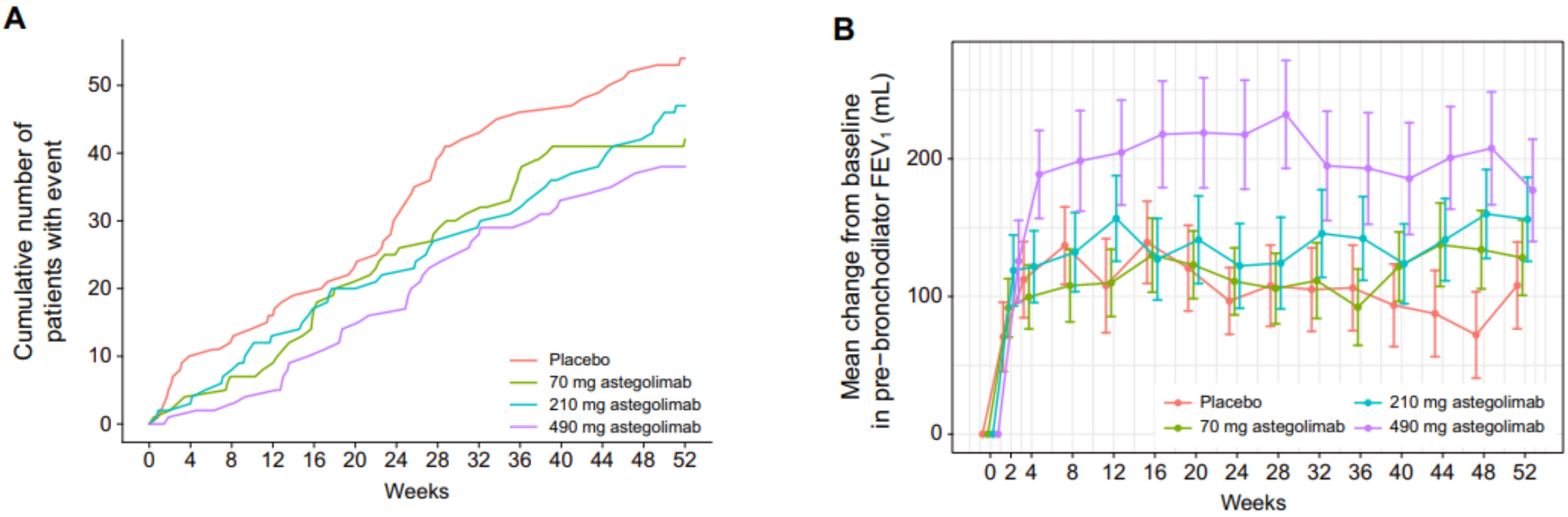




AER, asthma exacerbation rate; Eos-lo, <300 eosinophils/μL; Eos-hi, ≥300 eosinophils/μL; IL, interleukin; Q4W, every 4 weeks; SC, subcutaneous

J Allergy Clin Immunol 2021;148:790-8

Secondary outcomes. A, Cumulative number of patients with asthma exacerbations over the treatment period. B, Absolute change in FEV1 from baseline to week 54.



Conclusions: Astegolimab reduced AER in a broad population of patients, including those who were eosinophil-low, with inadequately controlled, severe asthma. Astegolimab was safe and well tolerated.

J Allergy Clin Immunol 2021;148:790-8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

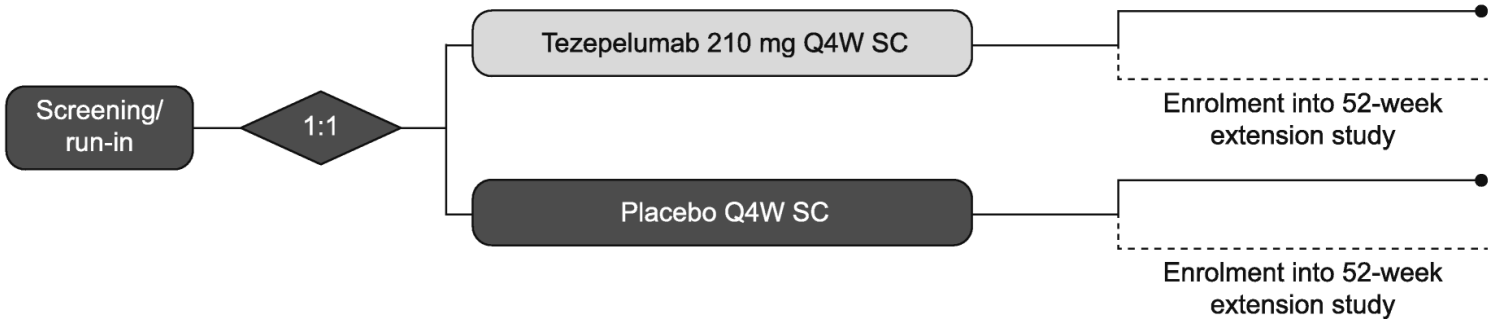
Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

NAVIGATOR trial

phase 3, multicenter, randomized, double-blind, placebo-controlled trial
November 23, 2017, to September 8, 2020 at 297 sites in 18 countries

Week	–5 to –6	0	2 to 48	52	58 to 64
	Screening/ run-in	Randomization	Treatment period	End of treatment	Follow-up or enrolment into separate extension study[a]



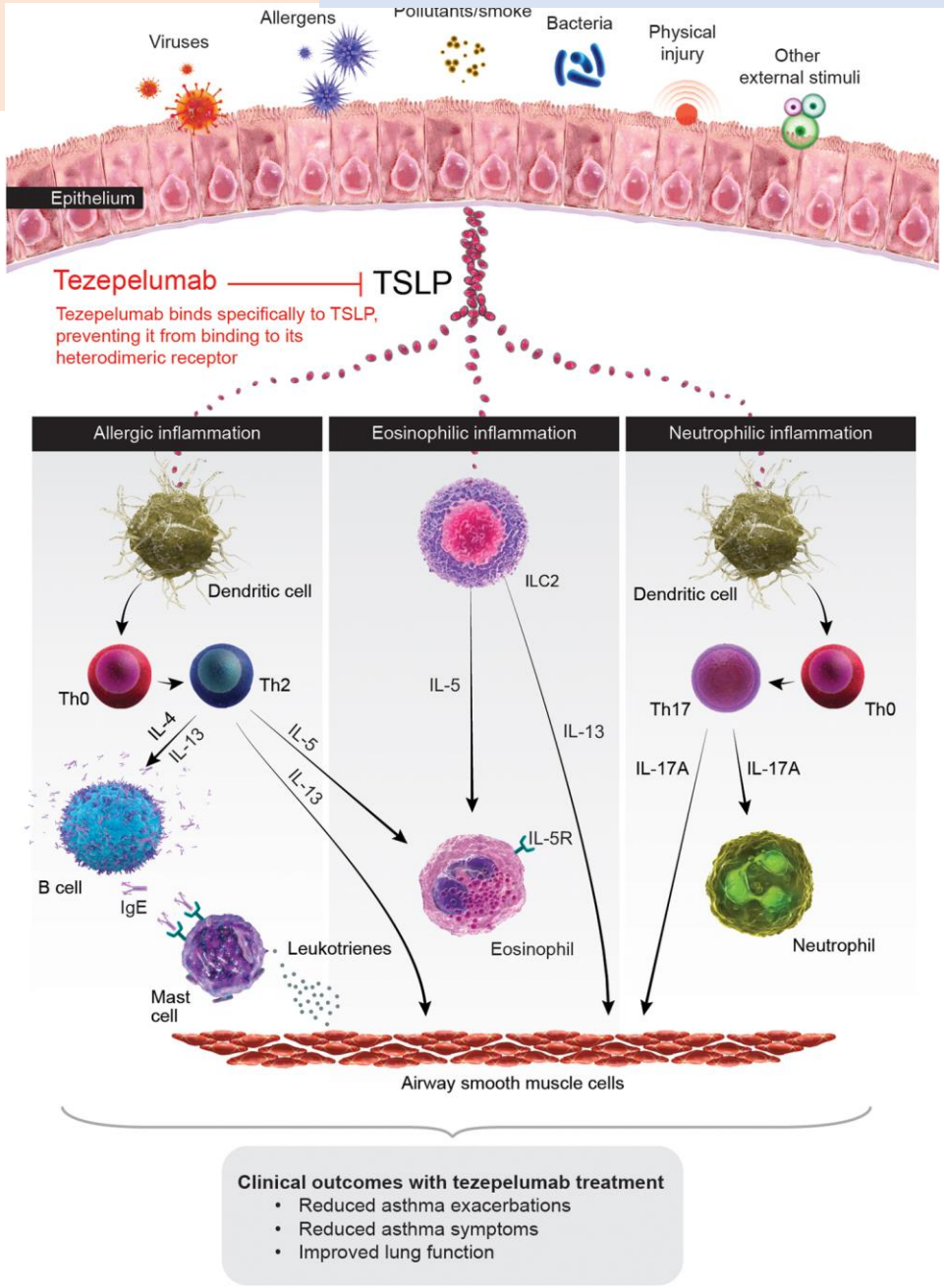
Andrew et al. N Engl J Med 2021; 384:1800-1809

Tezepelumab

- Human monoclonal antibody that blocks thymic stromal lymphopoietin (anti-TSLP), an epithelial-cell–derived cytokine implicated in the pathogenesis of asthma

- TSLP levels are correlated with airway obstruction, disease severity, and glucocorticoid resistance

- In addition to driving T2 inflammation of the airway, TSLP has been shown to mediate interactions between airway structural cells and immune cells, which are not exclusively driven by T2 inflammation



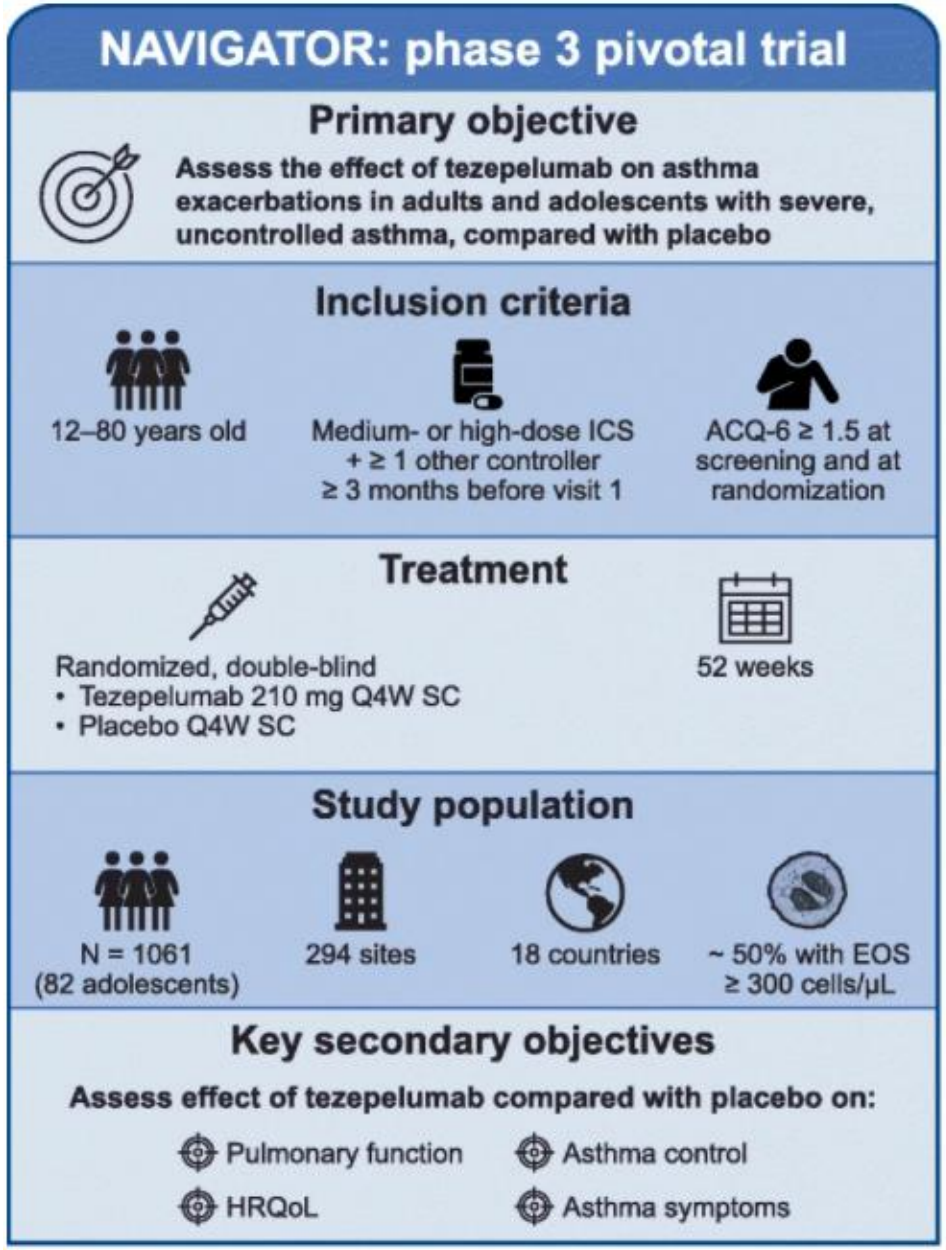
Respiratory Research **volume 21**, Article number: 266 (2020)

Tezepelumab - Phase 2b PATHWAY trial

- Annualized rate of asthma exacerbations was up to 71% lower with tezepelumab than with placebo among patients with severe, uncontrolled asthma.

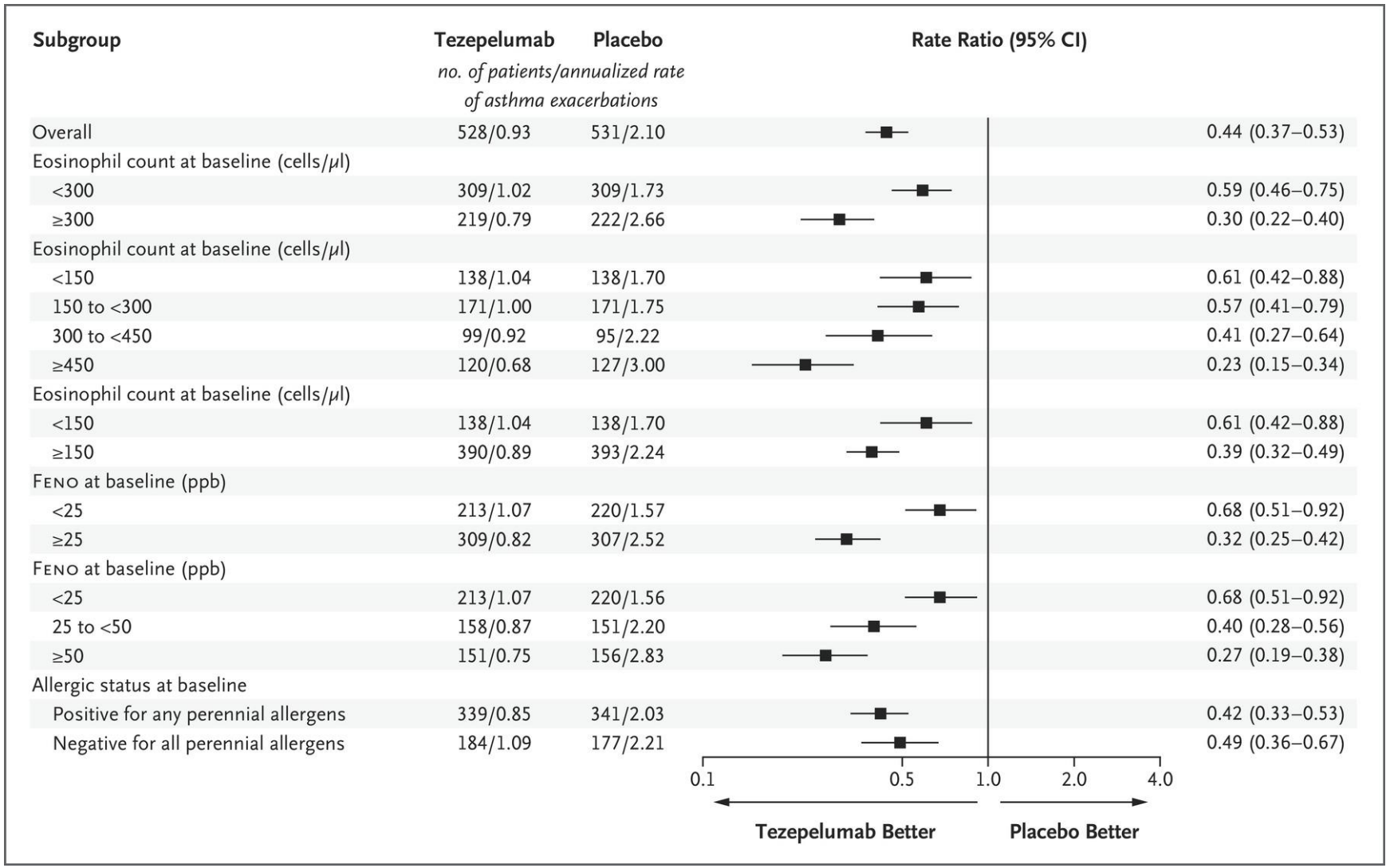
- Exacerbations were reduced irrespective of baseline levels of inflammatory biomarkers (including fraction of exhaled nitric oxide [FENO], blood eosinophils, and IgE) and allergic status

N Engl J Med 2017; 377:936-946



characteristic	tezepelumab (N=528)	Placebo (N=531)	Total (N=1059)
Age — yr	49.9±16.3	49.0±15.9	49.5±16.1
Male sex — no. (%)	193 (36.6)	194 (36.5)	387 (36.5)
White race — no. (%)†	332 (62.9)	327 (61.6)	659 (62.2)
Body-mass index‡	28.7±7.1	28.3±6.9	28.5±7.0
Dose of inhaled glucocorticoids — no. (%)			
Low	0	1 (0.2)	1 (0.1)
Medium	131 (24.8)	132 (24.9)	263 (24.8)
High	397 (75.2)	398 (75.0)	795 (75.1)
Use of oral glucocorticoids — no. (%)			
Yes	49 (9.3)	51 (9.6)	100 (9.4)
No	479 (90.7)	480 (90.4)	959 (90.6)
Prebronchodilator FEV_1 (%)	62.8±18.0	62.7±18.0	62.7±18.0
ACQ-6 score§	2.8±0.8	2.8±0.8	2.8±0.8
AQLQ(S)+12 overall score¶			
No. of patients evaluated	527	529	1056
Mean	3.9±1.0	3.9±1.0	3.9±1.0
F^{ENO} level			
No. of patients evaluated	522	527	1049
Mean — ppb	41.4±36.3	46.3±44.7	43.8±40.8
Median (range) — ppb	31.0 (5.0–235.0)	30.0 (5.0–265.0)	30.0 (5.0–265.0)
<25 ppb — no. (%)	213 (40.8)	220 (41.7)	433 (41.3)
≥25 ppb — no. (%)	309 (59.2)	307 (58.3)	616 (58.7)
Blood eosinophil count			
Mean — cells/µl	327±293	353±488	340±403
Median (range) — cells/µl	250 (0–3650)	250 (0–8170)	250 (0–8170)
<300 cells/µl — no. (%)	309 (58.5)	309 (58.2)	618 (58.4)
≥300 cells/µl — no. (%)	219 (41.5)	222 (41.8)	441 (41.6)
Serum total IgE — IU/ml			
Mean	515.7±959.8	614.1±1159.5	565.0±1065.2
Median (range)	194.9 (1.5–	196.7 (1.5–9740.9)	195.6 (1.5–12 823.2)

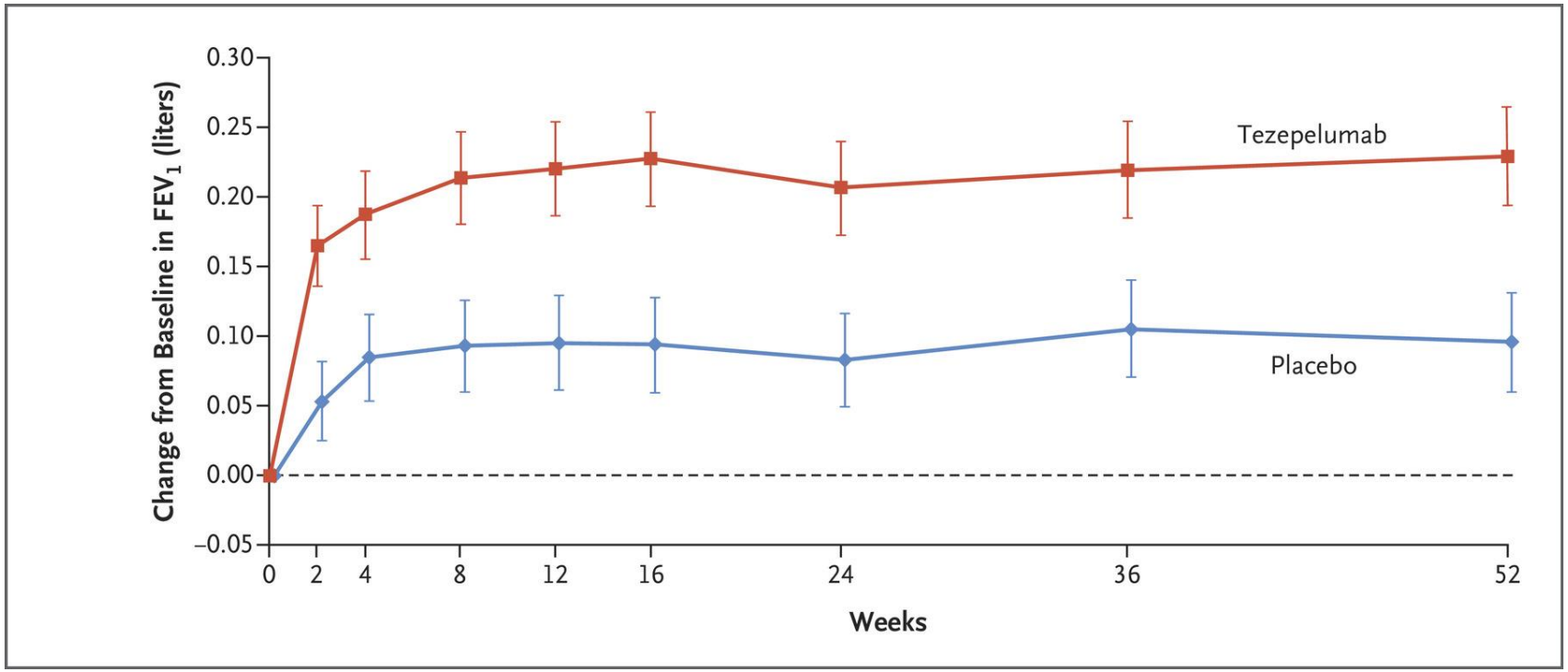
Annualized Rate of Asthma Exacerbations over a Period of 52 Weeks in the Overall Population and According to Baseline Biomarker Category or Allergic Status.



Andrew et al. N Engl J Med 2021; 384:1800-1809

- **Change from Baseline to Week 52 in Prebronchodilator FEV_1.**

Prebronchodilator FEV_1‡		
Mean at baseline — liters	1.8±0.7	1.9±0.7
Change from baseline at wk 52		
No. of patients evaluated	528	531
Least-squares mean — liters	0.23±0.02	0.09±0.02
Least-squares mean difference vs. placebo (95% CI) — liters	0.13 (0.08 to 0.18)§	



Andrew et al. N Engl J Med 2021; 384:1800-1809

Variable	Tezepelumab (N=528)	Placebo (N=531)
FENO level		
Mean at baseline — ppb	41.4±36.3	46.3±44.7
Change from baseline at wk 52		
No. of patients evaluated	440	426
Least-squares mean — ppb	−17.3±1.2	−3.5±1.2
Least-squares mean difference vs. placebo (95% CI) — ppb	−13.8 (−17.1 to −10.6)	
Blood eosinophil count		
Mean at baseline — cells/μl	327±293	353±488
Change from baseline at wk 52		
No. of patients evaluated	458	451
Least-squares mean — cells/μl	−170±9	−40±9
Least-squares mean difference vs. placebo (95% CI) — cells/μl	−130 (−156 to −104)	
Serum total IgE		
Mean at baseline — IU/ml	515.7±959.8	614.1±1159.5
Change from baseline at wk 52		
No. of patients evaluated	482	471
Least-squares mean — IU/ml	−164.4±34.4	43.6±34.5
Least-squares mean difference vs. placebo (95% CI) — IU/ml	−208.0 (−303.7 to −112.3)	

Andrew et al. N Engl J Med 2021; 384:1800-1809

- ACQ-6 (−1.55 vs. −1.22; difference, −0.33; 95% CI, −0.46 to −0.20; P<0.001)
- AQLQ (1.49 vs. 1.15; difference, 0.34; 95% CI, 0.20 to 0.47; P<0.001)
- Asthma symptom diary(ASD) (−0.71 vs. −0.59; difference, −0.12; 95% CI, −0.19 to −0.04;P = 0.002)

CONCLUSIONS

- Safety-no differences between placebo
- Patients with severe, uncontrolled asthma who received tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life than those who received placebo

Andrew et al. N Engl J Med 2021; 384:1800-1809

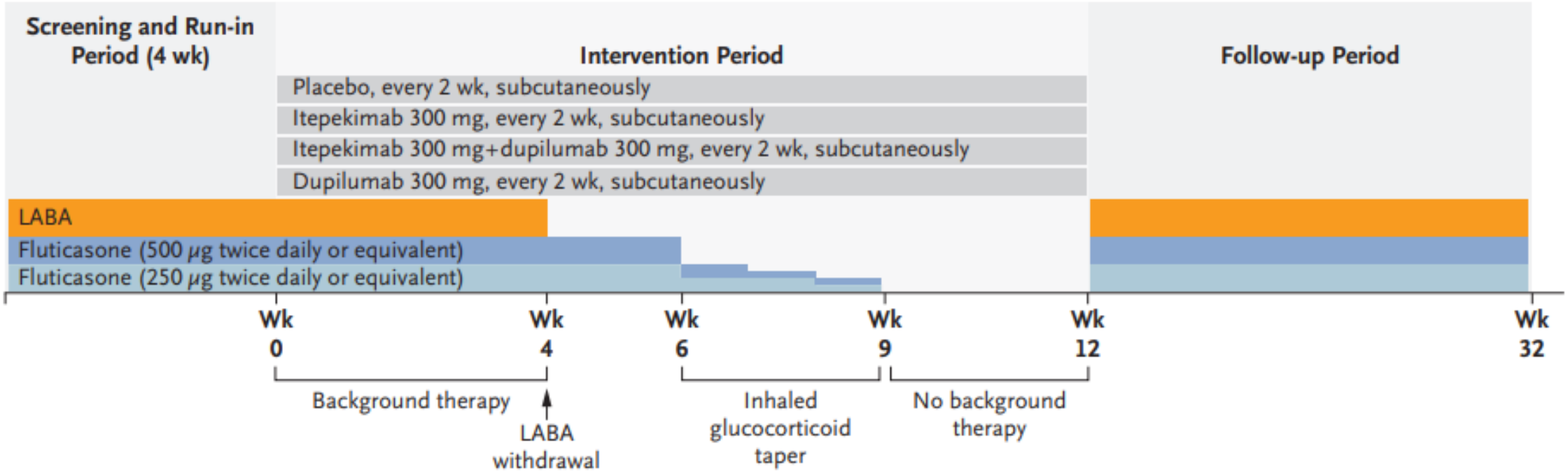
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

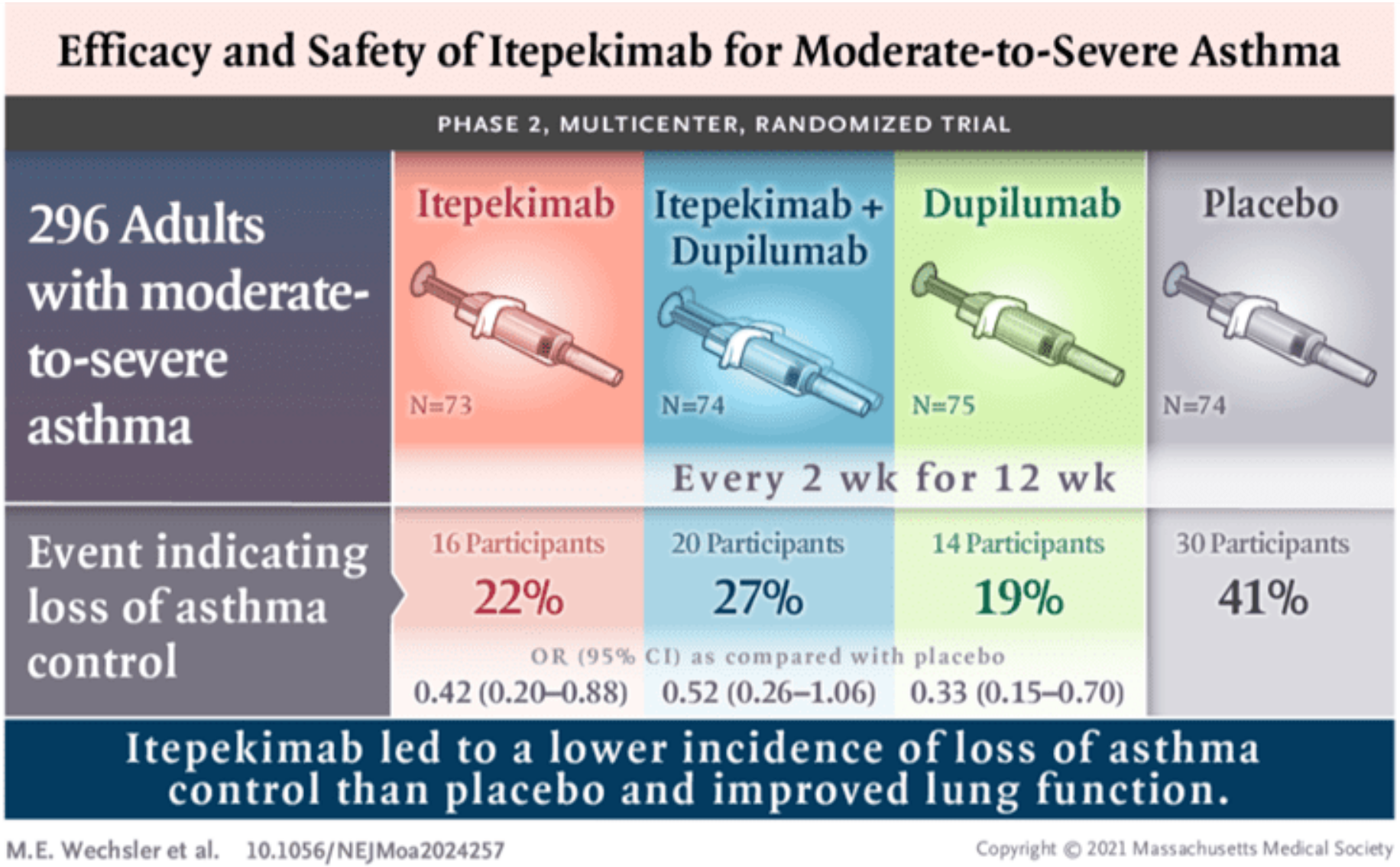
Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

Itepekimab

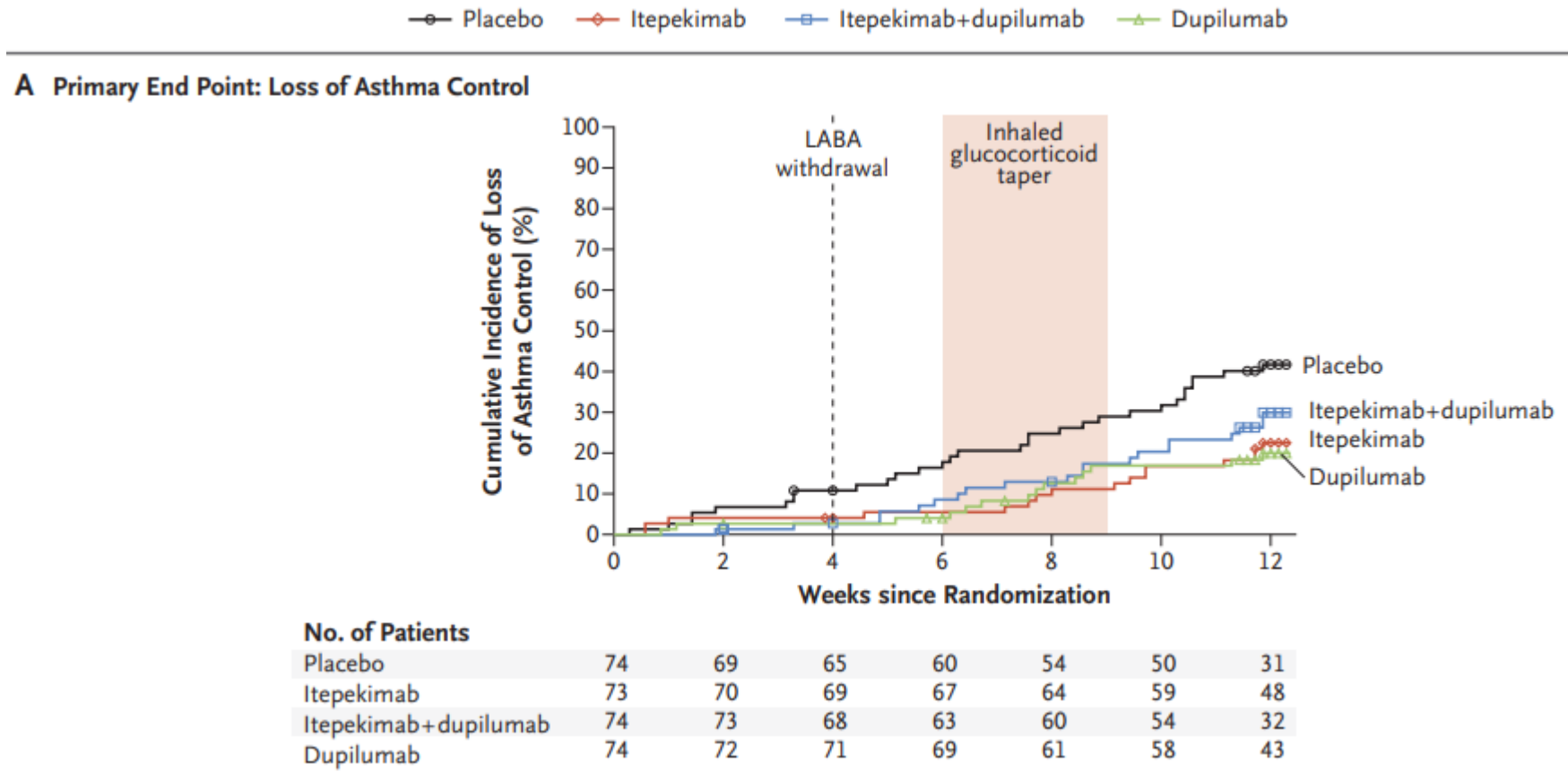
- new human IgG4P monoclonal antibody against the upstream alarmin **interleukin-33**
- phase 2 trial



Michael et al. N Engl J Med 2021;385:1656-68



Michael et al. N Engl J Med 2021;385:1656-68



Conclusion : Itepekimab monotherapy led to a lower incidence of events indicating loss of asthma control and to improved lung function,
findings that are consistent with a role for interleukin-33
in the pathogenesis of exacerbations and airflow limitation in asthma.

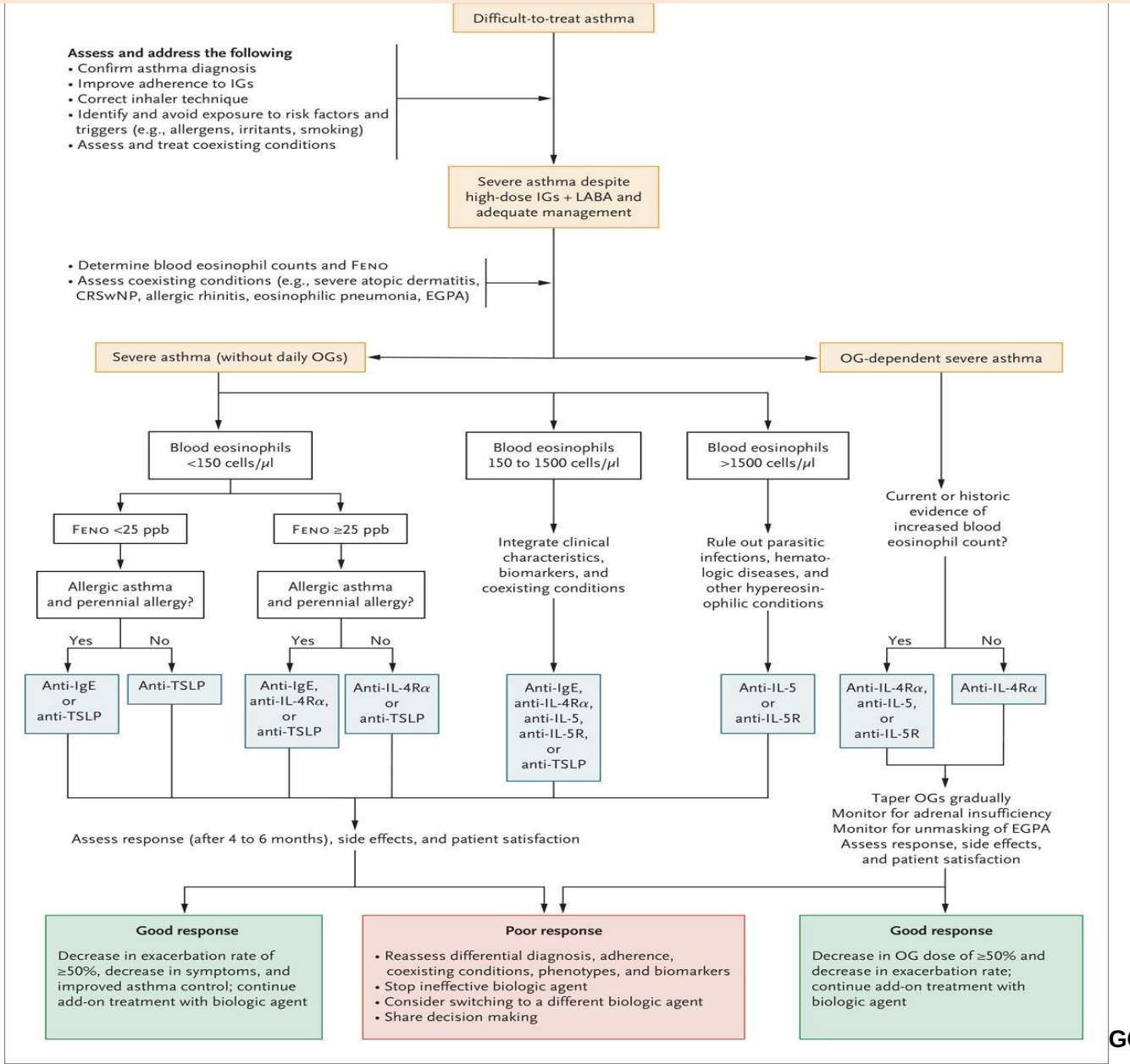
Michael et al. N Engl J Med 2021;385:1656-68

Biologic Agents Approved by the FDA for the Treatment of Severe Asthma.*

Biologic Agent (Therapeutic Target and Mechanism of Action)	Route of Administration and Dose†	Forms	Indication	Patient Yr of Age†	Efficacy	Safety Concerns
Benralizumab (interleukin-5Rα)	SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma	≥12	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs
Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, **inhibiting interleukin-4 and interleukin-13** signaling in hematopoietic cells)	•Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-to-severe atopic dermatitis, initial dose of 600 mg, followed by 300 mg every 2 wk •Children, ages 6–11 yr: SC; dose depends on body weight‡	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis	≥6	Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis
Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5)	•Adults and adolescents: SC; 100 mg every 4 wk •Children, ages 6–11 yr: SC; 40 mg every 4 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome	≥6	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare)
Omalizumab (IgE; antibody binds to Fc part of free IgE)	SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE	Prefilled syringe	Severe allergic asthma; other indication: chronic idiopathic urticaria	≥6	Reduced exacerbations, reduced symptoms, small effect on FEV_1; improved quality of life	Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients)
Reslizumab (interleukin-5; antibody binds to circulating interleukin-5)	IV; 3 mg/kg every 4 wk	IV infusion	Severe eosinophilic asthma	≥18	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; improved quality of life	Helminthic infections, abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.3% of patients)
Tezepelumab (TSLP)	SC; 210 mg every 4 wk	Prefilled syringe	Severe asthma	≥12	Reduced exacerbations, reduced symptoms, improved lung function; improved quality of life	Pharyngitis, arthralgia, back pain

Guy G. Brusselle, N Engl J Med 2022; 386:157-171

Algorithm for the Assessment and Treatment of Adults with Uncontrolled Severe Asthma.



GG Brusselle, GH Koppelman. N Engl J Med 2022;386:157-171.

Take Home Messages

- **Guidelines**
  - GINA treatment figure now shows two ‘tracks’
  - Severe asthma definition
  - Step for add-on LAMA have been expanded to include combination ICS-LABA-LAMA
  - Add-on azithromycin three days a week
- **Treatment – single inhaler triple therapy vs ICS/LABA vs ICS/LABA/LAMA**
  - FEV1 improvement
  - Reduction moderate to severe exacerbation
- **Treatment – Biologics**
  - Astegolimab in severe asthma
  - Tezepelumab in severe uncontrolled asthma
  - Itepekimab in moderate to severe asthma
  - Long-term safety and efficacy of dupilumab
- **COVID-19 & Asthma**

：severe asthma had increased mortality, lower mortality risk if asthma patients had used ICS