Respiratory Review of 2023: Asthma

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Global Initiative for Asthma (GINA)

What's new in GINA 2022?

GINA Global Strategy for Asthma Management and Prevention

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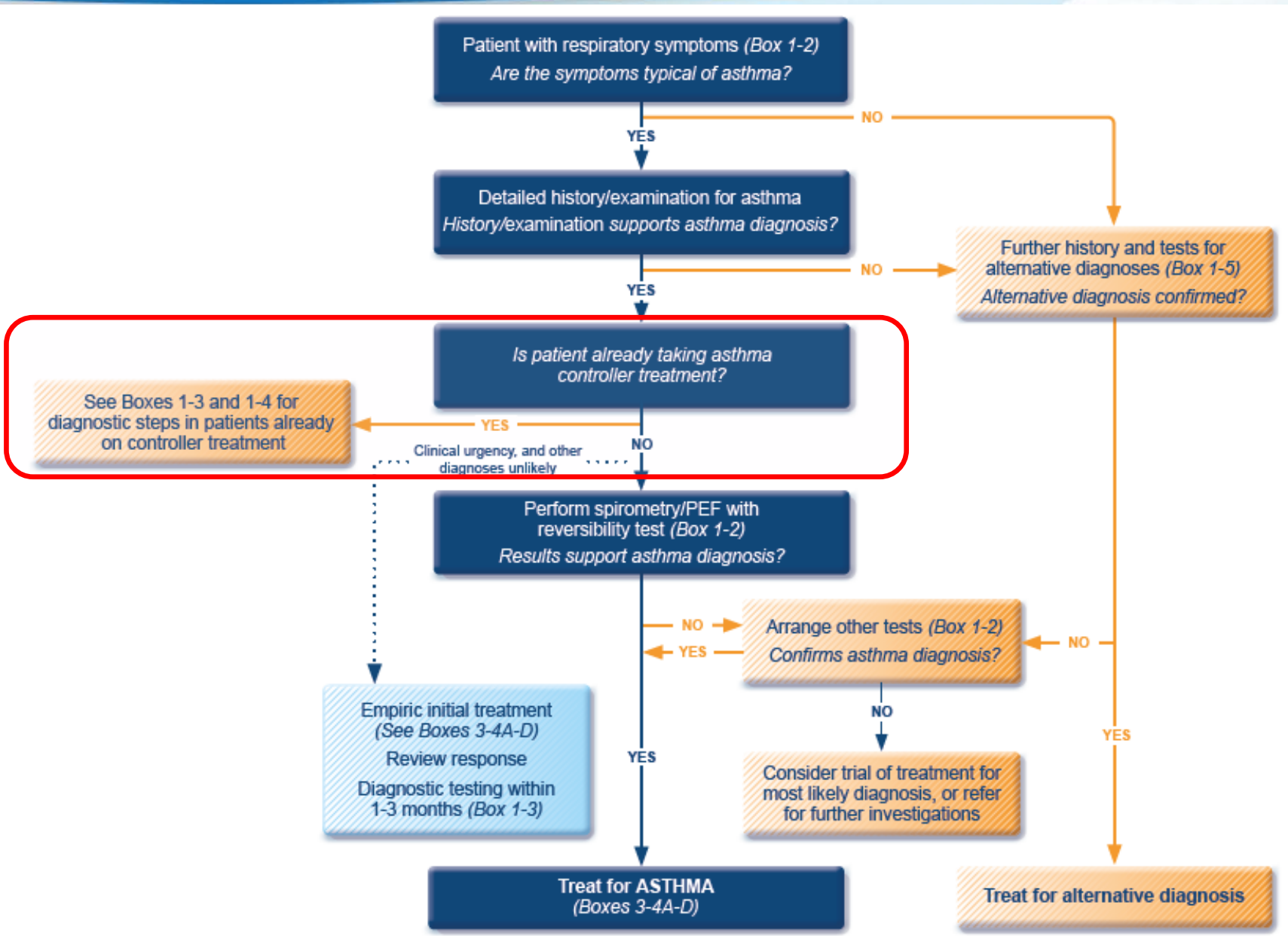
Diagnosis in GINA 2022

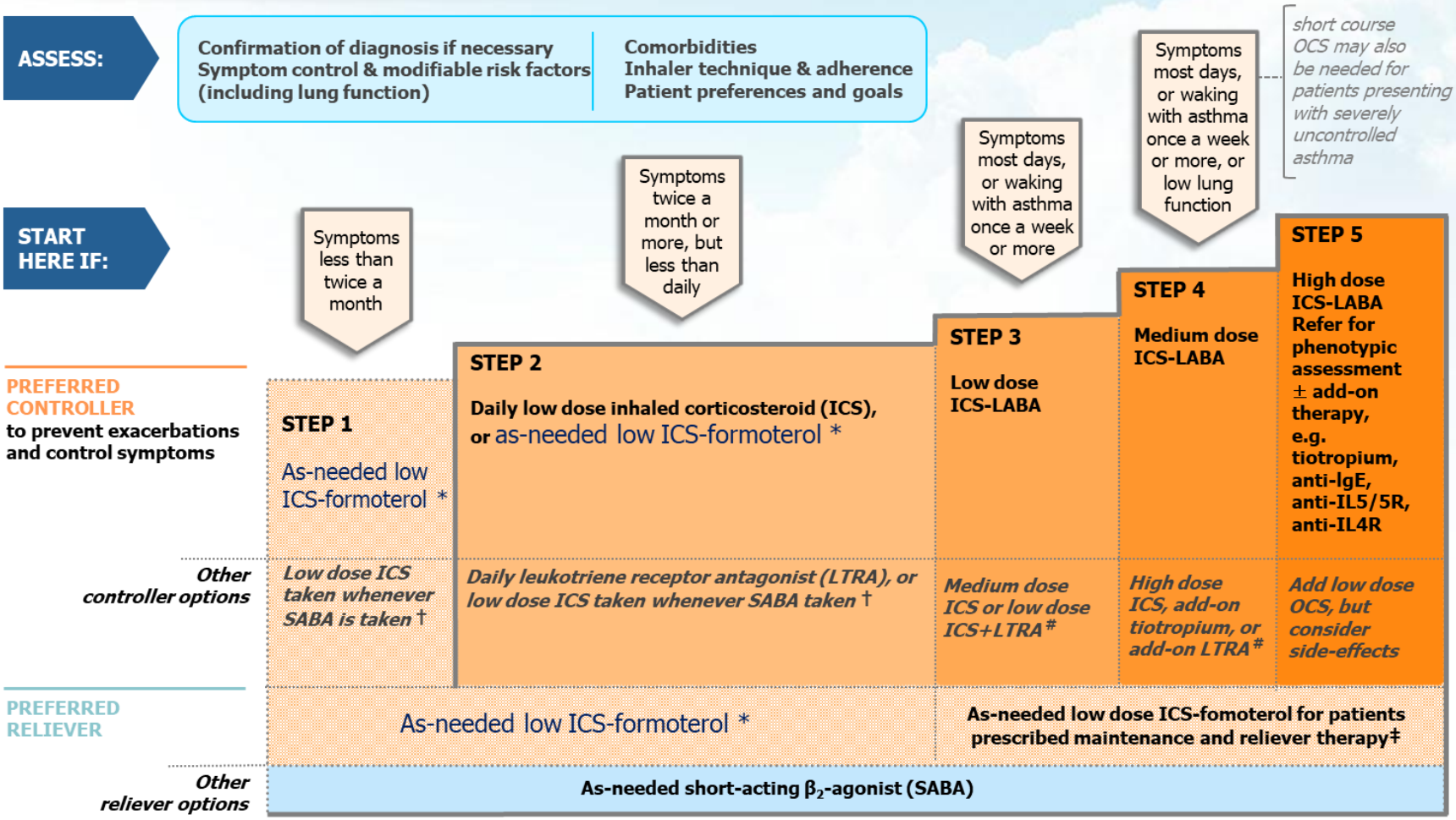


Diagnosis in GINA 2022

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2) and review controller treatment (Box 3-5).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 hrs for SABA, 24 hrs for twice-daily ICS-LABA, 36hrs for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-5). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1-5). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist. 'Variable airflow limitation' refers to expiratory airflow.

Treatment in GINA 2020



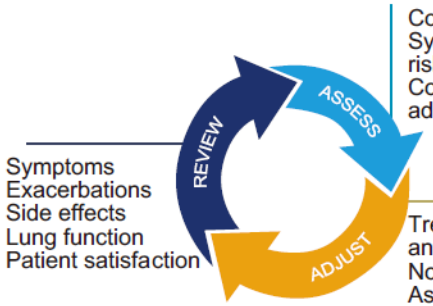
** Data only with budesonide-formoterol (bud-form)*
† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy
 # consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1>70% predicted

Treatment in GINA 2021-

Adults and adolescents 12+ years

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



Confirmation of diagnosis if necessary
Symptom control and modifiable risk factors
Comorbidities Inhaler technique and adherence Patient preferences and goals

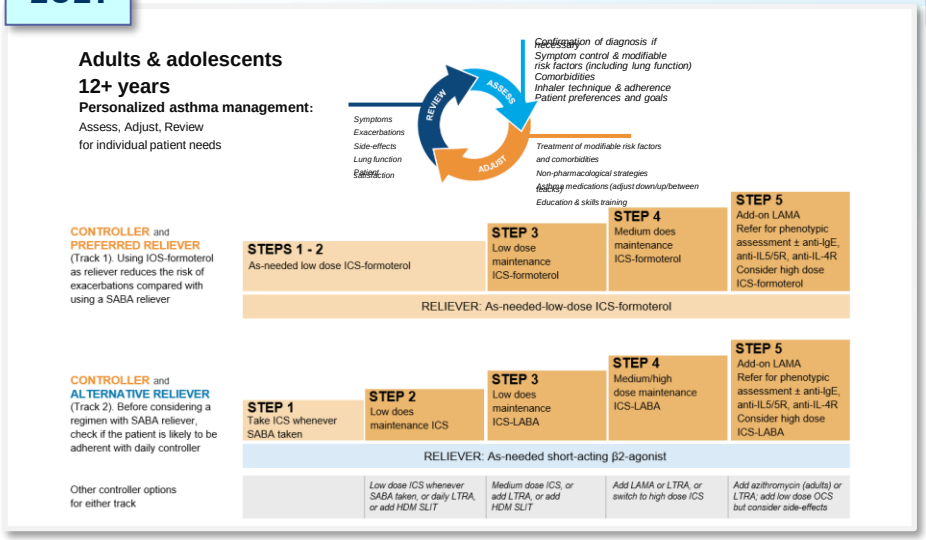
Symptoms
Exacerbations
Side effects
Lung function
Patient satisfaction

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

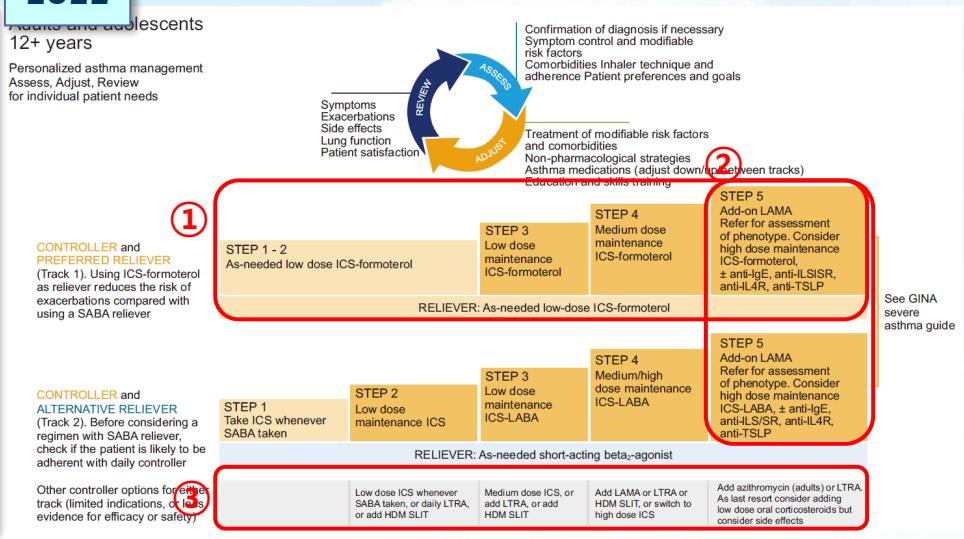
CONTROLLER and PREFERRED RELIEVER (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever	STEP 1 - 2 As-needed low dose ICS-formoterol	STEP 3 Low dose maintenance ICS-formoterol	STEP 4 Medium dose maintenance ICS-formoterol	STEP 5 Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-ILSISR, anti-IL4R, anti-TSLP	See GINA severe asthma guide
	RELIEVER: As-needed low-dose ICS-formoterol				
CONTROLLER and ALTERNATIVE RELIEVER (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller	STEP 1 Take ICS whenever SABA taken	STEP 2 Low dose maintenance ICS	STEP 3 Low dose maintenance ICS-LABA	STEP 4 Medium/high dose maintenance ICS-LABA	STEP 5 Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-ILS/SR, anti-IL4R, anti-TSLP	
	RELIEVER: As-needed short-acting beta$_2$-agonist				
Other controller options for either track (limited indications, or less evidence for efficacy or safety)		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. As last resort consider adding low dose oral corticosteroids but consider side effects	

Treatment in GINA 2022

2021



2022

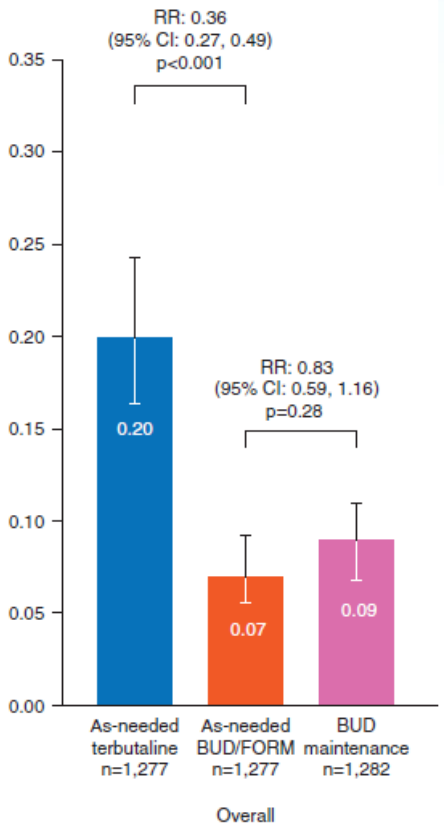


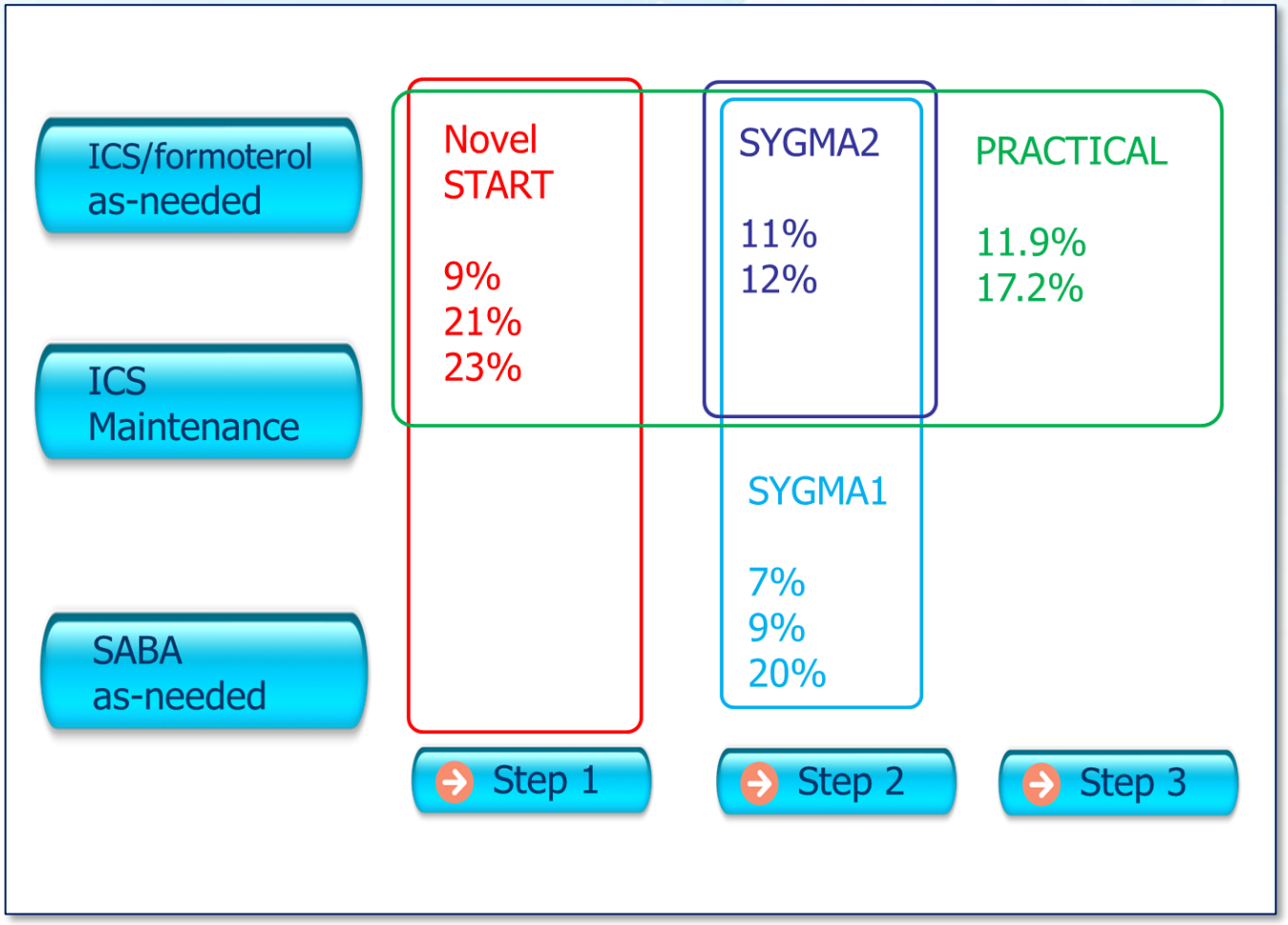
The rationale for two treatment tracks has been reinforced

- Track 1, with as-needed ICS-formoterol as reliever across treatment step, is preferred based on evidence for lower risk of exacerbation and similar or better symptom control compared with using SABA as reliever.
- Include anti-thymic stromal lymphopoietin (anti-TSLP; Tezepelumab) as a new biologic therapy for severe asthma in Step 5
- The 'other controller options' have been clarified as those that either have specific indications or have less evidence for safety and/or efficacy than the treatments in Track 1 or Track 2

Severe Exacerbation Rate

SYGMA 1





Bateman ED, et al. Ann Am Thorac Soc 2021;18:2007-17

As-needed Low Dose ICS-Formoterol in Mild Asthma

Compared with as-needed SABA

- The risk of severe exacerbations was reduced by 60–64% (SYGMA 1, Novel START)

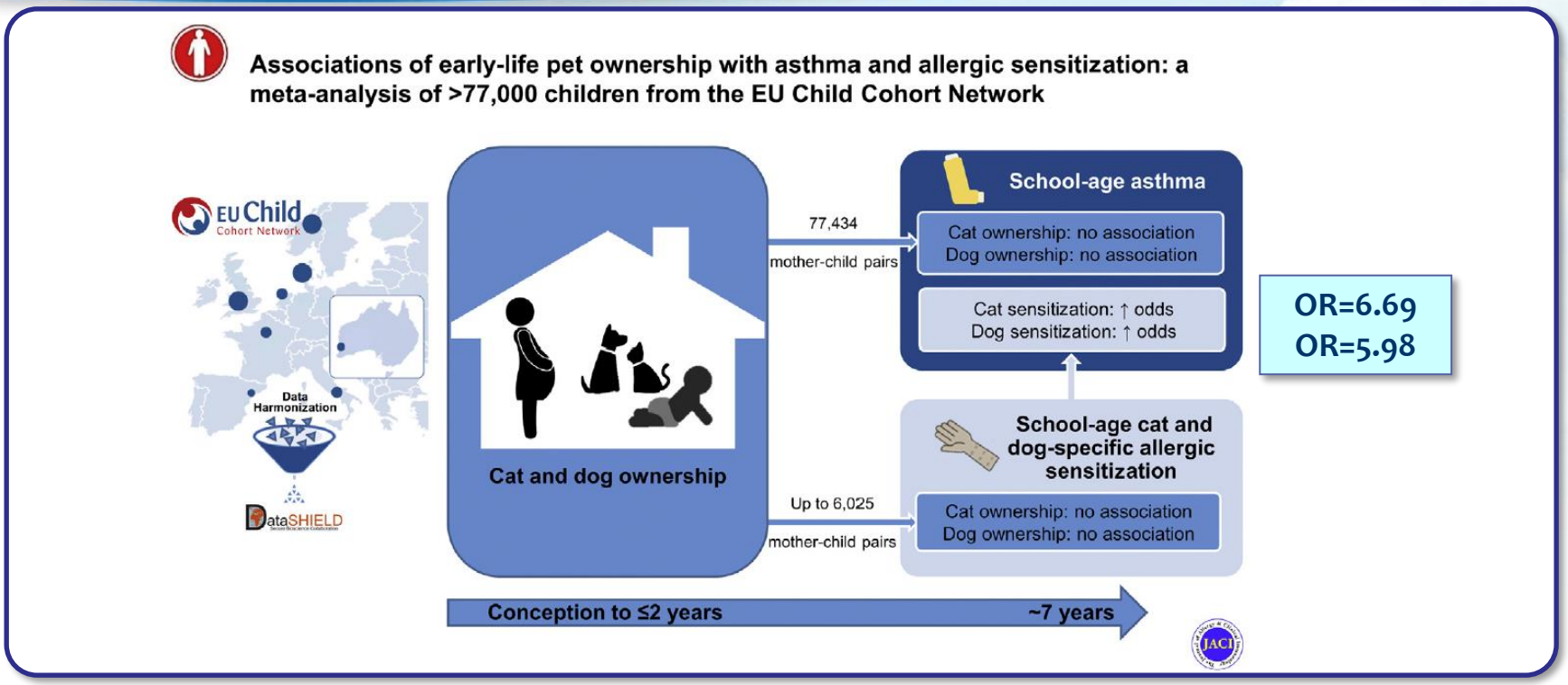
Compared with maintenance low dose ICS

- The risk of severe exacerbations was similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- Small differences in other asthma outcomes, favoring maintenance ICS, but all were less than the minimal clinically important difference
  - ACQ-5 mean difference ~ 0.15 (MCID 0.5)
  - FEV1 mean difference ~30-50 mL
  - FeNO mean difference ~10ppb (Novel START, PRACTICAL)
  - No evidence of progressive worsening over 12 months
- A Cochrane review (Crossingham I, et al. 2021)
  - moderate to high certainty evidence that as needed ICS-formoterol was clinically effective in mild asthma, significantly reducing important clinical outcomes including need for OCS, severe exacerbation rates, and ER visits or admissions compared with daily ICS (Evidence A)

GINA 2022

1. Risk Factors and Phenotype
2. Diagnosis
3. Inhaled Therapies
4. Biologics
5. COVID-19 and Asthma

Risk Factors: Pet Ownership



- 77,434 mother-child dyads from 9 birth cohorts in the EU Child Cohort Network
- Cat or dog ownership during pregnancy or early childhood

- Early-life cat or dog ownership in themselves are unlikely to increase the risk of school-age asthma.

Pinot de Moira A, et al. J Allergy Clin Immunol 2022;105:82-92

Risk Factors: Respiratory Tract Infections

Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150 000 European children

Evelien R. van Meel[1,2], Sara M. Mensink-Bout[1,2], Herman T. den Dekker[1,2,3], Tarunveer S. Ahluwalia[4,5], Isabella Annesi-Maesano[6], Syed Hasan Arshad[7,8,9], Nour Baïz[6], Henrique Barros[10,11], Andrea von Berg[12], Hans Bisgaard[4], Klaus Bønnelykke[4], Christian J. Carlsson[4], Maribel Casas[13,14,15], Leda Chatzi[16], Cecile Chevrier[17], Geertje Dalmeijer[18], Carol Dezateux[19], Karel Duchen[20], Merete Eggesbø[21], Cornelis van der Ent[22], Maria Fantini[23], Claudia Flexeder[24], Urs Frey[25], Fransesco Forastiere[26], Ulrike Gehring[27], Davide Gori[23], Raquel Granell[28], Lucy J. Griffiths[29], Hazel Inskip[9,30], Joanna Jerzynska[31], Anne M. Karvonen[32], Thomas Keil[33,34,35], Cecily Kelleher[36], Manolis Kogevinas[13,14,37,38], Gudrun Koppen[39], Claudia E. Kuehni[40,41], Nathalie Lambrechts[39], Susanne Lau[42], Irina Lehmann[43], Johnny Ludvigsson[20], Maria Christine Magnus[28,44], Erik Mélen[45], John Mehegan[36], Monique Mommers[46], Anne-Marie Nybo Andersen[47], Wenche Nystad[48], Eva S.L. Pedersen[40], Juha Pekkanen[32,49], Ville Peltola[50], Katharine C. Pike[51], Angela Pinot de Moira[49], Costanza Pizzi[52], Kinga Polanska[31], Maja Popovic[52], Daniela Porta[26], Graham Roberts[7,8,9], Ana Cristina Santos[10], Erica S. Schultz[45], Marie Standl[24,53], Jordi Sunyer[13,14,15,38], Carel Thijs[46], Laura Toivonen[50], Eleonora Uphoff[54], Jakob Usemann[25], Marina Vafeidi[55], John Wright[54], Johan C. de Jongste[2], Vincent W.V. Jaddoe[1,3,56] and Liesbeth Duijts[2,57]

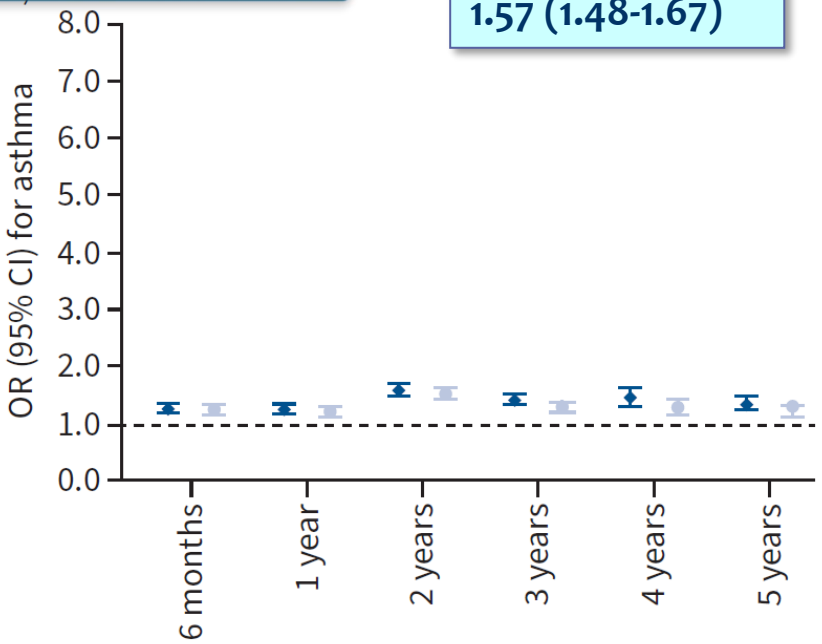
- 150,090 children from 38 cohorts in the EU Child Cohort Network
- To examine if children with early-life respiratory track infections (RTI) have increased risks of asthma at school age

van Meel ER, et al. Eur Respir J 2022;60:2102395

Respiratory Tract Infections and Asthma

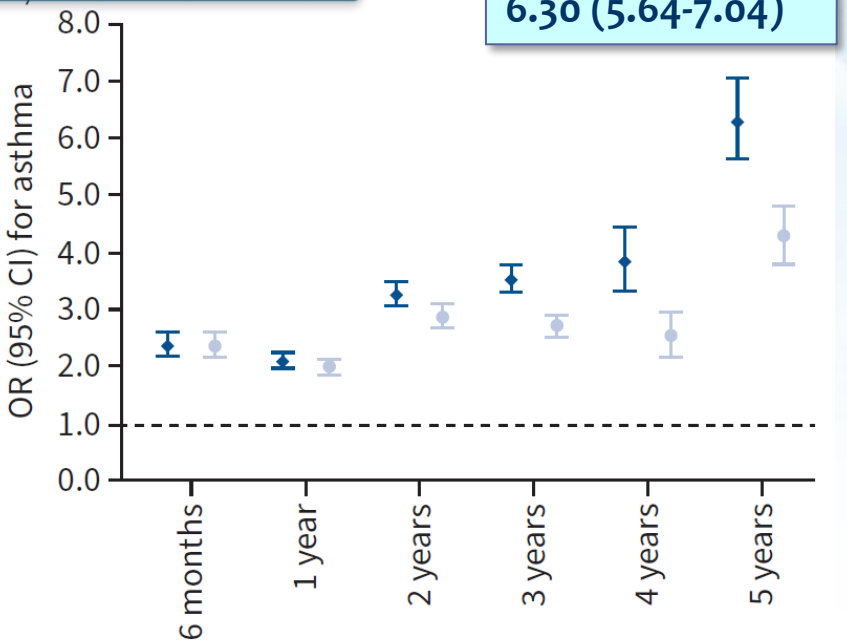
Upper RTI

OR :
1.25 (1.18-1.32) to
1.57 (1.48-1.67)



Lower RTI

OR :
2.10 (1.98-2.22) to
6.30 (5.64-7.04)



- Early-life respiratory tract infections affect development of asthma in later life, with the strongest effects for lower respiratory tract infections.

van Meel ER, et al. Eur Respir J 2022;60:2102395

Patients Characteristics by Age of Onset

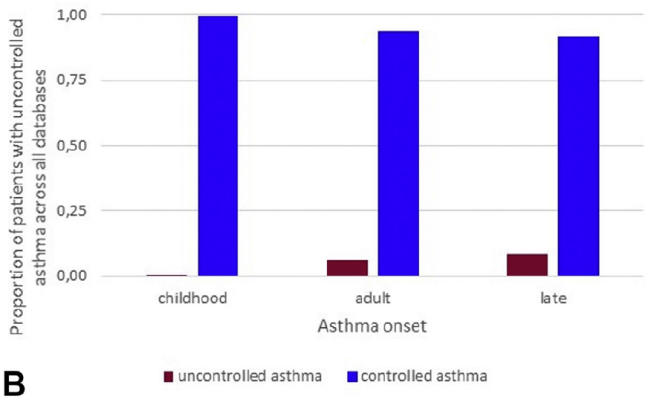
Characterization of Asthma by Age of Onset: A Multi-Database Cohort Study

Esmé J. Baan, MD[a,*], Emmely W. de Roos, MD[b,c,*], Marjolein Engelkes, MD, PhD[a], Maria de Ridder, PhD[a], Lars Pedersen, PhD[d], Klara Berencsi, MD, PhD[d,e], Dani Prieto-Alhambra, MD, PhD[a,f,g], Francesco Lapi, PhD[h], Melissa K. Van Dyke, PhD[i], Peter Rijnbeek, PhD[a], Guy G. Brusselle, MD, PhD[b,c,j], and Katia M.C. Verhamme, MD, PhD[a,k] *Rotterdam, The Netherlands; Ghent, Belgium; Aarhus, Denmark; Oxford, United Kingdom; Barcelona, Spain; Florence, Italy; Collegeville, Pa*

- 586,436 asthma patients from 5 European electronic databases

Category based on onset age

- Childhood-onset (age at onset < 18 y) : 81,691
- Adult-onset (age at onset 18~40 y): 218,184
- Late-onset (age at onset ≥ 40 y): 286,561



Baan EJ, et al. J Allergy Clin Immunol Pract 2022;10:1825-34

Patients Characteristics by Age of Onset

TABLE II. OR of having various characteristics, meta-analysis result of crude and adjusted models

	Adult- vs childhood-onset							
	Crude model				Adjusted model*			
Variables	OR	95%	CI	*P* value	OR	95%	CI	*P* value
Uncontrolled asthma	15.80	9.48	26.31	<.0001	**43.05**	**20.64**	**89.81**	**<.0001**
Atopic disorder	0.82	0.74	0.91	.0001	**0.81**	**0.69**	**0.95**	**.0084**
Chronic rhinosinusitis	1.08	0.68	1.74	.7347	**0.56**	**0.33**	**0.95**	**.0299**
Nasal polyposis	2.41	2.15	2.70	<.0001	1.04	0.79	1.37	.7863
Overweight/obesity	2.37	1.96	2.86	<.0001	**1.38**	**1.08**	**1.76**	**.0090**
Diabetes mellitus	3.32	3.01	3.66	<.0001	0.90	0.80	1.02	.0944
GERD	2.73	2.24	3.33	<.0001	1.30	0.97	1.74	.0771
Smoking: current	1.45	1.15	1.82	.0016	**1.51**	**1.21**	**1.89**	**.0003**
Smoking: past	2.54	1.84	3.49	<.0001	**1.73**	**1.34**	**2.23**	**<.0001**
	Late- vs adult-onset							
	Crude model				Adjusted model*			
	OR	95%	CI	*P* value	OR	95%	CI	*P* value
Uncontrolled asthma	1.68	1.24	2.27	.0007	**2.77**	**1.69**	**4.53**	**.0001**
Atopic disorder	0.53	0.49	0.59	<.0001	0.92	0.72	1.17	.4832
Chronic rhinosinusitis	1.37	1.22	1.53	<.0001	1.13	0.87	1.47	.3486
Nasal polyposis	2.13	1.72	2.64	<.0001	**1.76**	**1.19**	**2.61**	**.0047**
Overweight/obesity	2.17	1.62	2.91	<.0001	**1.29**	**1.20**	**1.38**	**<.0001**
Diabetes mellitus	7.84	4.98	12.36	<.0001	**2.28**	**1.82**	**2.87**	**<.0001**
GERD	2.34	2.14	2.57	<.0001	**1.42**	**1.20**	**1.69**	**.0001**
Smoking: current	0.49	0.36	0.67	<.0001	**1.51**	**1.16**	**1.97**	**.0024**
Smoking: past	1.55	1.13	2.11	.0061	**1.59**	**1.12**	**2.26**	**.0094**

Baan EJ, et al. J Allergy Clin Immunol Pract 2022;10:1825-34

Persistent Airflow Limitation (PAL) Phenotype

Predictors and associations of the persistent airflow limitation phenotype in asthma: a post-hoc analysis of the ATLANTIS study

Tessa M Kole, Elise Vanden Berghe, Monica Kraft, Judith M Vonk, Martijn C Nawijn, Salman Siddiqui, Kai Sun, Leonardo M Fabbri, Klaus F Rabe, Kian Fan Chung, Gabriele Nicolini, Alberto Papi, Chris Brightling, Dave Singh, Thys van der Molen, Sven-Erik Dahlén, Alvar Agusti, Rosa Faner, Jadwiga A Wedzicha, Gavin C Donaldson, Ian M Adcock, Lies Lahousse, Huib A M Kerstjens, Maarten van den Berge, on behalf of ATLANTIS, U-BIOPRED, and CADSET investigators

- Some patients with long-standing asthma develop airflow limitation that is persistent or incompletely reversible. This is thought to be due to airway wall remodeling. –GINA 2022
- PAL is defined as a post-bronchodilator FEV1/FVC of less than the lower limit of normal at recruitment
- 760 patients in the ATLANTIS study had post-bronchodilator FEV1/FVC data
- 248 (33%) had PAL

Kole TM, et al. Lancet Respir Med 2023;11:55-64

	Asthma with PAL (n=248)	Asthma without PAL (n=512)	p value
Mean post-bronchodilator FEV_1/FVC ratio (SD)	0·62 (0·08)	0·79 (0·07)	..
Mean age, years (SD)	46·15 (12·49)	43·48 (13·12)	0·0078
Age at diagnosis, years			
n	247	509	..
Median (IQR)	17·80 (5·62 to 38·77)	27·00 (12·00 to 41·54)	<0·0001
Duration of asthma, years			
n	248	511	..
Median (IQR)	24·03 (10·29 to 35·75)	12·13 (4·43 to 24·76)	<0·0001
Sex			
Men	126 (51%)	193 (38%)	0·00079
Women	122 (49%)	319 (62%)	..
BMI, kg/m²	..	..	0·122
≤18	1 (<1%)	7 (1%)	..
>18 to ≤25	89 (36%)	214 (42%)	..
>25 to ≤30	100 (40%)	165 (32%)	..
>30 to ≤40	51 (21%)	103 (20%)	..
>40	7 (3%)	23 (4%)	..
Positive specific IgE blood screening (Phadiatop)	163/195 (84%)	283/360 (79%)	0·194
Smoking status	..	..	0·206
Current smoker	12 (5%)	15 (3%)	..
Former smoker	56 (23%)	99 (19%)	..
Never-smoker	180 (73%)	398 (78%)	..

Kole TM, et al. Lancet Respir Med 2023;11:55-64

Pack-years in current and former smokers			
n	68	114	..
Median (IQR)	4·55 (2·00 to 8·00)	4·00 (2·00 to 7·15)	0·532
GINA step	..	..	<0·0001
1	21 (8%)	112 (22%)	..
2	24 (10%)	59 (12%)	..
3	62 (25%)	143 (28%)	..
4	111 (45%)	183 (36%)	..
5	30 (12%)	15 (3%)	..
LAMA use	17 (7%)	11 (2%)	0·0025
Use of biologics	22 (9%)	9 (2%)	<0·0001
Systemic corticosteroids use	13 (5%)	9 (2%)	0·014
Daily ICS dose (beclomethasone equivalent)*, µg			
n	212	374	..
Mean (SD)	897 (646)	768 (557)	0·012
Median ACQ6 score (IQR)	0·83 (0·33 to 1·66)	0·67 (0·17 to 1·50)	0·021
Blood eosinophil count, × 10^9 cells per L			
n	245	509	..
Median (IQR)	0·27 (0·17 to 0·40)	0·20 (0·12 to 0·34)	<0·0001
Blood neutrophil count, × 10^9 cells per L			
n	246	509	..
Median (IQR)	3·82 (3·11 to 4·90)	3·53 (2·90 to 4·54)	0·0055

- 16% of step 1
- 29% of step 2

Kole TM, et al. Lancet Respir Med 2023;11:55-64

Asthma with PAL

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
PAL	2·04 (1·46–2·86)	<0·0001	1·73 (1·22–2·48)	0·0017
Age (per 5-year increment)	1·12 (1·05–1·20)	0·0012	1·08 (1·01–1·16)	0·036
Male sex	0·60 (0·41–0·85)	0·0048	0·57 (0·39–0·83)	0·0025
Former smoking	1·03 (0·68–1·55)	0·909	0·88 (0·57–1·54)	0·559
Current smoking	0·60 (0·19–1·87)	0·376	0·77 (0·24–2·46)	0·657
GINA step 4–5	3·18 (2·21–4·59)	<0·0001	2·43 (1·67–3·54)	<0·0001
Blood eosinophils	4·14 (2·59–6·63)	<0·0001	3·15 (1·89–5·25)	<0·0001
Blood monocytes	2·41 (1·25–4·63)	0·0087	1·83 (0·72–4·73)	0·212
Blood neutrophils	1·11 (1·02–1·22)	0·022	1·04 (0·93–1·16)	0·534

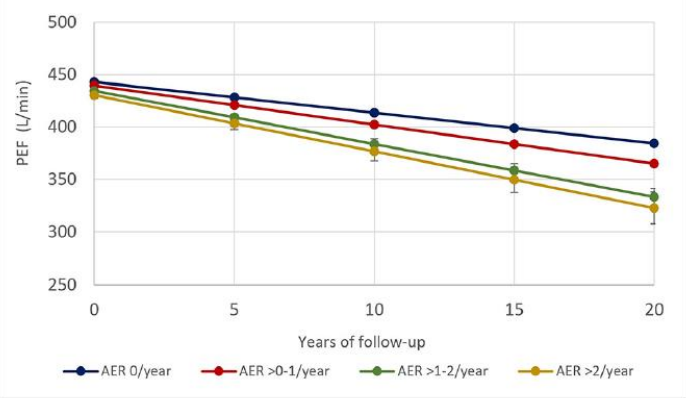
- PAL is not only present in severe disease, but also in a considerable proportion of patients with milder disease.
- PAL is associated with eosinophilic inflammation and a higher risk of exacerbations.

Kole TM, et al. Lancet Respir Med 2023;11:55-64

Exacerbation and Lung Function Decline

Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study

Seyi Soremekun ,[1] Liam G Heaney,[2] Derek Skinner,[3,4] Lakmini Bulathsinhala,[3,4] Victoria Carter,[3,4] Isha Chaudhry,[3,4] Naeimeh Hosseini ,[3,4] Neva Eleangovan,[3,4] Ruth Murray,[3,4] Trung N Tran,[5] Benjamin Emmanuel,[5] Esther Garcia Gil,[6] Andrew Menzies-Gow,[7] Matthew Peters,[8] Njira Lugogo,[9] Rupert Jones,[4,10] David B Price [4,11,12]

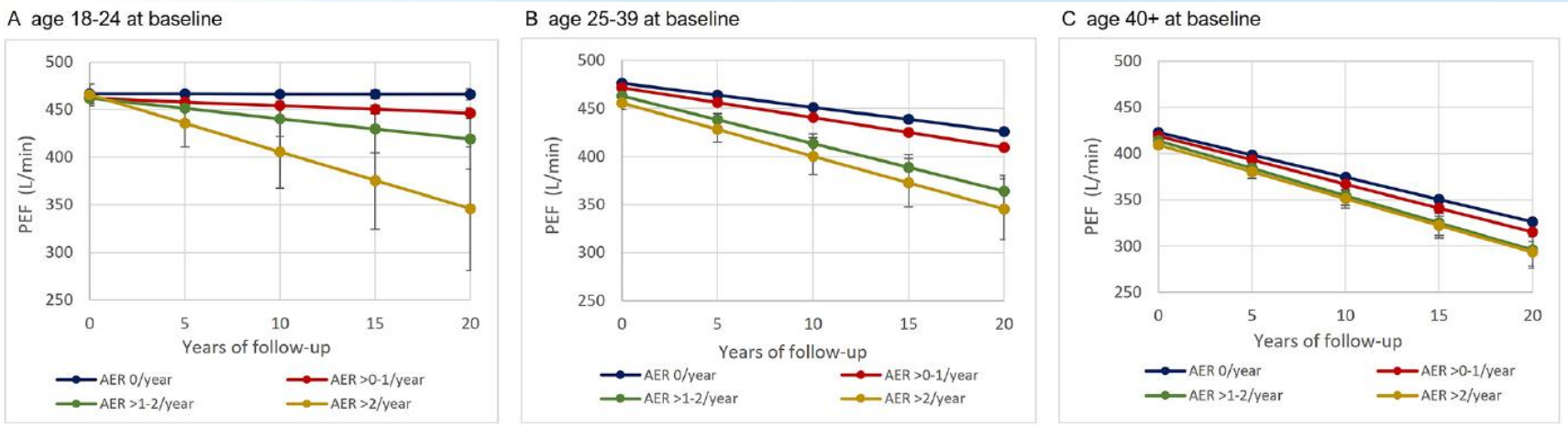


Annual exacerbation rate	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline between AER categories (95% CI; p)
0/yr	**-2.93** L/min/yr (-3.04, -2.82)	
>0-1/yr	**-3.74** L/ min/yr (-3.84, -3.64)	-0.81 L (-0.93, -0.70) p ≤0.001
>1-2/yr	**-5.05** L/ min/yr (-5.38, -4.73)	-2.13 L (-2.46, -1.80) p ≤0.001
>2/yr	**-5.38** L/ min/yr (-5.98, -4.78)	-2.46 L (-3.06, -1.85) p ≤0.001

- UK-side cohort study
- 109, 182 asthma patients with follow-up ranging from 5 to 50 years

For each additional exacerbation, an estimated additional -1.34 L/min PEF per year (95% CI -1.23 to -1.50) were lost.

Soremekun S, et al. Thorax 2022. Epub



AER	18 – 24 years old at baseline		25 – 39 years old at baseline		40+ years old at baseline	
	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline (95% CI; p)
0/yr	**-0.02** L/min/yr (-0.26, 0.22)	**comparator**	**-2.52** L/min/yr (-2.67, -2.36)	**comparator**	**-4.82** L/min/yr (-4.94, -4.7)	**comparator**
>0-1/yr	**-0.77** L/min/yr (-1.00, -0.54)	**-0.75** L/min/yr (-1.08, -0.41) p<0.001	**-3.11** L/min/yr (-3.24, -2.98)	**-0.59** L/min/yr (-0.79, -0.39) p<0.001	**-5.20** L/min/yr (-5.29, -5.11)	**-0.38** L/min/yr (-0.53, -0.23) p<0.001
>1-2/yr	**-2.15** L/min/yr (-3.43, -0.88)	**-2.13** L/min/yr (-3.43, -0.83) p = 0.001	**-4.93** L/min/yr (-5.57, -4.28)	**-2.41** L/min/yr (-3.07, -1.75) p<0.001	**-5.89** L/min/yr (-6.25, -5.53)	**-1.07** L/min/yr (-1.45, -0.69) p<0.001
>2/yr	**-5.98** L/min/yr (-8.64, -3.31)	**-5.95** L/min/yr (-8.63, -3.28) p<0.001	**-5.51** L/min/yr (-6.75, -4.27)	**-2.99** L/min/yr (-4.24, -1.74) p<0.001	**-5.82** L/min/yr (-6.5, -5.14)	**-1.00** L/min/yr (-1.69, -0.31) p = 0.005

- Asthma exacerbations are associated with faster LF decline.
- This was more prominent in younger patients
- Earlier intervention with appropriate management in younger patients with asthma could be of value to prevent excessive LF decline

Soremekun S, et al. Thorax 2022. Epub

1 Risk Factors and Phenotype

2 Diagnosis

3 Inhaled Therapies

4 Biologics

5 COVID-19 and Asthma

Diagnosis of Asthma

European Respiratory Society guidelines for the diagnosis of asthma in adults

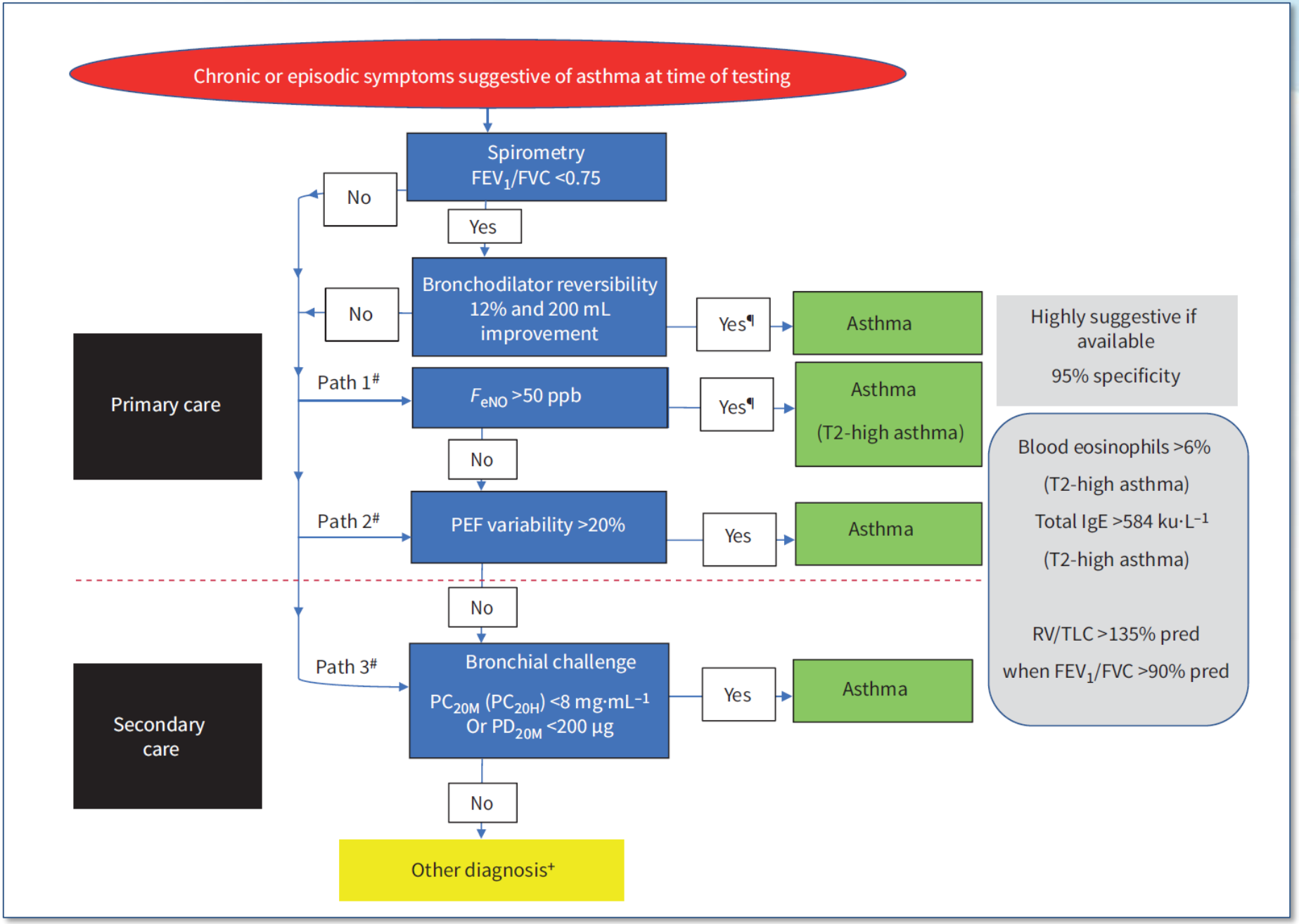
Renaud Louis[1,22], Imran Satia[2,23], Inigo Ojanguren[3,23], Florence Schleich[4,23], Matteo Bonini[5,23], Thomy Tonia[6], David Rigau[7], Anne ten Brinke[8], Roland Buhl[9], Stelios Loukides[10], Janwillem W. H. Kocks[11], Louis-Philippe Boulet[12], Arnaud Bourdin[13], Courtney Coleman[14], Karen Needham[14], Mike Thomas[15], Marco Idzko[16], Alberto Papi[17], Celeste Porsbjerg[18], Daniel Schuermans[19], Joan B. Soriano[20] and Omar S. Usmani[21,24]

- Eight PICO questions

FeNO

- A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity, while a cut-off of 50 ppb has a high specificity close to 90% and is supportive of a diagnosis of asthma
- A FeNO value <40 ppb does not rule out asthma; similarly, high FeNO levels themselves do not define asthma.
- FeNO values are markedly reduced by smoking, impaired airway calibre, treatment with ICS or anti-IL4/IL13-receptor-α antibody

Louis R, et al. Eur Respir J 2022;60:2101585



Louis R, et al. Eur Respir J 2022;60:2101585

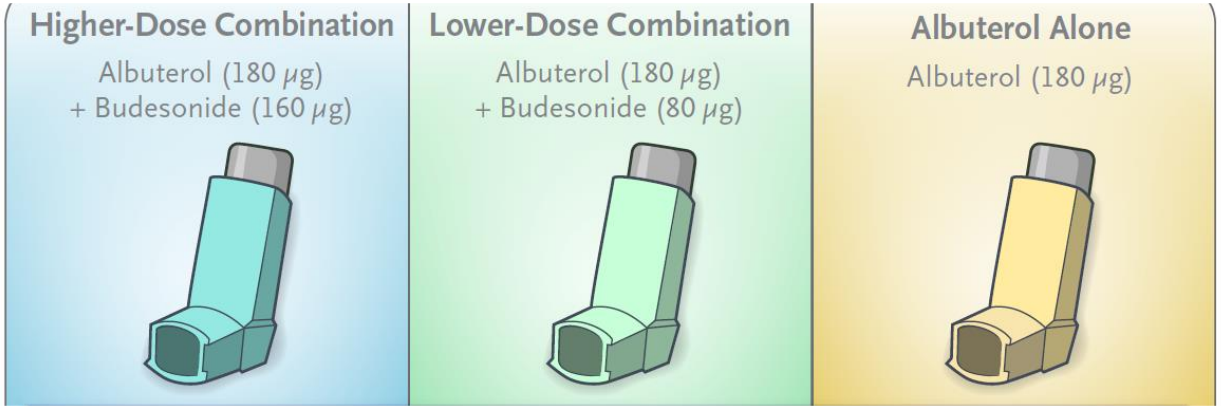
1. Risk Factors and Phenotype
2. Diagnosis
3. **Inhaled Therapies**
   - Albuterol-budesonide inhaler
   - Triple combination inhaler
4. Biologics
5. COVID-19 and Asthma

SABA-ICS as Rescue Inhaler

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

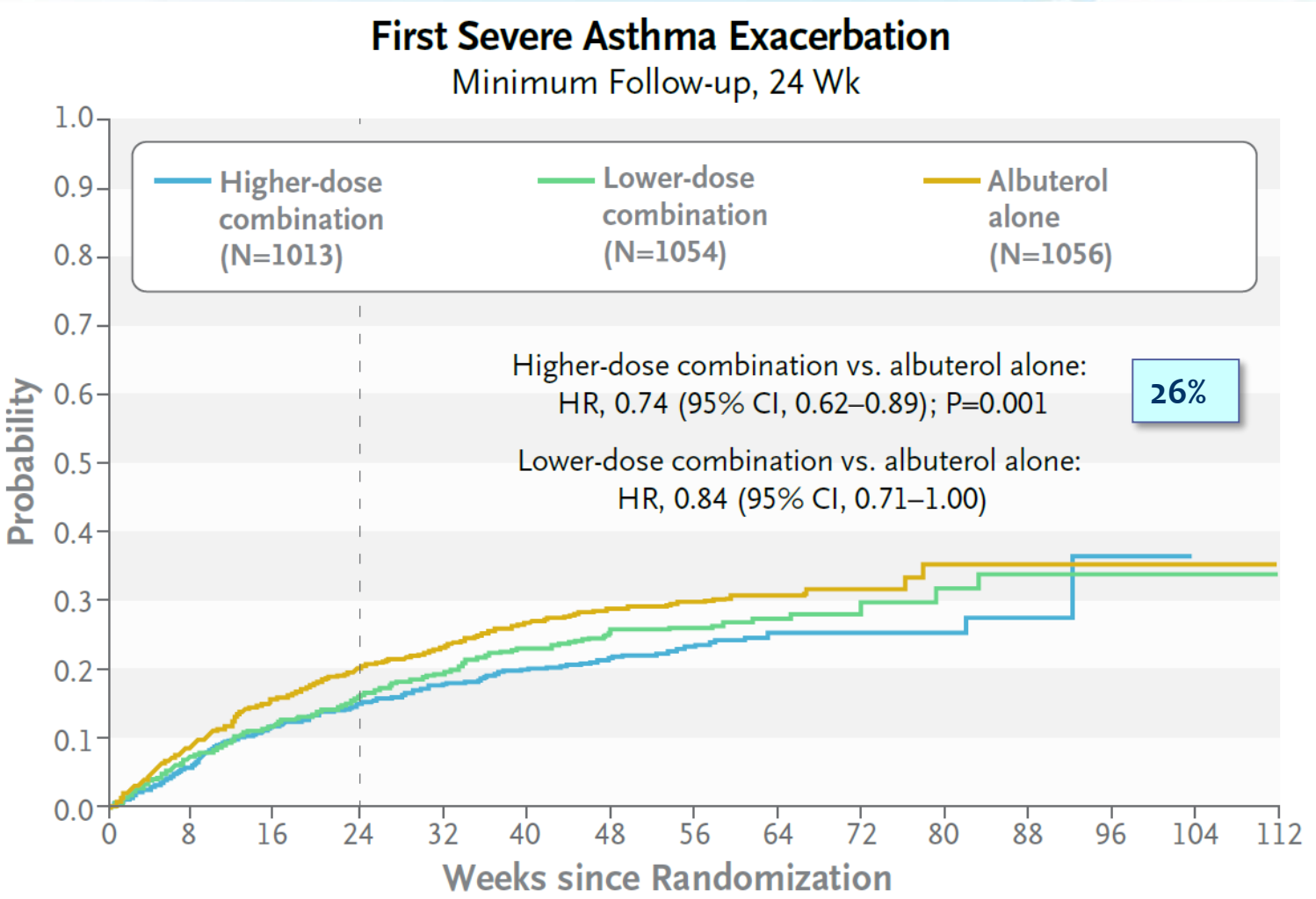
Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

- Multinational, phase 3, double-blind, RCT (MANDALA trial)
- The safety and efficacy of as-needed use of a fixed-dose combination of albuterol and budesonide in patients with moderate-to-severe asthma receiving ICS
- 3,132 patients from 295 clinical center



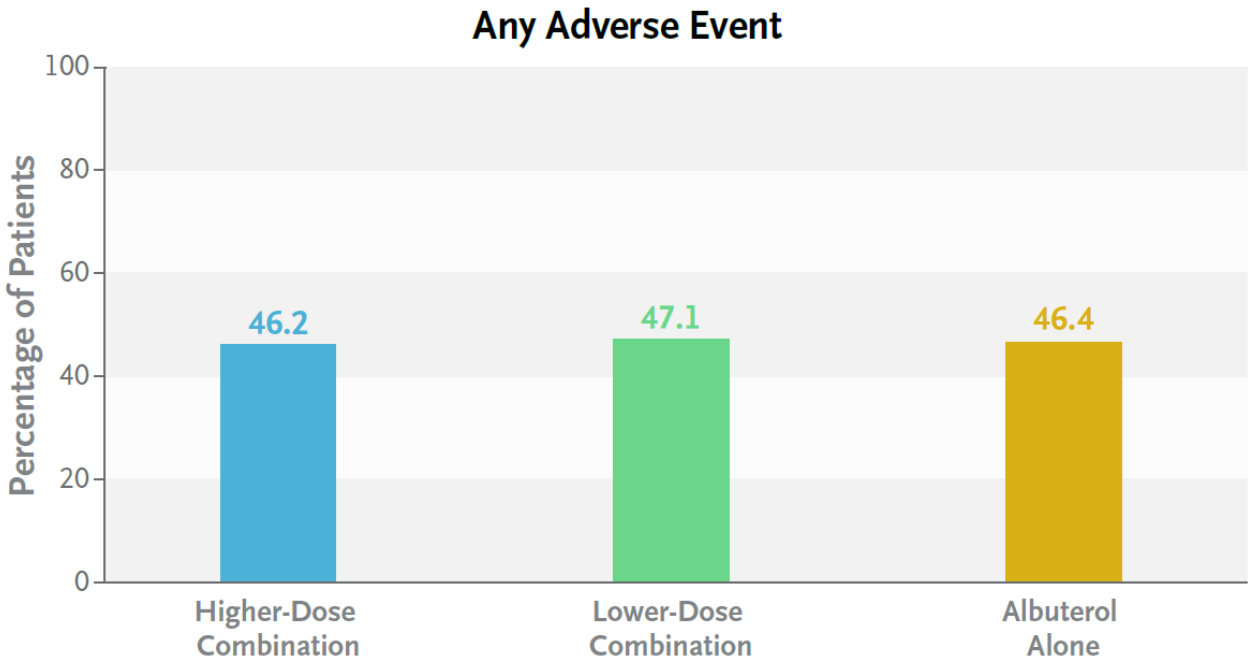
Papi A, et al. N Engl J Med 2022;386:2071-83

SABA-ICS as Rescue Inhaler



Papi A, et al. N Engl J Med 2022;386:2071-83

SABA-ICS as Rescue Inhaler



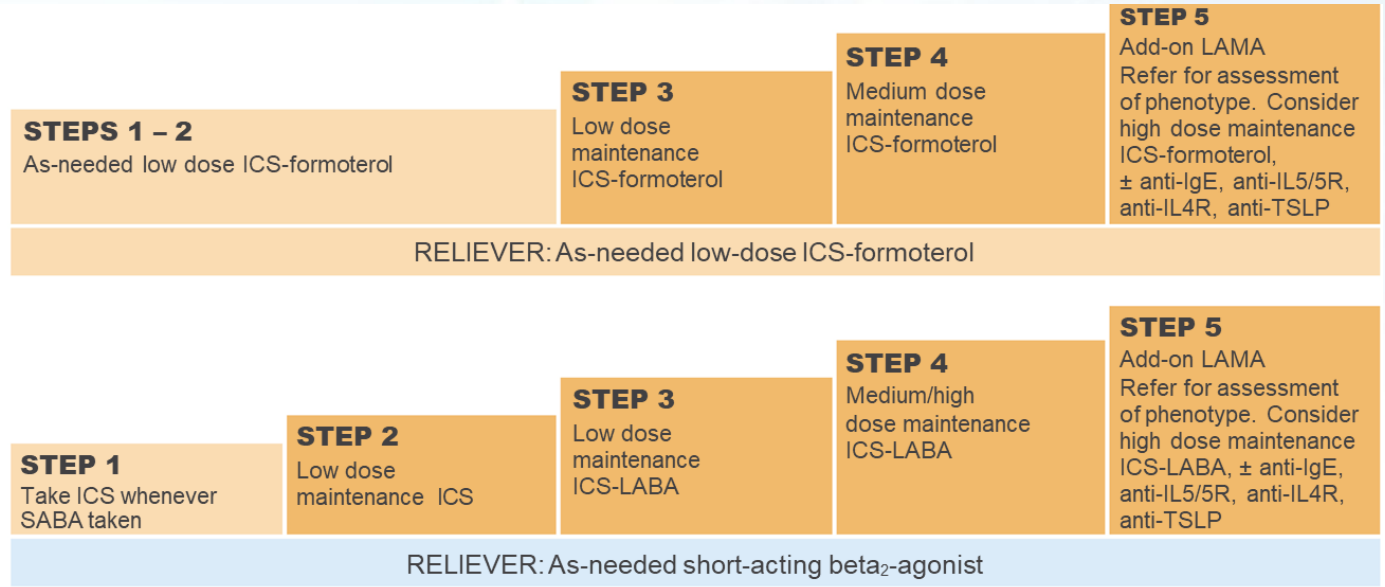
Limitations

- FeNO level was not measured, a limitation that precludes direct assessment of anti-inflammatory effects.
- Head-to-head studies of the same ICS combined with either formoterol or albuterol as rescue therapy will be needed

Papi A, et al. N Engl J Med 2022;386:2071-83

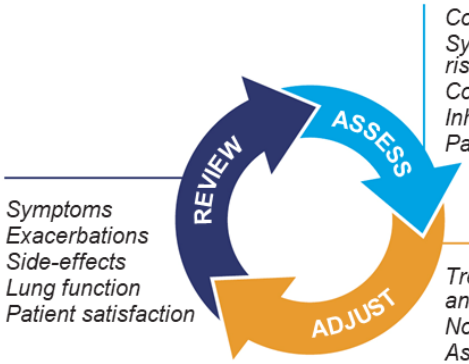
Another Reliever in Asthma

GINA 2022: Personalized Asthma Management



As-needed ICS-SABA

GINA 2022: Personalized Asthma Management



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

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

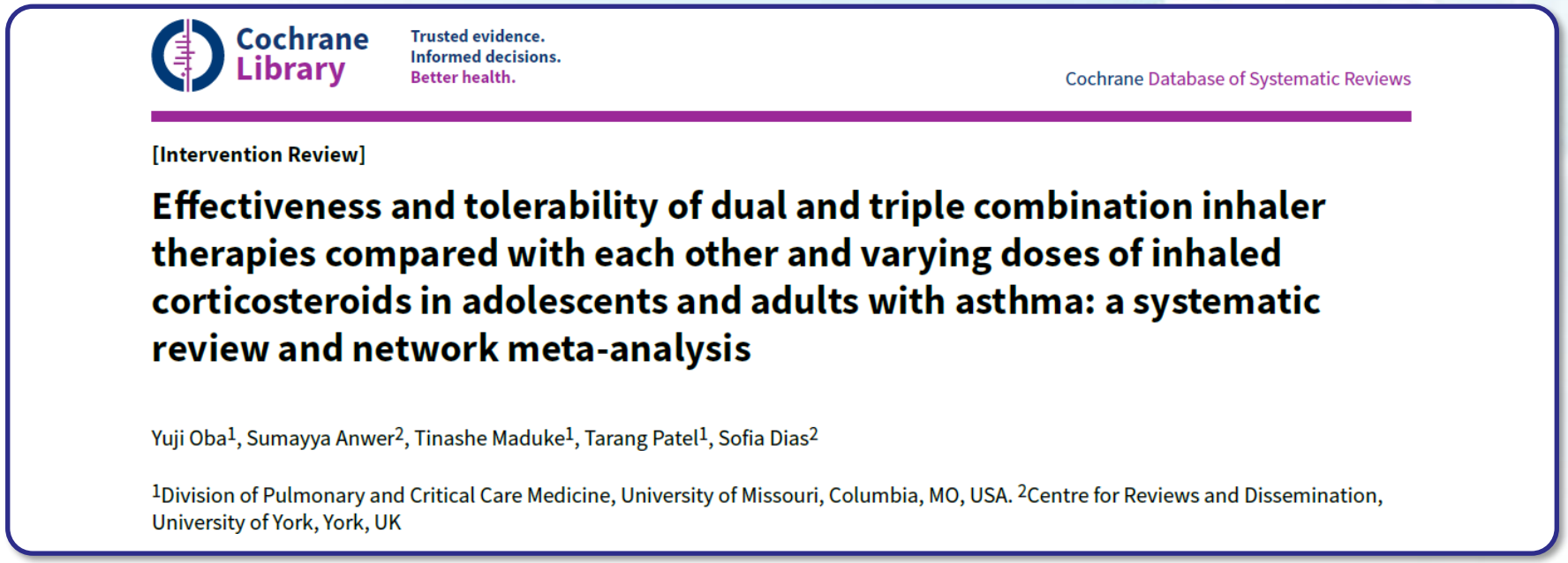
STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed 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 assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)	*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. As last resort consider adding low dose OCS but consider side-effects*

Triple Combination Inhaler



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[Intervention Review]

Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis

Yuji Oba[1], Sumayya Anwer[2], Tinashe Maduke[1], Tarang Patel[1], Sofia Dias[2]

[1]Division of Pulmonary and Critical Care Medicine, University of Missouri, Columbia, MO, USA. [2]Centre for Reviews and Dissemination, University of York, York, UK

- To assess the effectiveness and safety of dual (ICS/LABA) and triple therapies (ICS/LABA/LAMA) compared with each other and with varying doses of ICS
- 17,161 patients from 17 studies (median duration 26 weeks)

Oba Y, et al. Cochrane Database Syst Rev. 2022;12:CD013799

Moderate to Severe (Steroid-Requiring) Exacerbations

Total studies: 10 RCTs **Total Participants**: 12407	**Hazard ratio** (95% CrI)	**Anticipated absolute effect at the end of 1 year***(95% CrI)		**Certainty of the evidence**
		With intervention	**Difference compared to MD-ICS/LABA**	
HD-ICS/LABA (Direct evidence; 6 RCTs; 5452 participants)	**0.90** (0.77 to 1.04)	176 per 1000	20 per 1000 fewer (from 45 fewer to 8 more)	⊕⊕⊕⊕ **High**
MD-TRIPLE (Direct evidence; 3 RCTs; 3184 participants)	**0.84** (0.71 to 0.99)	165 per 1000	31 per 1000 fewer (from 2 fewer to 57 fewer)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]
HD-TRIPLE (Direct evidence; 2 RCTs; 2037 participants)	**0.69** (0.58 to 0.82)	135 per 1000	61 per 1000 fewer (from 35 fewer to 82 fewer)	⊕⊕⊕⊕ **High**
MD-ICS/LABA	Reference Comparator	196 per 1000[2]	Reference Comparator	Reference Comparator

Oba Y, et al. Cochrane Database Syst Rev. 2022;12:CD013799

Asthma-Related Hospitalizations

Total studies: 8 RCTs **Total Participants:** 9983	**Hazard ratio**** (95% CrI)	**Anticipated absolute effect at the end of 1 year***(95% CrI)		**Certainty of the evidence**	**Ranking****** (95% CrI)	**Interpretation of Findings**
		With intervention ***(With MD-ICS/LABA)***	**Difference**			
HD-ICS/LABA (Direct evidence; 7 RCTs; 7023 participants)	**1.43** (0.76 to 2.77)	15 per 1000	5 per 1000 more (from 2 fewer to 18 more)	⊕⊕⊕◯ **Moderate** Due to substantial heterogeneity[1]	**3.0** (1.0 to 4.0)	Probably little or no difference
MD-TRIPLE (Direct evidence; 2 RCTs; 1023 participants)	**1.73** (0.90 to 3.32)	18 per 1000	8 per 1000 more (from 1 fewer to 24 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**4.0** (1.0 to 4.0)	Suggest little or no difference
HD-TRIPLE (Direct evidence; 2 RCTs; 1024 participants)	**1.14** (0.54 to 2.41)	12 per 1000	2 per 1000 more (from 4 fewer to 15 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**2.0** (1.0 to 4.0)	Suggest little or no difference
MD-ICS/LABA	Reference Comparator	(10 per 1000)[3]	Reference Comparator	Reference Comparator	**1.0** (1.0 to 3.0)	Reference Comparator

Oba Y, et al. Cochrane Database Syst Rev. 2022;12:CD013799

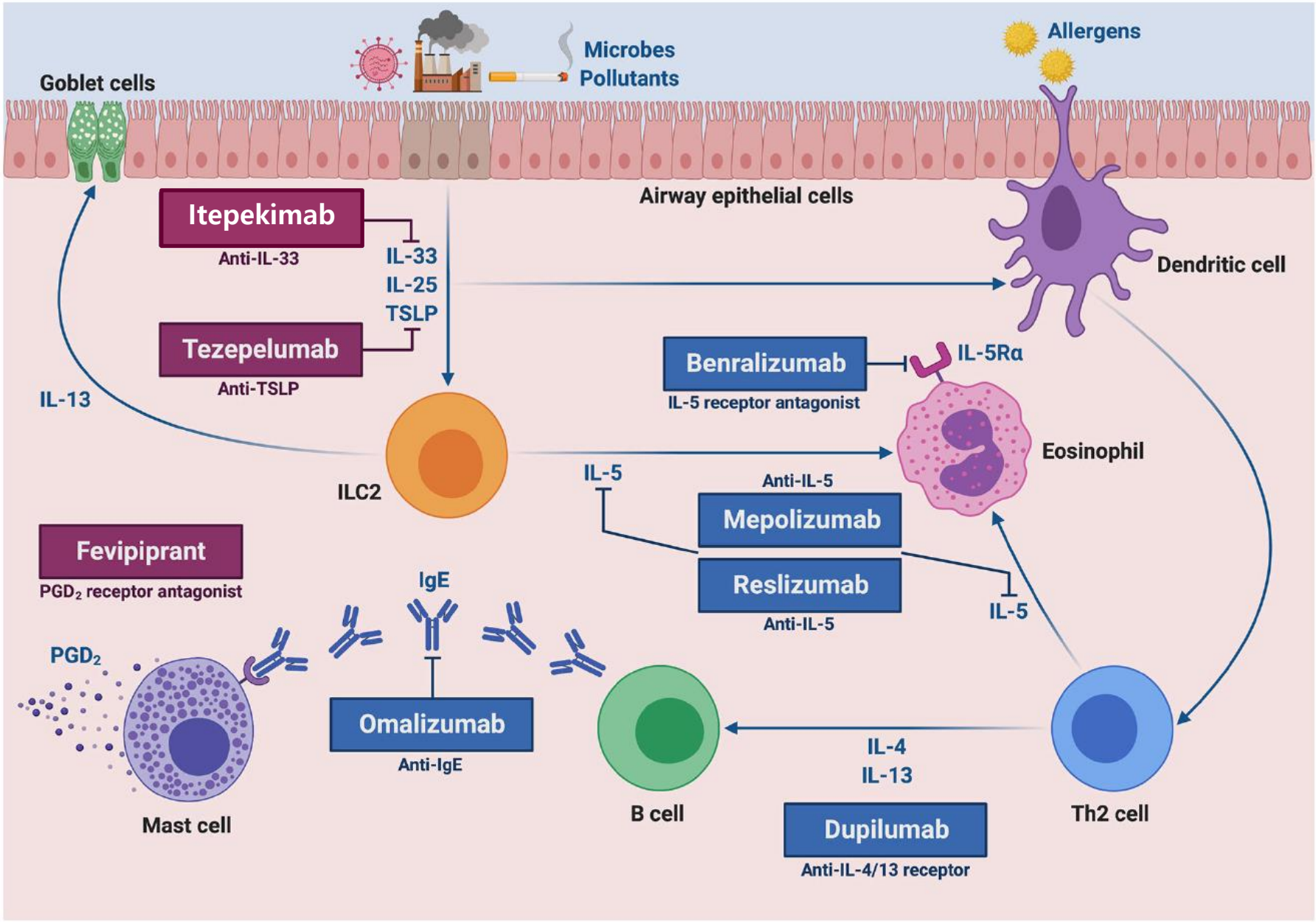
Changes in ACQ Scores at 12 Months

Total studies: 5 RCTs **Total Participants**: 5440	**Relative effect** (95% CrI)	**Anticipated absolute effect****(95% CrI)**		**Certainty of the evidence**	**Ranking***** (95% CrI)	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA***[1]			
HD-ICS/LABA (Direct evidence; 3 RCTs; 3152 participants)	**0.00** (-0.06 to 0.06)	**1.00** (0.94 to 1.06)	Change from baseline in ACQ score was 0.00 (0.06 lower to 0.06 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**3.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
MD-TRIPLE (Direct evidence; 2 RCTs; 1366 participants)	**0.02** (-0.07 to 0.11)	**0.98** (0.89 to 1.07)	Change from baseline in ACQ score was 0.08 higher (0.01 lower to 0.17 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**4.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
HD-TRIPLE (Direct evidence; 2 RCTs; 1379 participants)	**-0.08** (-0.16 to 0.00)	**1.08** (1.00 to 1.16)	Change from baseline in ACQ score was 0.08 higher (0.00 lower to 0.16 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**1.0** (1.0 to 2.0)	Probably little or no clinically meaningful difference[3]
MD-ICS/LABA	Reference	1.00	Reference Comparator	Reference Comparator	3.0 (2.0 to 4.0)	Reference Comparator

- Triple inhaled therapy, especially high-dose formulations, reduces asthma flare-ups, but may or may not to improve symptoms or quality of life compared to dual therapy.
- Immuno-modulators may be considered if asthma symptoms are not well controlled or for those requiring asthma-related hospitalizations despite being on medium-dose dual inhaled therapy.

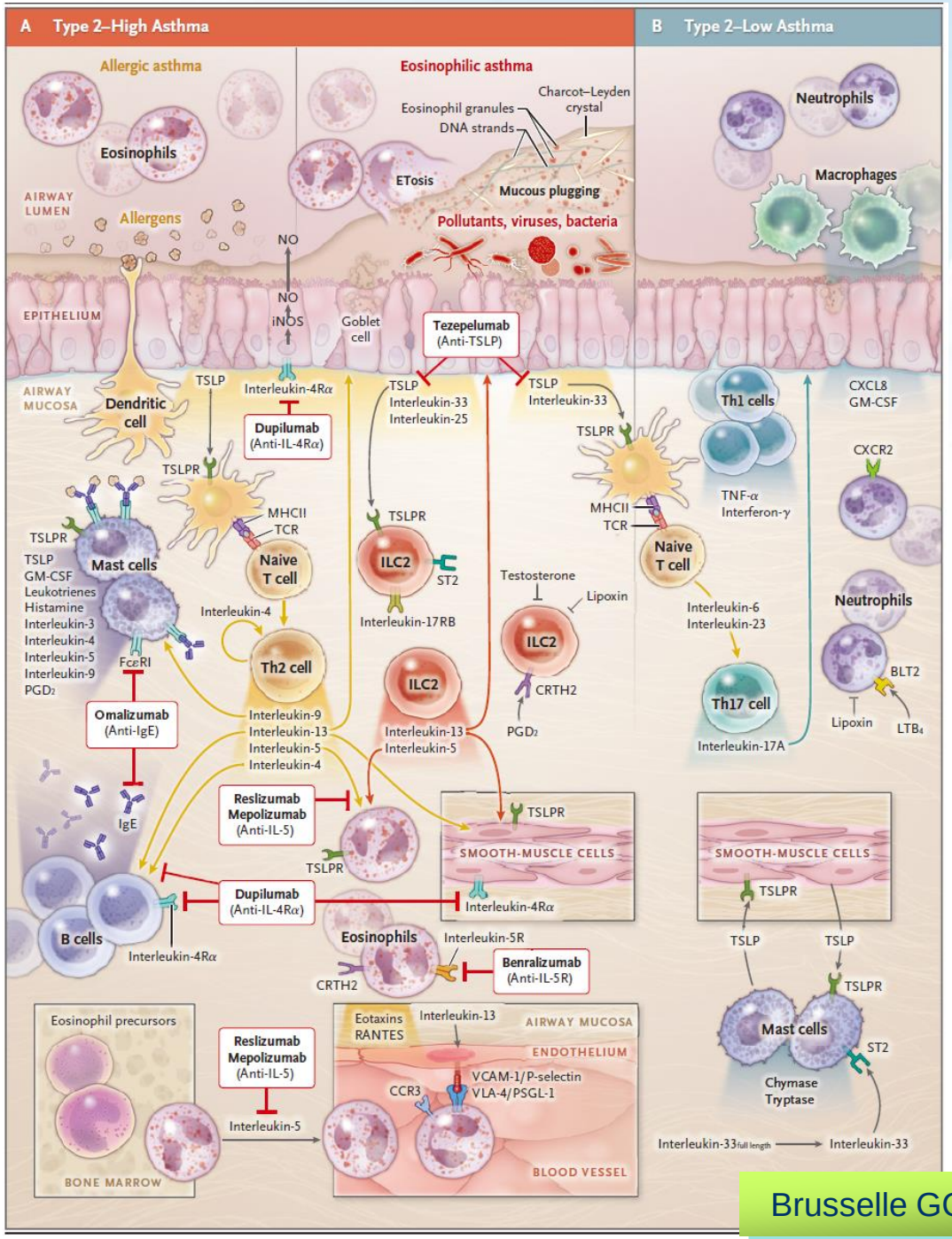
Oba Y, et al. Cochrane Database Syst Rev. 2022;12:CD013799

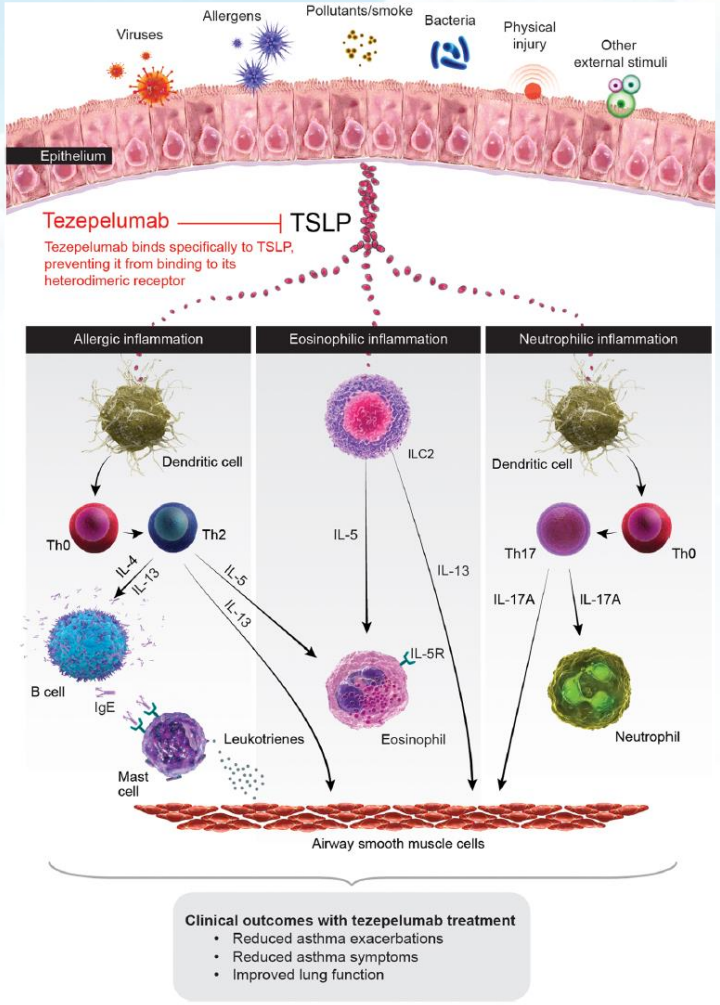
1. Risk Factors and Phenotype
2. Diagnosis
3. Inhaled Therapies
4. **Biologics**
   - Anti-TSLP :Tezepelumab
   - Stopping mepolizumab
5. COVID-19 and Asthma



Pelaia C, et al. Front Immunol 2020;11:603312

Upstream epithelial alarmin

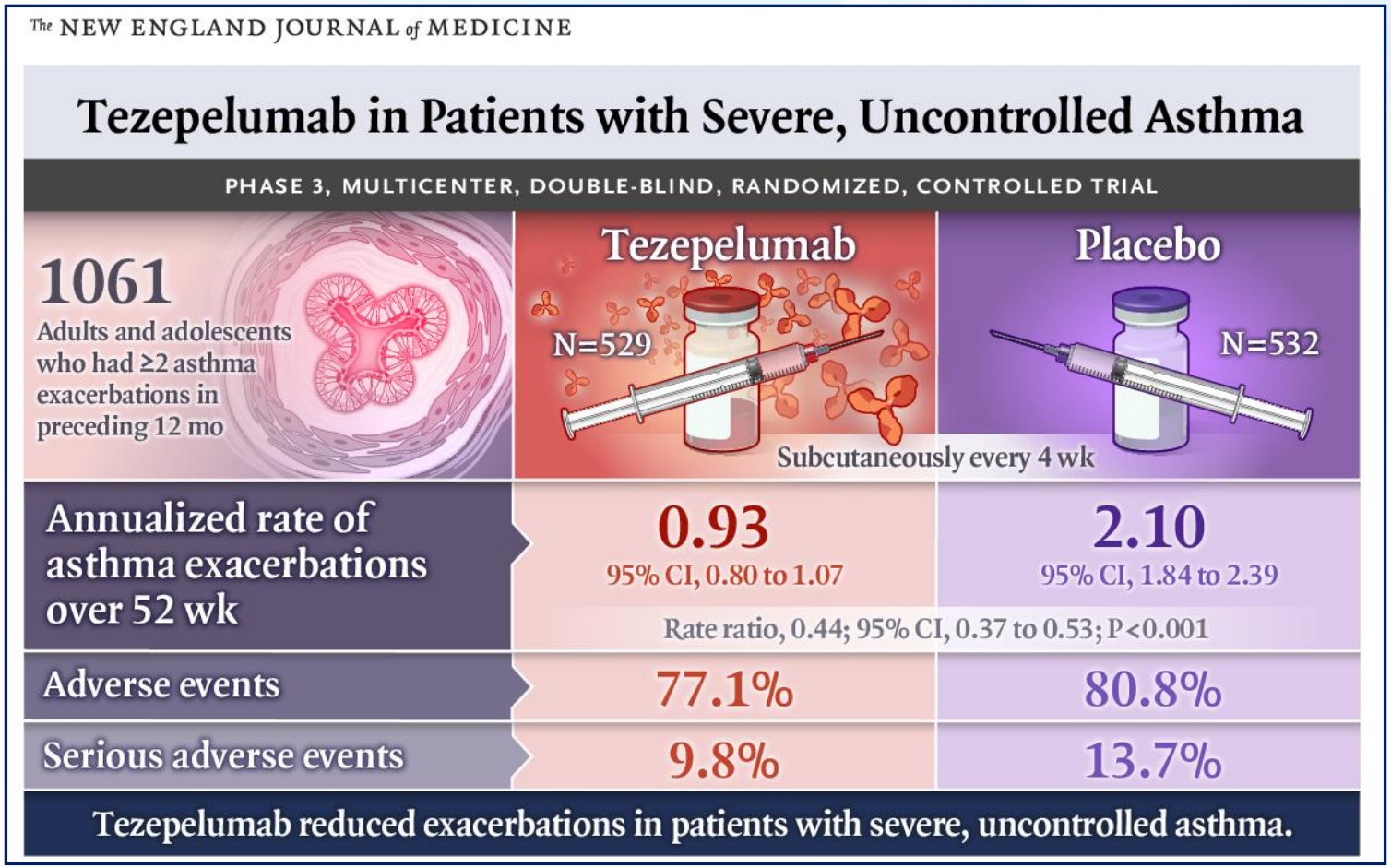




Brusselle GG, et al. N Eng J Med 2022;386:157-71

Tezepelumab: Anti-TSLP (Thymic Stromal Lymphopoietin)

NAVIGATOR trial



Menzies-Gow A, et al. N Eng J Med 2021;384:1800-9

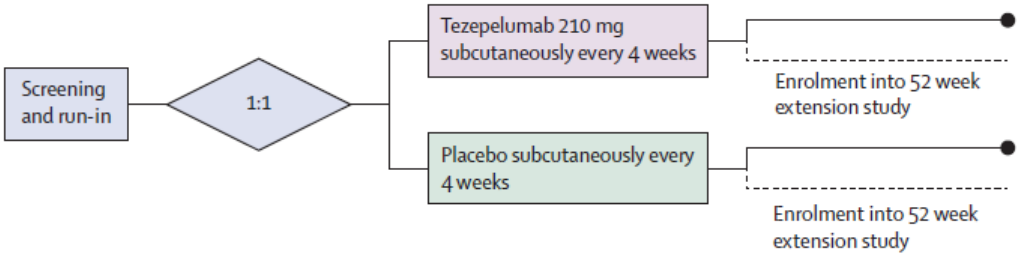
SOURCE: Oral Corticosteroid-Sparing Effect of Tezepelumab

Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study

*Michael E Wechsler, Andrew Menzies-Gow, Christopher E Brightling, Piotr Kuna, Stephanie Korn, Tobias Welte, Janet M Griffiths, Kinga Sałapa, Åsa Hellqvist, Gun Almqvist, Harbans Lal, Primal Kaur, Tor Skärby, Gene Colice, on behalf of the SOURCE study group**

- Phase 3, multicentre, double-blind RCT (n=150)

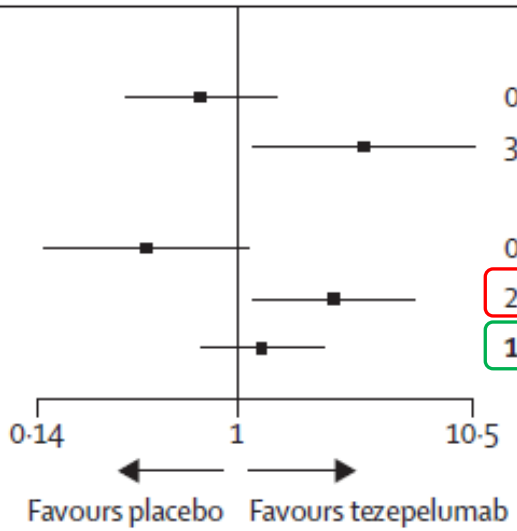
Weeks −10 to −8	Weeks −8 to 0	Week 0	Weeks 0–48			Weeks 48–60
Screening and run-in	Oral corticosteroid optimisation phase	Randomisation	Treatment period			Follow-up or enrolment into separate extension study*
			0–4	4–40	40–48	
			Induction phase	Oral corticosteroid reduction phase	Maintenance phase	



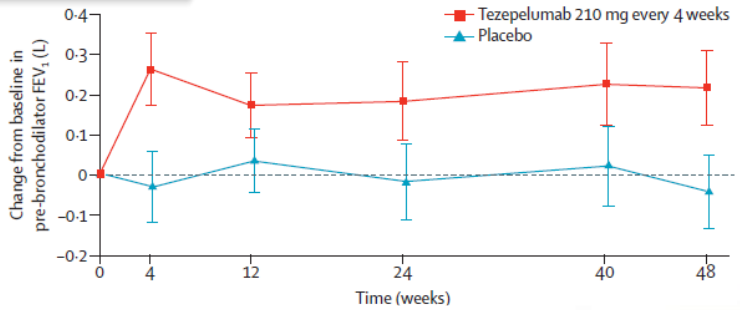
Wechsler ME, et al. Lancet Respir Med 2022:10:650-60

Percentage Reduction in OCS Dose at Week 48

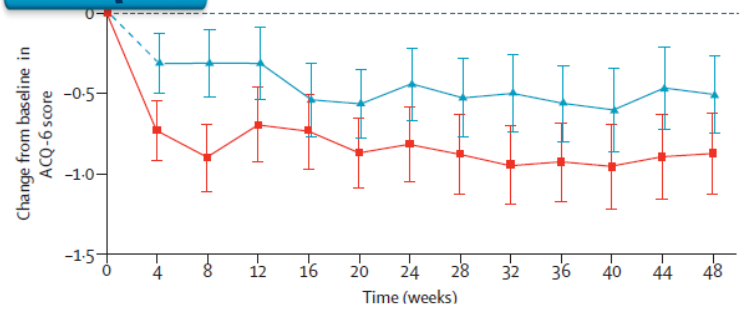
	Tezepelumab 210 mg every 4 weeks, n (%)	Placebo, n (%)	Cumulative OR (95% CI)
Baseline blood eosinophil count			
<300 cells per µL	46 (62·2)	52 (68·4)	0·70 (0·33–1·47)
≥300 cells per µL	28 (37·8)	24 (31·6)	3·49 (1·16–10·49)
Baseline blood eosinophil count			
<150 cells per µL	27 (36·5)	24 (31·6)	0·40 (0·14–1·13)
≥150 cells per µL	47 (63·5)	52 (68·4)	2·58 (1·16–5·75)
Overall	**74 (100·0)**	**76 (100·0)**	**1·28 (0·69–2·35)**



FEV1



ACQ-6



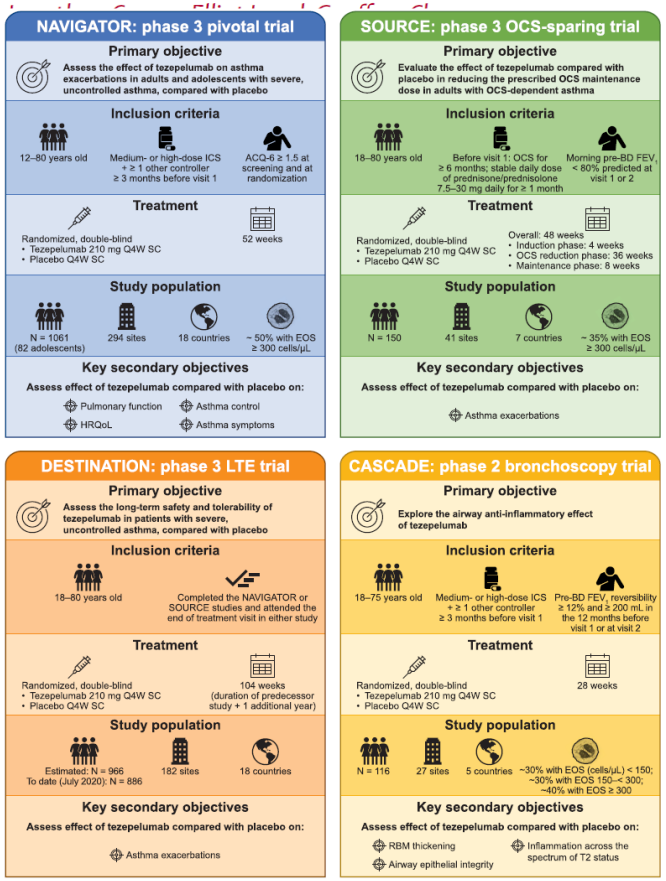
Wechsler ME, et al. Lancet Respir Med 2022:10:650-60

Long Term Safety and Efficacy of Tezepelumab

Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study

*Andrew Menzies-Gow, Michael E Wechsler, Christopher E Brightling, Stephanie Korn, Artur Bednarczyk, Sandhia Ponnarambil, Scott Caveney, Gun Almqvist, Monika Gołc Gene Colice on behalf of the DESTINATION study investigators**

- Extension study recruited from phase 3 NAVIGATOR (52-week) and SOURCE (48-week) studies (104 weeks)
- 1059 participants from NAVIGATOR and 150 participants from SOURCE



Menzies-Gow A, et al. Lancet Respir Med. 2023. Epub

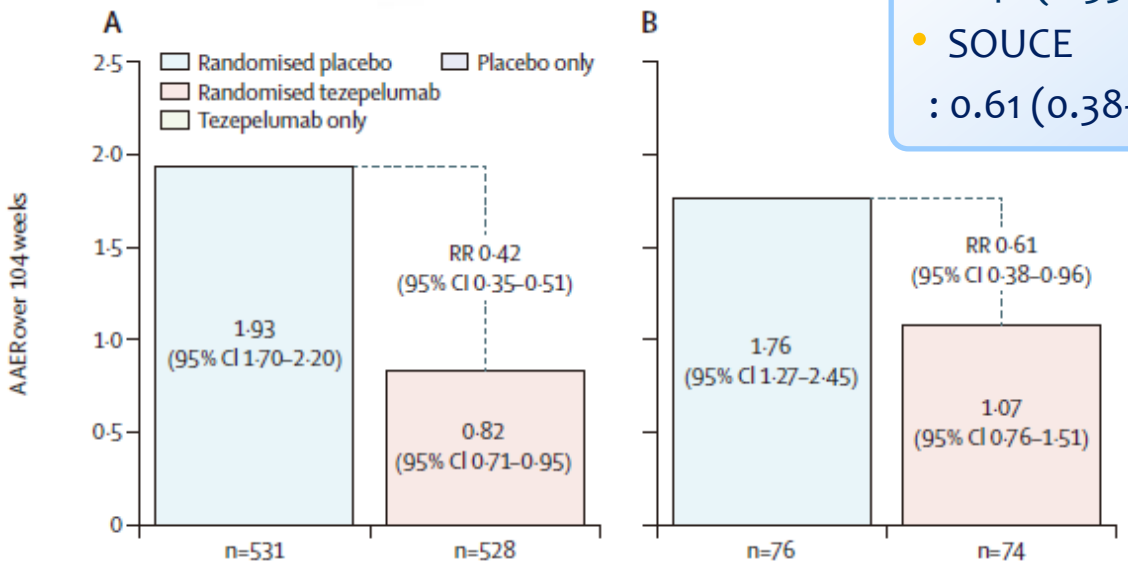
Incidence of adverse event

	NAVIGATOR tezepelumab and placebo groups	SOURCE tezepelumab and placebo groups
Any adverse event	−13·04 (−17·83 to −8·18)	−22·82 (−34·77 to −10·01)
Any adverse event resulting in death	0·62 (−0·10 to 1·44)	1·55 (−2·19 to 5·47)
Any serious adverse event	−4·59 (−7·69 to −1·65)	−4·85 (−14·88 to 4·53)
Any adverse event leading to discontinuation of treatment	−1·37 (−3·05 to 0·08)	−0·45 (−5·62 to 3·74)

- Nasopharyngitis, upper respiratory tract infection, headache, asthma

Annualized Asthma Exacerbation Rate

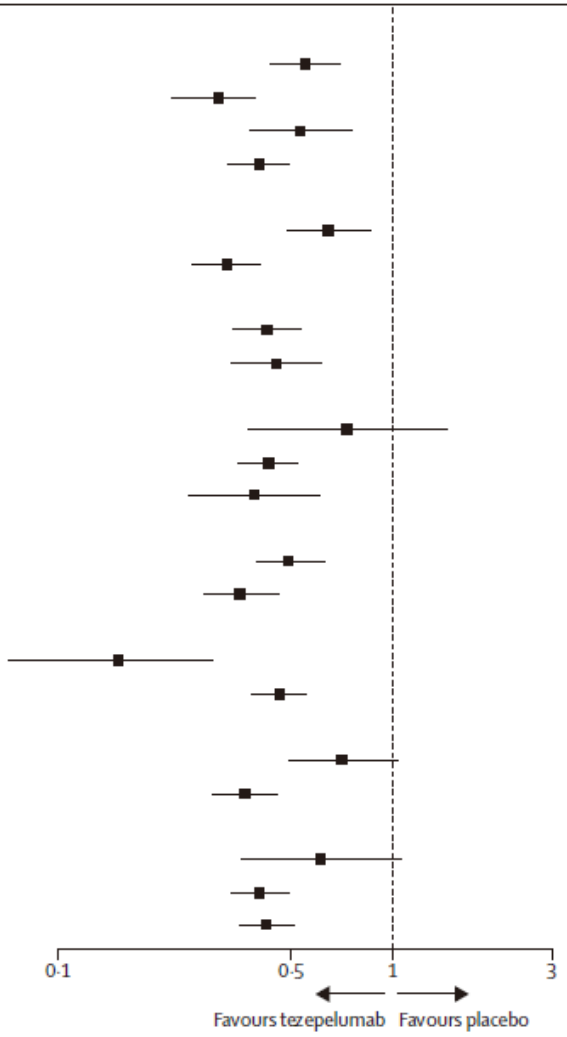
- NAVIGATOR
  : 0.42 (0.35-0.51)
- SOUCE
  : 0.61 (0.38-0.96)



Menzies-Gow A, et al. Lancet Respir Med. 2023. Epub

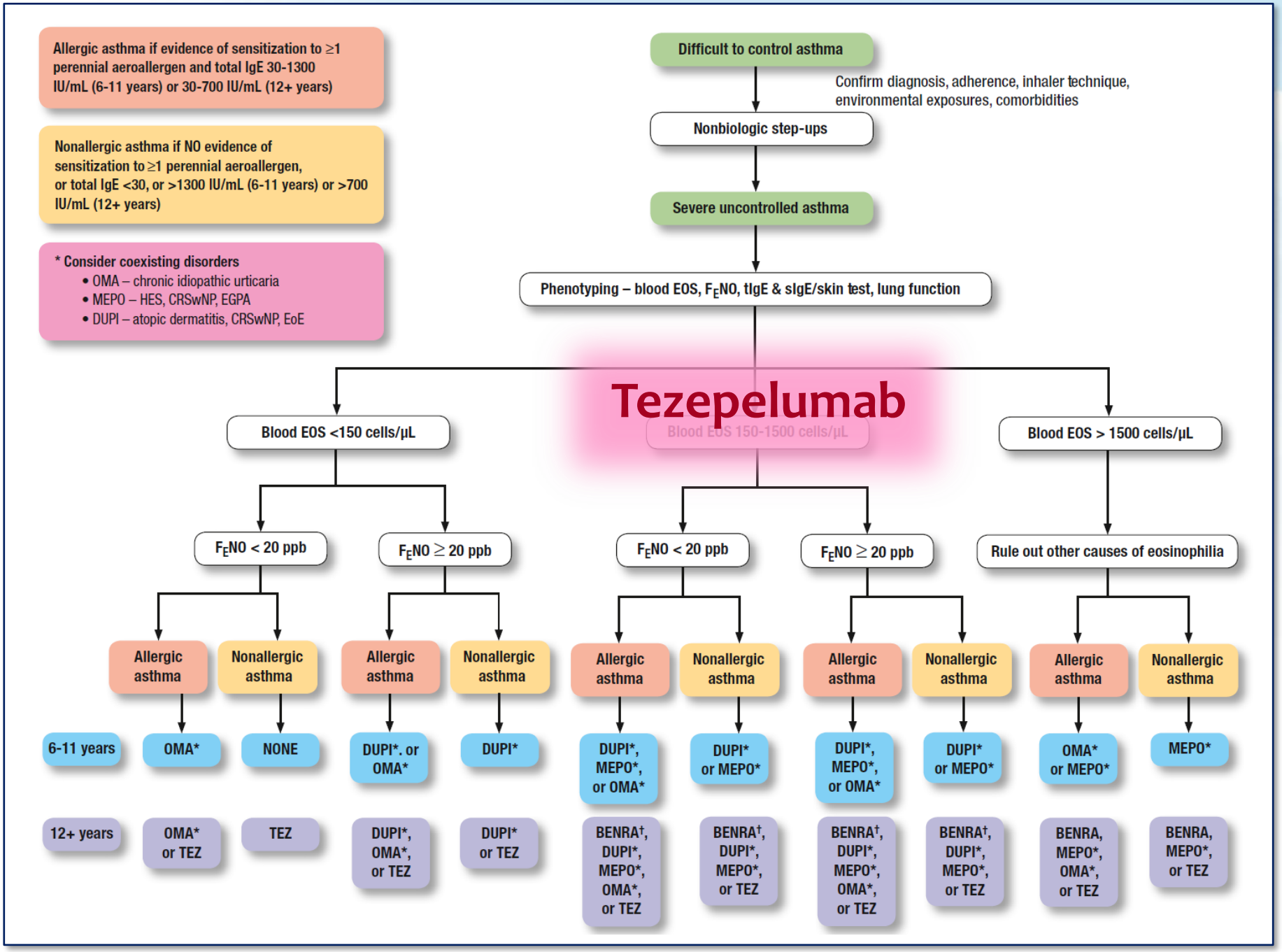
Annualized Asthma Exacerbation Rate

	Randomised tezepelumab n/estimate	Randomised placebo n/estimate	Rate ratio (95% CI)
Baseline blood eosinophil count			
<300 cells per µL	309/0·88	309/1·60	0·55 (0·44–0·70)
≥300 cells per µL	219/0·73	222/2·46	0·30 (0·22–0·39)
<150 cells per µL	138/0·82	138/1·55	0·53 (0·37–0·76)
≥150 cells per µL	390/0·82	393/2·08	0·40 (0·32–0·49)
Baseline FeNO level			
<25 ppb	213/0·90	220/1·40	0·64 (0·48–0·86)
≥25 ppb	309/0·75	307/2·37	0·32 (0·25–0·40)
Allergy status			
FEIA positive for any perennial aeroallergen	339/0·77	341/1·84	0·42 (0·33–0·53)
FEIA negative for all perennial aeroallergens	184/0·94	177/2·09	0·45 (0·33–0·61)
Age at study entry			
Adolescent (≥12 to <18 years)	41/0·56	41/0·78	0·72 (0·36–1·45)
Adult (≥18 to <65 years)	391/0·88	416/2·11	0·42 (0·34–0·51)
Older adult (≥65 years)	96/0·65	74/1·73	0·38 (0·24–0·60)
Number of asthma exacerbations in the year before study entry			
≤2	310/0·61	325/1·23	0·49 (0·39–0·63)
>2	218/1·10	206/1·11	0·35 (0·27–0·46)
Nasal polyps in the 2 years before randomisation			
Yes	42/0·39	41/2·65	0·15 (0·07–0·29)
No	486/0·86	490/1·88	0·46 (0·38–0·55)
Inhaled corticosteroid dose group			
Medium	131/0·85	132/1·18	0·71 (0·49–1·04)
High	397/0·81	398/2·22	0·36 (0·29–0·45)
Maintenance oral corticosteroid use			
Yes	49/1·85	51/3·01	0·61 (0·35–1·07)
No	479/0·73	480/1·82	0·40 (0·33–0·49)
Overall	**528/0·82**	**531/1·93**	



0.42 (0.35-0.51)

Menzies-Gow A, et al. Lancet Respir Med. 2023. Epub



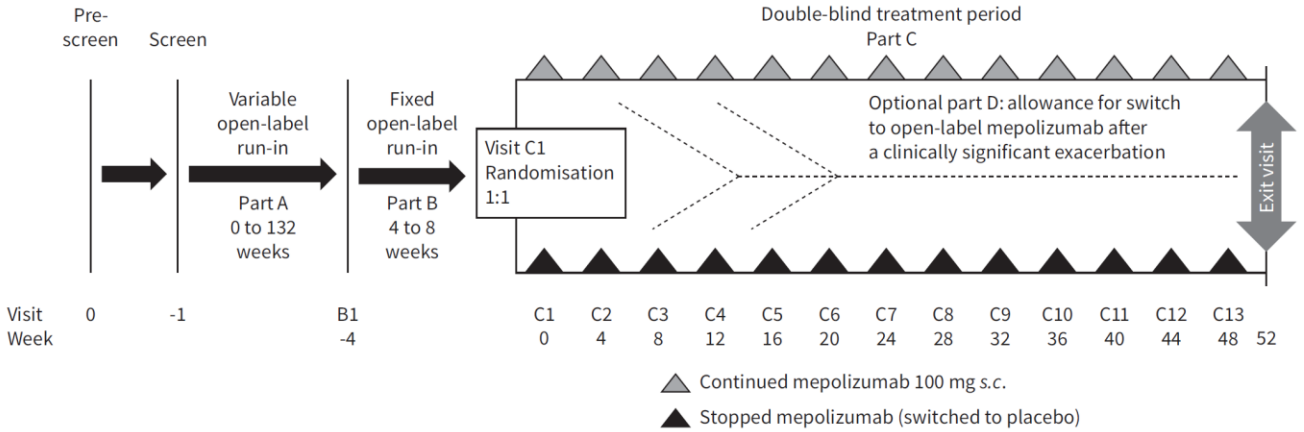
Bacharier LB, et al. J Allergy Clin Immunol 2023;151:581-9

Stopping Mepolizumab

Stopping *versus* continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study)

Wendy C. Moore[1], Oliver Kornmann[2], Marc Humbert[3,4,5], Claude Poirier[6], Elisabeth H. Bel[7], Norihiro Kaneko[8], Steven G. Smith[9], Neil Martin[10,11], Martyn J. Gilson[12], Robert G. Price[13], Eric S. Bradford[9] and Mark C. Liu[14]

- Multicenter, double-blind RCT (295 patients in 75 centers)
- Patients who had completed COLUMBA or COSMEX and received continuous mepolizumab treatment for ⩾3 years

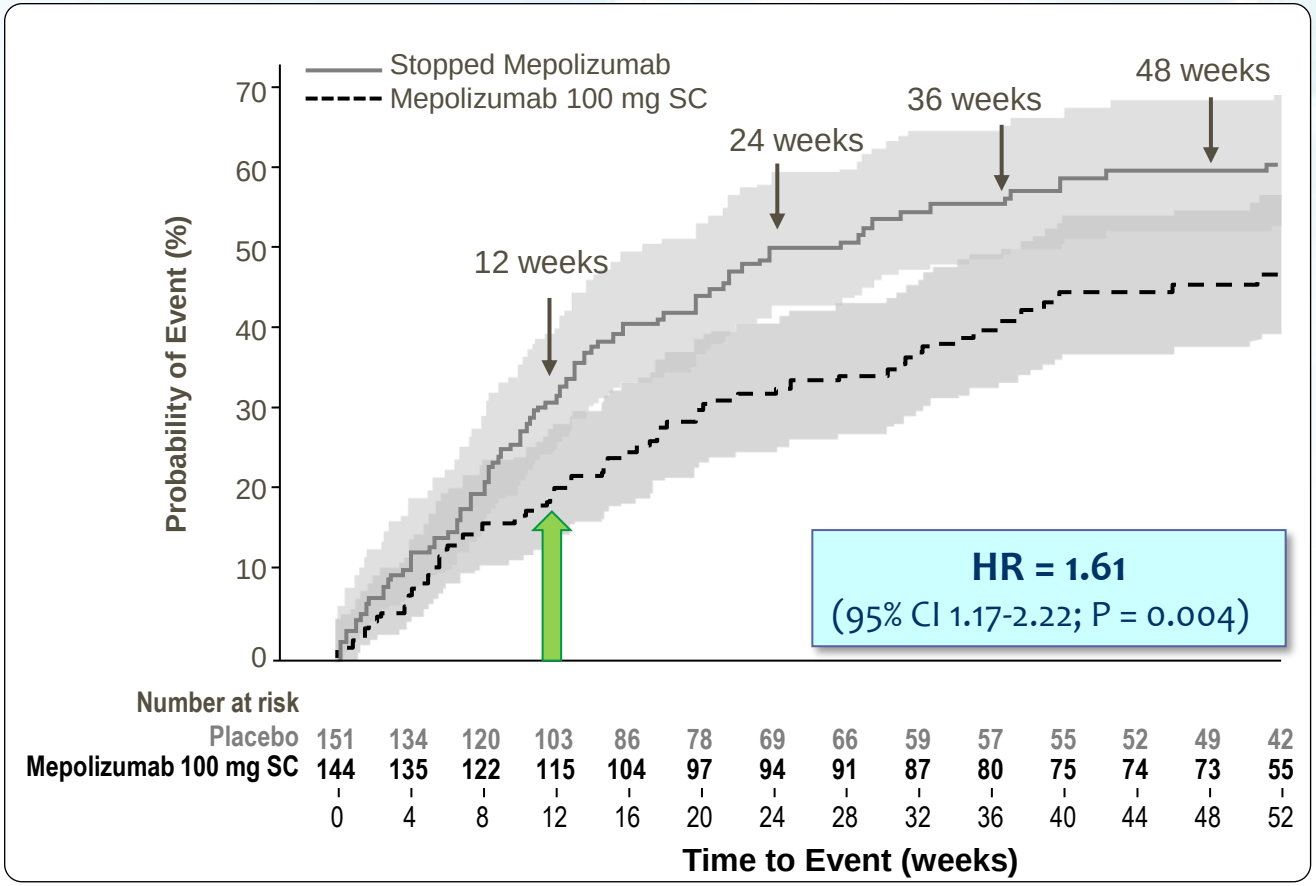


Moore WC, et al. Eur Respir J 2022;59:2100396

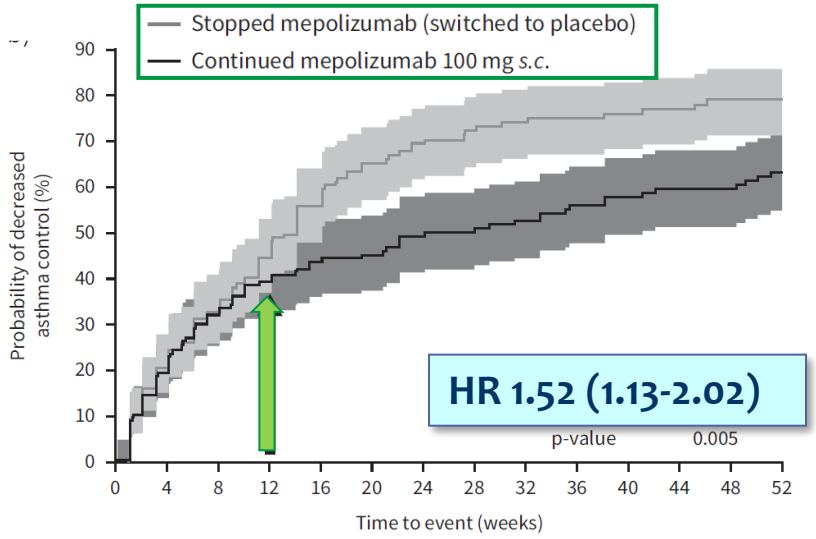
Time to First Exacerbation

Patients who continued mepolizumab treatment had a 38% lower risk of experiencing an exacerbation

: Equivalent to 61% increase in risk of first exacerbation after cessation of mepolizumab (HR = 1.61)

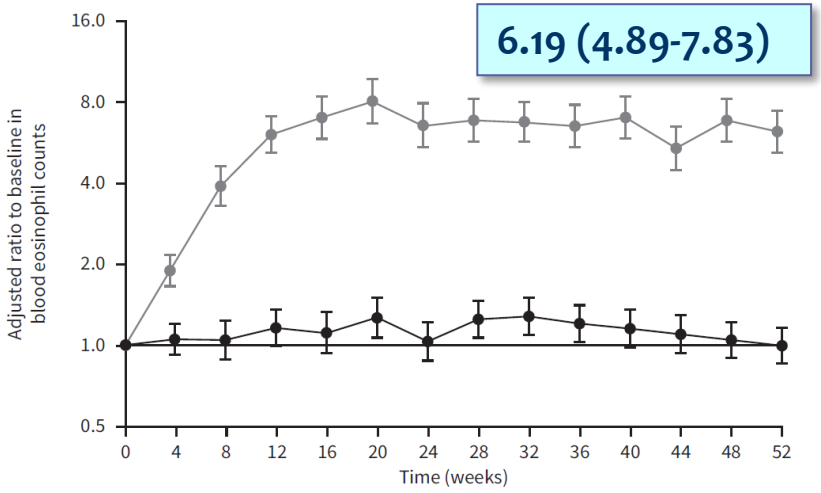


Moore WC, et al. Eur Respir J 2022;59:2100396



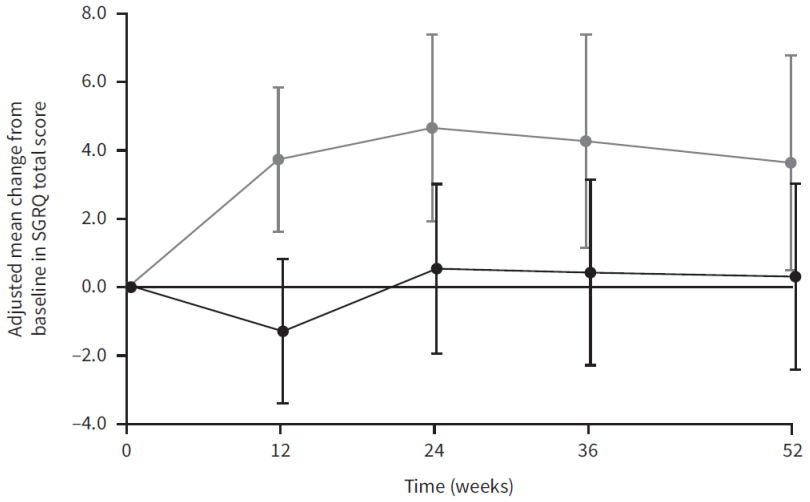
Number at risk

Placebo	151	119	100	76	58	42	35	31	28	26	24	23	20	19
Mepolizumab 100 mg s.c.	144	116	96	84	73	70	62	60	57	50	48	46	45	32



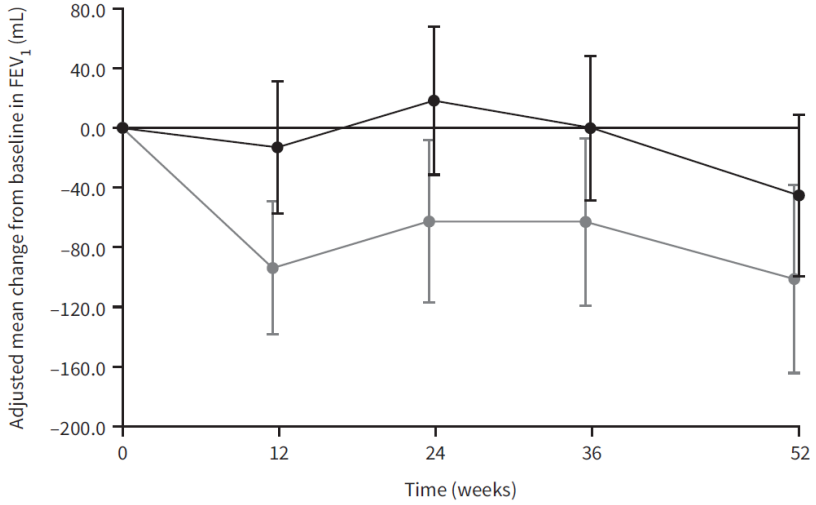
Number of patients at each time point

Placebo	150	145	136	121	103	84	79	77	75	65	68	66	60	60
Mepolizumab 100 mg s.c.	141	137	133	120	114	102	106	101	99	99	93	92	86	92



Number of patients at each time point

Placebo	151	137	92	74	65
Mepolizumab 100 mg s.c.	144	141	117	106	94



Number of patients at each time point

Placebo	150	137	93	75	65
Mepolizumab 100 mg s.c.	144	139	116	106	94

Moore WC, et al. Eur Respir J 2022;59:2100396

1. Risk Factors and Phenotype
2. Diagnosis
3. Inhaled Therapies
4. Biologics
5. **COVID-19 and Asthma**

COVID-19 and Asthma: GINA 2022

- What are the implications for asthma management?
  - It is important to continue good asthma management, with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimise the need for OCS.

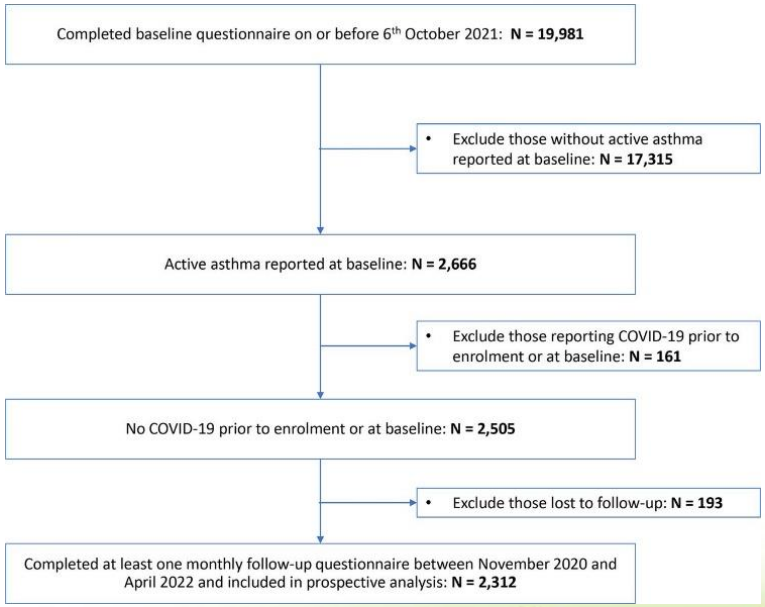
- More asthma exacerbations during the pandemic?
  - No: in 2020–21, many countries saw a decrease in asthma exacerbations and influenza-related illness
  - The reasons are not precisely known, but may be due to public health measures such as handwashing, masks and social/physical distancing that reduced the incidence of other respiratory infections, including influenza.

Relaxation of COVID-19 Restrictions

Rebound in asthma exacerbations following relaxation of COVID-19 restrictions: a longitudinal population-based study (COVIDENCE UK)

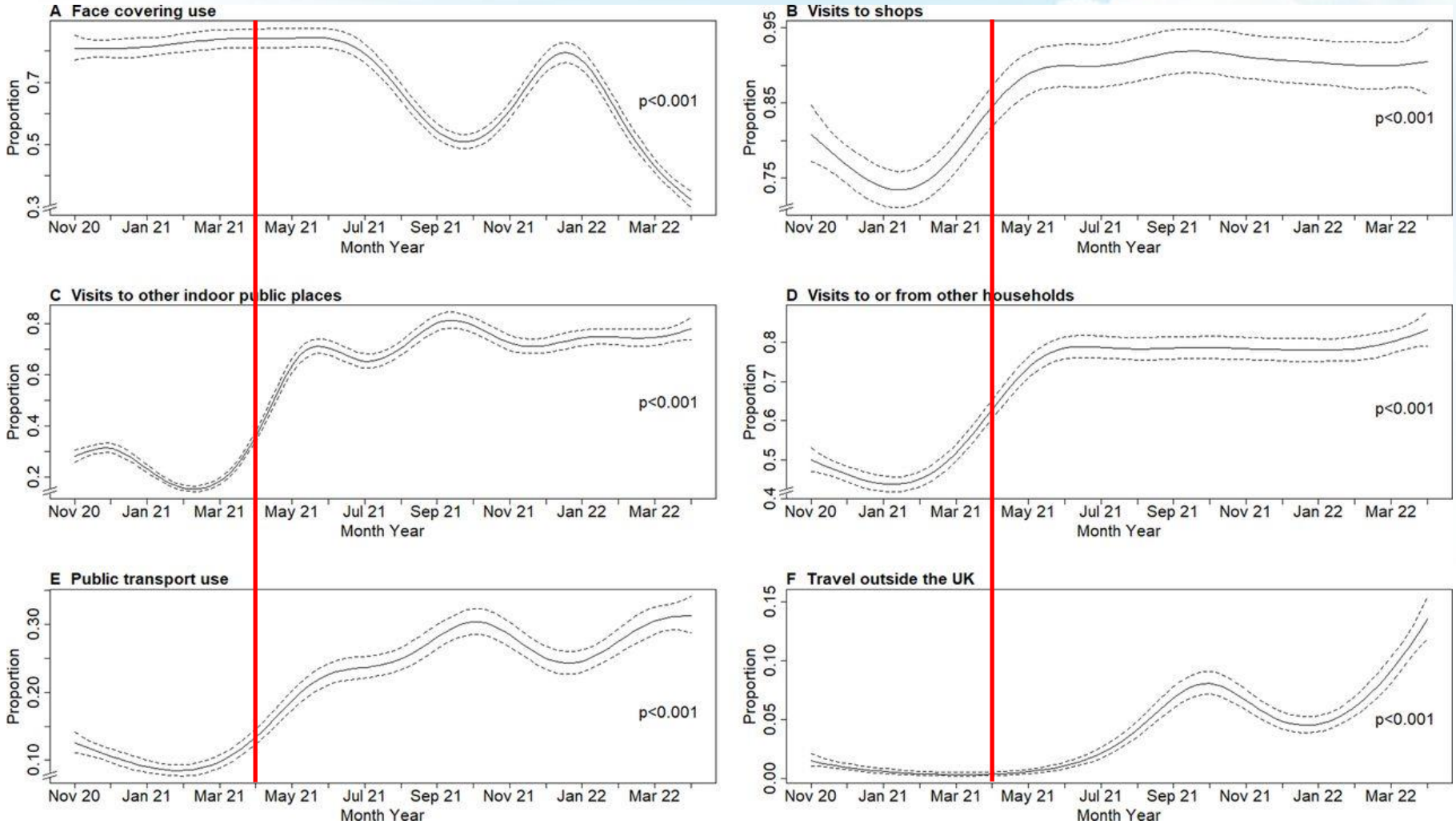
Florence Tydeman,[1] Paul E Pfeffer ,[2,3] Giulia Vivaldi,[1,4] Hayley Holt,[1,4] Mohammad Talaei ,[4] David Jolliffe ,[1,4] Gwyneth Davies ,[5,6] Ronan A Lyons ,[5] Christopher Griffiths,[4,7] Frank Kee ,[8] Aziz Sheikh ,[9,10] Seif O Shaheen ,[4] Adrian R Martineau [1,3,7]

- Population-based longitudinal study in 2,312 UK adults with asthma



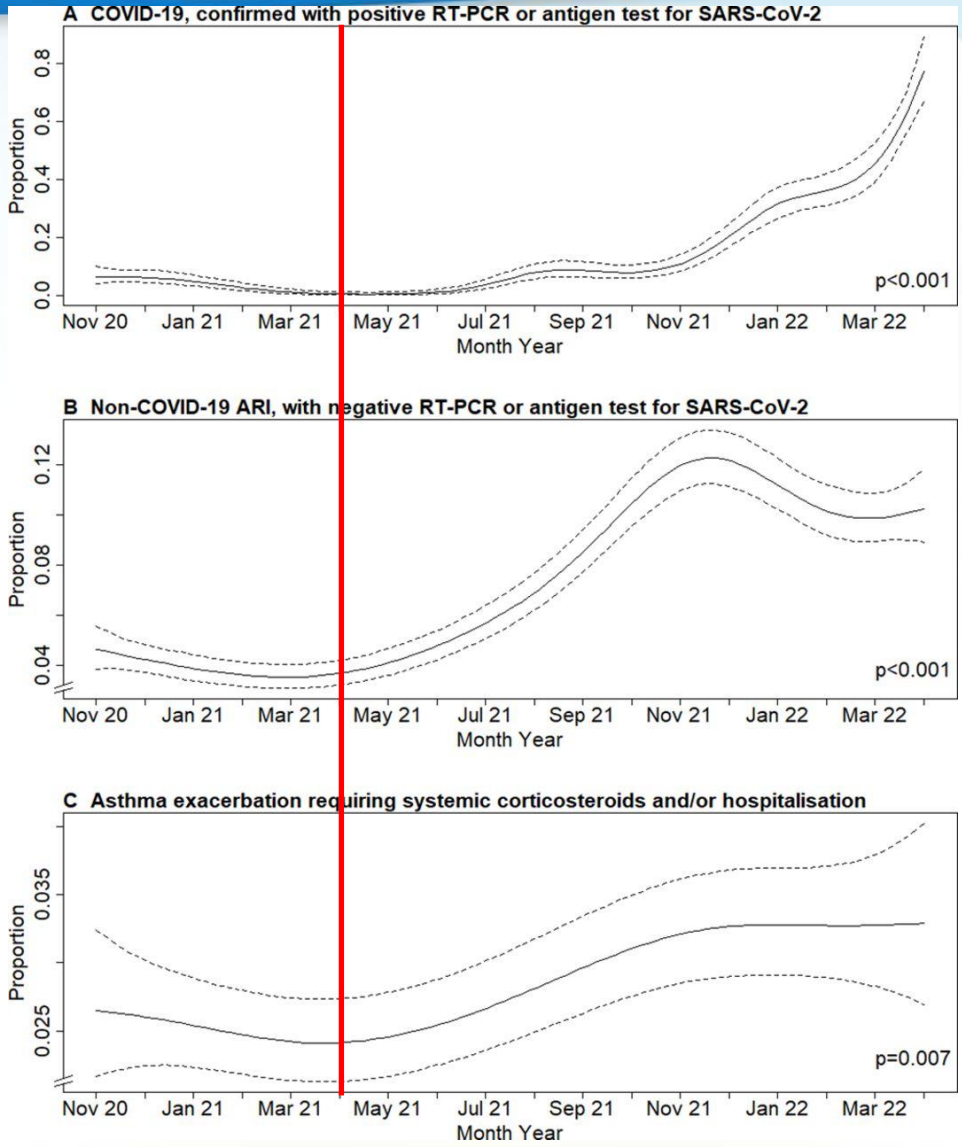
Tydeman F, et al. Thorax 2022. Epub

Temporal Trends in Behaviours



Tydeman F, et al. Thorax 2022. Epub

Temporal Trends in Acute Respiratory Infections (ARI) and Asthma Exacerbations



Tydeman F, et al. Thorax 2022. Epub

Determinants of Severe Asthma Exacerbation Risk

Primary course of SARS-CoV-2 vaccination				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	1.35 (1.13 to 1.61)	0.001	1.12 (0.84 to 1.48)	0.466
Incident COVID-19				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes, before December 2021	4.09 (2.22 to 7.53)	<0.001	5.89 (3.45 to 10.04)	<0.001
Yes, on/after December 2021	4.17 (2.77 to 6.27)	<0.001	5.69 (3.89 to 8.31)	<0.001
Incident non-COVID-19 ARI				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	4.53 (3.72 to 5.52)	<0.001	5.75 (4.75 to 6.97)	<0.001

Omicron variant

- Relaxation of COVID-19 restrictions coincided with decreased face covering use, increased social mixing and a rebound in ARI and asthma exacerbations.
- Associations between incident ARI and risk of severe asthma exacerbation were similar for non-COVID-19 ARI and COVID-19.

Tydeman F, et al. Thorax 2022. Epub

SUMMARY

- Risk Factors
  - Early-life pet ownership, lower respiratory tract infections
- Phenotype
  - Patient characteristics and comorbidities by onset age
  - Persistent airflow limitation phenotype
- Diagnosis: ERS guidelines
- Inhaler therapies
  - Albuterol-budesonide fixed dose combination rescue inhaler
  - Triple combination inhaler
- Biologics
  - Tezepelumab: OCS-sparing effect, long term safety and efficacy
  - Stopping long-term mepolizumab
- COVID-19 and asthma
  - Asthma exacerbations following relaxation of COVID-19 restrictions

Thank You for Your Attention