천식 진료 지침 최신 지견

- What is new in GINA 2022? -

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Diagnosis of asthma

- The diagnosis of asthma is based on a history of **variable respiratory symptoms** and demonstration of **variable expiratory airflow limitation**

- Many patients (25-35%) with a diagnosis of asthma in primary care cannot be confirmed as having asthma

- GINA 2022 emphasized **different approach** for initial diagnosis of asthma in patients **already taking controller treatment for asthma**

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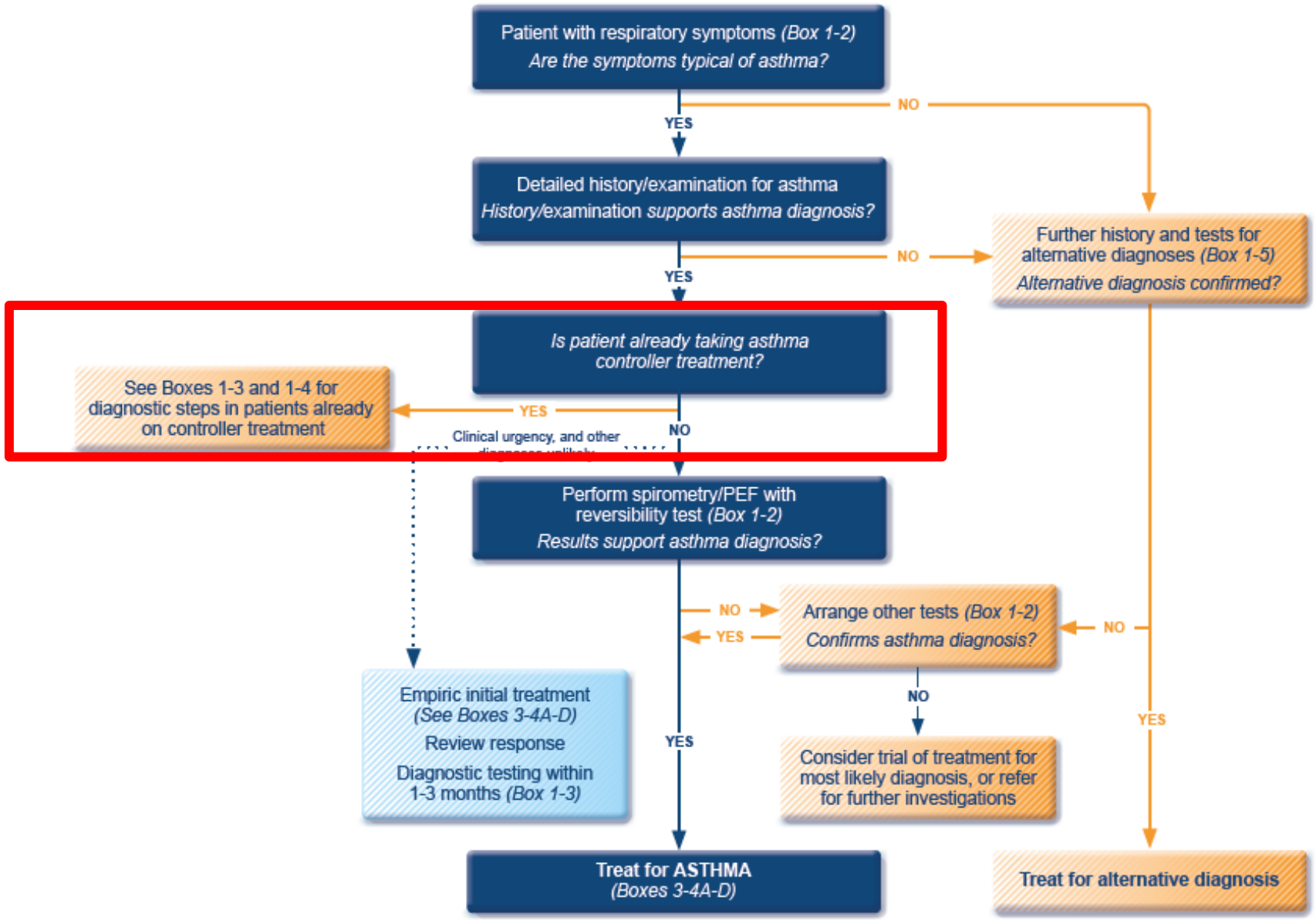
		Specialist/allergy department		
		Asthma	No asthma	Total
Asthma				
Asthma group (n = 99)	Estimated[a]	24	7	31
Primary health care	Verified	52	16	68
No asthma				
Control group (n = 2926)	Estimated[a]	50	2709	2759
Primary health care	Verified	3	164	167
Overall total				3025

Overdiagnosis: 23.5%
Underdiagnosis: 1.7%

Fam Pract. 2002 Aug;19(4):365-8.

Diagnostic steps of asthma



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Diagnosis of asthmatics on controller treatment

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.

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Variable symptoms and lung function

- With **variable respiratory symptoms** and **variable airflow limitation**

  ➔ **Asthma is diagnosed**

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).

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Few symptoms and stable lung function

- With **few respiratory symptoms** and **no variable airflow limitation**

  Step 1) **Withhold bronchodilator** & **repeat lung function examination with BDR test**

  ➔ If normal, then asthma unlikely

  Step 2) **Step down controller treatment**

  a) If symptom emerge and lung function falls ➔ **Asthma is diagnosed**

  b) If no symptom or no lung function decline ➔ **Monitor 12months**

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).

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Persistent symptoms and reduced lung function

- With **persistent respiratory symptoms** and **persistent airflow limitation**

  ➔ **Stepping up controller treatment for 3 months**

  If no response, then **resume previous treatment** and **check other conditions including COPD**

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.

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Variable symptoms but stable lung function

- With **variable respiratory symptoms**, **but no variable airflow limitation**

  Step 1) **Withhold bronchodilator** & **repeat lung function examination with BDR test**

  ➔ **Check between visit variability and BDR positivity**

  ➔ If normal, then asthma unlikely

  Step 2) After bronchodilator withdrawal

  a) If **FEV_1>70%** ➔ **Step down controller treatment**

  ➔ **Bronchial provocation test and repeating BDR test**

  b) If **FEV_1<70%** ➔ **Step up controller treatment for 3 months**

  ➔ **If no response,** then **resume previous treatment** and **check other conditions including COPD**

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Diagnosis of asthma in low-/mid-income countries

- **Asthma is often under-diagnosed in low- and middle-income countries**
  - ✓ Access to lung function testing is limited
  - ✓ Differential diagnosis of other infectious respiratory diseases (tuberculosis, HIV/AIDS-associated lung disease, parasitic or fungal lung disease)

- GINA recommends confirmation of asthma diagnosis with lung function testing, whenever possible, before commencing long-term treatment
  - ✓ Spirometry-based testing if available
  - ✓ **Peak expiratory flow (PEF)**
    - >20% increase in PEF, 15 minutes after 2 puffs of salbutamol = asthma likely (WHO-PEN)
    - Improvement of symptoms and PEF after 4 weeks ICS treatment

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Contents

- Diagnosis
- **Assessment of asthma control / severity**
- Treatment: Reliever
- Treatment: Add-on therapy (LAMA & Biologic agent)
- Management of asthma during COVID-19

Frequency of reliever use

- **Frequency of SABA reliever** (<2 or ≥2/week) is included in assessment of asthma control
  - ✓ If SABA was used ≥2/week, patients need to start controller treatment or increase the dose.

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA reliever for symptoms more than twice/week?*	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

- **Should frequency of as-needed ICS-formoterol be included in assessment of asthma control?**

  ➔ **No,** frequency of as-needed ICS-formoterol (<2 or ≥2/week) is not included in assessment of asthma control

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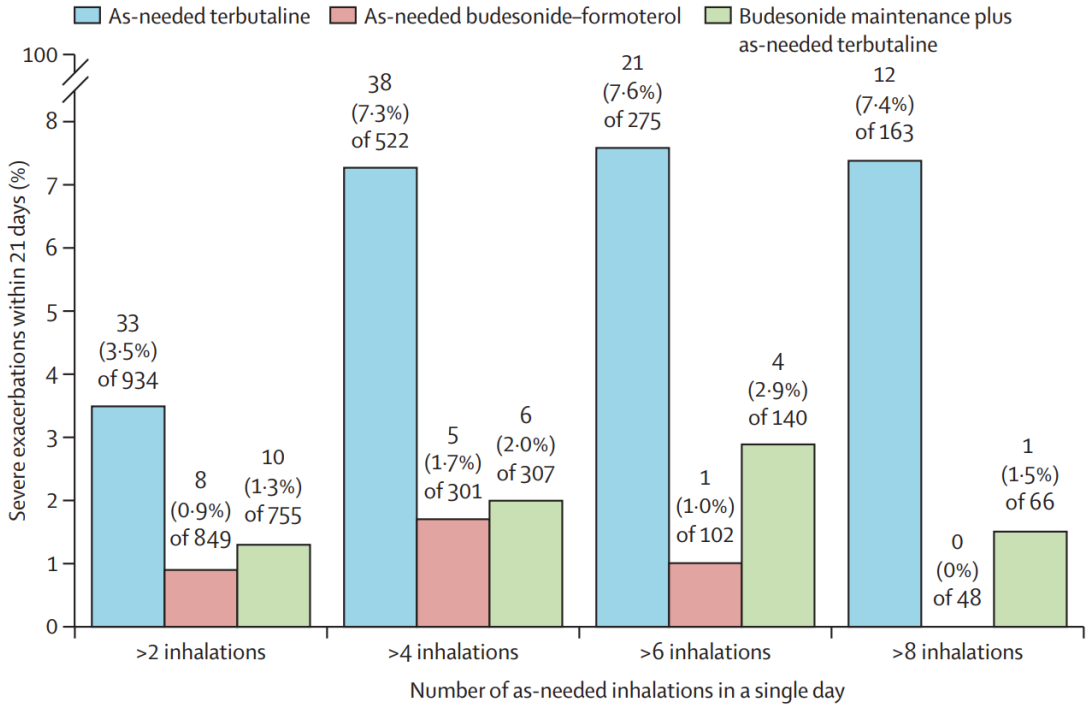
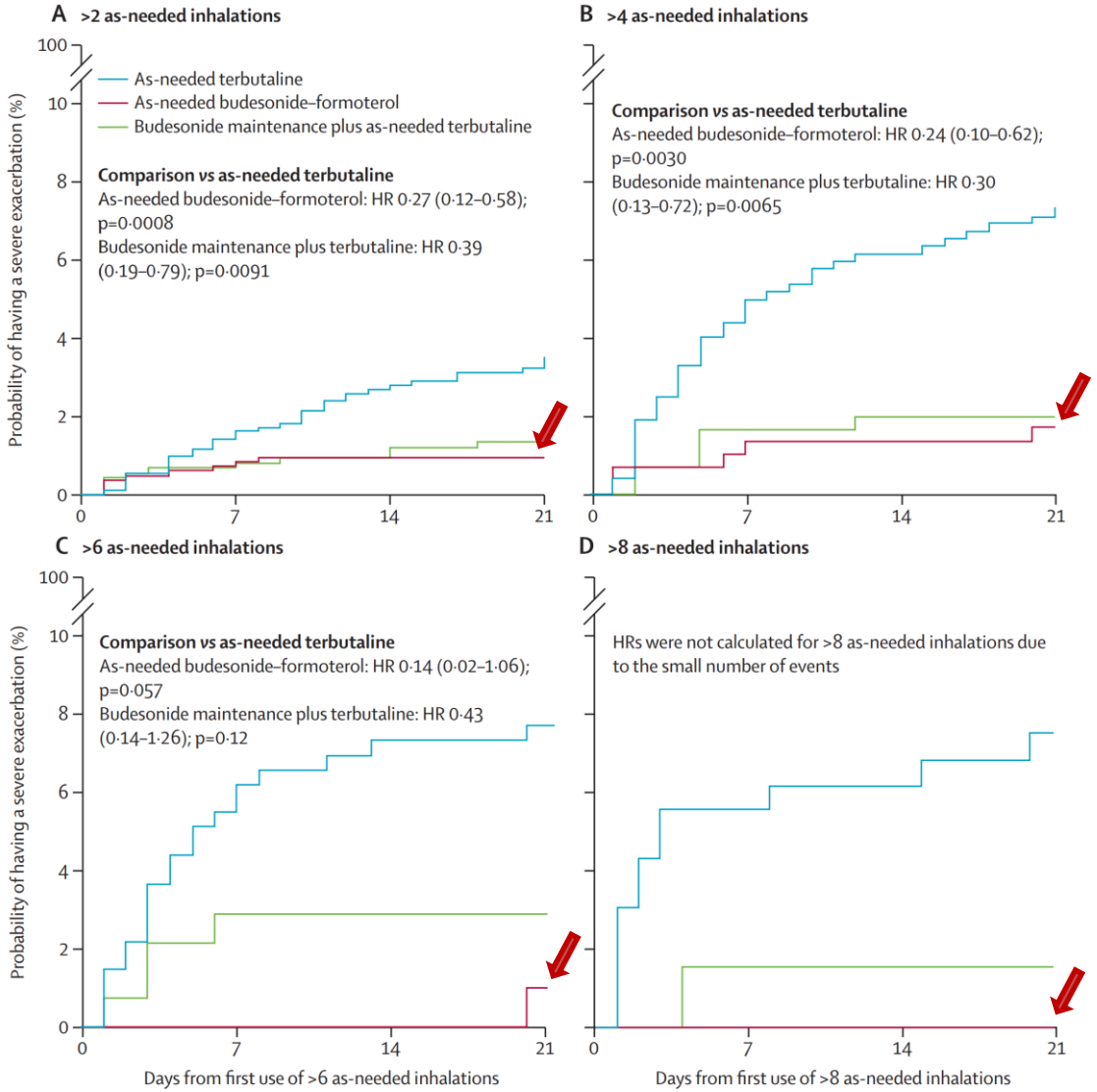
Frequency of as-needed ICS-formoterol

- Post-hoc analysis of the SYGMA 1 study
- **Increasing use of as-needed ICS-formoterol** is associated with a **significantly lower risk of severe exacerbation**





Lancet Respir Med. 2021 Feb;9(2):149-158.

Severity of asthma

- **Severe asthma**: Uncontrolled despite optimized treatment with high-dose ICS/LABA or that requires high-dose ICS/LABA to prevent it from becoming uncontrolled
- **Moderate asthma**: Well-controlled with Step 3 or 4 treatment (low-to-moderate dose ICS/LABA)
- **Mild asthma**: Well-controlled with Step 1 or 2 treatment (low-dose ICS or as needed low-dose ICS/LABA)

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The definition of mild asthma

- While severe asthma has been widely accepted in guidelines and clinical practice, **the clinical utility or relevance of the definition of mild asthma is much less clear**
  - Up to 30% of asthma deaths are in asthma patients with infrequent symptoms
  - Mild asthma can be defined only after several months of treatment
    (many patients with well-controlled asthma have not had their treatment stepped down)
  - Retrospective definition of mild asthma is of little value in deciding future treatment.

- **GINA recommends the term "mild asthma" should generally be avoided in clinical practice**

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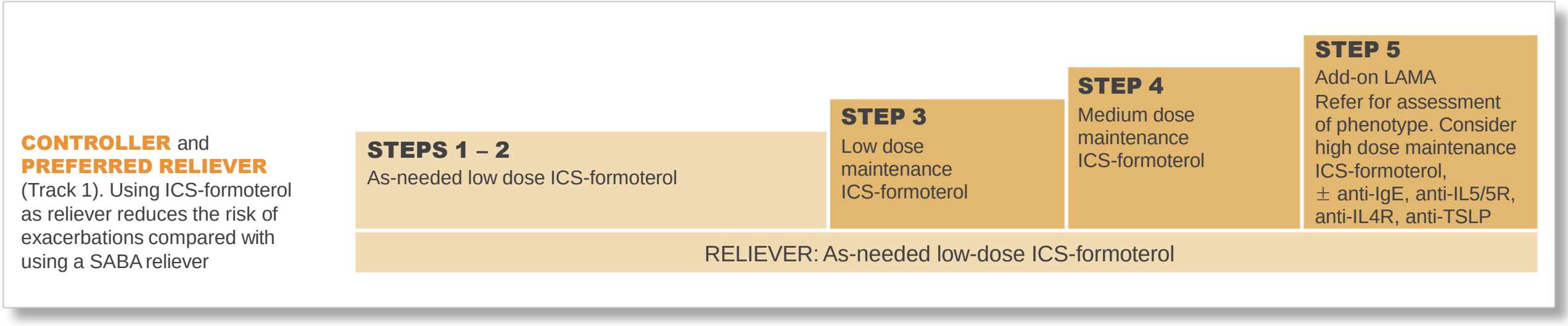
Contents

- Diagnosis
- Assessment of asthma control / severity
- **Treatment: Reliever**
- Treatment: Add-on therapy (LAMA & Biologic agent)
- Management of asthma during COVID-19

GINA treatment options: Two tracks for reliever

- **Track 1 with low dose ICS-formoterol as the reliever**
  - **Track 1 is preferred** because using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and lung function.



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GINA treatment options: Two tracks for reliever

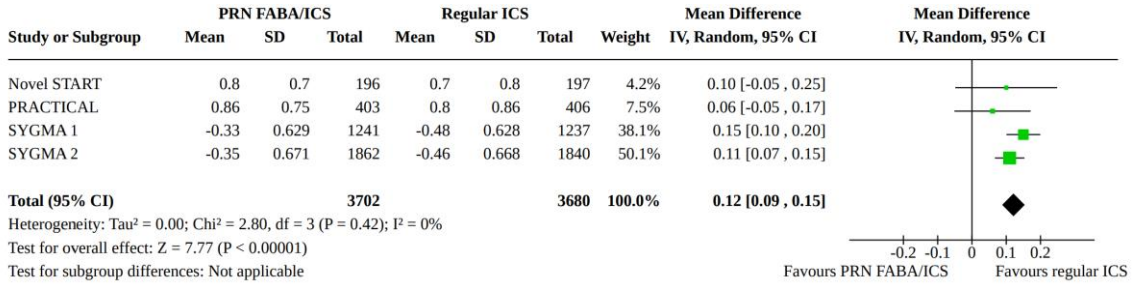
- **ACQ-5, FEV_1, FeNO**

  : as needed Budesonide + Formoterol < Budesonide maintenance + as needed albuterol

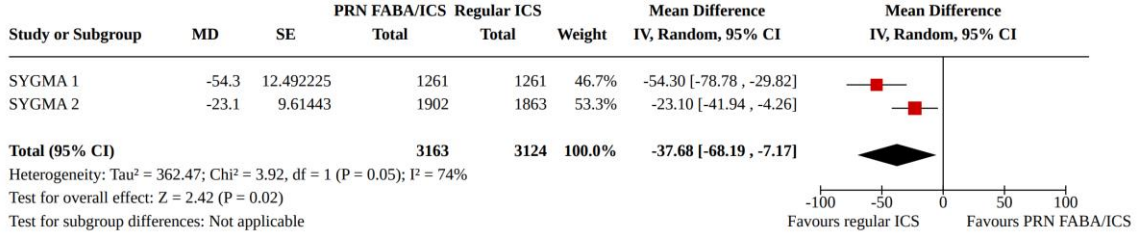
- Meta-analysis of all four RCTs, n=9,565
  - ✓ ACQ-5 mean difference 0.15 (MCID 0.5)
  - ✓ FEV_1 mean difference ~54 mL
  - ✓ FeNO mean difference ~10ppb

- Small differences but all were less than the minimal clinically important difference (MCID)

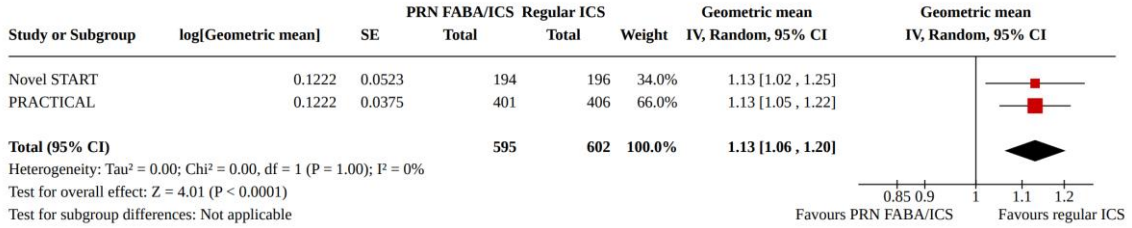
ACQ-5



FEV_1



FeNO



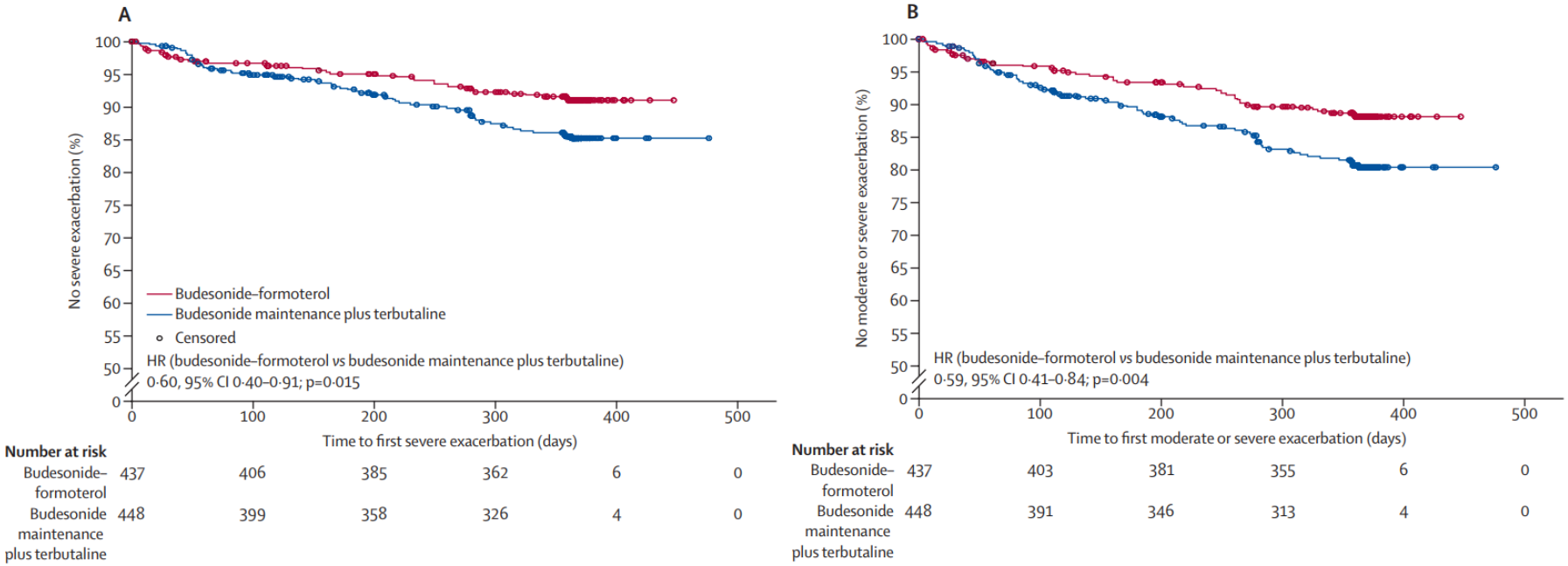
Cochrane Database Syst Rev. 2021 May 4;5(5):CD013518.

GINA treatment options: Two tracks for reliever

- **Severe exacerbation**

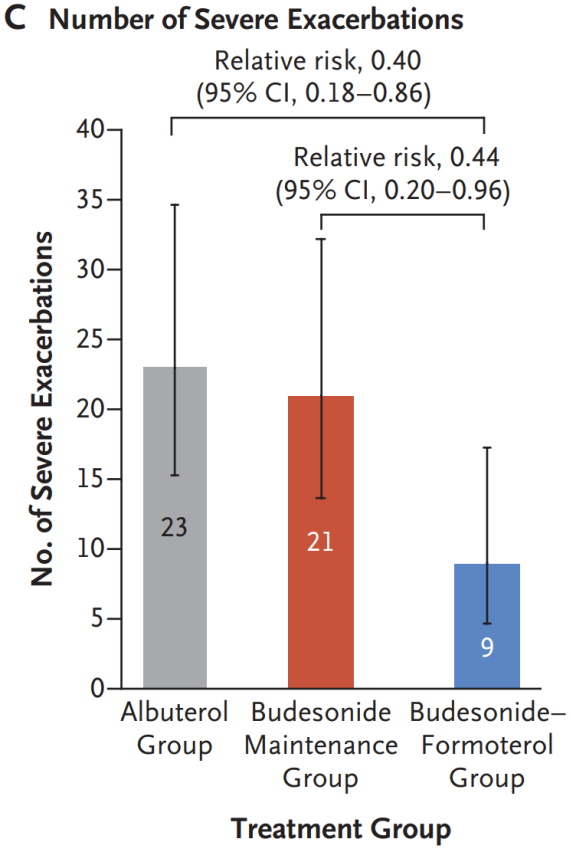
  : as needed Budesonide + Formoterol >= Budesonide maintenance + as needed albuterol

PRACTICAL trial



Lancet. 2019 Sep 14;394(10202):919-928.

Novel START trial



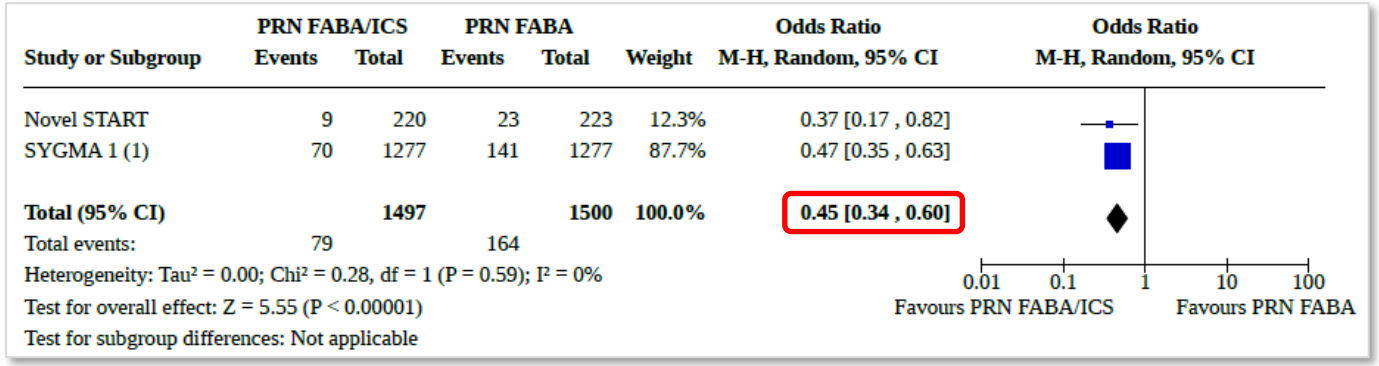
N Engl J Med 2019; 380:2020-2030

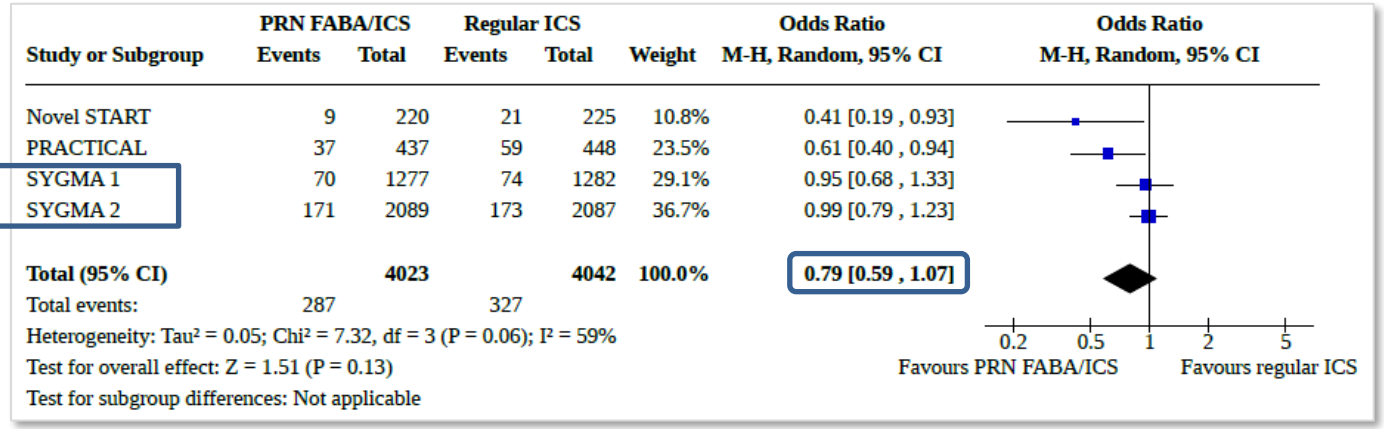
GINA treatment options: Two tracks for reliever

- **Severe exacerbation**

  : as needed Budesonide + Formoterol >= Budesonide maintenance + as needed albuterol

- Meta-analysis of all four RCTs, n=9,565
  - ✓ **55% reduction in severe exacerbations compared with SABA alone**
  - ✓ **Similar risk of severe exacerbations as with daily ICS + SABA reliever**





SYGMA I & II study

: **Both** previously **controlled & uncontrolled** patients were included.

➔ Are there different results in **uncontrolled patients**?

Cochrane Database Syst Rev. 2021 May 4;5(5):CD013518.

GINA treatment options: Two tracks for reliever

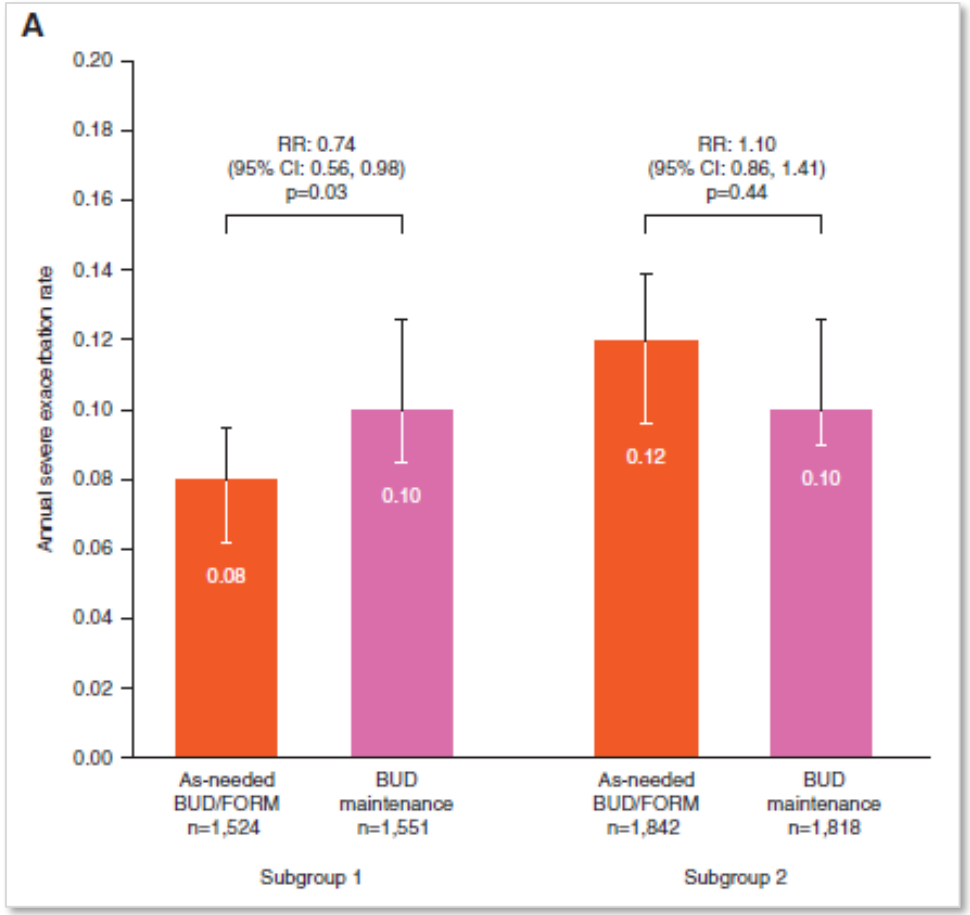
- **Severe exacerbation**

  : as needed Budesonide + Formoterol >= Budesonide maintenance + as needed albuterol

- Post-hoc analysis of SYGMA I & II
  - Subgroup 1: **previously uncontrolled on as-needed SABA**
  - Subgroup 2: **previously controlled on LD-ICS or LTRA**

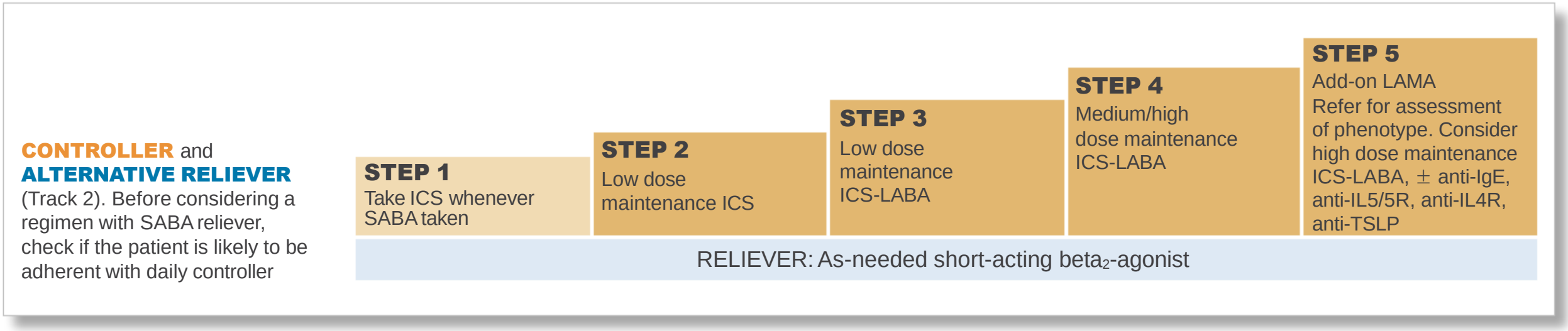
- Patients previously taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA

Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017.



GINA treatment options: Two tracks for reliever

- **Track 2, with SABA as the reliever, is an 'alternative' (non-preferred) strategy**
  - Use Track 2
    - ✓ If Track 1 is not possible or not preferred.
    - ✓ If a patient has good adherence with their controller, and had no exacerbations in the last 12 months



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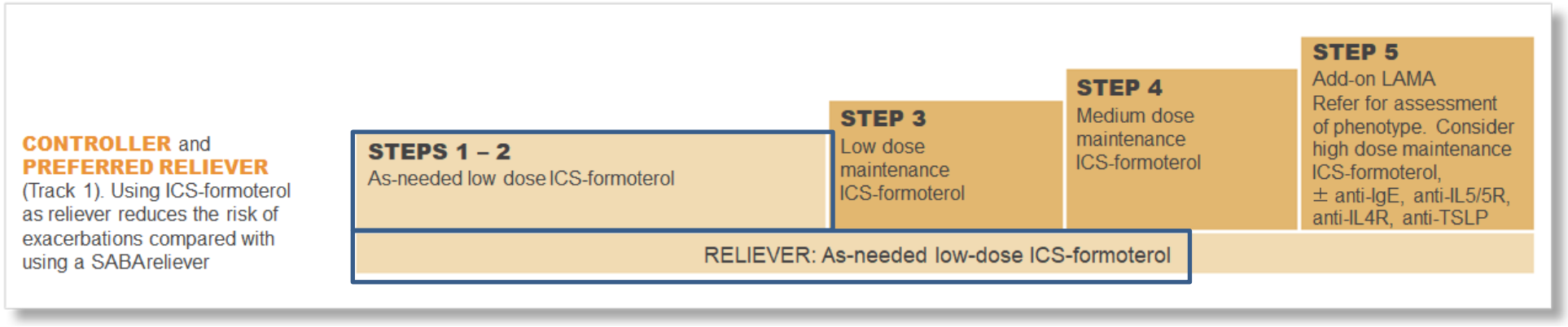
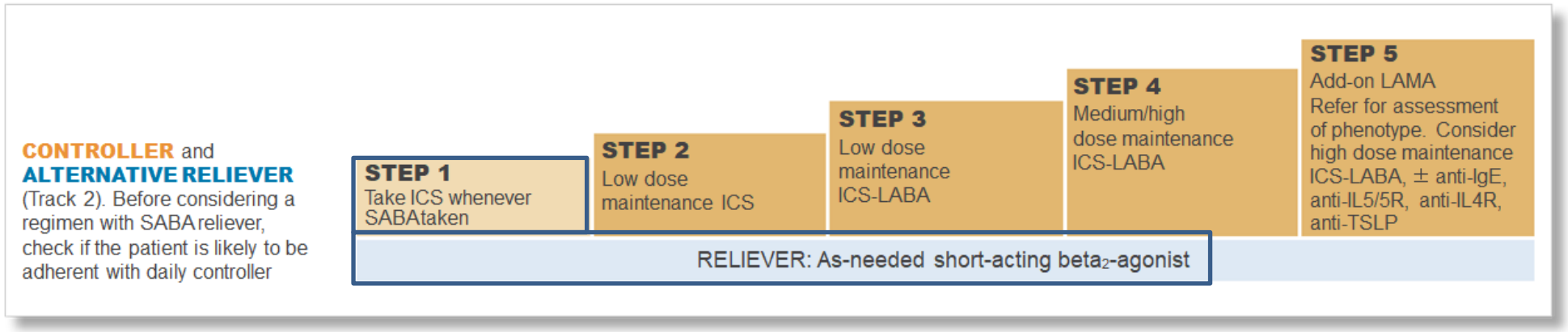
Other treatment options

- **Other controller/reliever options**
  - Limited indications, or less evidence for efficacy and/or safety than Track 1 or 2 options





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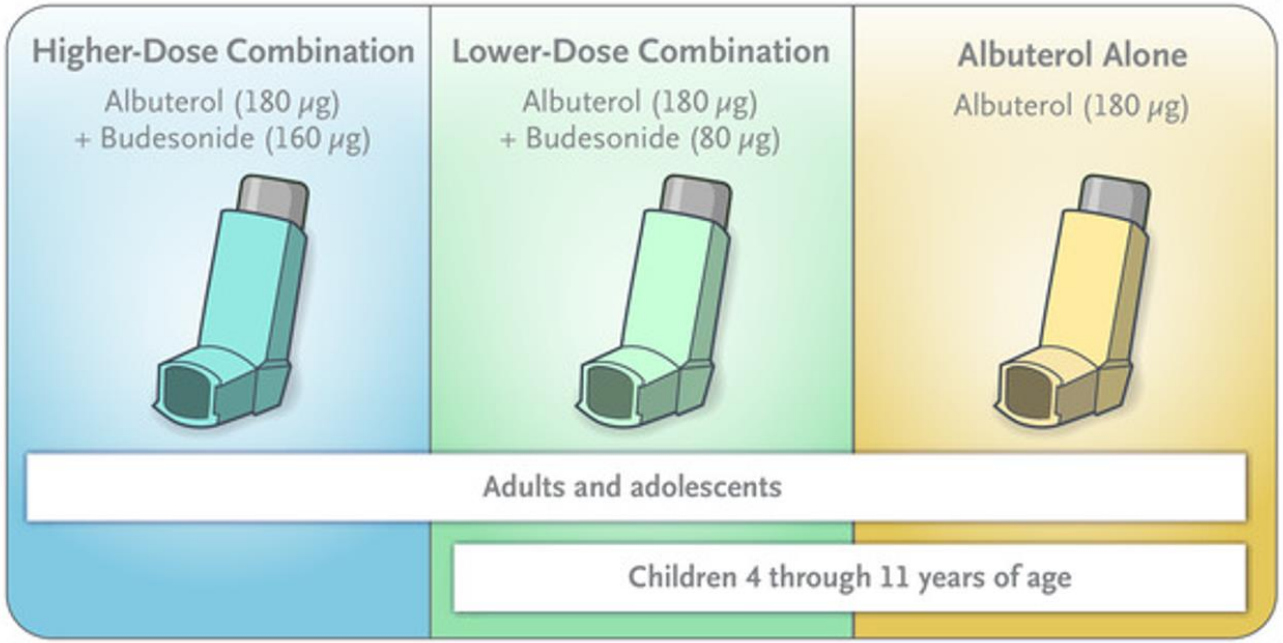
As needed ICS + SABA

- MANDALA trial
- Phase 3, Double-blind, Randomized controlled trial
- Uncontrolled moderate-to-severe asthma patients, ≥4 years old, previous history of ≥1 exacerbation
- **Maintenance treatment**: medium-to-high dose ICS or low-to-high dose ICS/LABA

Intervention: Three reliever (as needed therapy)

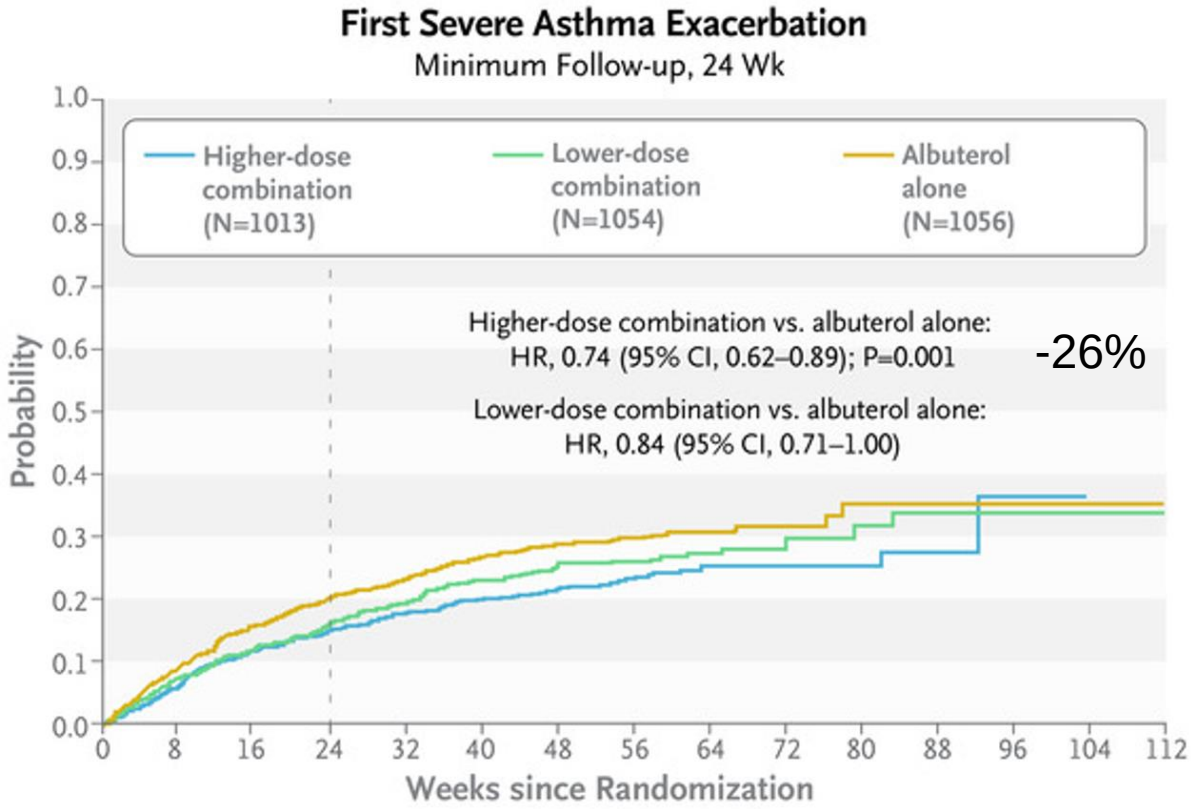


N Engl J Med. 2022 Jun 2;386(22):2071-2083.

As needed ICS + SABA > SABA alone

Table 1. Demographic and Clinical Characteristics of the Patients at Screening.*

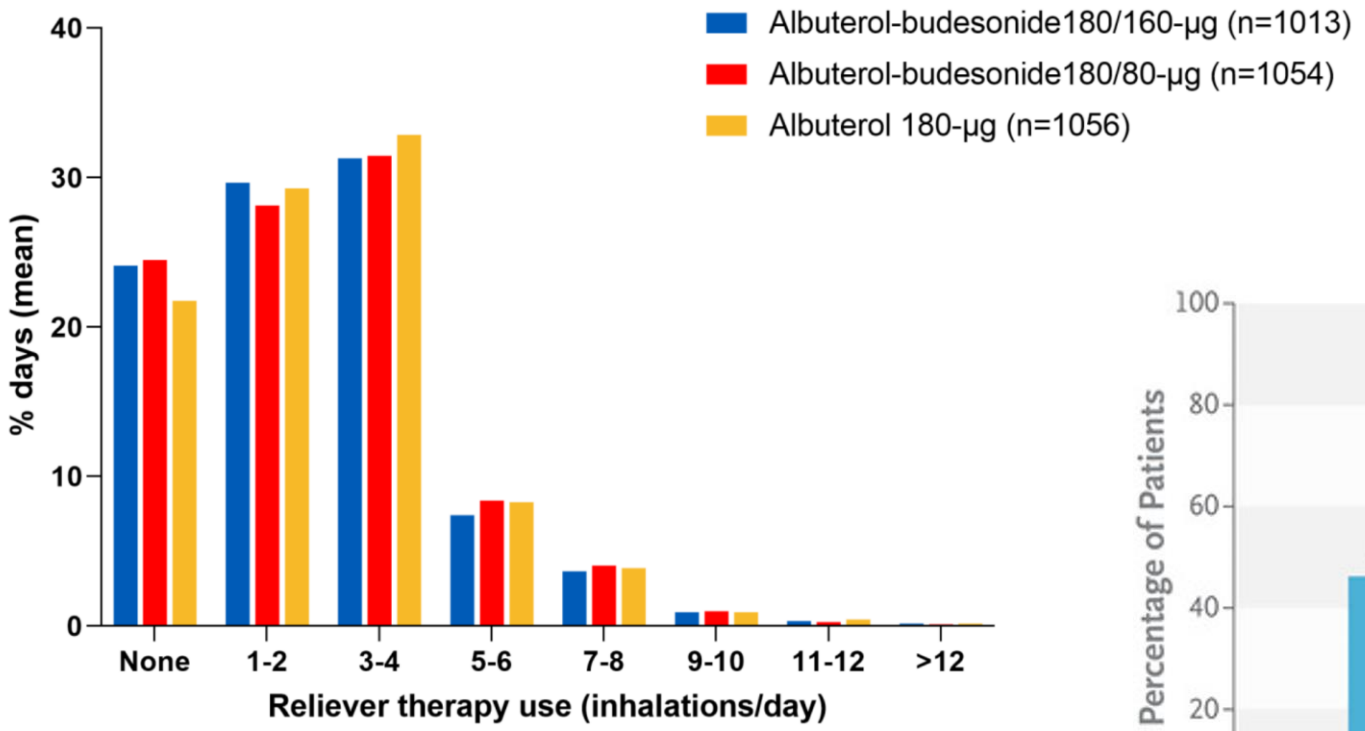
Characteristic	Albuterol (180 μg)–Budesonide (160 μg) (N=1013)	Albuterol (180 μg)–Budesonide (80 μg) (N=1054)	Albuterol (180 μg) (N=1056)	All Patients (N=3123)
Maintenance treatment — no. (%)				
Low-dose inhaled glucocorticoid–LABA or medium-dose inhaled glucocorticoid	314 (31.0)	334 (31.7)	308 (29.2)	956 (30.6)
Medium-dose inhaled glucocorticoid–LABA or high-dose inhaled glucocorticoid	385 (38.0)	435 (41.3)	441 (41.8)	1261 (40.4)
High-dose inhaled glucocorticoid–LABA	295 (29.1)	267 (25.3)	285 (27.0)	847 (27.1)
Missing	19 (1.9)	18 (1.7)	22 (2.1)	59 (1.9)
Severe asthma exacerbations in the 12 mo before screening — no. (%)				
1	788 (77.8)	822 (78.0)	840 (79.5)	2450 (78.5)
2	185 (18.3)	185 (17.6)	164 (15.5)	534 (17.1)
3	27 (2.7)	38 (3.6)	45 (4.3)	110 (3.5)
≥4	13 (1.3)	9 (0.9)	7 (0.7)	29 (0.9)

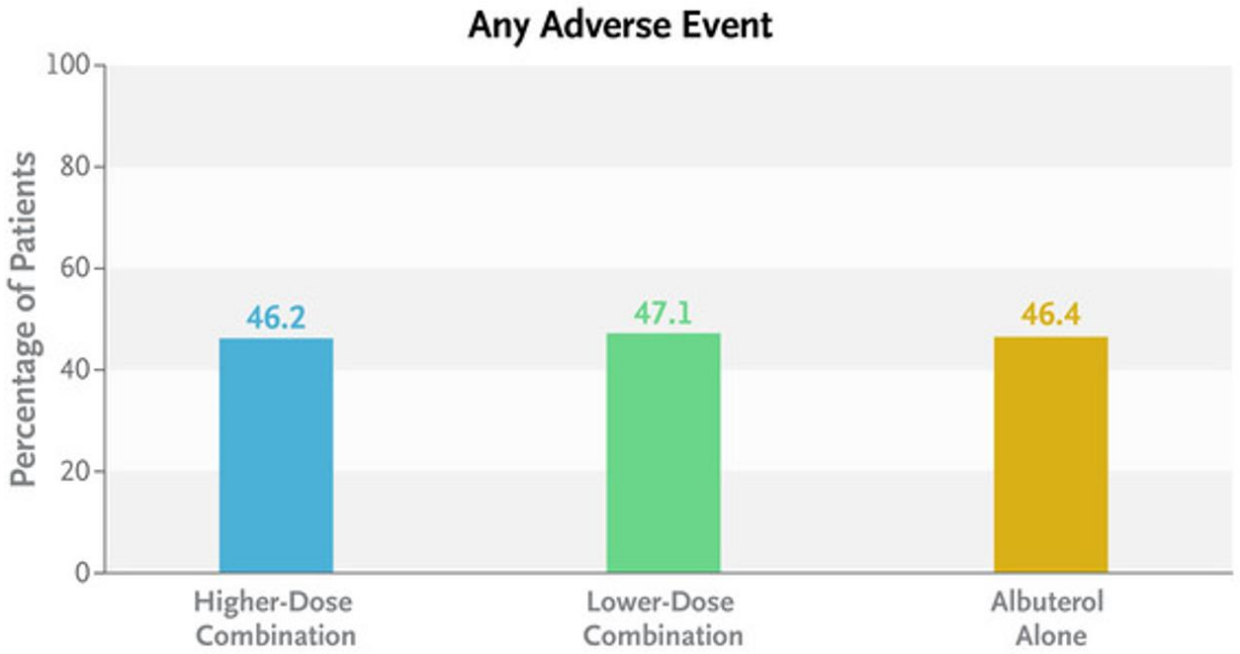


-26%

N Engl J Med. 2022 Jun 2;386(22):2071-2083.

Similar frequency of reliever and adverse events





N Engl J Med. 2022 Jun 2;386(22):2071-2083.

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- **Treatment: Add-on therapy (LAMA & Biologic agent)**
- Management of asthma during COVID-19

LAMA monotherapy for severe asthma

- In GINA 2022, **LAMA**, like LABA, **should not be used as monotherapy** without ICS in asthma

  ➔ **Increased risk of severe exacerbations**

	Treatment exposure periods (n = 329) considering mixed patients (n = 74) only		
	Relative Risk	95% CI	p-value
Mono therapy	**5.72**	**1.39-23.62**	**0.016**
Dual therapy	Ref	Ref	–
Triple therapy	N/A	N/A	N/A
Female sex	0.77	0.22-2.69	0.677
Age	0.95	0.89-1.00	0.065
History of exacerbations	2.14	0.92-5.01	0.079
Allergic rhinitis	0.86	0.27-2.70	0.793
Sinusitis	0.00	0.00-∞	1.00
Depression	**5.09**	**1.27-20.35**	**0.021**
Lower respiratory tract infection	**6.04**	**1.53- 23.90**	**0.011**
Smoking: never	ref		
Smoking: current	0.24	0.048-1.20	0.083
Smoking: past	0.00	0.00-∞	1.000
Smoking: unknown	0.00	0.00-∞	1.000

Pulm Pharmacol Ther. 2021 Dec;71:102074.

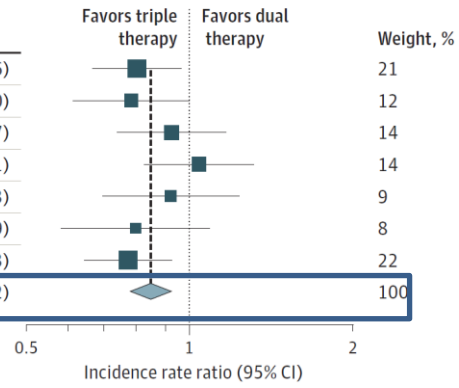
Add-on LAMA for severe asthma

- Reinforced evidence on add-on therapy of **LAMA to MD- or HD-ICS/LABA** in severe asthma
  - ➢ Recent systematic review and meta-analysis confirmed previous findings

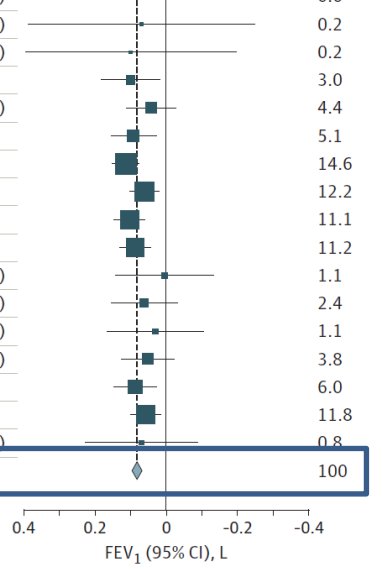
    : Add-on LAMA **reduced 15% of exacerbation rate / improved FEV_1 of 80mL** compared to ICS/LABA

A Incidence rate ratio of exacerbations

Source	Mean annualized exacerbation rate[a] Triple	Dual	Incidence rate ratio (95% CI)	Weight, %
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)	21
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)	12
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)	14
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)	14
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)	9
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)	8
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)	22
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)	100



Source	Triple therapy No.	Triple therapy FEV_1, mean (SD), L	Dual therapy No.	Dual therapy FEV_1, mean (SD), L	FEV_1, mean difference (95% CI), L	Weight, %
Hamelmann et al,[50] 2017	256	0.31 (0.78)	132	0.23 (0.55)	0.08 (-0.05 to 0.22)	1.2
Hoshino et al,[51] 2018	29	0.11 (0.08)	30	0.02 (0.11)	0.09 (0.04 to 0.14)	8.6
Ishiura et al,[52] 2019	17	0.20 (0.28)	17	0.07 (0.29)	0.13 (-0.06 to 0.32)	0.6
Ishiura et al,[53] 2020	19	0.10 (0.29)	19	-0.01 (0.29)	0.11 (-0.07 to 0.29)	0.6
Jabbal et al,[47] 2017	14	0.15 (0.43)	14	0.08 (0.43)	0.07 (-0.25 to 0.39)	0.2
Jabbal et al,[54] 2020	16	0.21 (0.43)	16	0.11 (0.42)	0.10 (-0.20 to 0.40)	0.2
Kerstjens et al,[48] 2011	67	0.15 (0.25)	33	0.05 (0.17)	0.10 (0.02 to 0.18)	3.0
Kerstjens et al,[46] 2012[a]	237	0.13 (0.39)	222	0.09 (0.37)	0.04 (-0.03 to 0.11)	4.4
Kerstjens et al,[46] 2012[a]	216	0.16 (0.34)	232	0.06 (0.35)	0.09 (0.03 to 0.16)	5.1
Kerstjens et al,[55] 2020[a]	614	0.45 (0.37)	1213	0.34 (0.42)	0.11 (0.08 to 0.15)	14.6
Kerstjens et al,[55] 2020[a]	614	0.39 (0.35)	602	0.33 (0.38)	0.06 (0.02 to 0.10)	12.2
Lee et al,[56] 2020[a]	803	0.13 (0.44)	400	0.02 (0.31)	0.10 (0.06 to 0.15)	11.1
Lee et al,[56] 2020[a]	804	0.16 (0.44)	403	0.08 (0.31)	0.09 (0.04 to 0.13)	11.2
Pearl Therapeutics,[57] 2017	702	0.13 (1.77)	193	0.13 (0.32)	0.01 (-0.13 to 0.14)	1.1
Ohta et al,[58] 2015	228	0.14 (0.41)	57	0.08 (0.29)	0.06 (-0.03 to 0.15)	2.4
Singh et al,[59] 2014	152	0.14 (0.70)	49	0.11 (0.28)	0.03 (-0.11 to 0.17)	1.1
Szefler et al,[49] 2017	263	0.19 (0.43)	130	0.14 (0.31)	0.05 (-0.02 to 0.13)	3.8
Virchow et al,[45] 2019[a]	826	0.24 (0.71)	547	0.16 (0.41)	0.09 (0.03 to 0.15)	6.0
Virchow et al,[45] 2019[a]	557	0.18 (0.36)	553	0.13 (0.36)	0.06 (0.02 to 0.10)	11.8
Zhang et al,[62] 2018	40	0.75 (0.44)	40	0.68 (0.26)	0.07 (-0.09 to 0.23)	0.8
Overall: $I^2 = 0\%$	6474		4902		0.08 (0.07 to 0.10)	100



JAMA. 2021 Jun 22;325(24):2466-2479.

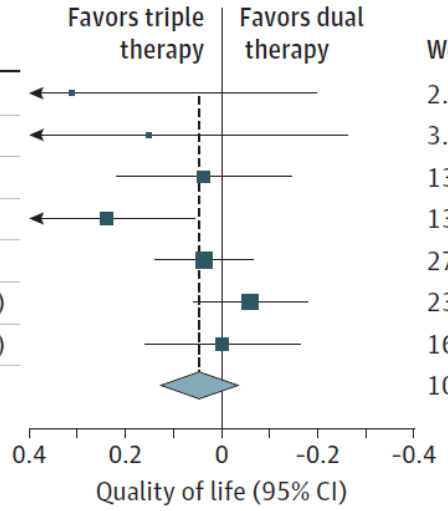
Add-on LAMA for severe asthma

- Reinforced evidence on add-on therapy of **LAMA to MD- or HD-ICS/LABA** in severe asthma
  - ➢ Recent systematic review and meta-analysis confirmed previous findings

    : **<u>No benefit for symptoms or quality of life ➔ Do not prescribe for dyspnea</u>**

B Quality of life

Source	Scale[a]	Triple therapy No.	Triple therapy Mean (SD)	Dual therapy No.	Dual therapy Mean (SD)	Standardized mean difference (95% CI)	Weight, %
Hoshino et al,[51] 2018	AQLQ	29	0.50 (1.00)	30	0.20 (0.90)	0.31 (-0.20 to 0.83)	2.4
Kerstjens et al,[48] 2011	Mini-AQLQ	67	0.21 (0.69)	33	0.11 (0.49)	0.15 (-0.26 to 0.57)	3.5
Kerstjens et al,[46] 2012[b]	AQLQ	237	0.55 (1.01)	222	0.51 (1.01)	0.04 (-0.15 to 0.22)	13.8
Kerstjens et al,[46] 2012[b]	AQLQ	216	0.48 (0.96)	232	0.24 (1.02)	0.24 (0.06 to 0.43)	13.5
Kerstjens et al,[55] 2020[b]	AQLQ	552	0.87 (0.82)	1093	0.83 (1.19)	0.04 (-0.07 to 0.14)	27.1
Kerstjens et al,[55] 2020[b]	AQLQ	535	0.76 (0.83)	536	0.81 (0.83)	-0.06 (-0.18 to 0.06)	23.3
Pearl Therapeutics,[57] 2017	AQLQ	667	0.95 (4.94)	188	0.96 (1.01)	-0.00 (-0.16 to 0.16)	16.4
Overall: $I^2 = 32\%$		2303		2334		0.05 (-0.03 to 0.13)	100



JAMA. 2021 Jun 22;325(24):2466-2479.

Safety of omalizumab in pregnant asthmatics

- **No increased risk of congenital malformations with use of omalizumab** compared with asthma population

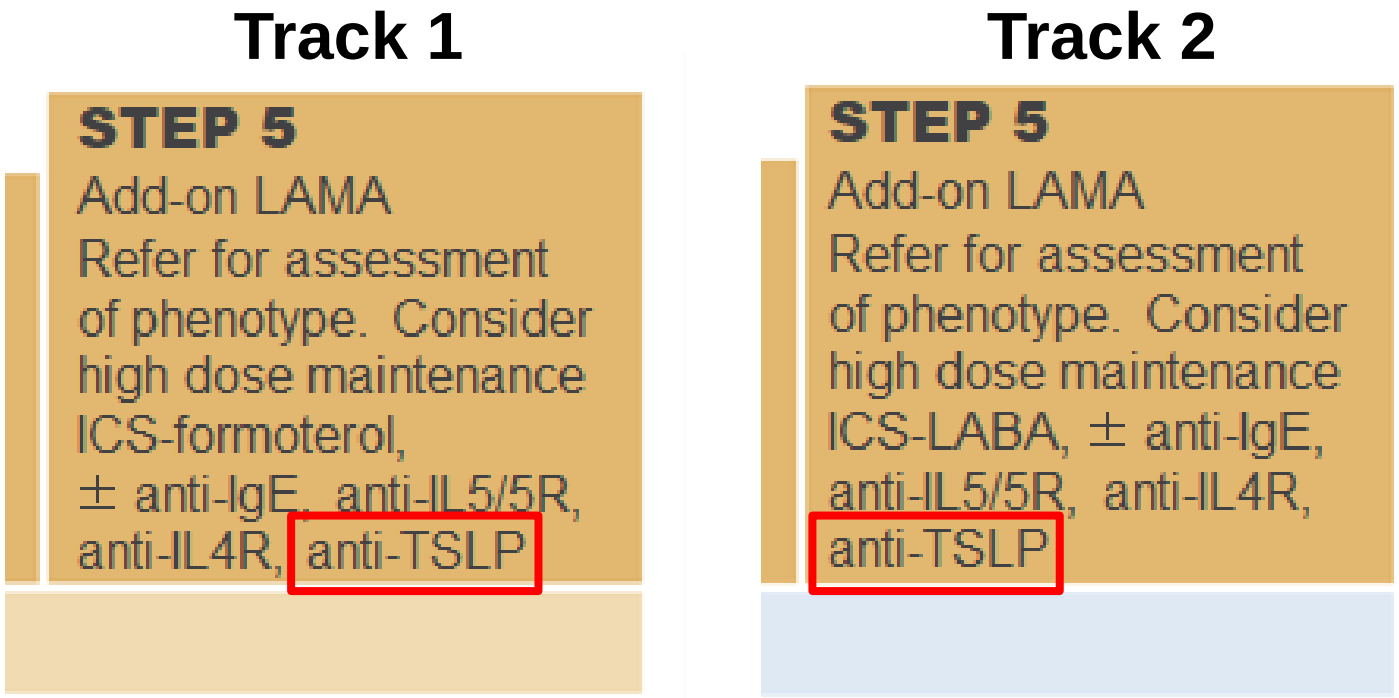
- The Xolair Pregnancy Registry (EXPECT)

Data source	Citation	Major congenital anomalies
EXPECT		4.4 (1.8-8.8)
General population		
MACDP	Correa 2007[32]; Rynn 2008[25]	2.8[32]
CBDMP	Calif Dept Public Health[33]	2.9
NYSCMR	NY Dept Public Health[34]	3.1
TBDR	Tex Dept State Health[35]	4.2
DNBR/DNPR	Pasternak 2013[18]	2.9
NCHS	Martin 2013[24]; MMWR[23]; MacDorman 2012[19]	
Kaiser Permanente	Ammon Avalos 2012[28]	
Asthma population		
ISQ	Blais 2009[16]; Blais 2007[17]	
MED-ECHO	All asthma	6.1[16]
RAMQ	ICS (≤1000 μg)	5.7[16]
	ICS (>1000 μg)	8.3[16]
	OCS	7.3[17]
	SABA	6.1[17]
	LABA	9.1[17]
OTIS Network	Bakhireva 2007[15]	
	β_2-agonists	3.9
	LTRAs	6.0
Soroka Univ Med Ctr	Sheiner 2005[27]	3.8
Int'l Teratogen Information Services	Sarkar 2009[26]	2.7
Health Improvement Network Database (UK)	Tata 2007[20]	

J Allergy Clin Immunol. 2015 Feb;135(2):407-12

Anti-TSLP for severe asthma

- **Add-on biologic therapy for severe asthma**
  - Anti-thymic stromal lymphopoietin (anti-TSLP agent, tezepelumab) as a new biologic therapy for severe asthma in Step 5



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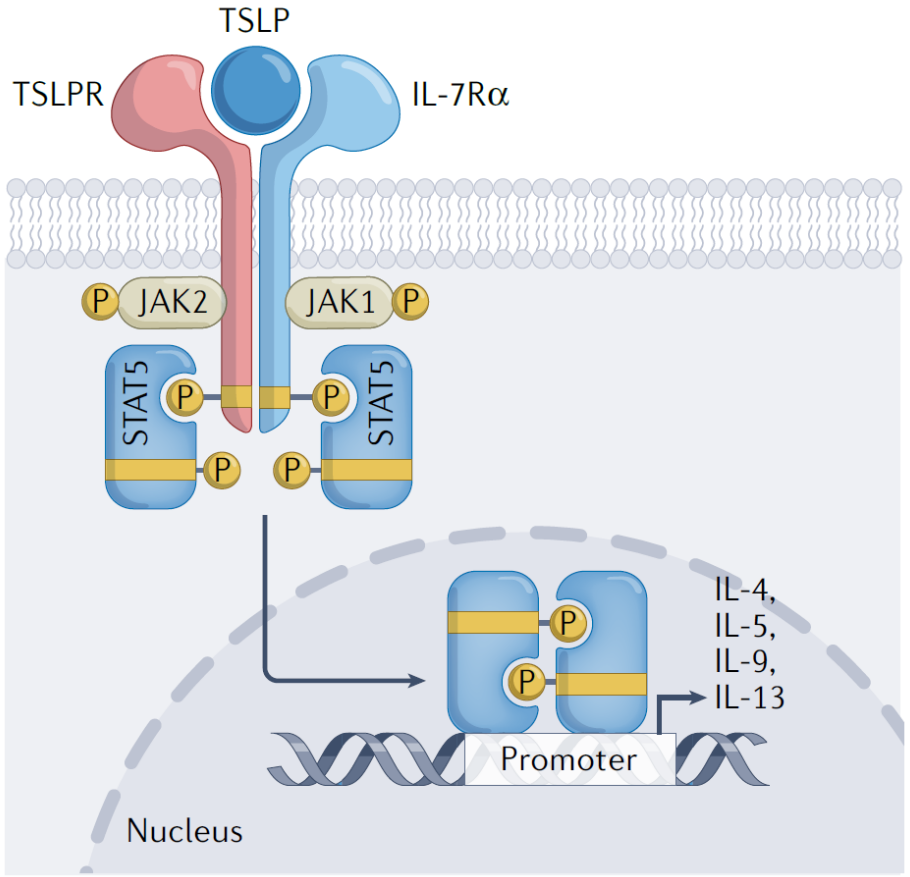
Thymic stromal lymphopoietin (TSLP)

- Initially isolated from a thymic stromal cell line supernatant

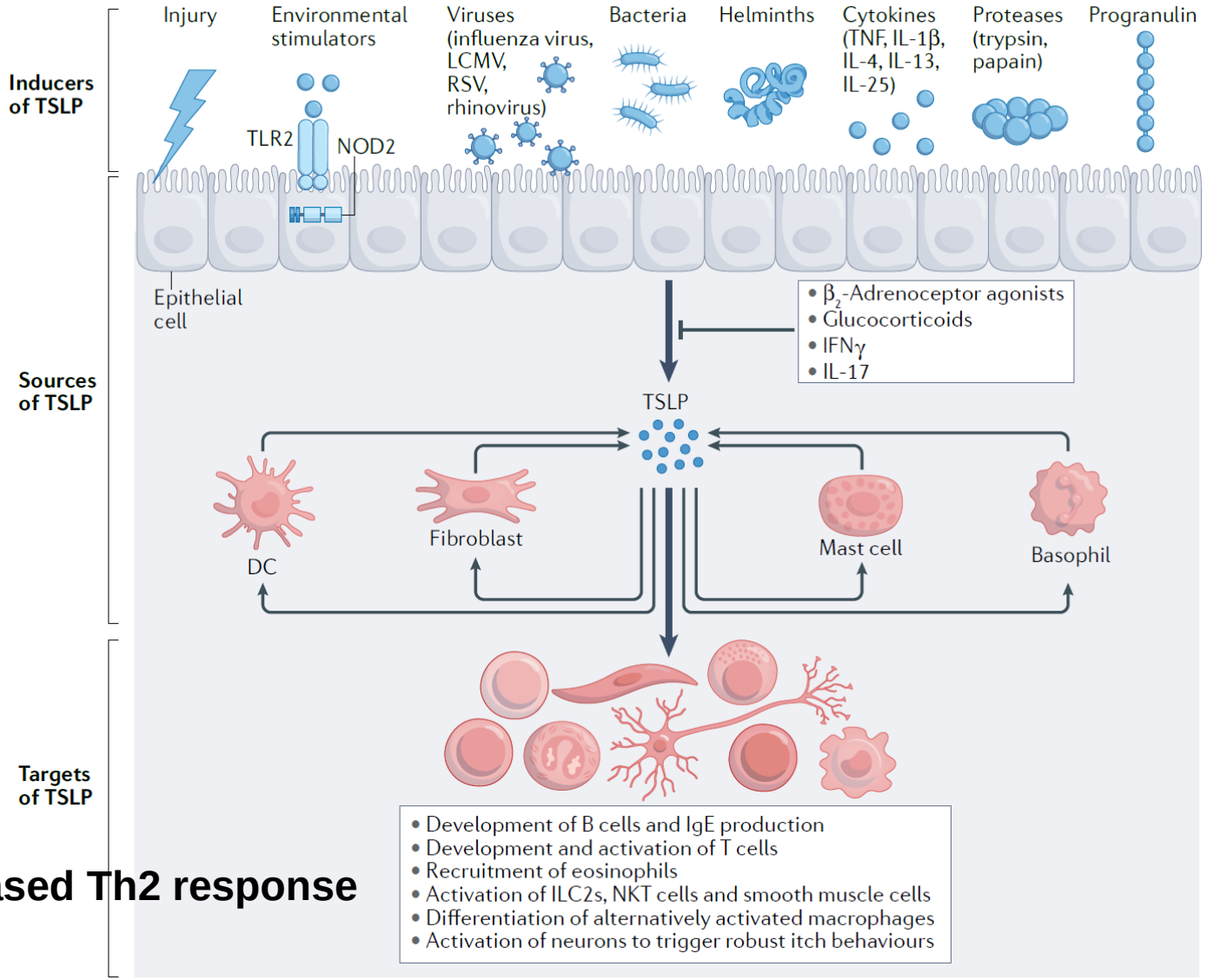
J Leukoc Biol. 2012;91(6):877–886.

- **IL-7 like hematopoietic cytokine**
  - ✓ IL-7: Lymphoid development & homeostasis
  - ✓ **TSLP: Related with allergic diseases**



Nat Rev Immunol. 2022 Jun 1;1-14.

Pathogenesis of TSLP



Increased Th2 response

Nat Rev Immunol. 2022 Jun 1;1-14.

Anti-TSLP in severe asthma

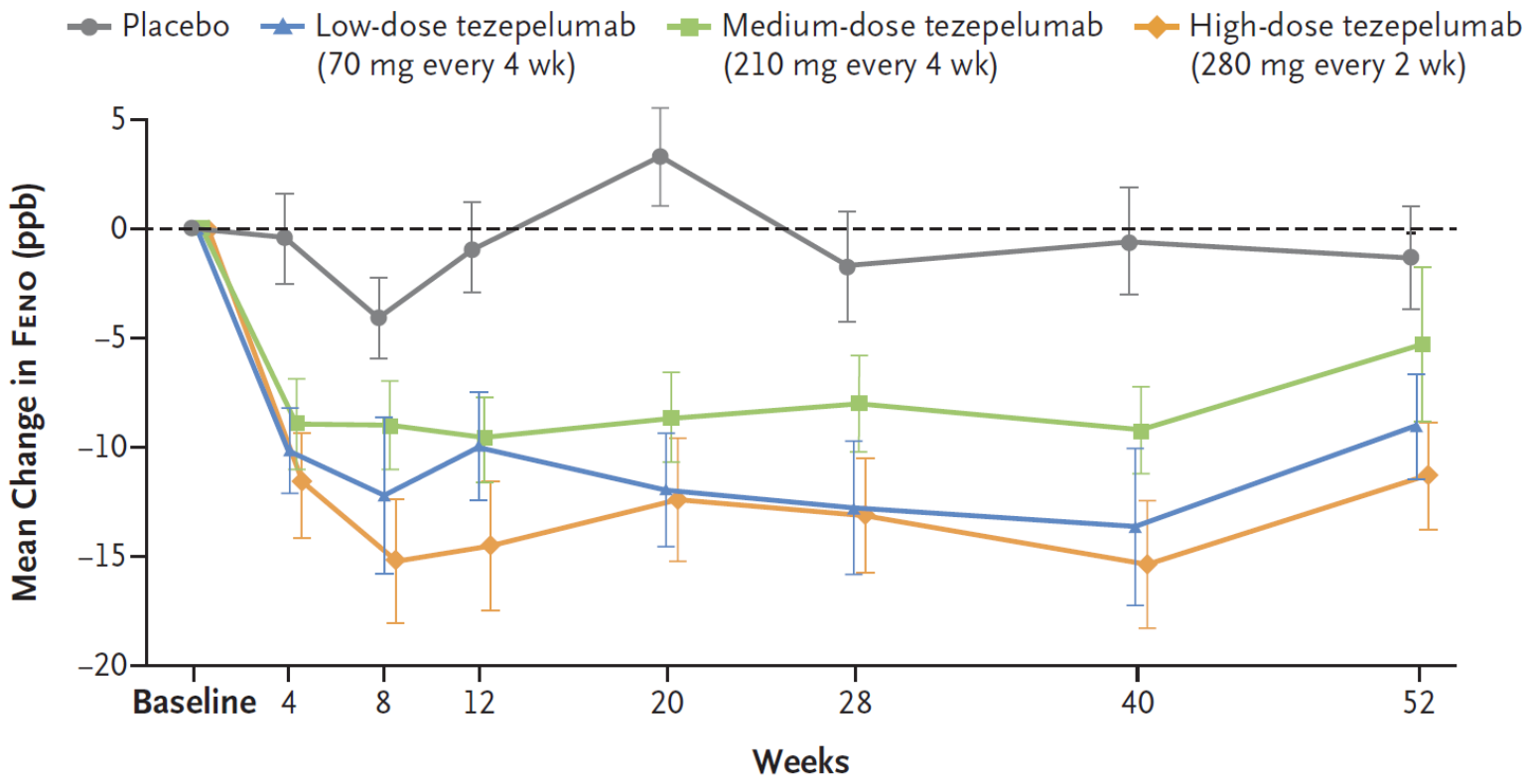
- PATHWAY trial, phase 2, RCT
- Current non-smoker, uncontrolled asthma with MD or HD-ICS/LABA
- Previous exacerbation: ≥2 moderate (steroid use) to ≥1 severe (hospitalization)
- **Placebo vs. Tezepelumab: 70 mg/4wk (low), 210 mg/4wk (medium), 280 mg/2wk (high) SC**
- 52 weeks

Variable	Placebo (N=138)	Low-Dose Tezepelumab (N=138)	Medium-Dose Tezepelumab (N=137)	High-Dose Tezepelumab (N=137)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.72 (0.61 to 0.86)	0.27 (0.20 to 0.36)	0.20 (0.14 to 0.28)	0.23 (0.17 to 0.32)
Relative reduction vs. placebo — % (90% CI)	—	62 (42 to 75)	71 (54 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001

N Engl J Med 2017; 377:936-946

Anti-TSLP reduced FeNO

B Change in FENO

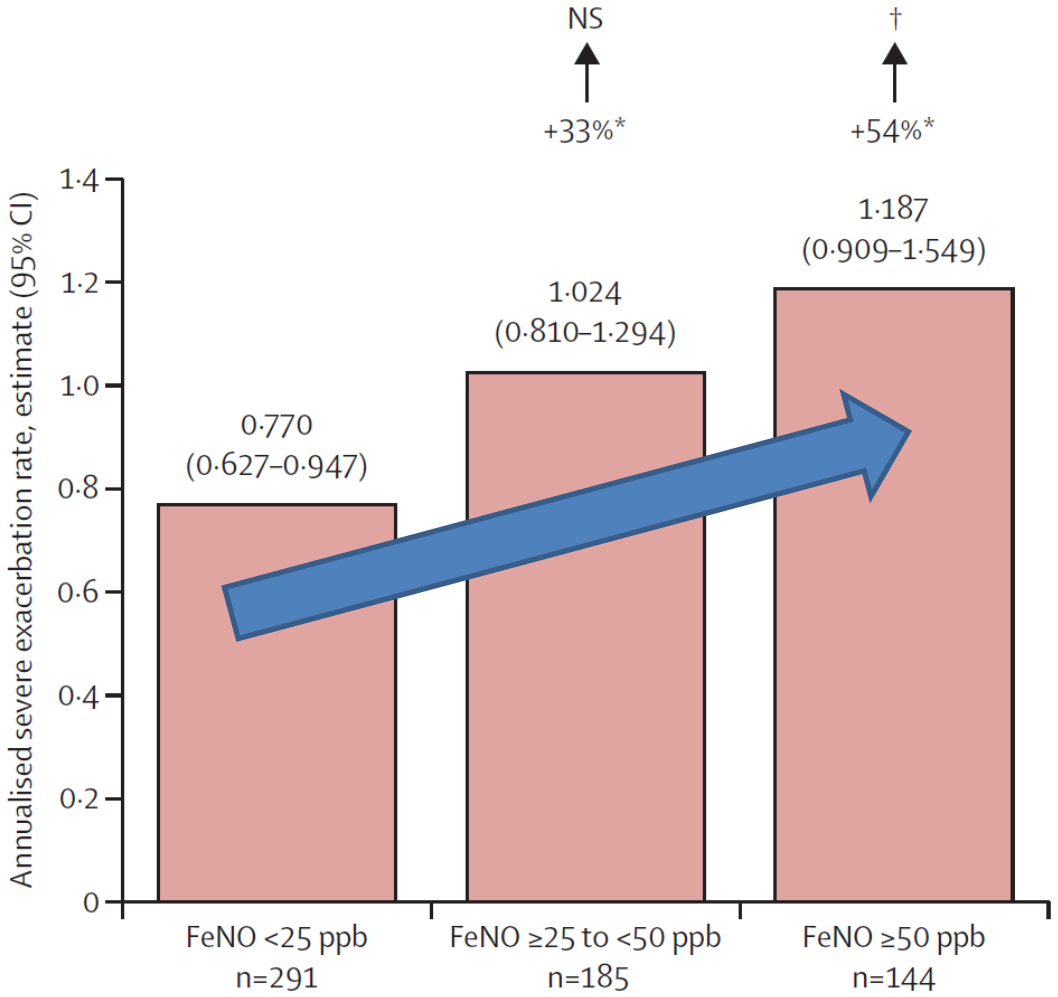


No. at Risk								
Placebo	137	113	113	114	109	107	111	108
Low-dose tezepelumab	137	106	103	107	102	111	101	104
Medium-dose tezepelumab	135	105	103	104	96	88	96	96
High-dose tezepelumab	133	103	102	106	87	96	97	99

N Engl J Med 2017; 377:936-946

FeNO as a prognostic marker

- Higher FeNO / eosinophil count are associated with greater risk of severe exacerbations (GINA 2022)
- Post-hoc analysis of LIBERTY ASTHMA QUEST study (Placebo vs. Dupilumab)



Blood eosinophil count (cells per µL)	FeNO <25 ppb	FeNO ≥25 to <50 ppb	FeNO ≥50 ppb
≥300	n=89 0·844 (0·589–1·210) p=0·2083*	n=97 1·235 (0·869–1·755) p=0·0186*	n=98 1·777 (1·245–2·536) p=0·0008*
≥150 to <300	n=96 0·818 (0·591–1·131) p=0·1504*	n=53 1·138 (0·761–1·701) p=0·0164*	n=25 0·475 (0·226–0·999) p=0·7164*
<150	n=106 0·556 (0·353–0·877)	n=35 0·616 (0·328–1·158) p=0·7490*	n=21 0·530 (0·235–1·195) p=0·9083*

FeNO (ppb)

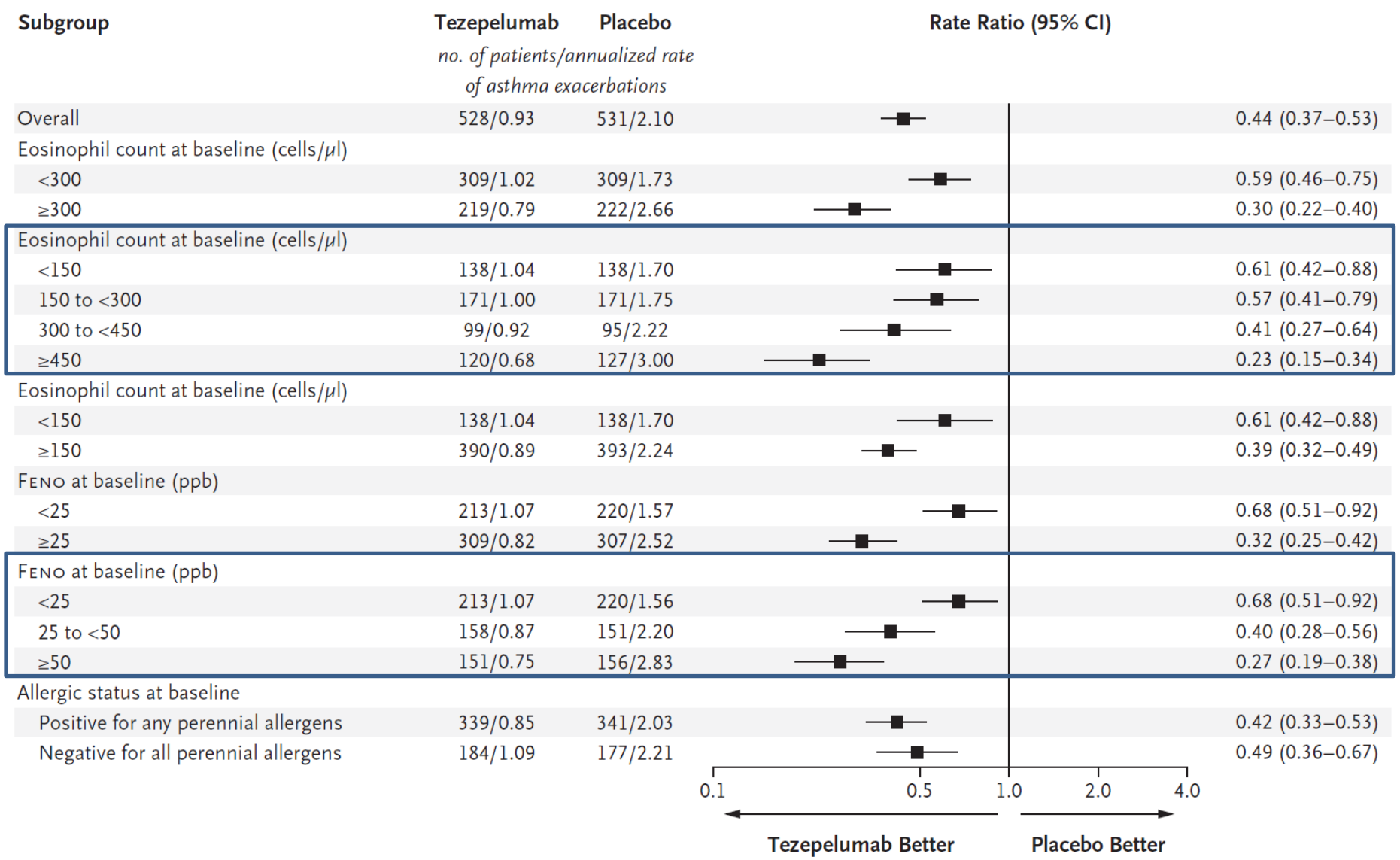
Lancet Respir Med 2021;9: 1165–73

Anti-TSLP in severe asthma

- NAVIGATOR trial, phase 3, RCT
- Uncontrolled asthma with MD or HD-ICS ± additional controller ± oral corticosteroid
- FEV_1<80%, BDR positivity (12% & 200ml), previous moderate-to-severe exacerbation ≥2
- Placebo vs. **Tezepelumab: 210 mg/4wk SC**
- 52 weeks

N Engl J Med 2021; 384:1800-1809

Anti-TSLP reduced acute exacerbation

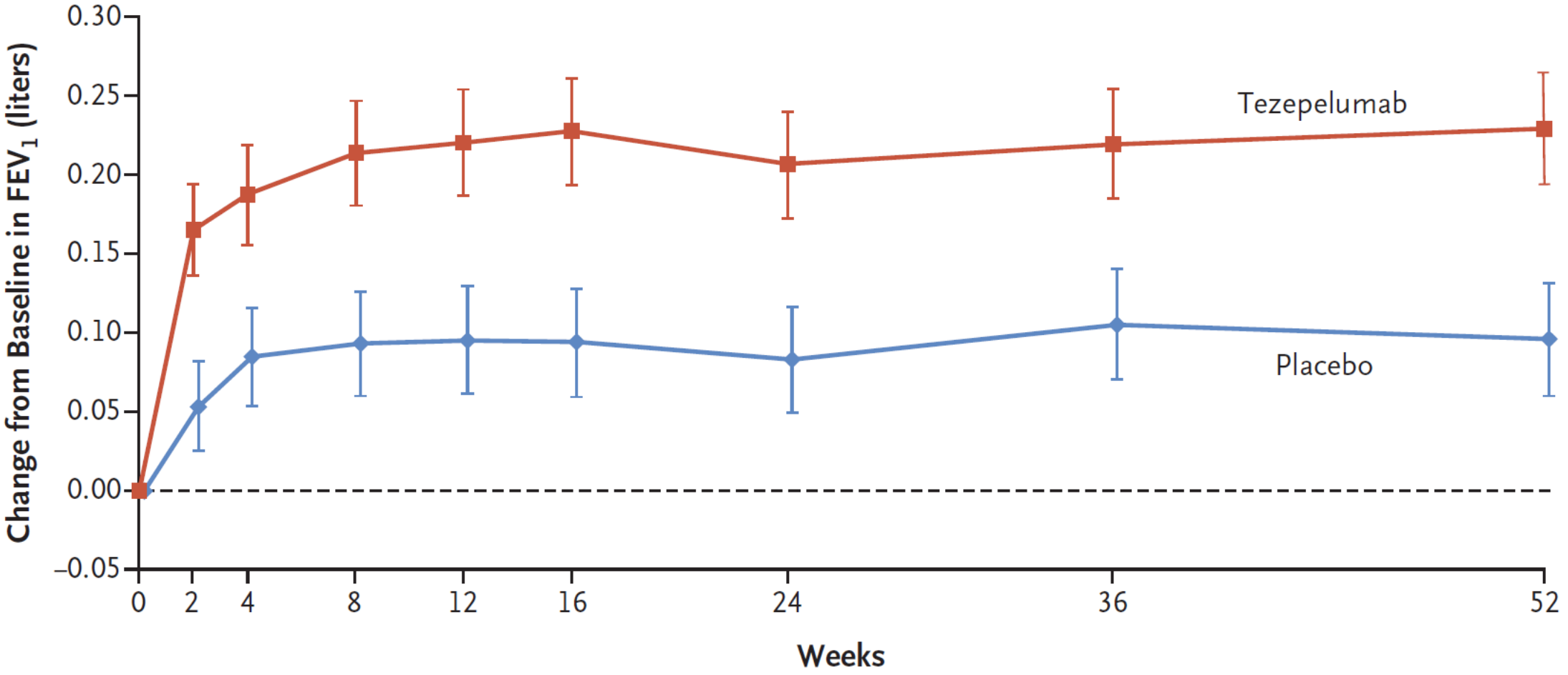


Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

-56%

N Engl J Med 2021; 384:1800-1809

Anti-TSLP improved FEV_1



N Engl J Med 2021; 384:1800-1809

Indication/Mechanism of Th2 biologic agents

Eligibility

Anti-IgE *(omalizumab)*

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

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

no / no

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

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

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

no / no

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

no / no

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

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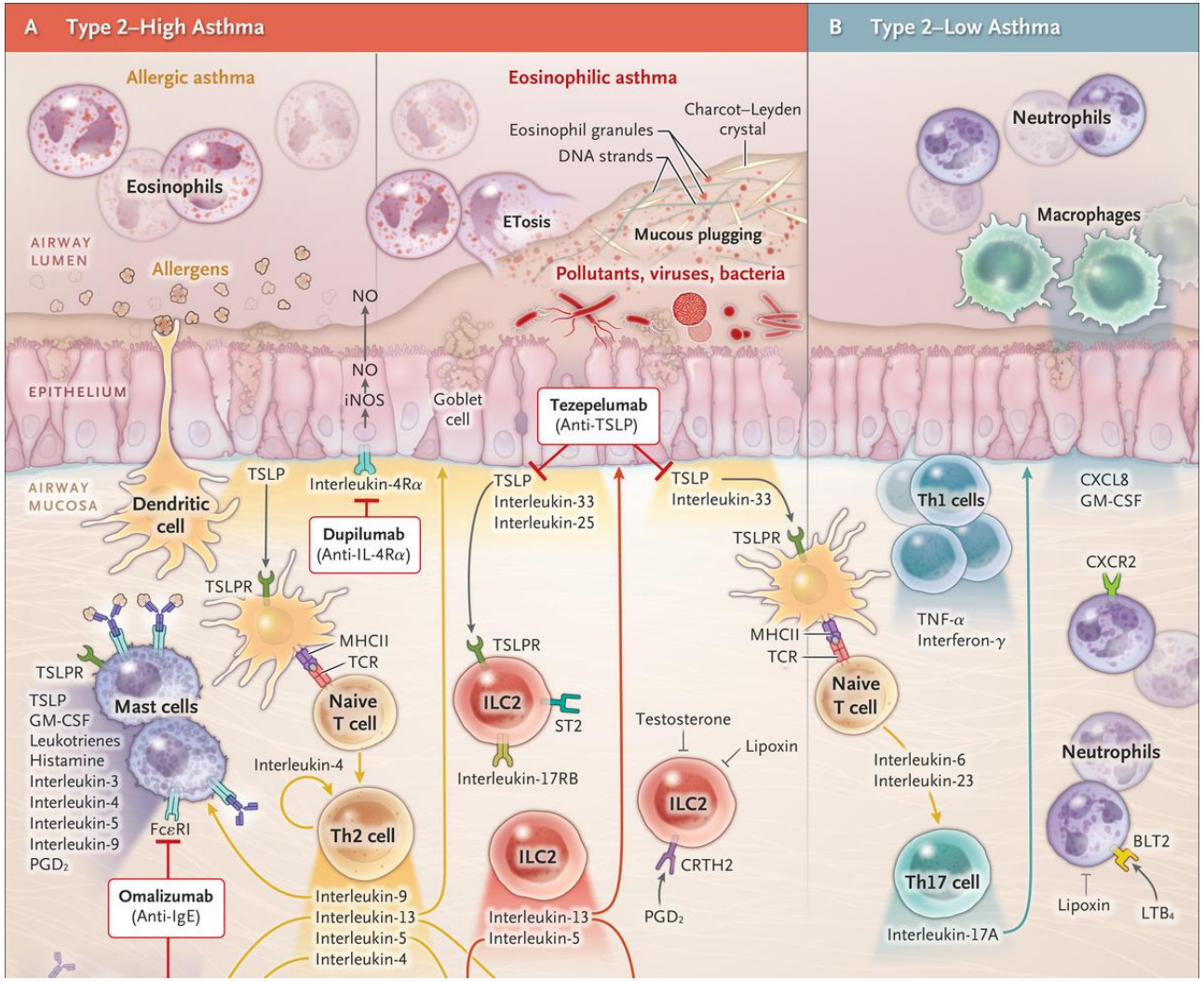


N Engl J Med 2022; 386:157-171

Anti-TSLP in non-TH2 asthma

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

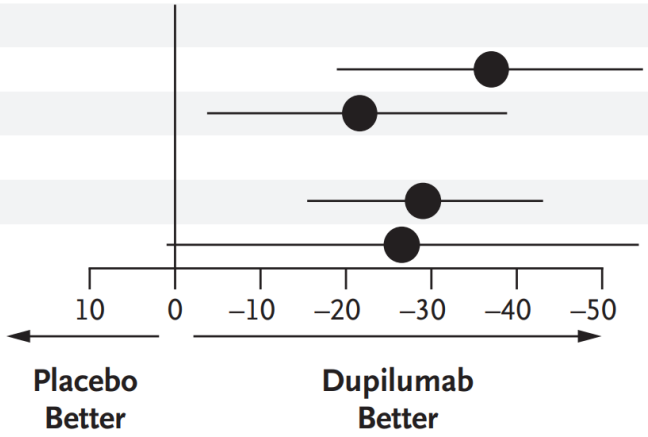
GINA report 2022

Anti-IL4R in asthmatics with OCS maintenance

- Phase 3, RCT
- Uncontrolled asthma with HD-ICS + controller (LABA or LTRA) & oral corticosteroid for ≥6 months
- FEV_1<80%, BDR positivity (12% & 200ml), or airway hyperresponsiveness
- No limitation regarding Th2 biomarker
- Placebo vs. **Dupilumab**
- 24 weeks

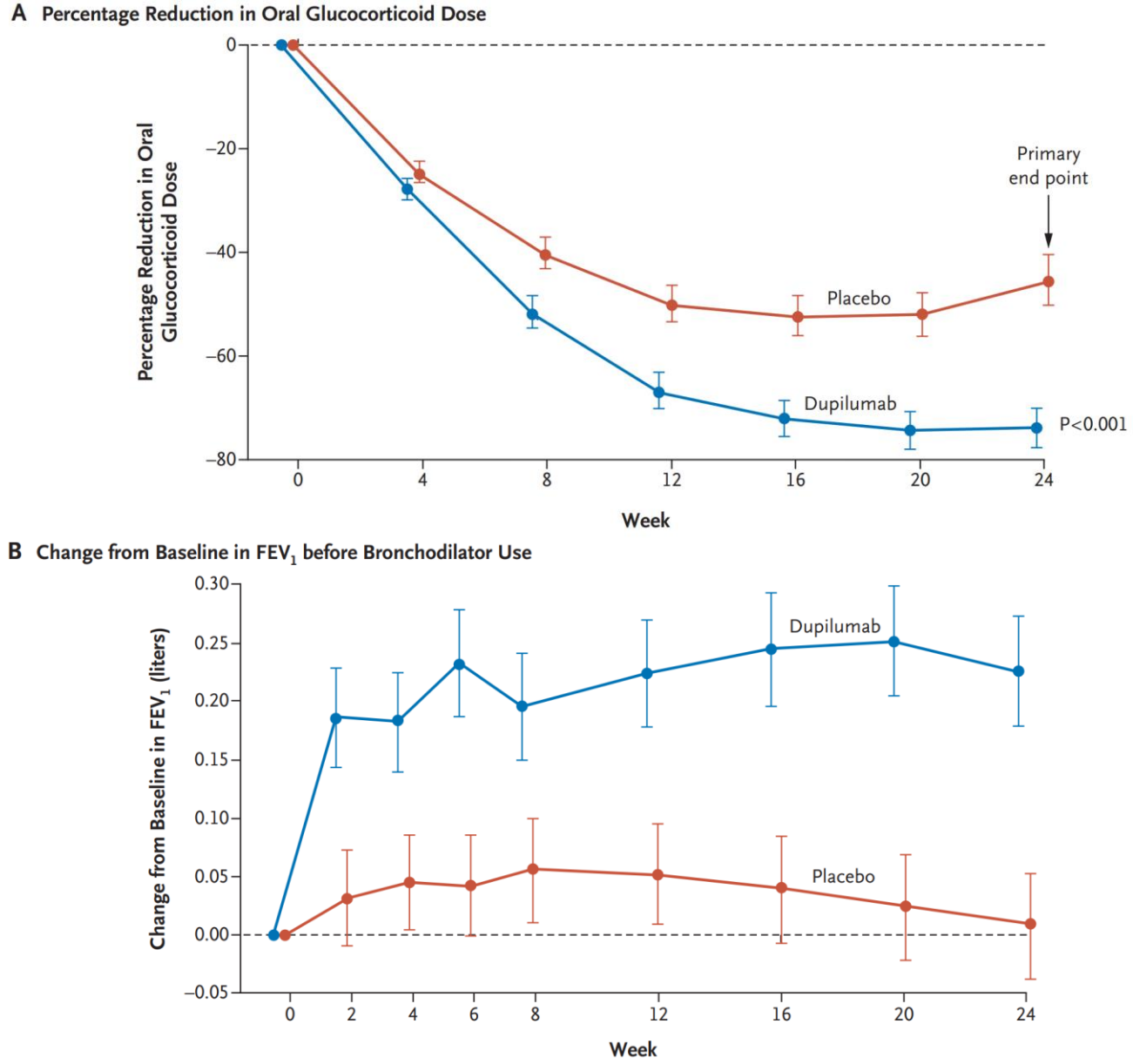
A **Percentage Reduction in Oral Glucocorticoid Dose, According to Blood Eosinophil Subgroup**

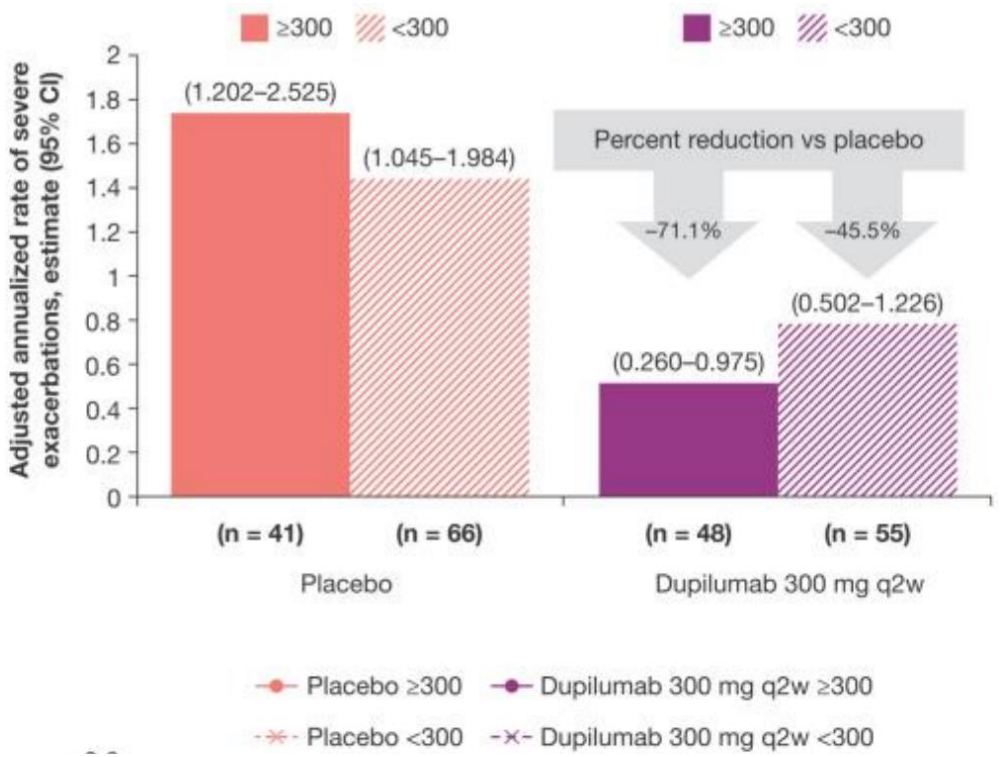
Subgroup	Placebo (N=107)	Dupilumab (N=103)	Least-Squares Mean Difference (95% CI)	Overall P Value for Interaction
	no. of patients		*percentage points*	
≥300 or <300 cells/mm³				0.24
≥300	41	48	−36.8 (−54.7 to −18.9)	
<300	66	55	−21.3 (−38.8 to −3.9)	
≥150 or <150 cells/mm³				0.71
≥150	69	81	−29.4 (−43.1 to −15.7)	
<150	38	22	−26.9 (−54.5 to 0.7)	



N Engl J Med. 2018 Jun 28;378(26):2475-2485

Anti-IL4R in asthmatics with OCS maintenance

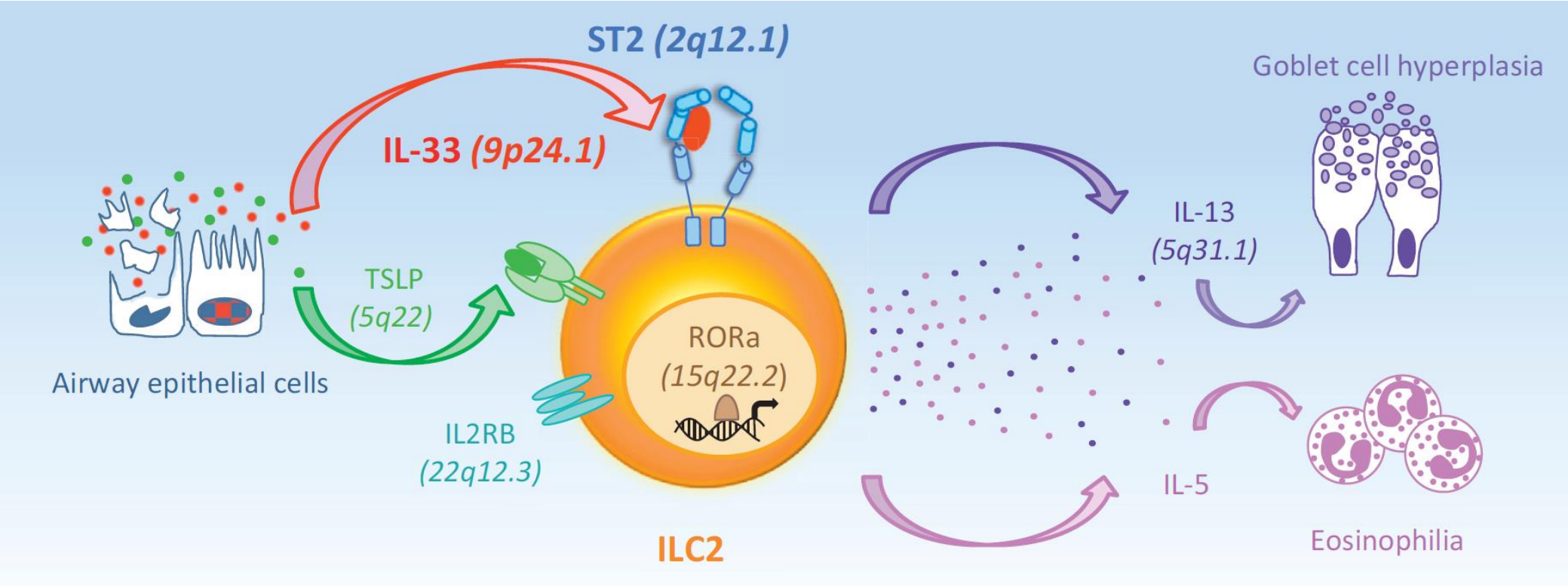




N Engl J Med. 2018 Jun 28;378(26):2475-2485

New targets for severe asthma treatment

- **Itepekimab**: human IgG_4P monoclonal antibody against IL-33
- **Astegolimab**: human IgG_2 monoclonal antibody against ST2 (Selective IL-33 inhibition)

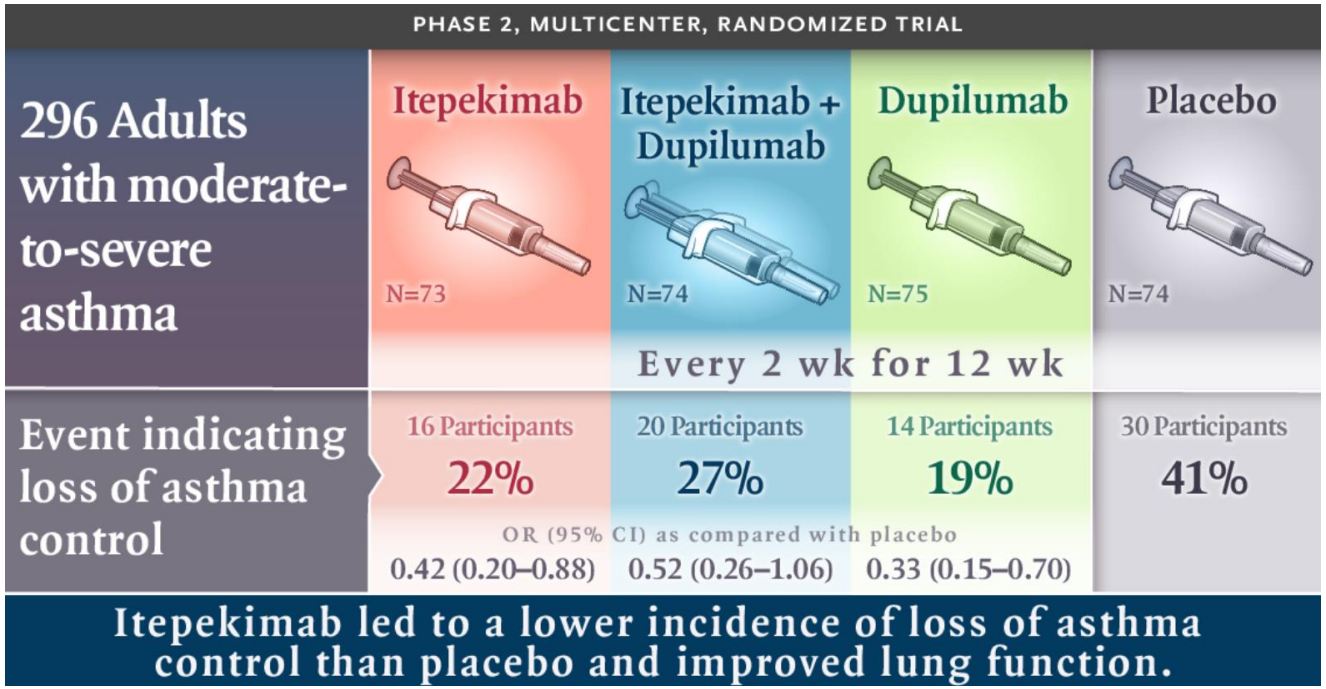


Curr Opin Immunol. 2014 Dec;31:31-7

Efficacy of Itepekimab (Anti-IL33)

- Phase 2 RCT, 12 weeks
- Severe asthma patients with MD- or HD-ICS/LABA, pre-BDR FEV_1: 50-85%, ≥1 moderate-to-severe exacerbation
- Placebo vs. **Itepekimab vs. Itepekimab + Dupilumab vs. Dupilumab**
- Primary outcome: loss of asthma control

- Definition of loss of asthma control
  - ✓ 30% reduction of morning PEF
  - ✓ ≥6 puffs of SABA
  - ✓ moderate-to-severe exacerbation



N Engl J Med 2021; 385:1656-1668

Itepekimab reduced loss of asthma control

End Point	Placebo (N=74)	Itepekimab (N=73)	Itepekimab plus Dupilumab (N=74)	Dupilumab (N=74)
Primary end point: event indicating loss of asthma control during 12-wk intervention period — no. (%)	30 (41)	16 (22)	20 (27)	14 (19)
Odds ratio vs. placebo (95% CI)		0.42 (0.20 to 0.88)	0.52 (0.26 to 1.06)	0.33 (0.15 to 0.70)
P value vs. placebo		0.02	0.07	NA†
Patients with baseline eosinophils <300 cells per mm^3 — no.	33	37	42	43
Primary end-point event — no. (%)	11 (33)	7 (19)	13 (31)	10 (23)
Odds ratio vs. placebo (95% CI)		0.46 (0.15 to 1.41)	0.92 (0.33 to 2.56)	0.62 (0.22 to 1.77)
Patients with baseline eosinophils ≥300 cells per mm^3 — no.	41	36	32	31
Primary end-point event — no. (%)	19 (46)	9 (25)	7 (22)	4 (13)
Odds ratio vs. placebo (95% CI)		0.39 (0.14 to 1.05)	0.30 (0.10 to 0.87)	0.17 (0.05 to 0.58)
Secondary end points				
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.05	0.10±0.05	0.06±0.05	0.12±0.05
Least-squares mean difference vs. placebo (95% CI)		0.14 (0.01 to 0.27)	0.10 (−0.03 to 0.23)	0.16 (0.03 to 0.29)
Patients with baseline eosinophils <300 cells per mm^3 — no.	19	32	30	31
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	0.03±0.07	0.06±0.06	0.02±0.06	0.02±0.06
Least-squares mean difference vs. placebo (95% CI)		0.03 (−0.14 to 0.20)	−0.01 (−0.18 to 0.16)	−0.01 (−0.18 to 0.15)
Patients with baseline eosinophils ≥300 cells per mm^3 — no.	22	26	19	25
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.07	0.18±0.07	0.15±0.08	0.30±0.08
Least-squares mean difference vs. placebo (95% CI)		0.22 (0.02 to 0.41)	0.19 (−0.01 to 0.40)	0.34 (0.14 to 0.54)

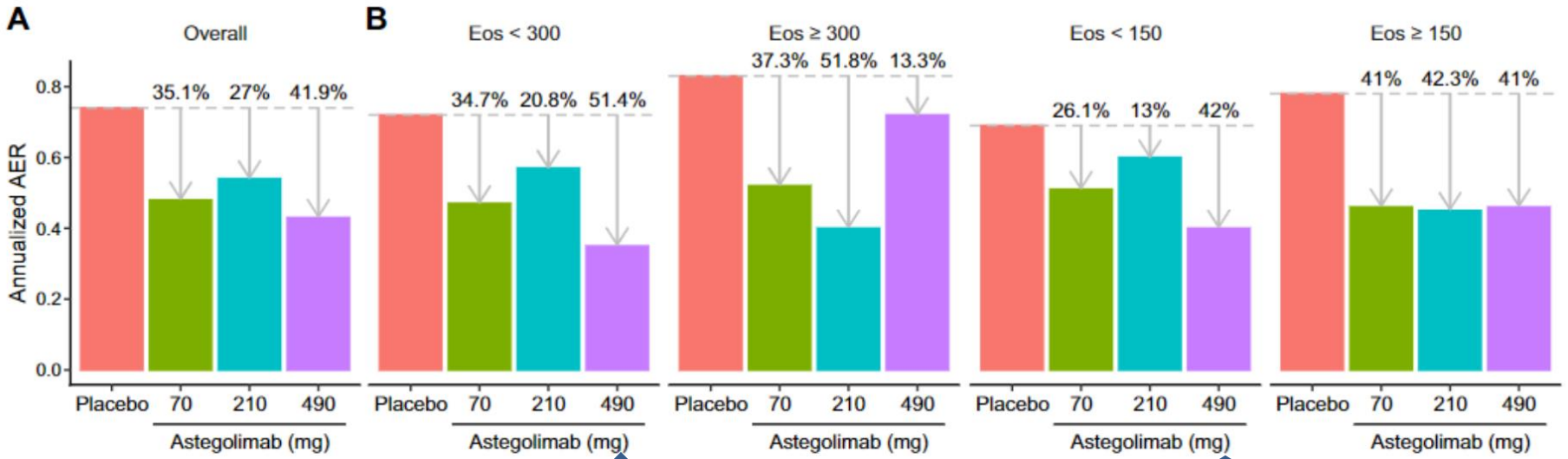
N Engl J Med 2021; 385:1656-1668

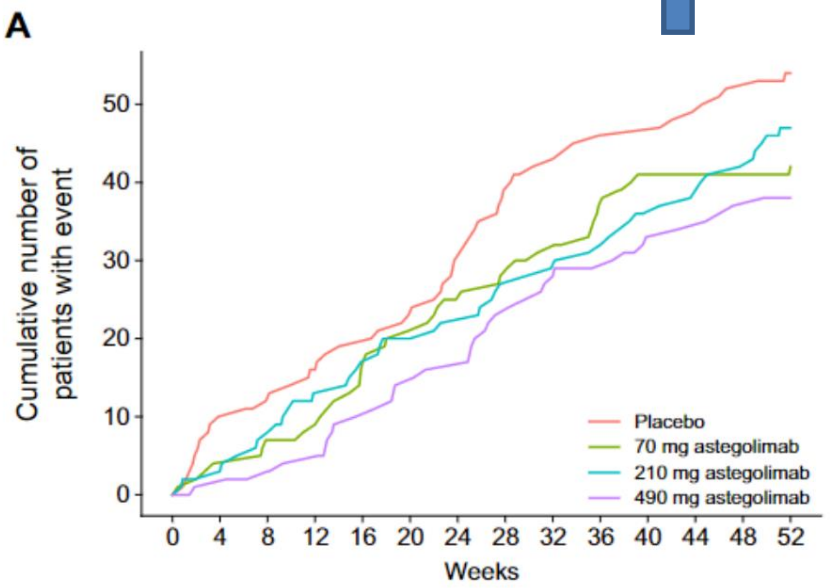
Efficacy of Astegolimab (Anti-ST2)

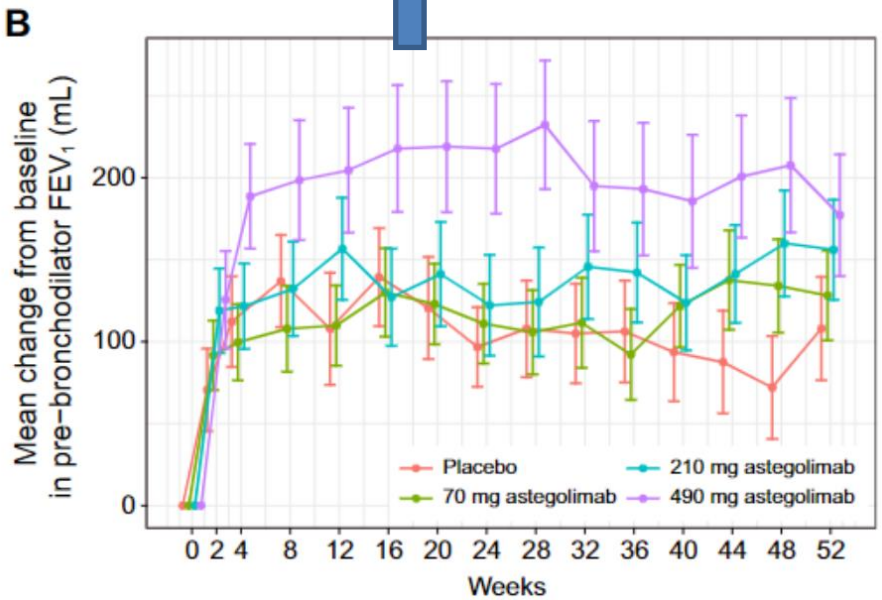
- Phase 2 RCT, 52 weeks
- Asthma patients with MD- or HD-ICS + additional controller, pre-BDR FEV_1: 40-80%, ACQ-5≥1.5, ≥1 moderate-to-severe exacerbation
- Placebo vs. **Astegolimab 70mg qw vs. Astegolimab 210mg qw vs. Astegolimab 490mg qw**
- Primary outcome: Annual acute exacerbation rate

J Allergy Clin Immunol. 2021 Sep;148(3):790-798.

Efficacy of Astegolimab (Anti-ST2)







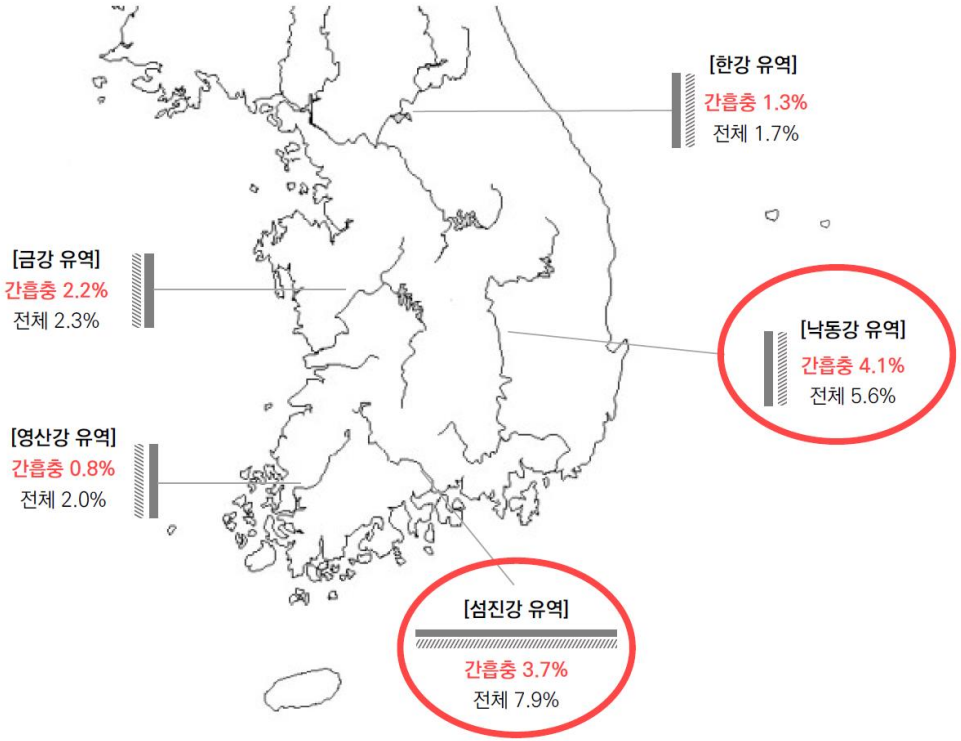
J Allergy Clin Immunol. 2021 Sep;148(3):790-798.

Eosinophilia (≥300/uL) in severe asthma

- In difficult-to-treat asthma and blood eosinophil ≥300/uL
- Before initiation of biologic agents, **investigate for non-asthma causes**

- **Parasites**
  - Strongyloides serology or **Stool examination**

지역	충란 양성률(%)	간흡충	장흡충	편충
경기도	0.3	0.1	0	0.2
충청북도	2.4	2.1	0.2	0
전라북도	4.3	3.0	1.1	0.1
전라남도	2.8	1.3	1.4	0.2
경상북도	2.7	2.3	0.2	0.1
경상남도	9.2	5.5	3.2	0.3



2019년 장내기생충 퇴치사업 현황, 질병관리본부

Eosinophilia (≥300/uL) in severe asthma

- **<u>Eosinophilic granulomatosis with polyangiitis (EPGA)</u>**

  : Consider EGPA if hypereosinophilia ≥1500/uL (GINA)

- **2022 ACR criteria for diagnosis of EGPA**

  : ≥6, sensitivity 85% & specificity 99%

- Anti-IL4R is preferably avoided in patients with hypereosinophilia ≥1500/uL

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Ann Rheum Dis. 2022;81(3):309-314.

Contents

COVID-19 and asthma

- **Are patients with asthma at increased risk of COVID-19, or severe COVID-19?**
  - ✓ **Not increased** risk of acquiring COVID-19
  - ✓ **Not increased** risk of severe COVID-19 in well-controlled, mild-to-moderate asthmatics

- **Are people with asthma at increased risk of COVID-19-related death?**
  - ✓ **Not increased** risk of COVID-19-related death in well-controlled asthmatics
  - ✓ Mortality appeared to **be lower** than in people without asthma

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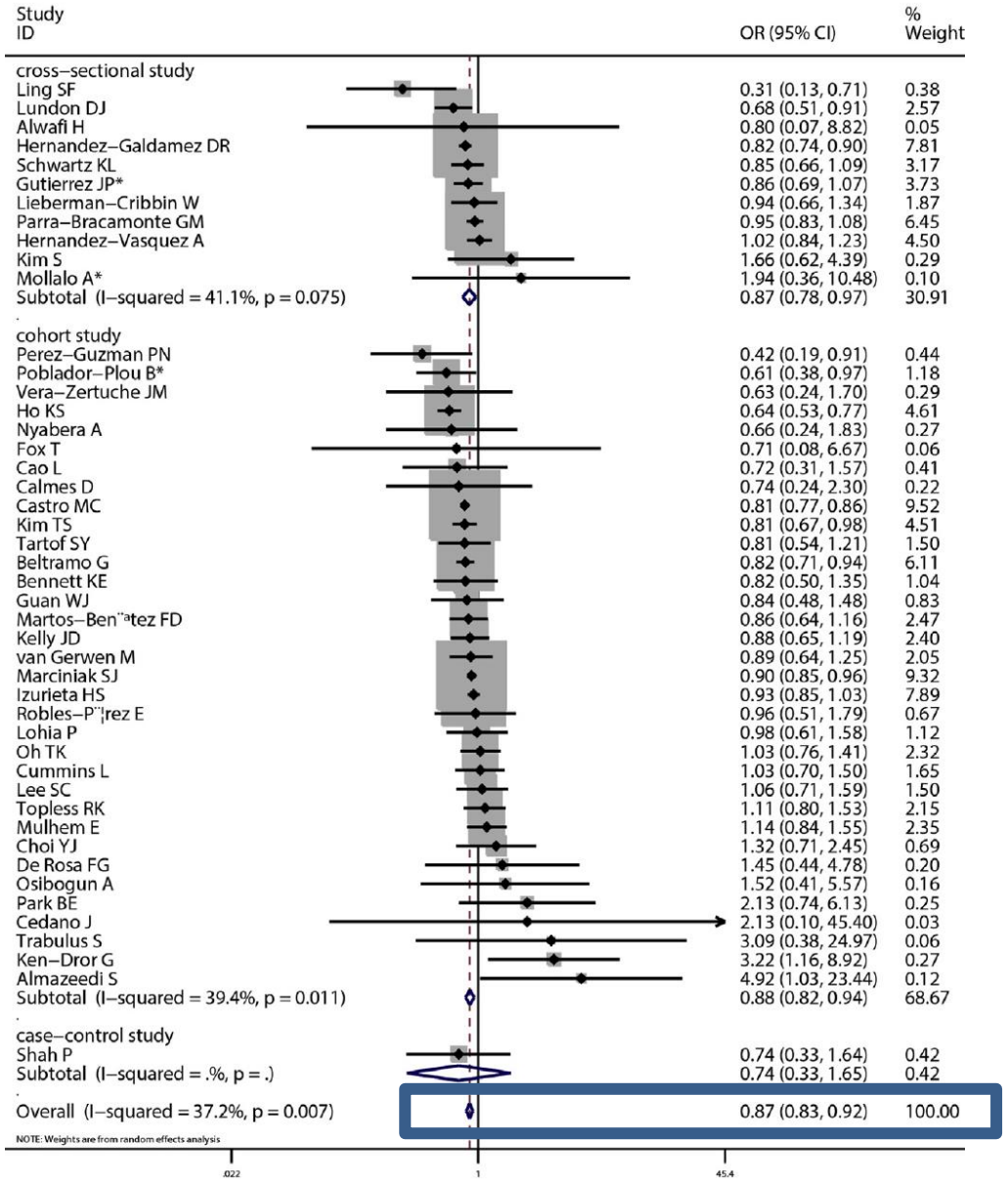
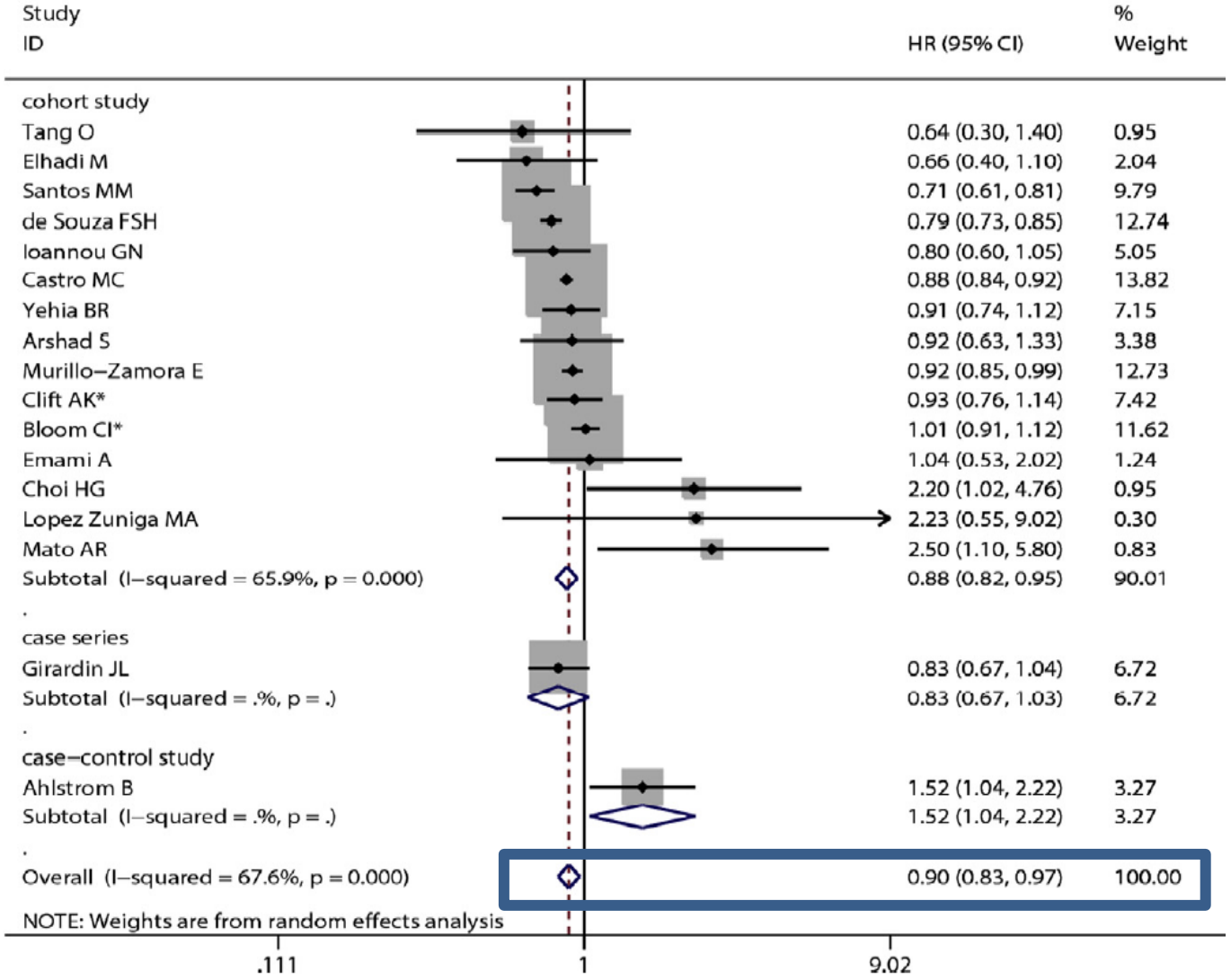
Lower COVID-19 related mortality in asthmatics



OR



HR

J Allergy Clin Immunol Pract. 2021 Nov; 9(11): 3944–3968.e5.

COVID-19 and asthma

- **Are patients with asthma at increased risk of COVID-19, or severe COVID-19?**
  - ✓ **Not increased** risk of acquiring COVID-19
  - ✓ **Not increased** risk of severe COVID-19 in well-controlled, mild-to-moderate asthmatics

- **Are people with asthma at increased risk of COVID-19-related death?**
  - ✓ **Not increased** risk of COVID-19-related death in well-controlled asthmatics
  - ✓ Mortality appeared to **be lower** than in people without asthma

- **However, higher mortality in patients who had recently needed OCS or hospitalized for their asthma**

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Higher mortality in uncontrolled asthmatics

HR for hospitalization

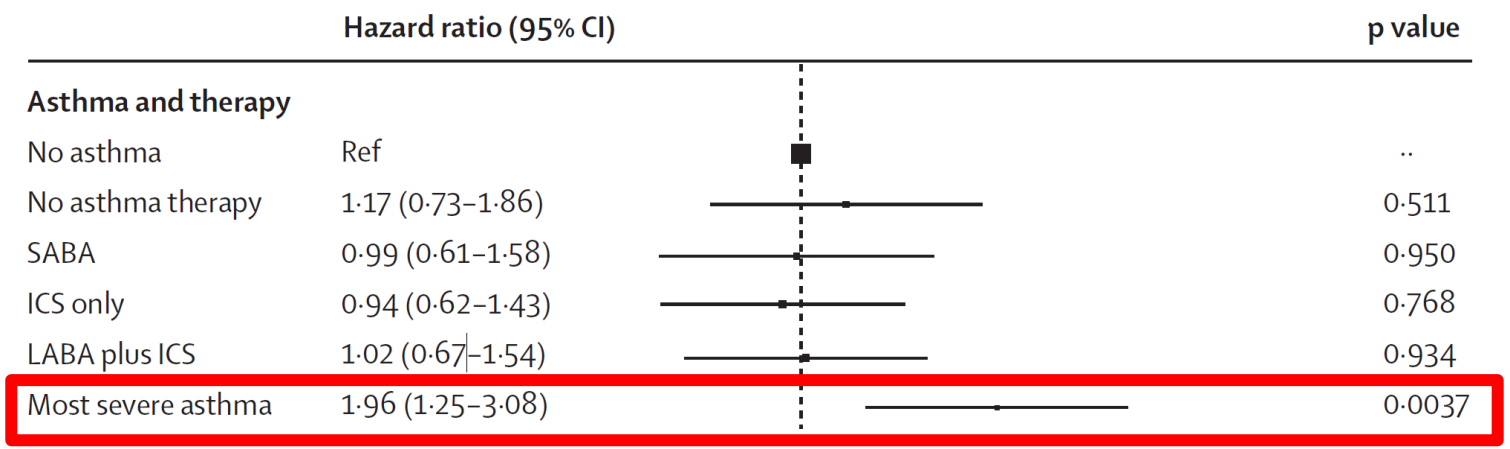
	Children aged 5–17 years with COVID-19 hospital admission	Adjusted HR (95% CI) for children aged 5–17 years	Adjusted HR (95% CI) for children aged 5–11 years	Adjusted HR (95% CI) for children aged 12–17 years
Using previous hospital admission for asthma as marker of uncontrolled asthma*				
No asthma	382	1 (ref)	1 (ref)	1 (ref)
Asthma without previous hospital admission	58	1·36 (1·02–1·80)	2·05 (1·35–3·12)	1·06 (0·73–1·54)
Asthma with previous hospital admission	9	6·40 (3·27–12·53)	3·78 (1·20–11·93)	10·04 (4·39–22·97)
Using previous prescribed oral corticosteroids as marker of uncontrolled asthma*				
No asthma	366	1 (ref)	1 (ref)	1 (ref)
Asthma with 0 courses of oral corticosteroids	47	1·34 (0·98–1·82)	2·18 (1·36–3·50)	1·03 (0·68–1·55)
Asthma with 1 course of oral corticosteroids	15	1·52 (0·90–2·57)	1·30 (0·61–2·79)	1·79 (0·88–3·67)
Asthma with 2 courses of oral corticosteroids	10	3·53 (1·87–6·67)	3·21 (1·31–7·87)	3·96 (1·61–9·73)
Asthma with ≥3 courses of oral corticosteroids	11	3·38 (1·84–6·21)	4·81 (2·33–9·92)	1·92 (0·60–6·10)

Lancet Respir Med. 2022 Feb;10(2):191-198

HR for mortality

Characteristic	Category	COVID-19 death HR (95% CI)	
		Adjusted for age and sex	Fully adjusted
Asthma[b] (versus none)	With no recent OCS use	1.13 (1.07–1.20)	0.99 (0.93–1.05)
	With recent OCS use	1.55 (1.39–1.73)	1.13 (1.01–1.26)

Nature. 2020 Aug;584(7821):430-436



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

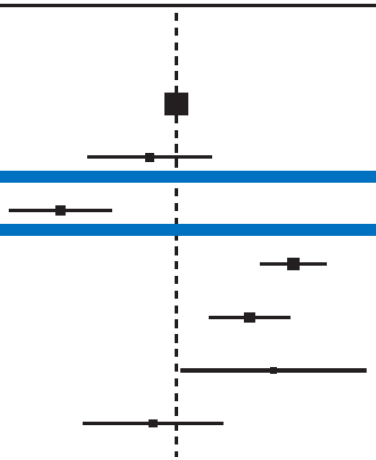
Mostly, oral corticosteroid user

Asthma medication in COVID-19 patients

- **ICS use** in patients with asthma was associated with **lower COVID-19 related mortality**

- **Continue** taking their prescribed **asthma medications**, especially **ICS** in COVID-19 patients
  - For patients with severe asthma, continue biologic therapy or OCS if prescribed

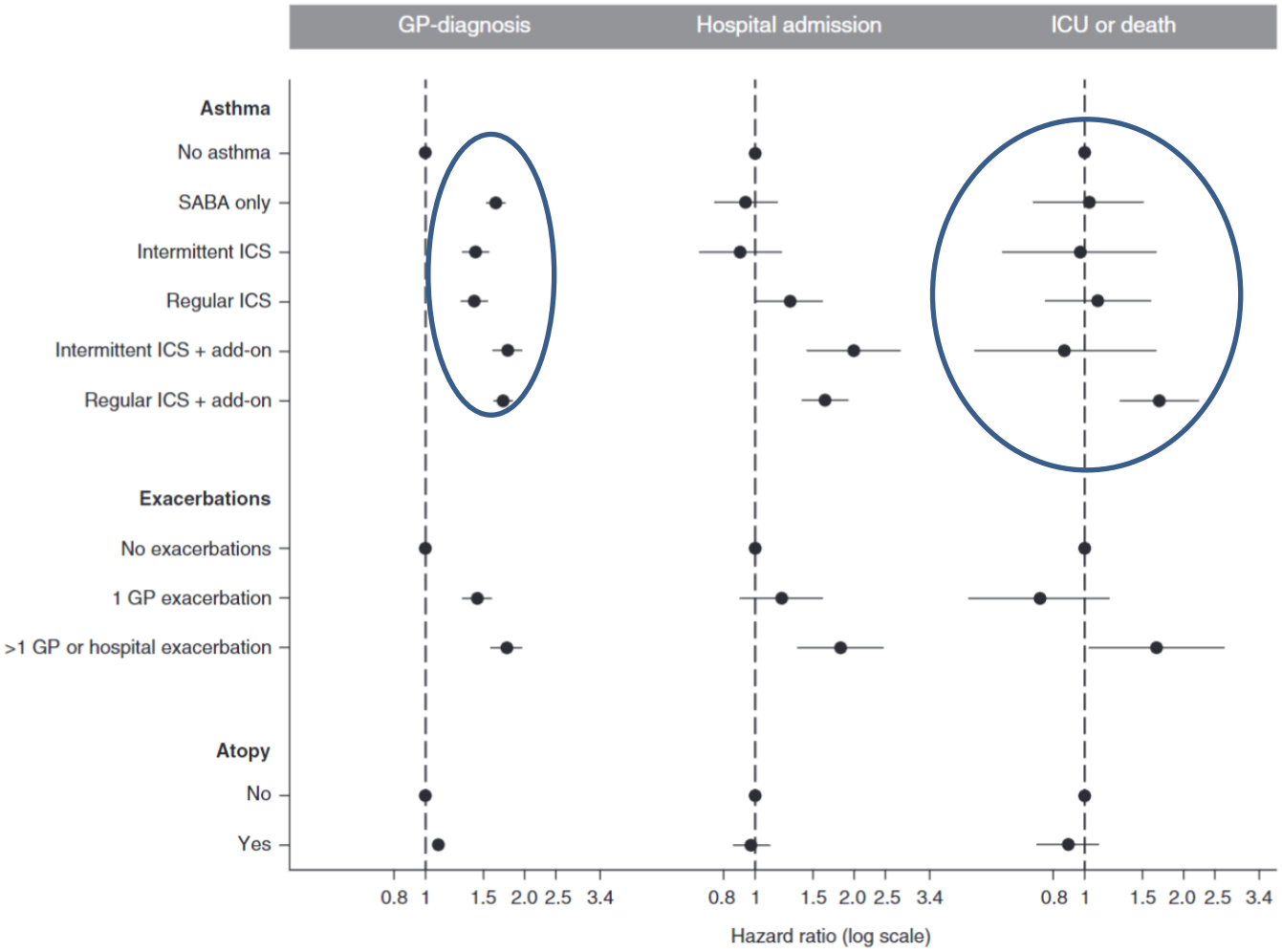
	Hazard ratio (95% CI)	p value
Respiratory disease		
No respiratory disease; no inhaled steroids	Ref	..
Asthma only; no inhaled ICS	0·97 (0·89–1·05)	0·391
Asthma only; on inhaled ICS	0·86 (0·80–0·92)	<0·0001
Chronic pulmonary disease only; no inhaled ICS	1·16 (1·12–1·22)	<0·0001
Chronic pulmonary disease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

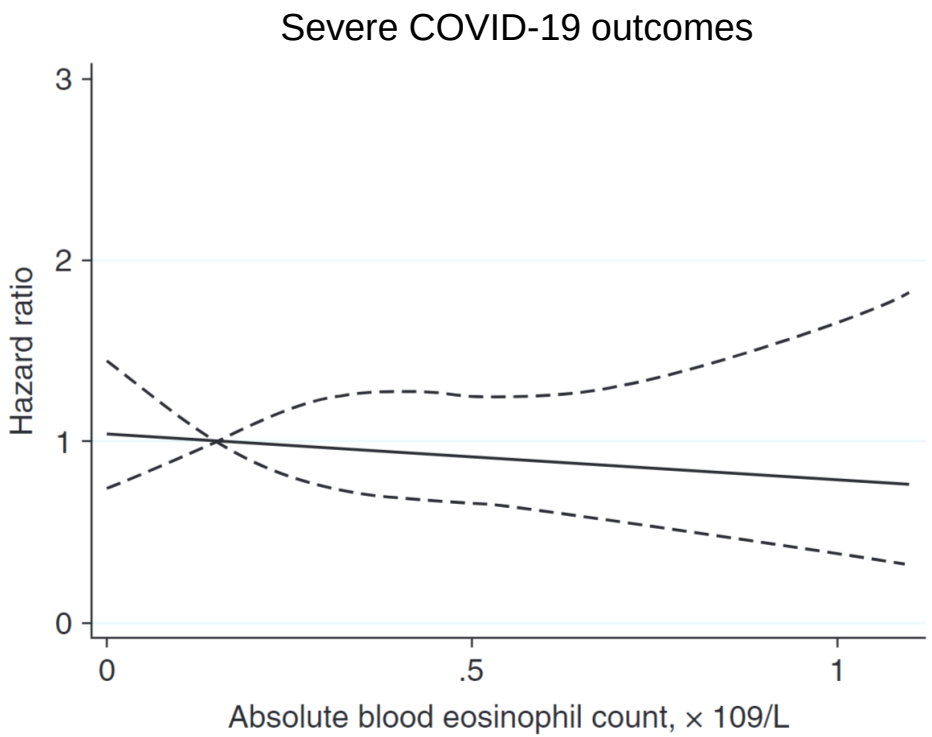


Lancet Respir Med. 2021 Jul;9(7):699-711.

Asthma medication in COVID-19 patients

- Asthma phenotypes and clinical outcomes
- 434,348 asthma patients vs. 748,327 general population, matched cohort





Am J Respir Crit Care Med. 2022 Jan 1;205(1):36-45.

Aerosol-generating procedures

- When **COVID-19** is confirmed or suspected, or local risk is moderate or high
  - ✓ **Avoid nebulizers** to reduce the risk of spreading virus, except AE-asthma
  - ✓ For bronchodilator administration, **pMDI via a spacer** is preferred.

- **Spirometry or peak flow measurement**
  - ✓ Use of an **in-line filter** minimizes the risk of transmission during spirometry
  - ✓ Coach the patient to stay on the mouthpiece if they feel the need to cough

GINA report 2022

COVID-19 vaccination

- GINA 2022 report **recommends** people with asthma should be up to date with COVID-19 vaccination **including boosting doses**

- The first dose of **biologic therapy** and **COVID-19 vaccine** **should not be given on the same day**
  - Adverse effects of either can be more easily distinguished

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Summary

- **Different approach for diagnosis of asthma in people already taking controller**
  - ✓ **Normal lung function with controller ➔ stop bronchodilator and repeat spirometry+BDR / step down controller**
  - ✓ **Variable symptom➔ check variable airflow limitation / If FEV_1>70%, step down controller**
  - ✓ **Persistent symptom / impaired FEV_1 ➔ step up controller / reassess variable airflow limitation**

- **Frequency of as-needed ICS-formoterol is not included in assessment of asthma control**

- **Track 1 (as needed ICS+LABA) is superior to Track 2 (ICS maintenance + as needed SABA) in reducing severe exacerbation, especially in uncontrolled asthma patients with SABA**

Summary

- **Like LABA, LAMA monotherapy is not recommended in asthma**
- **Anti-TSLP can be used in both Th2 and non-Th2 severe asthma**
- **Before initiating biologics in eosinophilic severe asthmatics, check non-asthma causes**
- **Continue taking their prescribed asthma medications during COVID-19, especially ICS**

Thank you for your attention