The Silent Burden:
The risks of “mild” asthma

Presenter: Hyun Woo Lee

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BORAMAE MEDICAL CENTER

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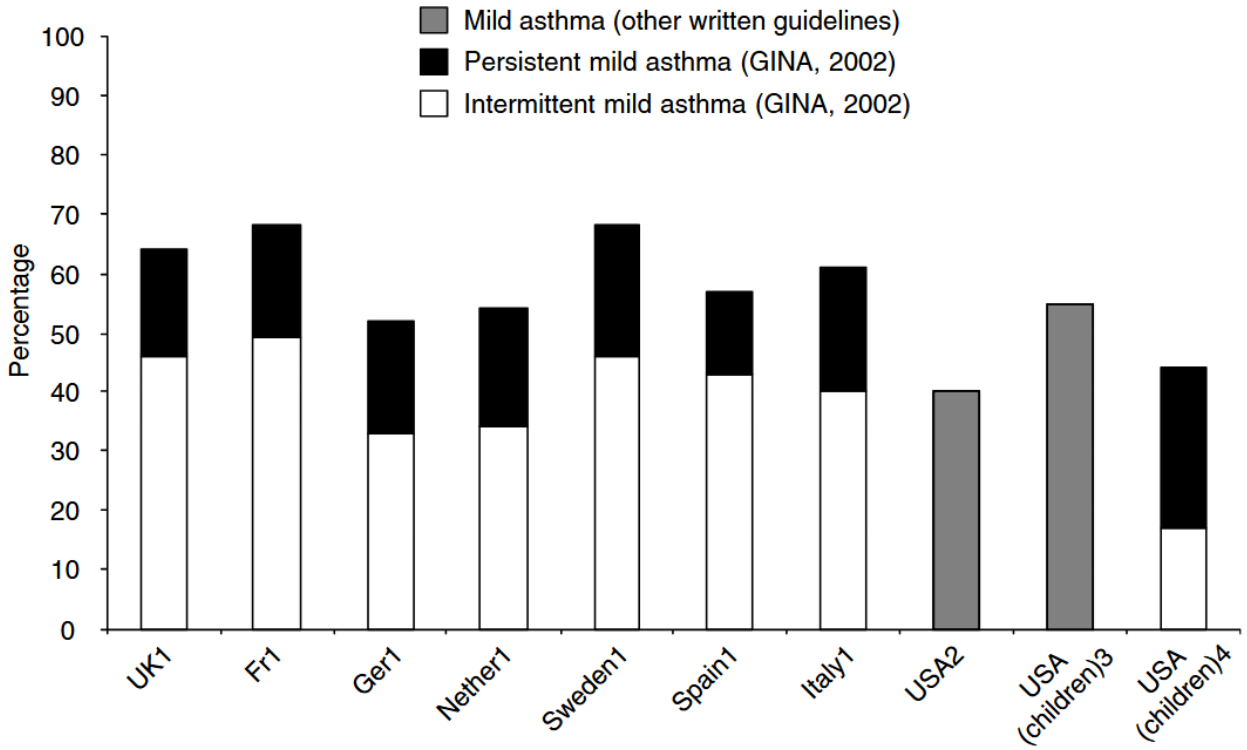
Epidemiology of mild asthma

- **Mild asthma accounts for**
  - ✓ About 3.3% of the general population

Allergy. 2007;62(6):591-604.

  - ✓ About 50% to 75% of all asthma cases

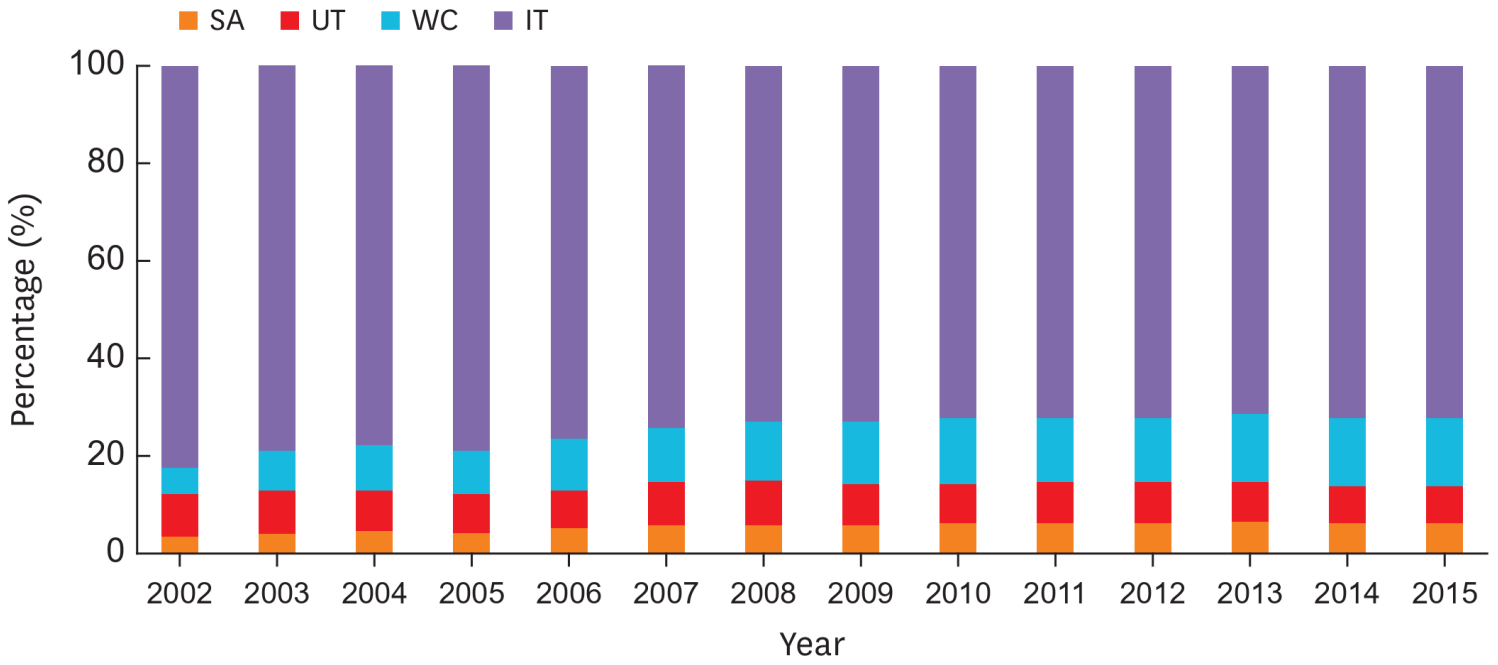
Int J Clin Pract. 2005 Jun;59(6):692-703.



Epidemiology of mild asthma in South Korea

- **Asthma accounts for**
  - ✓ About 3.2~4.7% of the general population

Tuberc Respir Dis (Seoul). 2023 May 30;86(3):158–165.



IT, **intermittently treated asthma (72~82%)**

WC, well-controlled asthma (6~14%)
UT, untreated asthma (7.5~8.5%)
SA, severe asthma

Allergy Asthma Immunol Res. 2020 May;12(3):467-484.

Controversies in defining mild asthma

- **What is mild asthma?**

  - Based on symptoms and lung function

  ➔ Meaning infrequent and mild symptom in context of normal lung function

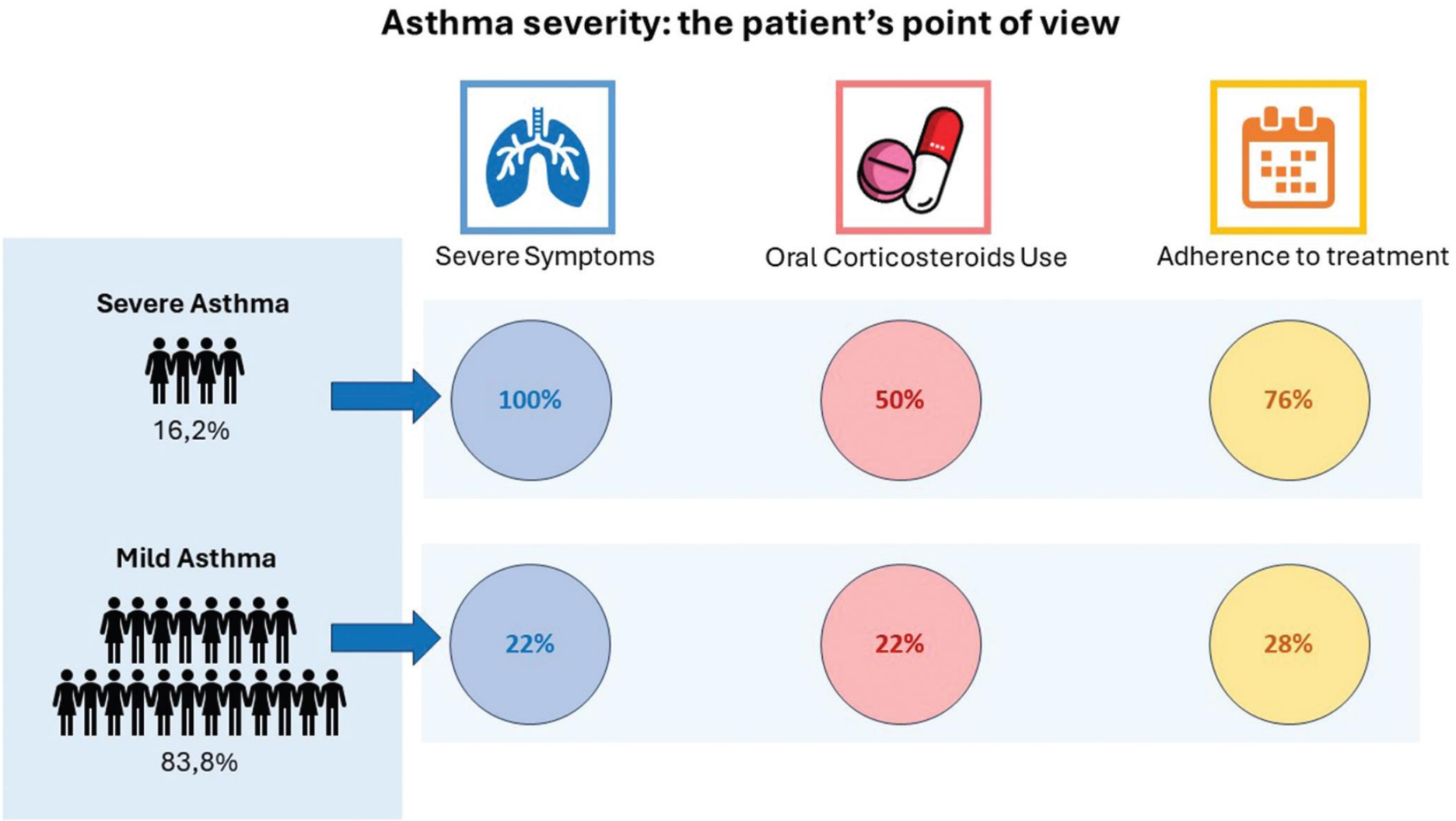
  ∴ Patients assuming not at risk or do not need ICS-containing treatment

  - Based on treatment response

  ➔ Retrospective label

  ∴ Cannot decide which patients are suitable to receive Step 1-2 or 3 treatment

Impact of perceiving asthma as mild in patients



Eur Clin Respir J. 2024 Aug 16;11(1):2381307.

Definition of mild asthma based on symptoms

- National Asthma Education Prevention Program (NAEPP)
- Expert panel report (EPR)-3 Focused updates 2020

- **Severity of asthma**

: Defined based on symptom, exacerbation, SABA use, Lung function

- ✓ **Intermittent**
- ✓ **Mild persistent**

} **Considered as mild asthma**

- ✓ Moderate persistent
- ✓ Moderate-to-severe persistent
- ✓ Severe persistent

Eur Respir J 2008; 31: 143–178

TABLE 2 Classification of asthma severity by clinical features before treatment

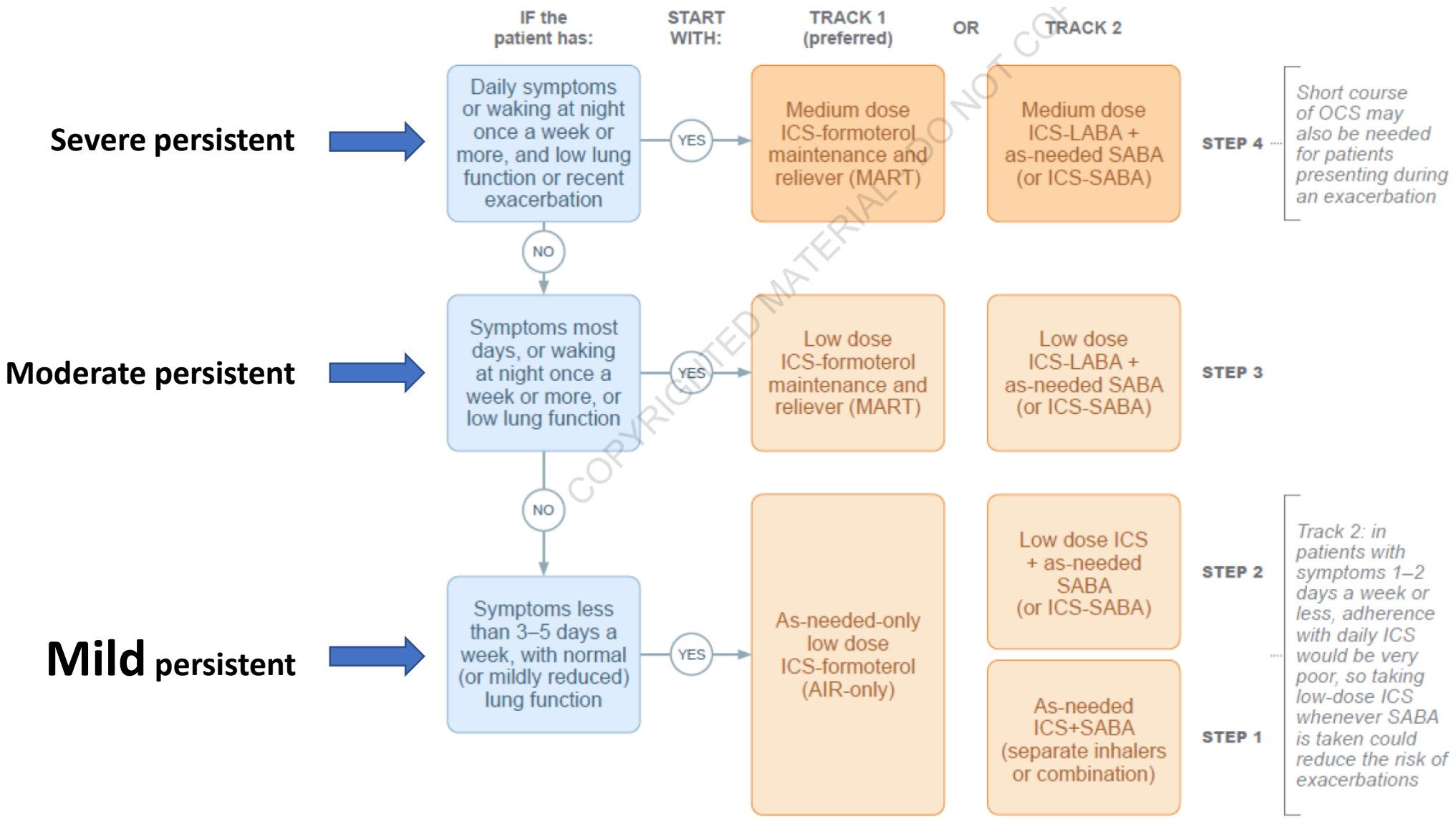
Intermittent
- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- FEV_1 or PEF ⩾80% pred
- PEF or FEV_1 variability <20%

Mild persistent
- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- FEV_1 or PEF ⩾80% pred
- PEF or FEV_1 variability <20–30%

Moderate persistent
- Symptoms daily
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week
- Daily use of inhaled short-acting β_2-agonist
- FEV_1 or PEF 60–80% pred
- PEF or FEV_1 variability >30%

Severe persistent
- Symptoms daily
- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Limitation of physical activities
- FEV_1 or PEF ⩽60% pred
- PEF or FEV_1 variability >30%

Initial treatment decision based on symptoms



GINA 2025 report

Do mild symptoms suggest mild asthma?

How mild is mild asthma?

A. R. RUBINFELD AND M. C. F. PAIN

From the Respiratory Unit, Royal Melbourne Hospital, Melbourne, Australia

Table 1 *Comparison of lung function indices in the baseline state and threshold state*

Lung function	*Baseline values*		*Values after methacholine provocation*		*t*	P
	Mean	SD	*Mean*	SD		
TLC	103.2	10.5	109.8	11.8	3.42	< 0.01
FRC	107.7	15.4	127.6	21.3	4.95	< 0.001
RV	141.4	33.5	181.3	41.2	4.53	< 0.001
FEV_1	90.6	16.9	73.4	17.9	6.43	< 0.001
Gaw	75.1	19.3	39.6	15.2	11.48	< 0.001

TLC, FRC, RV, FEV_1, Gaw expressed as % of predicted values.
t = value for paired Student's *t* test.
P = level of significance of *t* value.

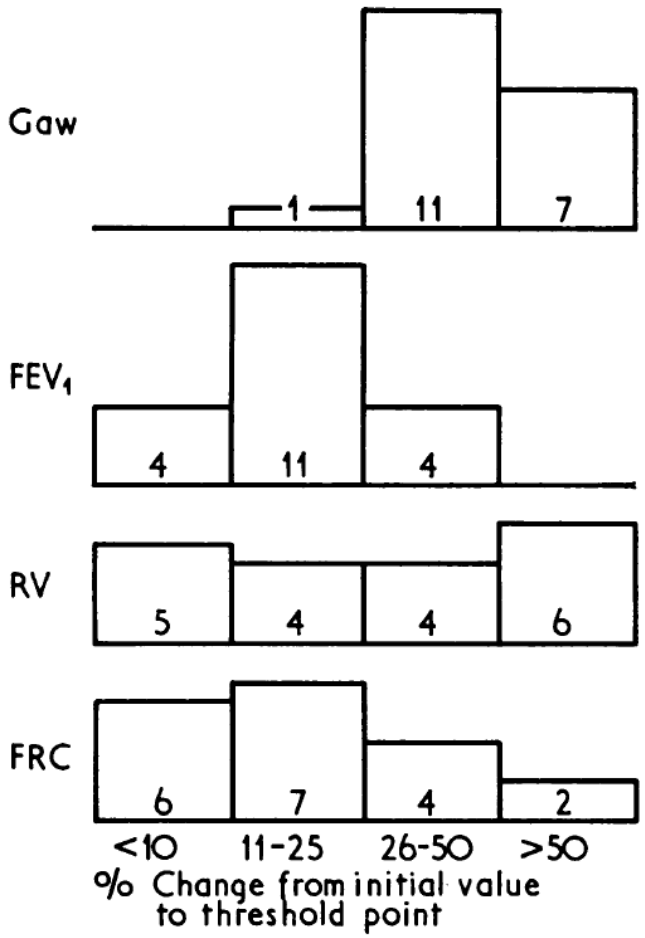


Fig. 2 *Distributions for changes in indices of lung function in moving from asymptomatic to threshold state.*

Thorax. 1977 Apr;32(2):177-81.

SAD is common in those with trivial symptoms

Small airway dysfunction is common even in mild asthma and suggests increased exacerbation risk

TABLE I. Small airway dysfunction defined by resistance at 5 Hz, difference between resistance at 5 and 20 Hz, area of reactance, and resonant frequency >95th percentile, and <5th percentile for X5 in patients with well-controlled (WC) not well-controlled (NWC) asthma

Variable	Well controlled (% small airway disease)			Not well controlled (% small airway disease)		
Impulse oscillometry metric	1	2	3	1	2	3
Resistance at 5 Hz	15.3	35.4	NT	57.4	48.1	NT
Difference between resistance at 5 and 20 Hz	11.9	45.6	29.9	65.4	66.7	100%
Area of reactance	NT	38.0	NT	NT	73.9	NT
X5	27.1	25.7	NT	59.4	63.8	NT
Resonant frequency	40.7	NT	NT	80.2	NT	NT

Study 1 by Jung et al.
Study 2 by Galant et al.
Study 3 by Cottini et al.

J Allergy Clin Immunol Pract. 2024 Jul;12(7):1946-1947.

Definition of mild asthma

- Global Initiative for Asthma (GINA)
- Global Strategy for Asthma Management and Prevention - Updates 2025

- **Severity of asthma** (Since GINA report 2014)

  : Defined as the difficulty in controlling asthma with treatment

  : Overwhelmingly focused on the **intensity of treatment required**

Am J Respir Crit Care Med. 2009 Jul 1;180(1):59-99.

✓ **Mild: well-controlled with Step 1-2 treatment**

✓ Moderate: well-controlled with Step 3-4 treatment

✓ Severe: uncontrolled despite Step 4-5 or requires Step 5 or higher intensity treatment

GINA 2025 report

Definition of mild asthma

- **Why** was the **definition** of asthma severity **changed?**

*"Patients with **few interval symptoms** can have **exacerbations triggered by external factors** such as viral infections or allergen exposure, and the **treatment** that was historically regarded as **the lowest intensity** – short-acting beta$_2$ agonist (**SABA**) alone – **actually increases the risk of exacerbations**."*

*"However, **up to 30% of asthma exacerbations and deaths** occur in people **with infrequent symptoms**, for example, less than weekly or only on strenuous exercise"*

= Asthma with mild severity (or intermittent)

GINA 2025 report

The silent risk of mild asthma

Therefore,

“Mild asthma” is not same with “Asthma not at risk” or

“Asthma without need for treatment”

“Mild asthma” means “Asthma requires low-dose ICS treatment for well-controlled condition”

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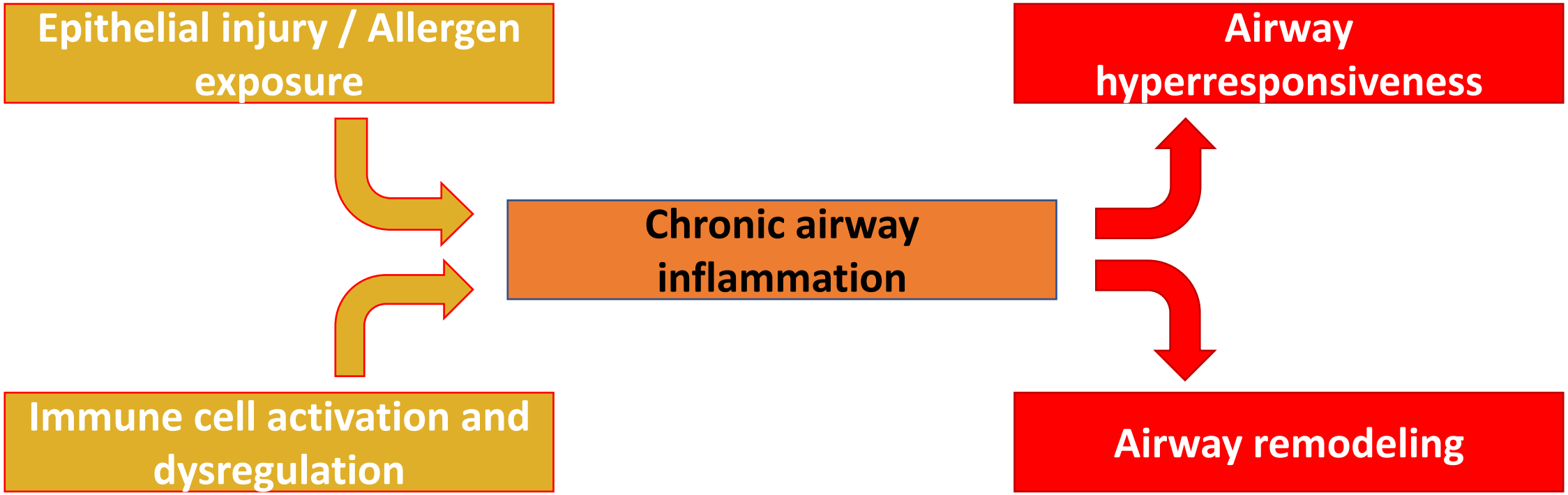
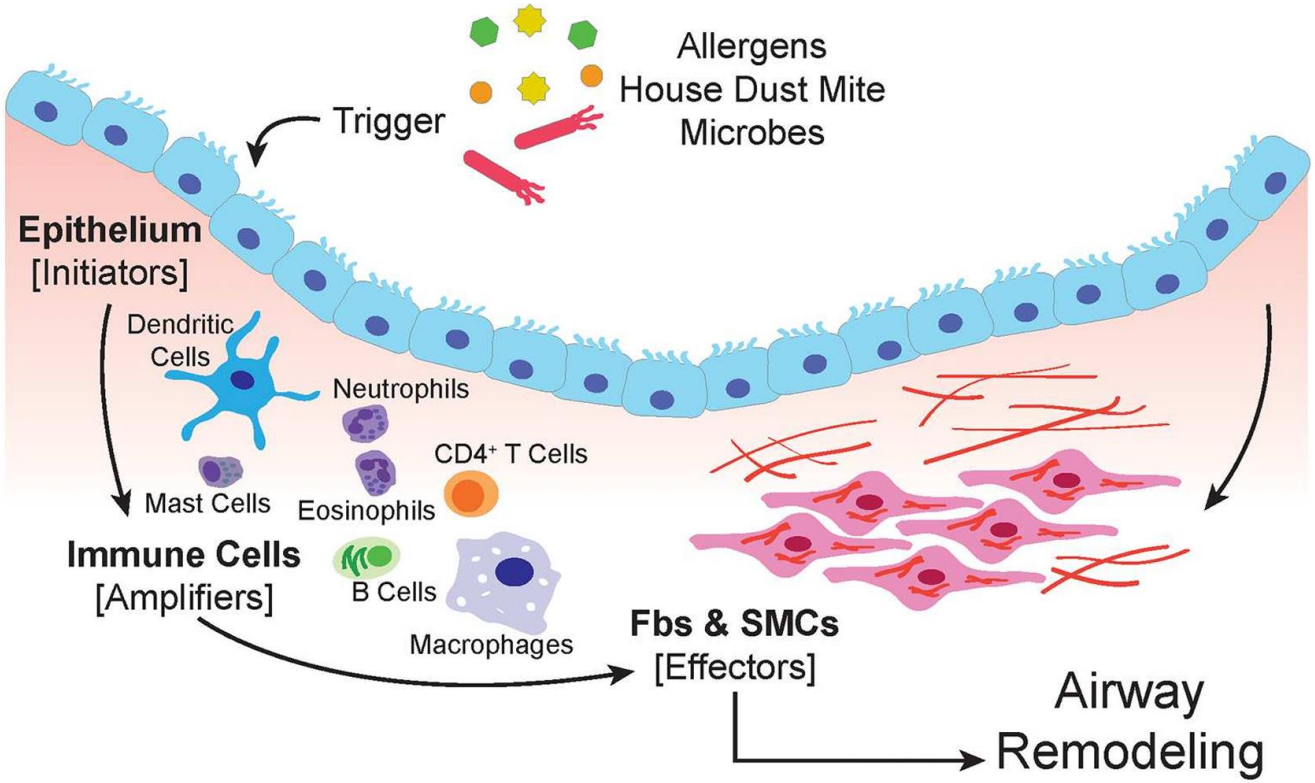
Pathogenesis of asthma

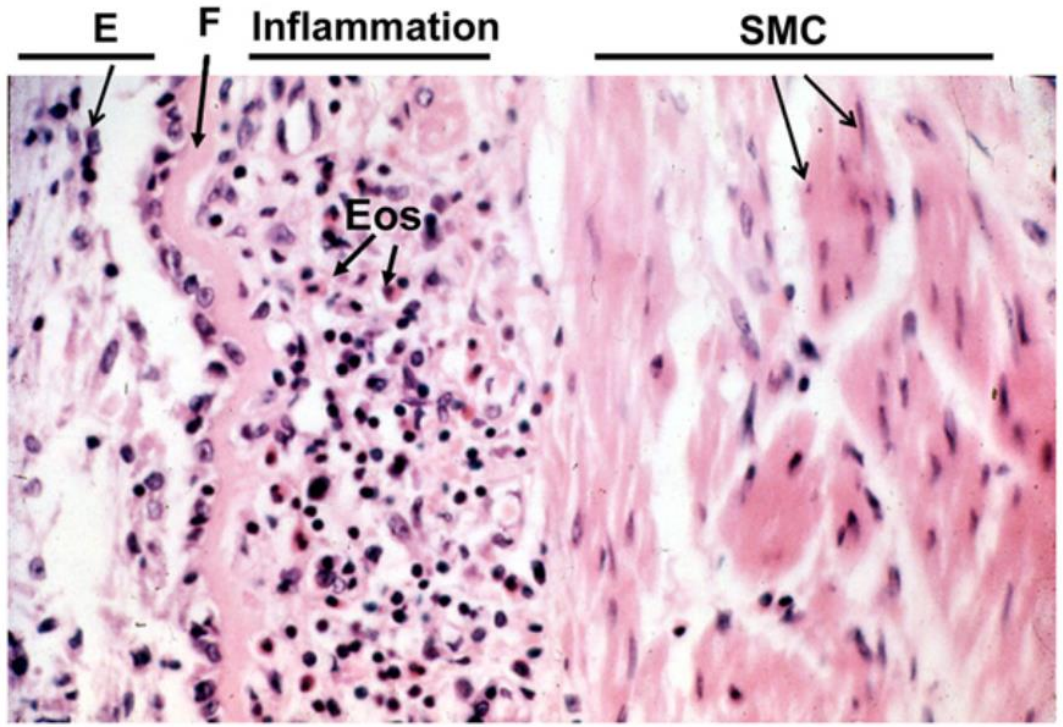
- Asthma was believed as a disease of bronchoconstriction
- Now, asthma is believed as a **disease of chronic airway inflammation**



Airways of mild asthma

- **Mild asthma** is characterized by the presence of **both chronic airway inflammation and airway remodeling**

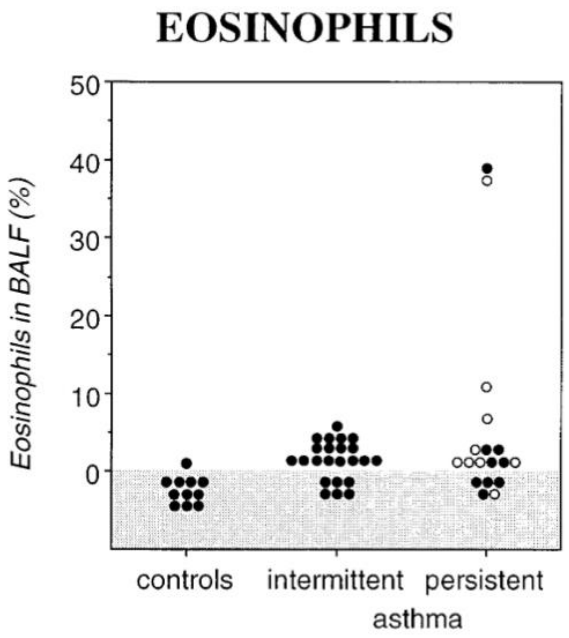


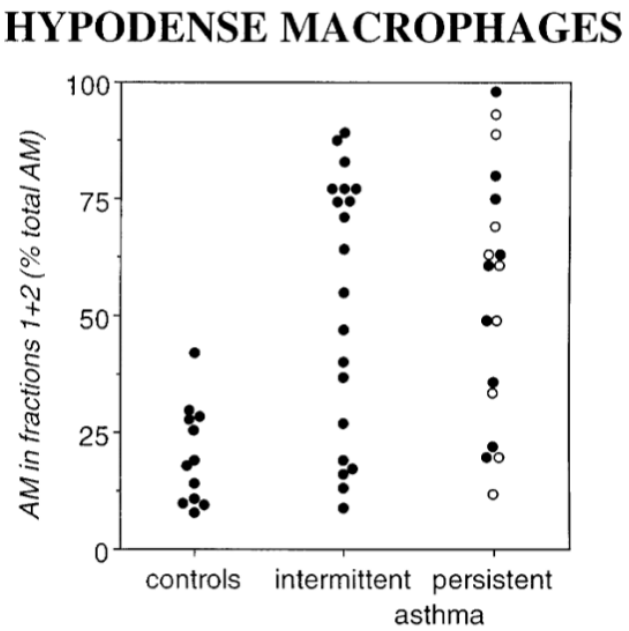


Am J Respir Cell Mol Biol. 2011 Feb;44(2):127-33.

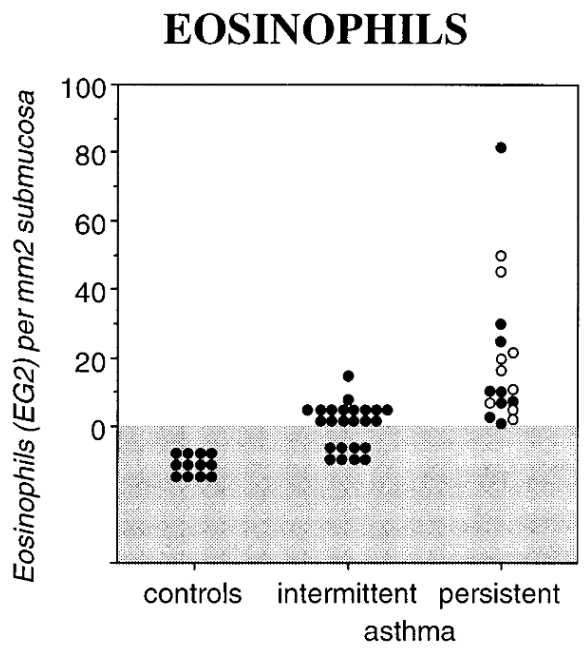
Airway inflammation in mild asthma

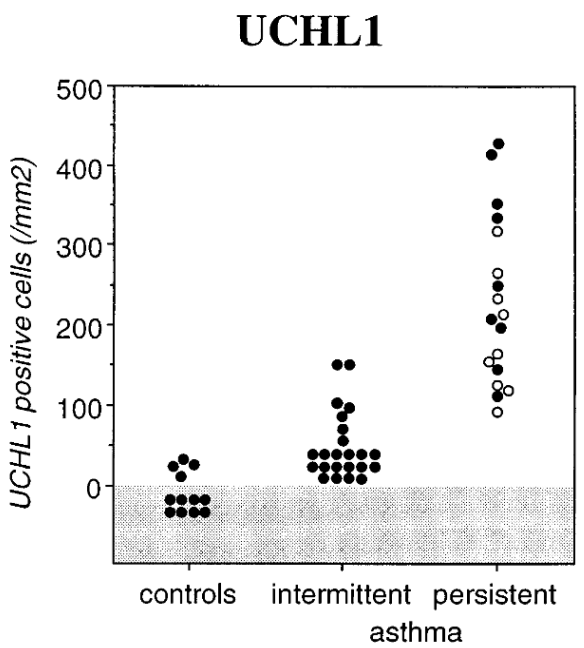
- Activated inflammatory cells are present even in mild intermittent asthma





Marker of mature T cell

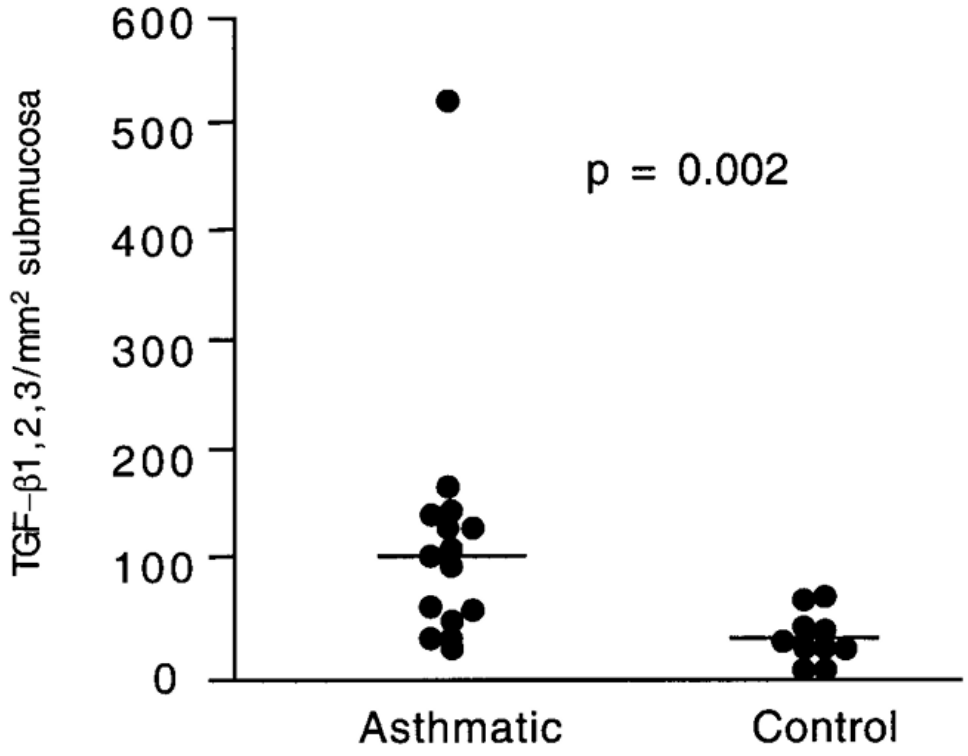


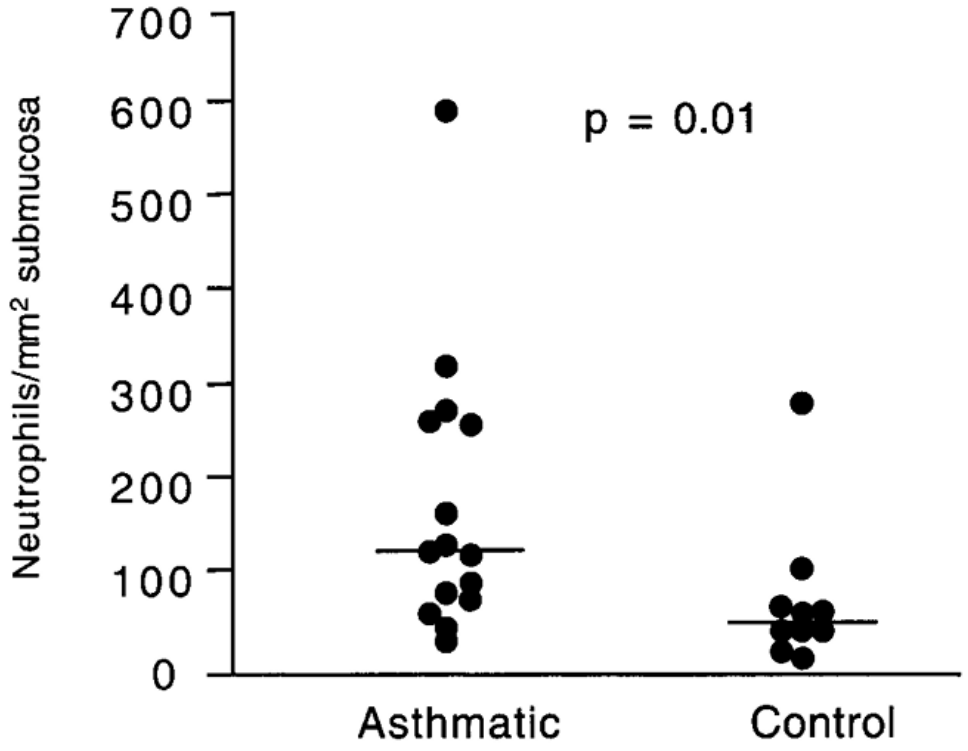


Am J Respir Crit Care Med. 1998 Feb;157(2):403-9.

Airway inflammation in mild asthma

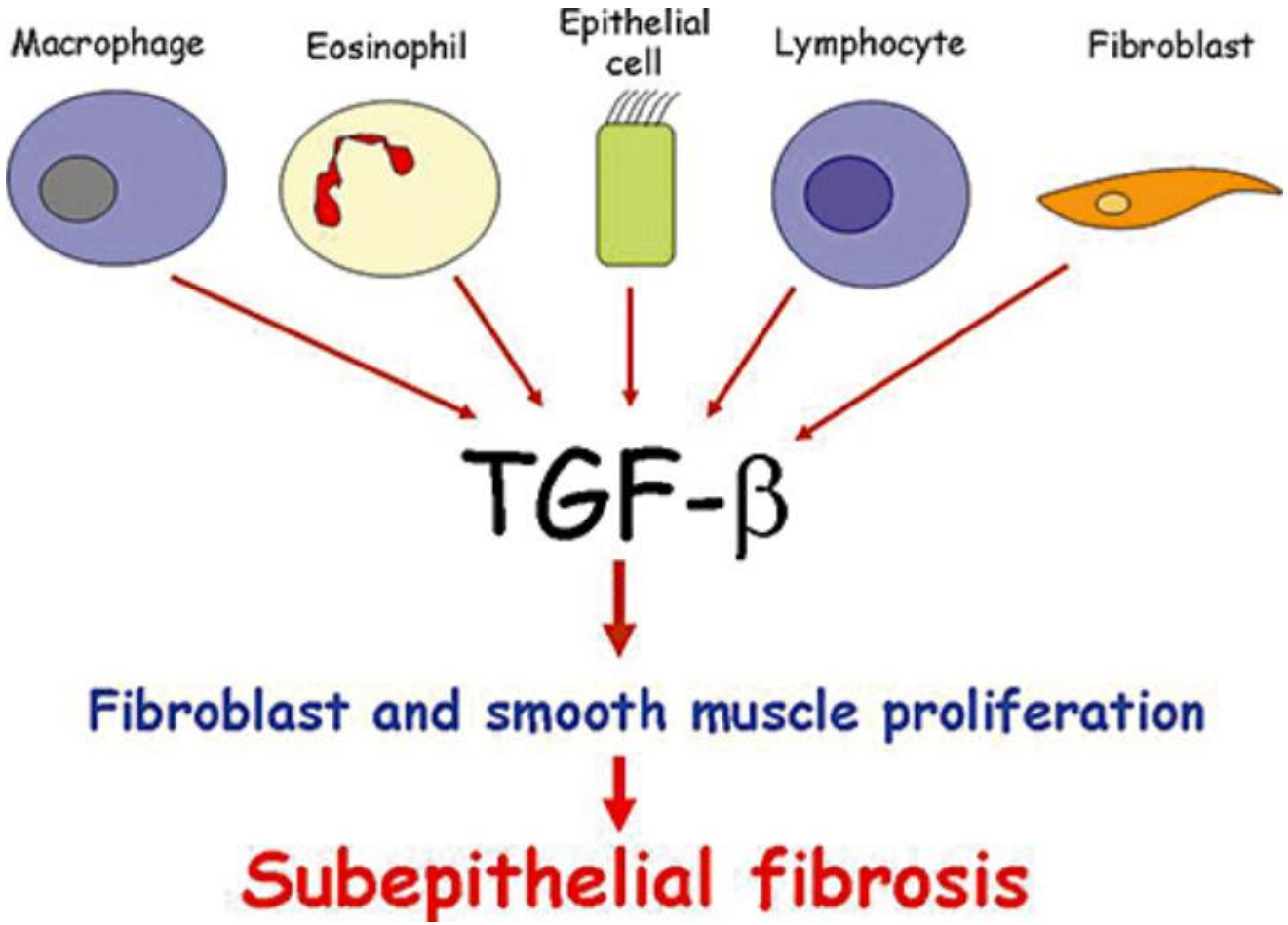
- TGF-β^{+} cells and neutrophils are elevated in asthma regardless of severity compared to controls





J Allergy Clin Immunol. 2000 Dec;106(6):1115-23.

Subepithelial fibrosis in asthma



Clin Respir J. 2010 May:4 Suppl 1:35-40.

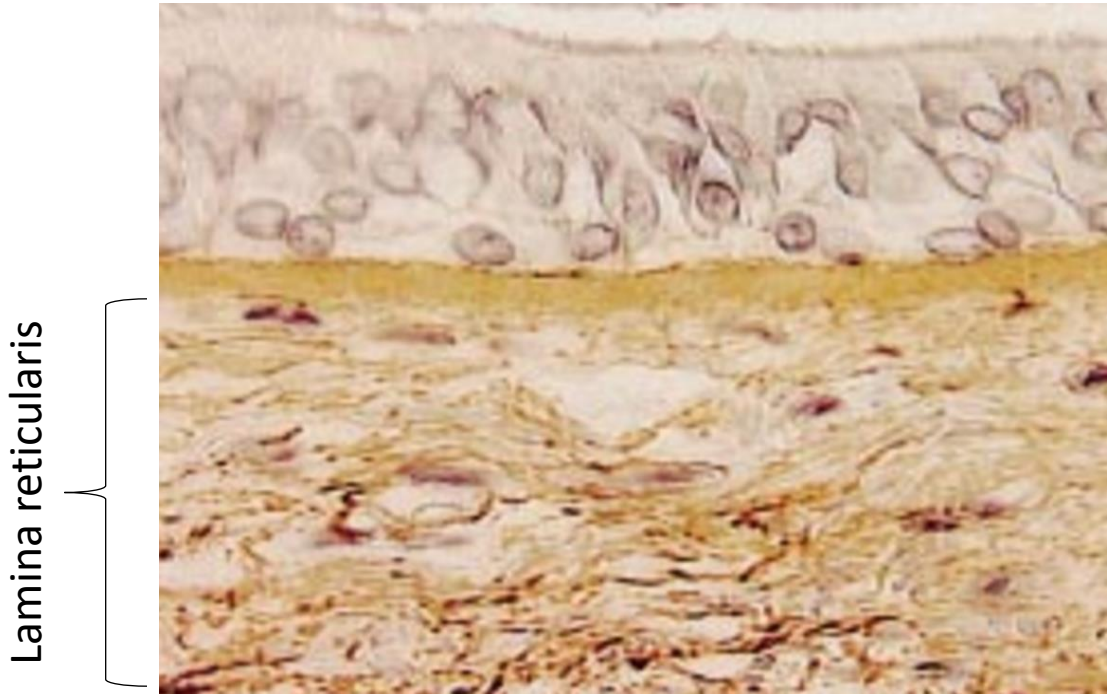
Airway remodeling in mild asthma

ORIGINAL ARTICLE

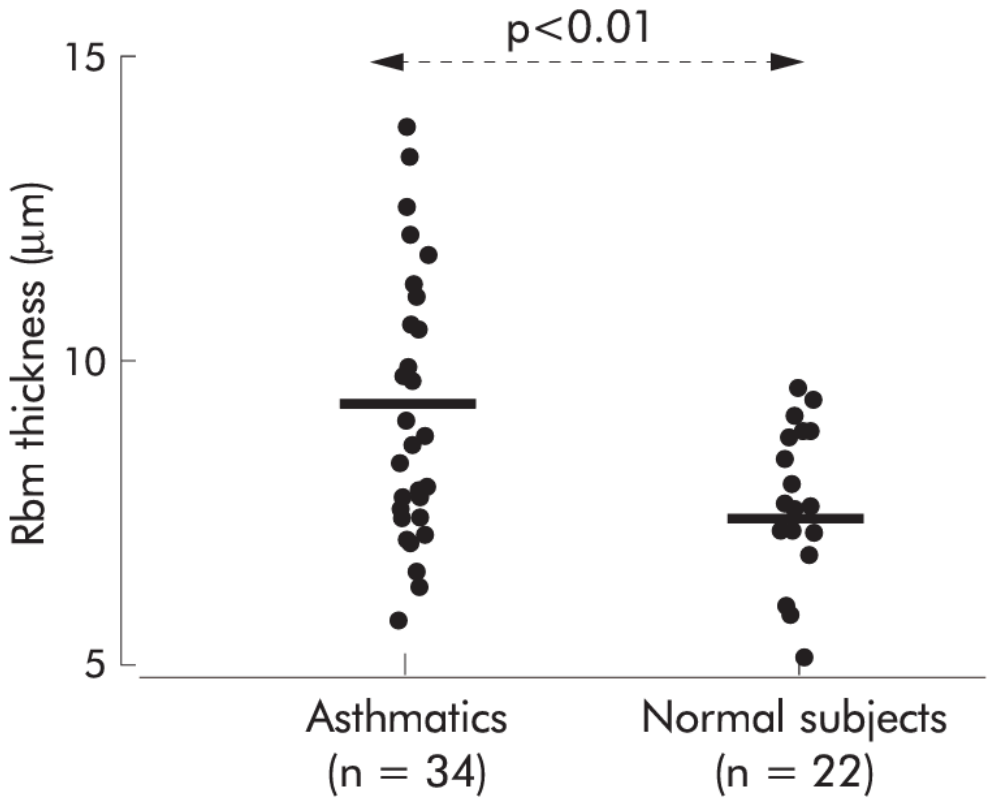
Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma

C Ward, M Pais, R Bish, D Reid, B Feltis, D Johns, E H Walters

Thorax 2002;**57**:309–316



Thickening of subepithelial reticular basement membrane **(RBM)**

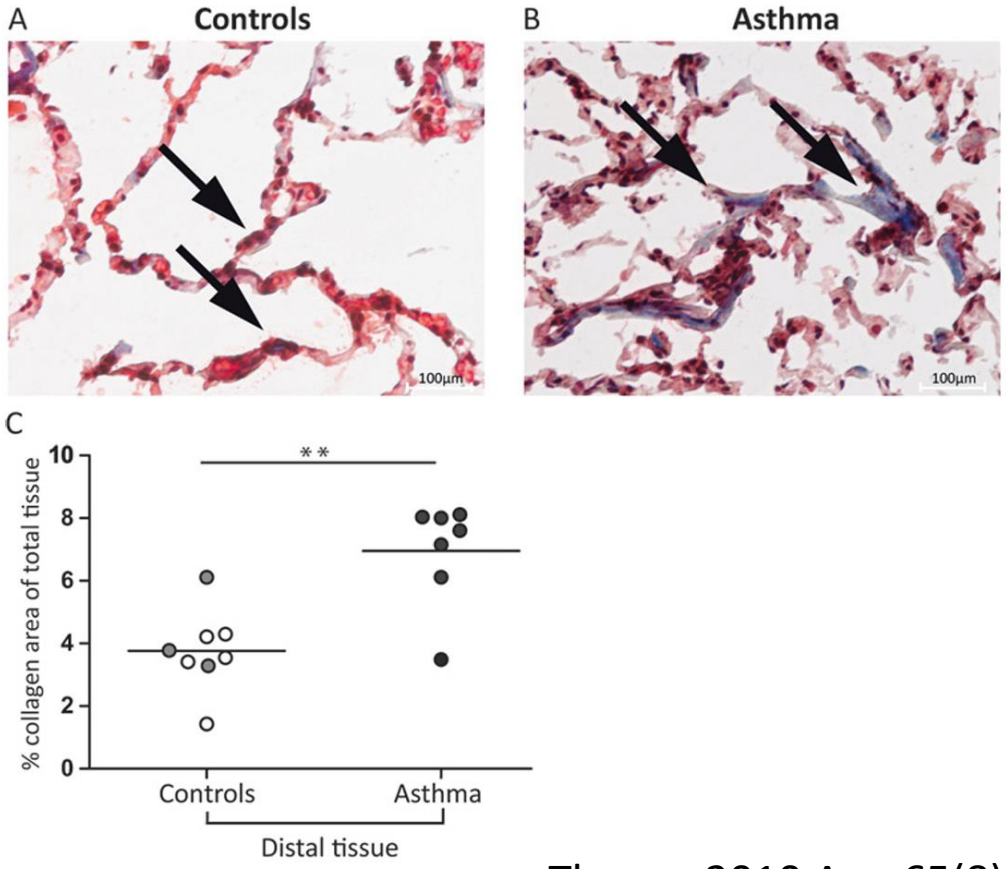


Thorax. 2002 Apr;57(4):309-16.

Airway remodeling in mild asthma

Altered matrix production in the distal airways of individuals with asthma

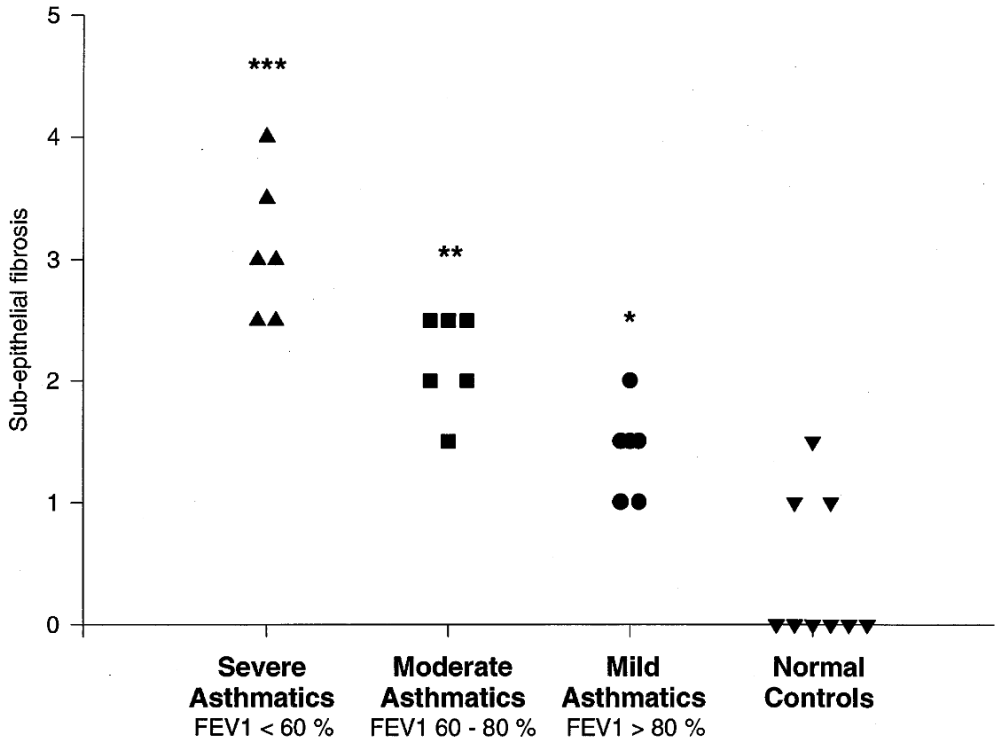
Kristian Nihlberg,[1] Annika Andersson-Sjöland,[2] Ellen Tufvesson,[2] Jonas S Erjefält,[1] Leif Bjermer,[2] Gunilla Westergren-Thorsson[1]



Thorax. 2010 Aug;65(8):670-6

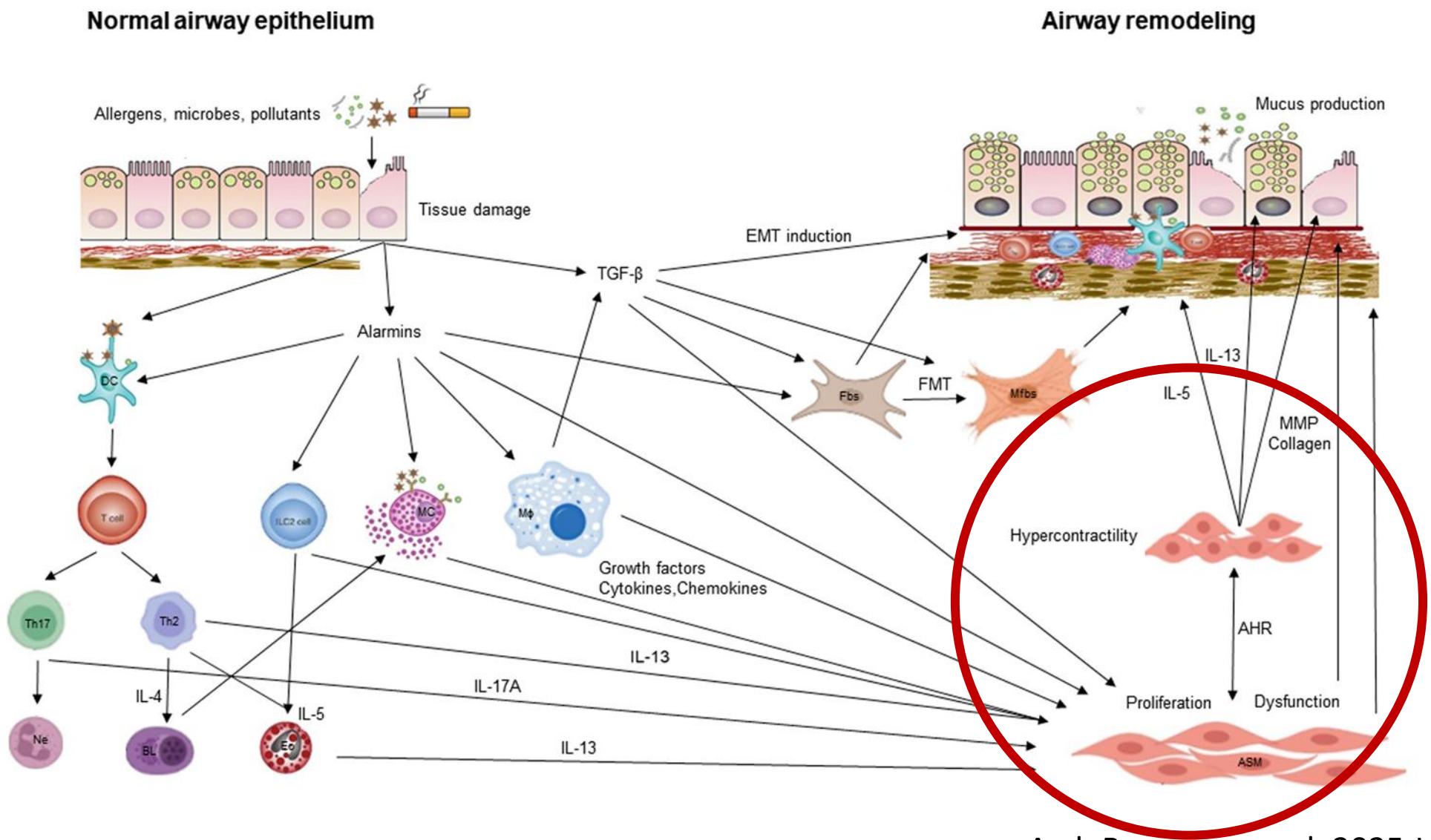
Eosinophil-associated TGF-β_1 mRNA Expression and Airways Fibrosis in Bronchial Asthma

Eleanor M. Minshall, Donald Y. M. Leung, Richard J. Martin, Yan Ling Song, Lisa Cameron, Pierre Ernst, and Qutayba Hamid



Am J Respir Cell Mol Biol. 1997 Sep;17(3):326-33.

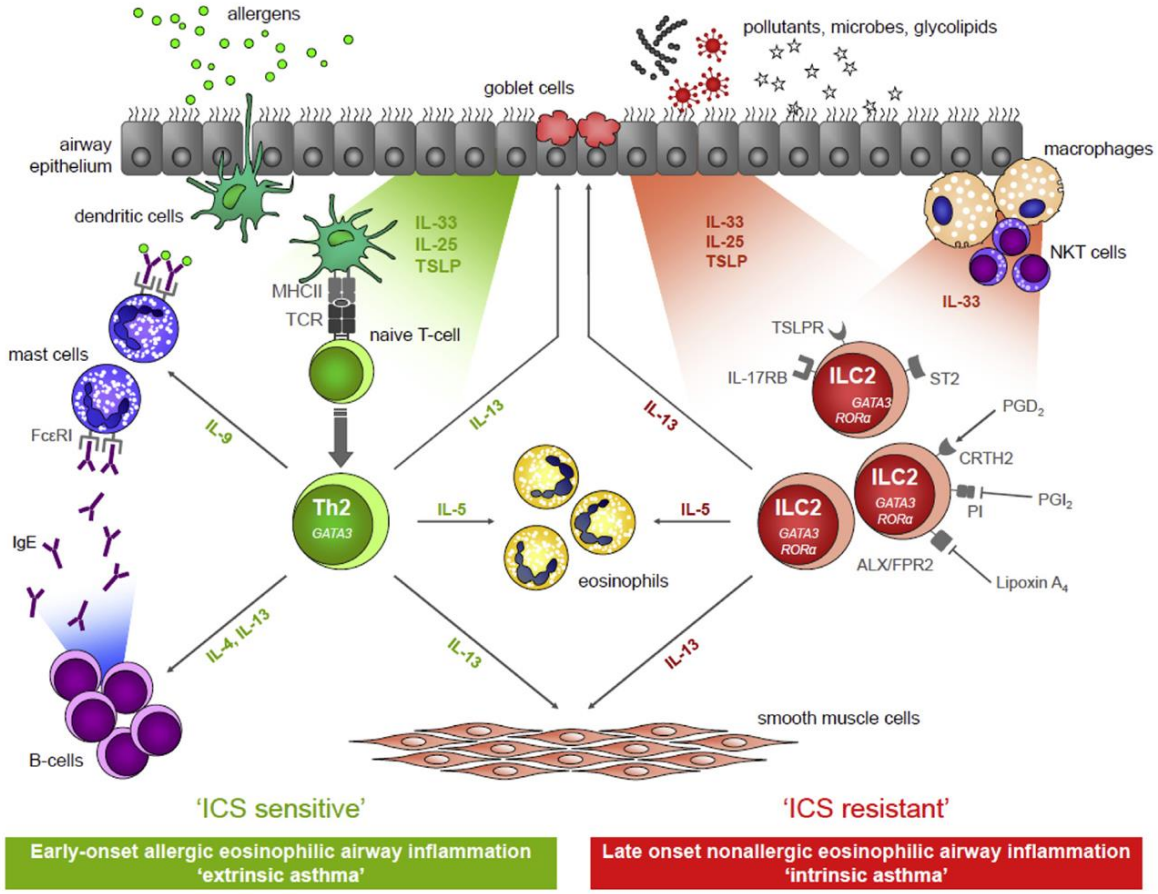
Airway hyperresponsiveness and smooth muscle

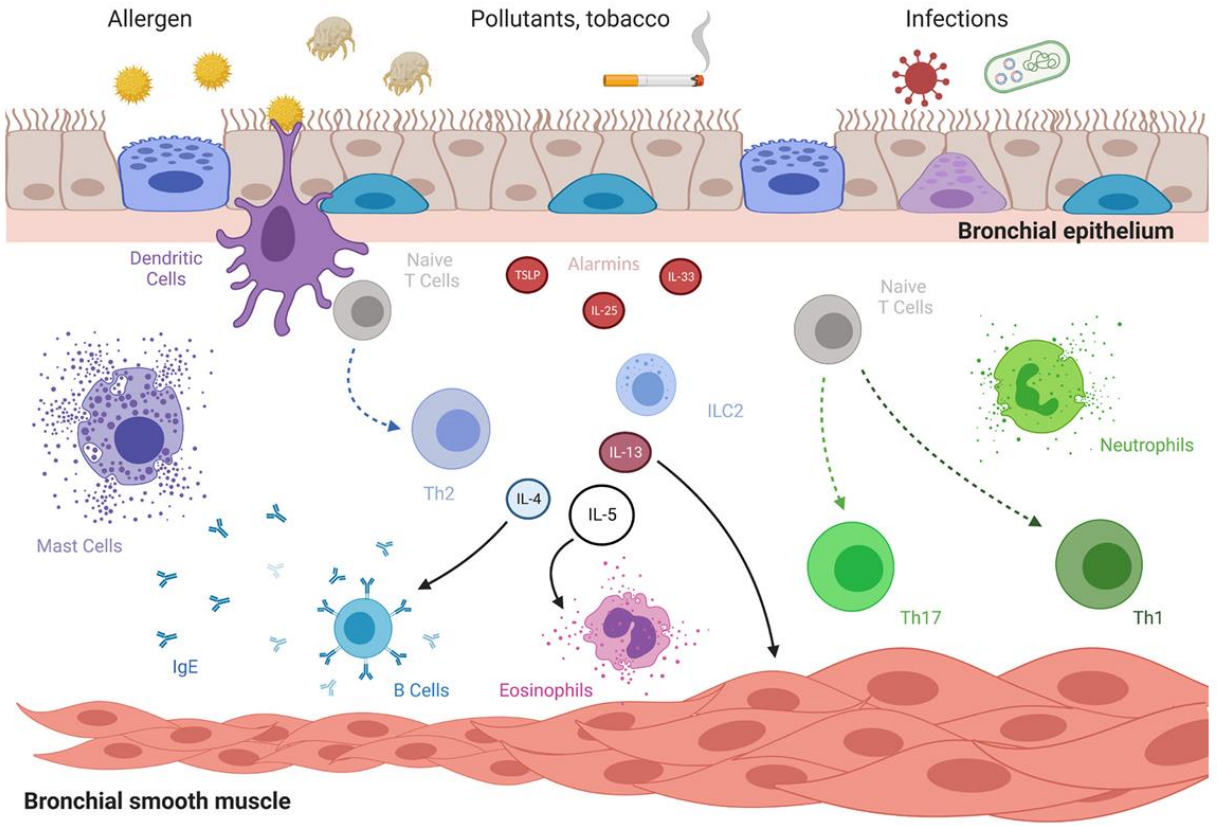


Arch Bronconeumol. 2025 Jan;61(1):31-40.

Smooth muscle hypertrophy in asthma

- **IL-13** induces proliferation and hypertrophy of airway smooth muscle cells





Chest. 2017 Dec;152(6):1276-1282.

BMJ Open Respir Res. 2022 Sep;9(1):e001351.

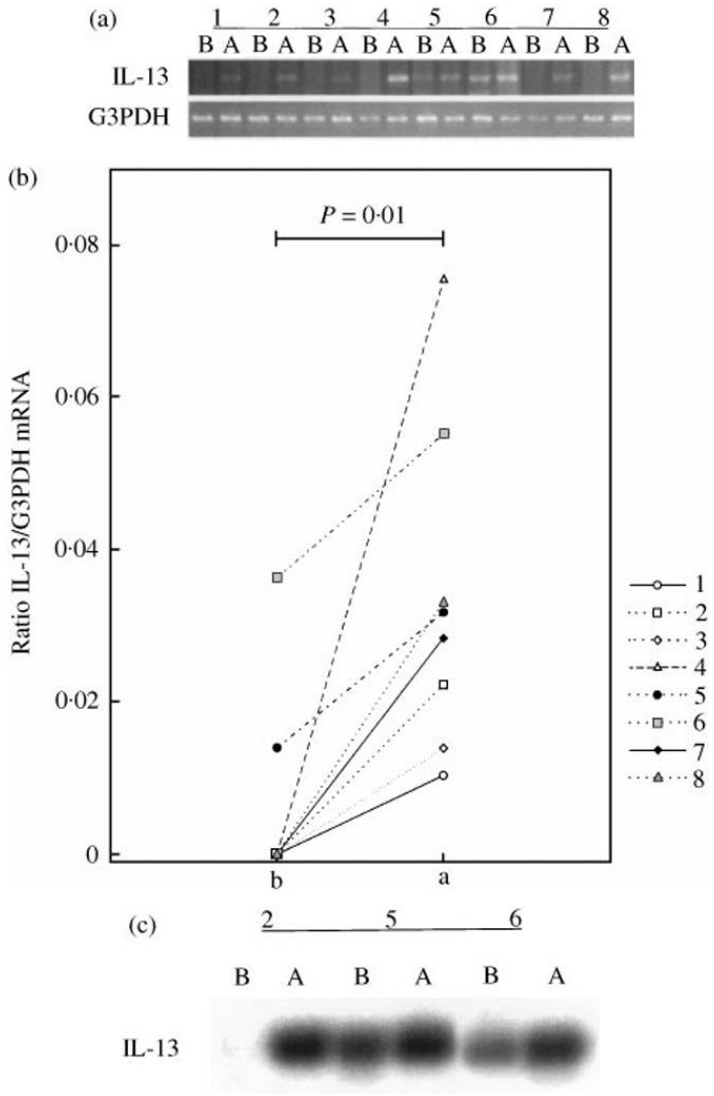
IL-13 elevation after allergen provocation

Respiratory Medicine (2000) **94,** 806–814
doi: 10.1053/rmed.2000.0826, available online at http://www.idealibrary.com on IDEAL®

Increased interleukin-13 mRNA expression in bronchoalveolar lavage cells of atopic patients with mild asthma after repeated low-dose allergen provocations

J. Prieto*, C. Lensmar*, A. Roquet*, I. van der ploeg†, D. Gigliotti‡, A. Eklund* and J. Grunewald*

- **IL-13 mRNA** in alveolar macrophage-enriched BAL cells is elevated in mild asthma **after low-dose allergen challenge**



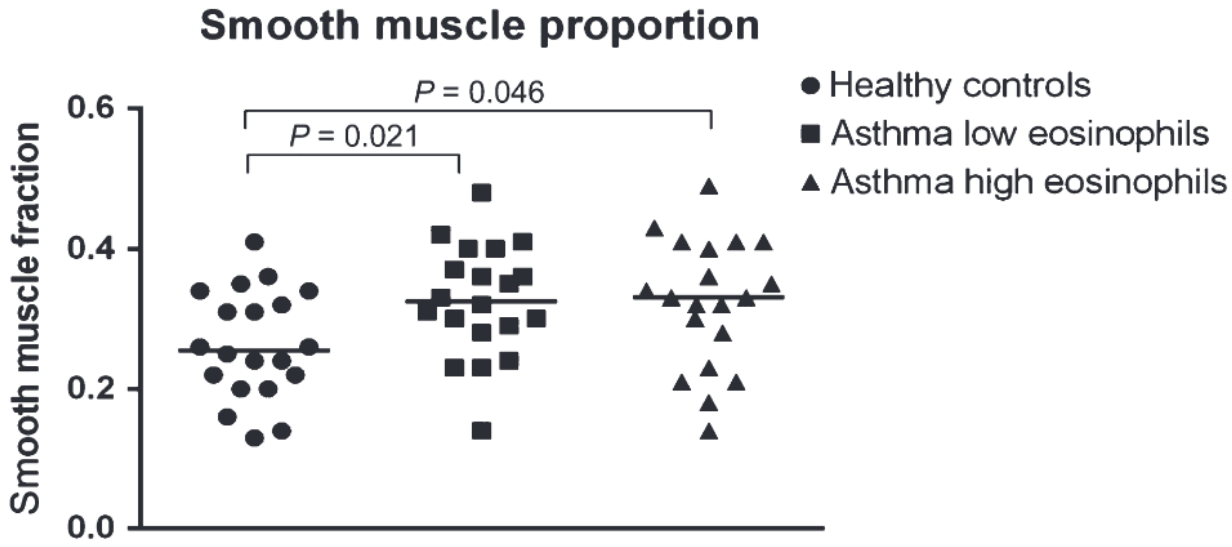
Respir Med. 2000 Aug;94(8):806-14.

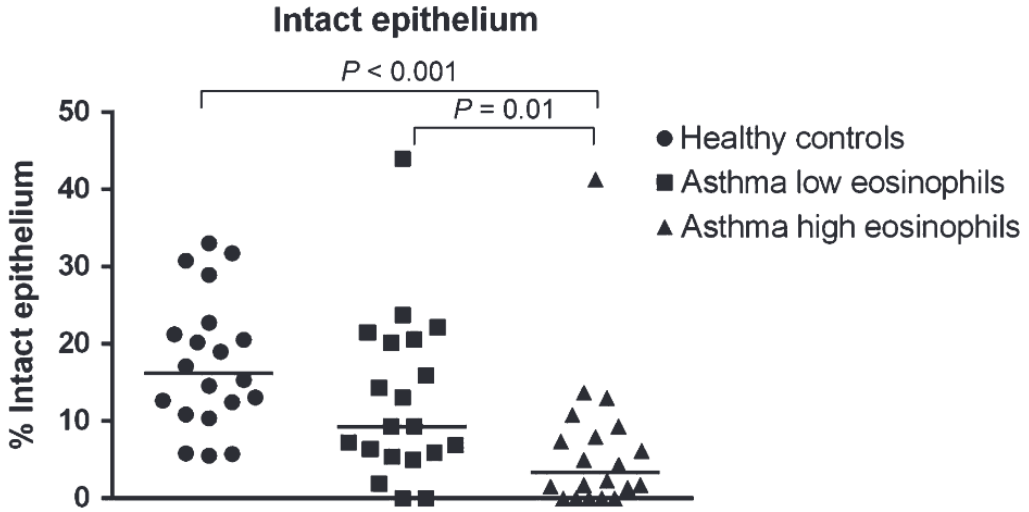
Smooth muscle hypertrophy in mild asthma

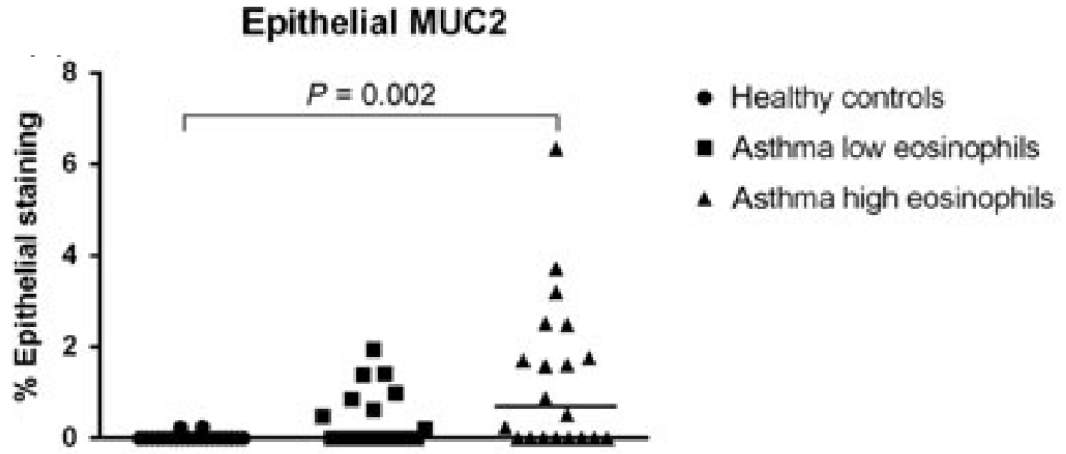
The relationship between eosinophilia and airway remodelling in mild asthma

S. J. Wilson[1], H. M. Rigden[1], J. A. Ward[1], M. Laviolette[2], N. N. Jarjour[3] and R. Djukanović[1,4]

[1]Academic Unit of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK, [2]Laval University, Quebec City, Canada, [3]University of Wisconsin, Madison, WI, USA and [4]NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK







Clin Exp Allergy. 2013 Dec;43(12):1342-50.

Contents

Challenges in mild asthma

Respir Med. 2023 Sep:216:107326.

Exacerbation burden in mild asthma

The burden of exacerbations in mild asthma: a systematic review

J. Mark FitzGerald [1], Peter J. Barnes [2], Bradley E. Chipps[3], Christine R. Jenkins [4], Paul M. O'Byrne [5], Ian D. Pavord [6] and Helen K. Reddel [7]

Main criteria for mild asthma	RCTs (n=54)		Observational/other studies (n=10)	
	All n (%)	Studies permitting past history of exacerbations n (%)	All n (%)	Studies permitting past history of exacerbations n (%)
1) Treatment level	3 (5.6)	0 (0)	5	2 (20.0)
2) Symptom frequency criteria	3 (5.6)	3 (5.6)	0	–
3) FEV_1 ⩾80% pred and symptoms<daily	19 (35.2)	15 (27.8)	2	1 (10.0)
4) FEV_1 >60–80% pred and symptoms<daily	15 (27.8)	13 (24.1)	1	1 (10.0)
5) Miscellaneous definitions#	9 (16.7)	8 (14.8)	0	–
6) Included patients aged <5 years	5 (9.3)	4 (7.4)	2	2 (20.0)

ERJ Open Res. 2020 Aug 11;6(3):00359-2019.

Severe exacerbations in mild asthma

- Proportion of patients who experienced **severe exacerbation in the previous year: 0~22.2%**
- Proportion of patients who experienced **severe exacerbation: 3.4%~33.3%**

- Annual severe exacerbation rates in placebo arms of RCTs
  - ✓ **SYGMA 1**: 0.20 per patient-year
  - ✓ **OPTIMA A**: 0.77 per patient-year
  - ✓ **CHUCHALIN et al.**: 0.33 per patient-year

ERJ Open Res. 2020 Aug 11;6(3):00359-2019.

Exacerbation risk of apparently mild asthma

- **“Apparently mild asthma”**
  - ✓ Few or intermittent symptoms but still at risk of severe exacerbations
  - ✓ Useful term to highlight the discordance between symptoms and risk
  - ✓ Should not be mistranslated into “Obviously mild asthma”

Since GINA 2021 report

- Patients with apparently mild asthma are still at risk of serious adverse events
  - ✓ 30–37% of adults with acute asthma
  - ✓ 16% of patients with near-fatal asthma
  - ✓ 15–27% of adults dying of asthma

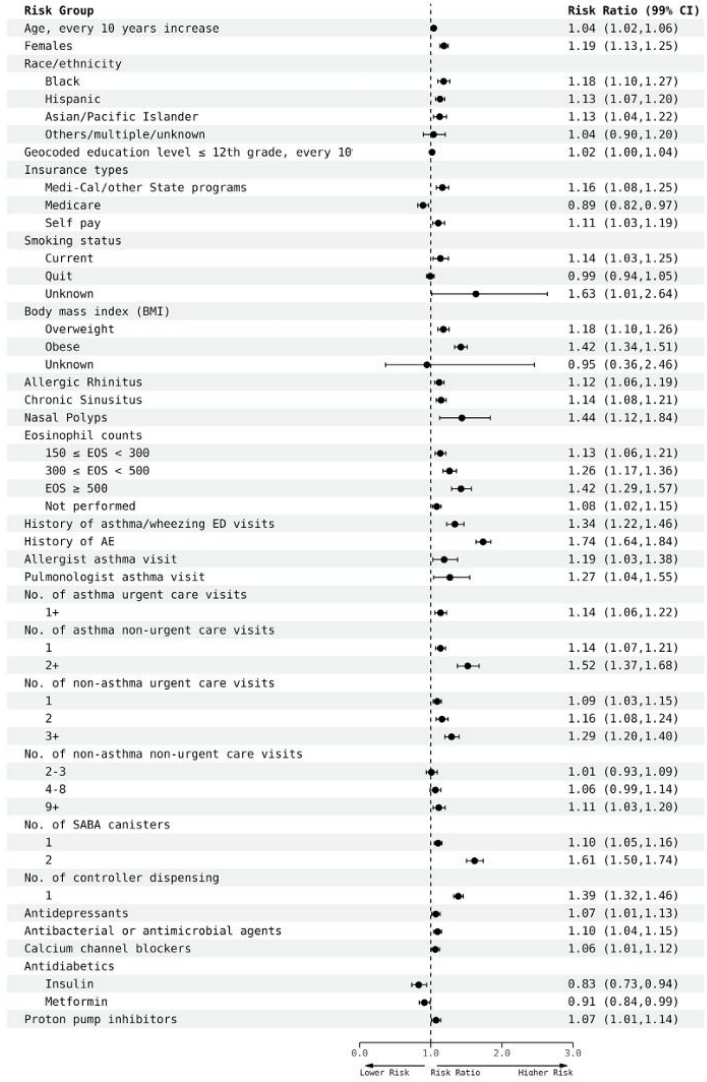
} had **symptoms less than weekly in previous 3 months**

Allergy. 2007 Jun;62(6):591-604.
Respir Med., 2008. 102: 1335-41.

Risk factors for exacerbations in mild asthma

- In multivariate models, predictors for future AE risk in mild asthma

  - ✓ Age (Older)
  - ✓ Sex (Female)
  - ✓ Current smoking
  - ✓ Body mass index (Higher)
  - ✓ Comorbidities (Rhinitis/Sinusitis/Nasal polyp)
  - ✓ Blood eosinophil count (Higher)
  - ✓ Prior acute asthma care
  - ✓ Antidepressant/Antibiotics/Anti-diabetics (no use), PPI



J Allergy Clin Immunol Pract. 2024 Oct;12(10):2705-2716.e6.

Mortality in mild asthma

- Depend on the age, study design, and healthcare settings,
  - ✓ ER visit rates were ranged from **13.7% to 41.3%**
  - ✓ hospitalization rates were ranged from **0% to 15.4%**

- About **5~13%** of investigated **deaths due to asthma** occurred in patients "being treated for mild asthma"

ERJ Open Res. 2020 Aug 11;6(3):00359-2019.

Assessment based on symptoms and AE history

Symptom control will be assessed using GINA recommendations.

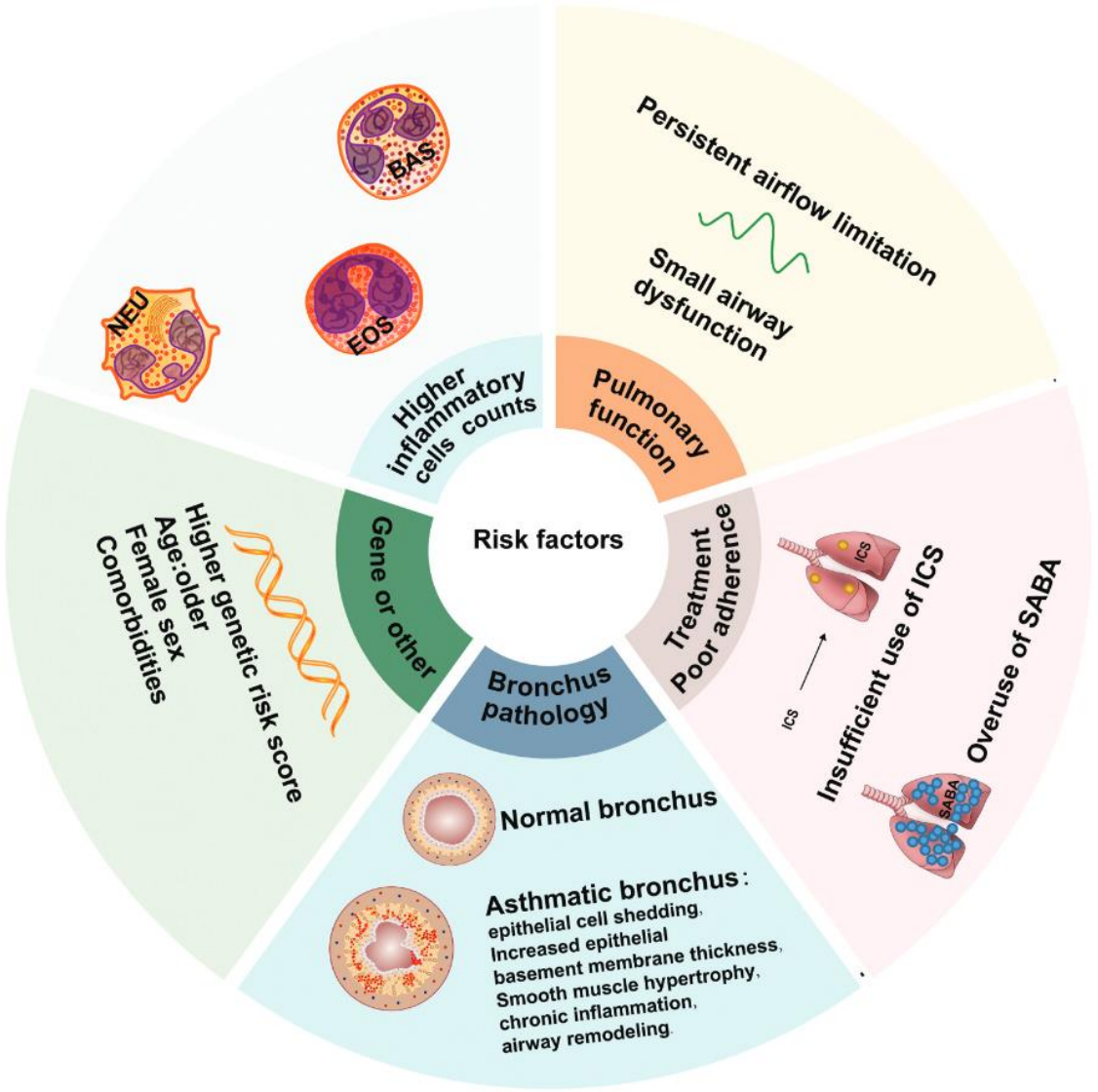
In the past 4 weeks, has the patient had:		**Level of asthma symptom control**		
		Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week?	Yes / No	None	1-2	3-4
Any night time waking due to asthma?	Yes / No			
SABA reliever needed more than twice/week?	Yes / No			
Any activity limitation due to asthma?	Yes / No			

Patient A = Low symptoms, low exacerbation Patient B = Low symptoms, high exacerbation Patient C = High symptoms, low exacerbation Patient D = High symptoms, high exacerbation		**Exacerbations**	
		Low (≤1 per year)	High (> 1 per year)
Control	Well controlled (0 points)	A	B
	Partly controlled or uncontrolled (1-4 points)	C	D

A: Ideal patient to be classified as mild, low symptoms and low risk.
B: May be classified as mild if exacerbation risk is underestimated. Should be treated with ICS to reduce exacerbation burden.
C: May be classified as mild if control improves after 6 months of therapy.
D: High symptom burden (poor control) and high exacerbation frequency, should not be considered mild asthma.

Respir Med. 2023 Sep:216:107326.

Risk factors for progression of mild asthma



Expert Rev Respir Med. 2023 Dec;17(12):1261-1271.

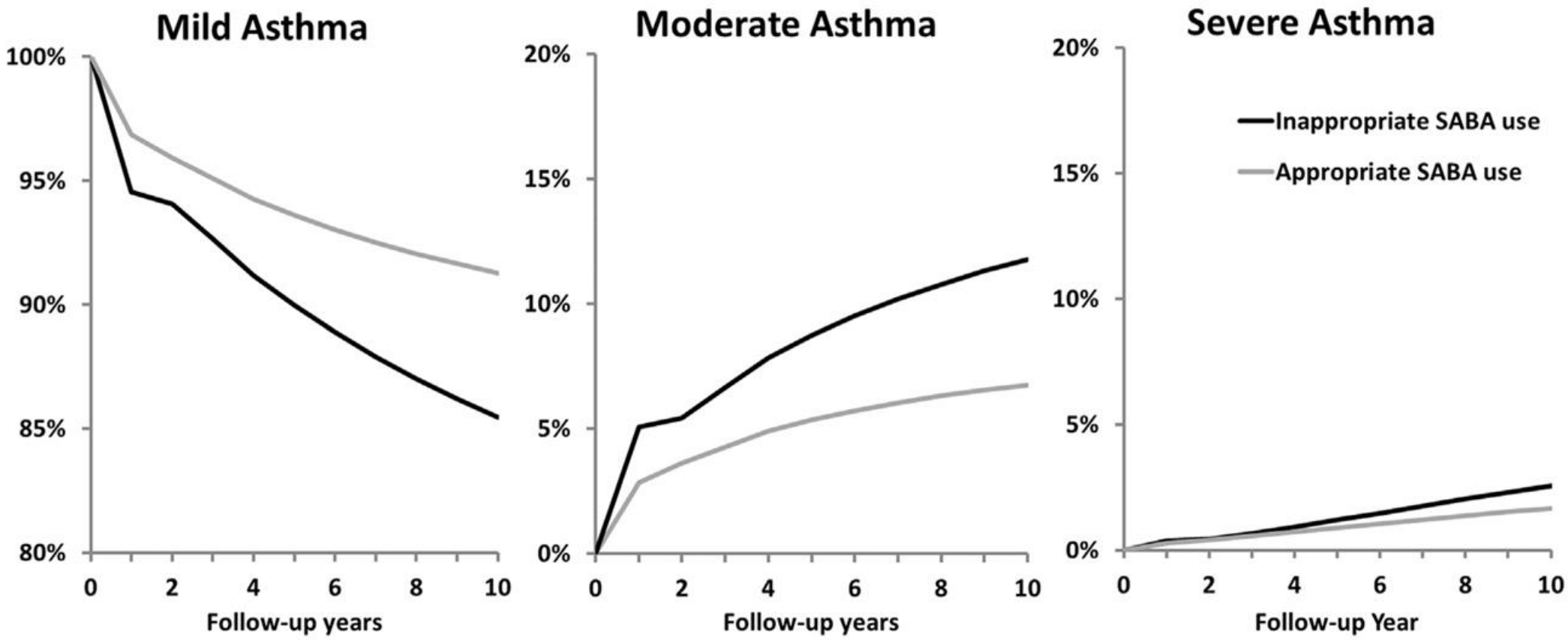
Progression of mild asthma to more severe status

Long-Term Trajectories of Mild Asthma in Adulthood and Risk Factors of Progression

Wenjia Chen, PhD[a], J. Mark FitzGerald, MD[b,c], Larry D. Lynd, PhD[a,d], Don D. Sin, MD[c,e], and Mohsen Sadatsafavi, MD, PhD[a,c] *Vancouver, BC, Canada*

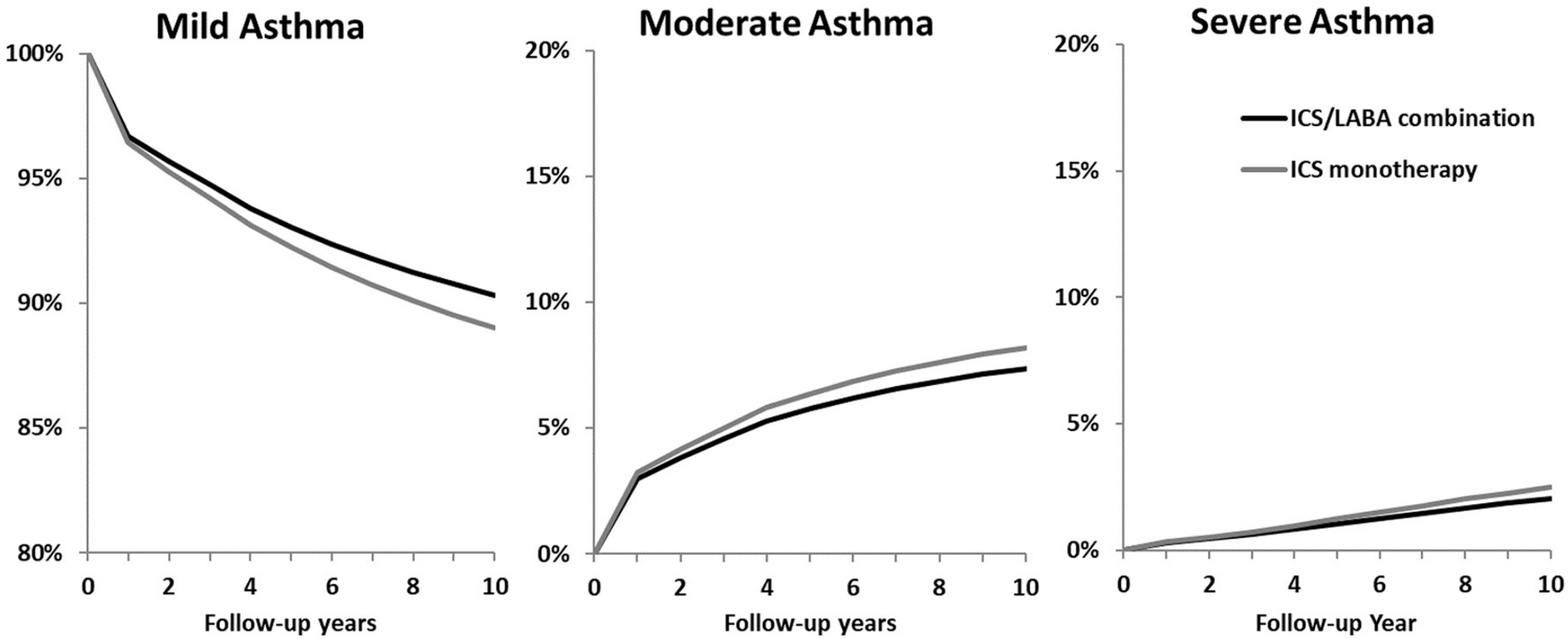
J Allergy Clin Immunol Pract. 2018 Nov-Dec;6(6):2024-2032.e5.

Inadequate treatment can lead to progression of mild asthma



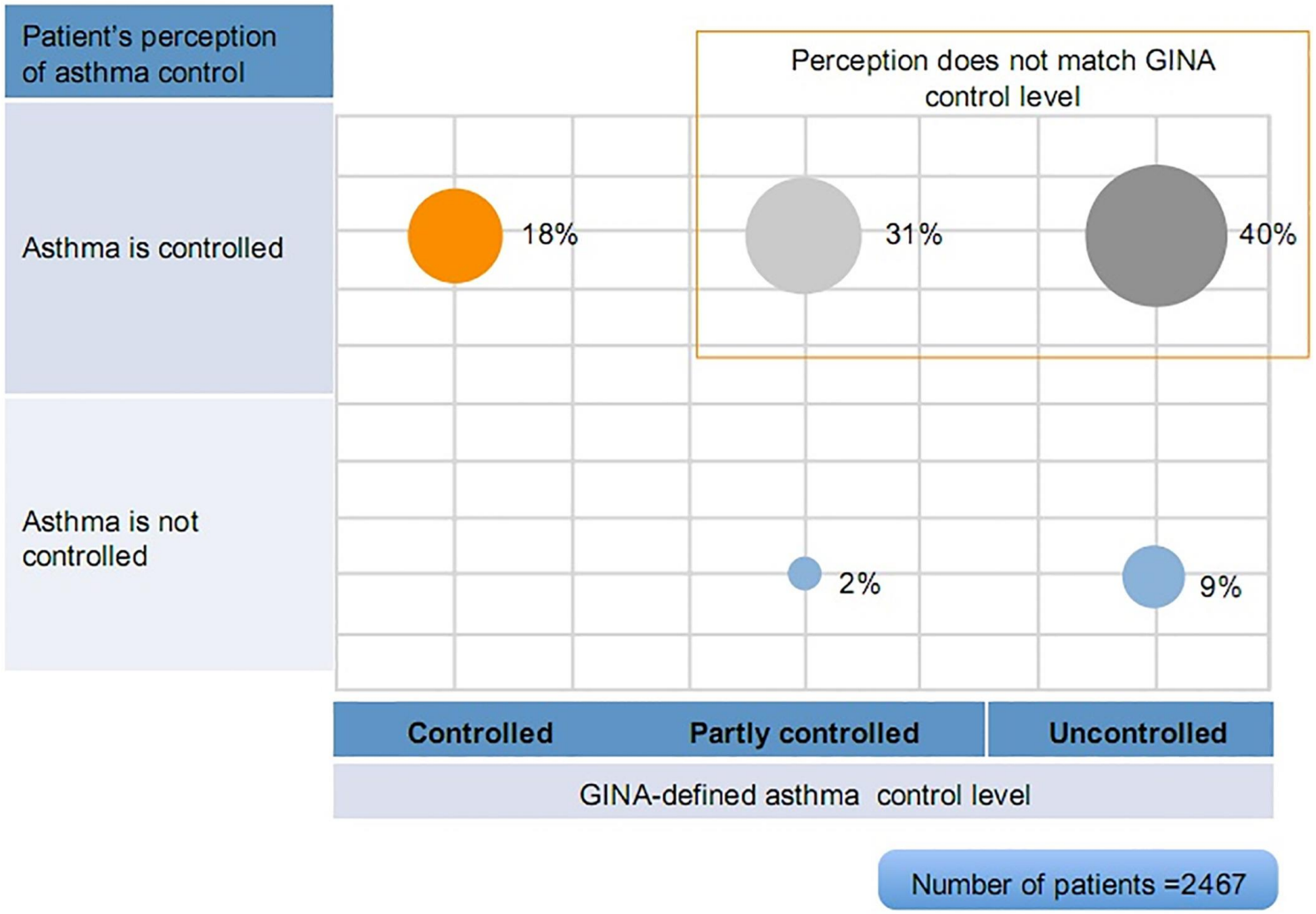
J Allergy Clin Immunol Pract. 2018 Nov-Dec;6(6):2024-2032.e5.

ICS/LABA *vs.* ICS in terms of asthma progression



J Allergy Clin Immunol Pract. 2018 Nov-Dec;6(6):2024-2032.e5.

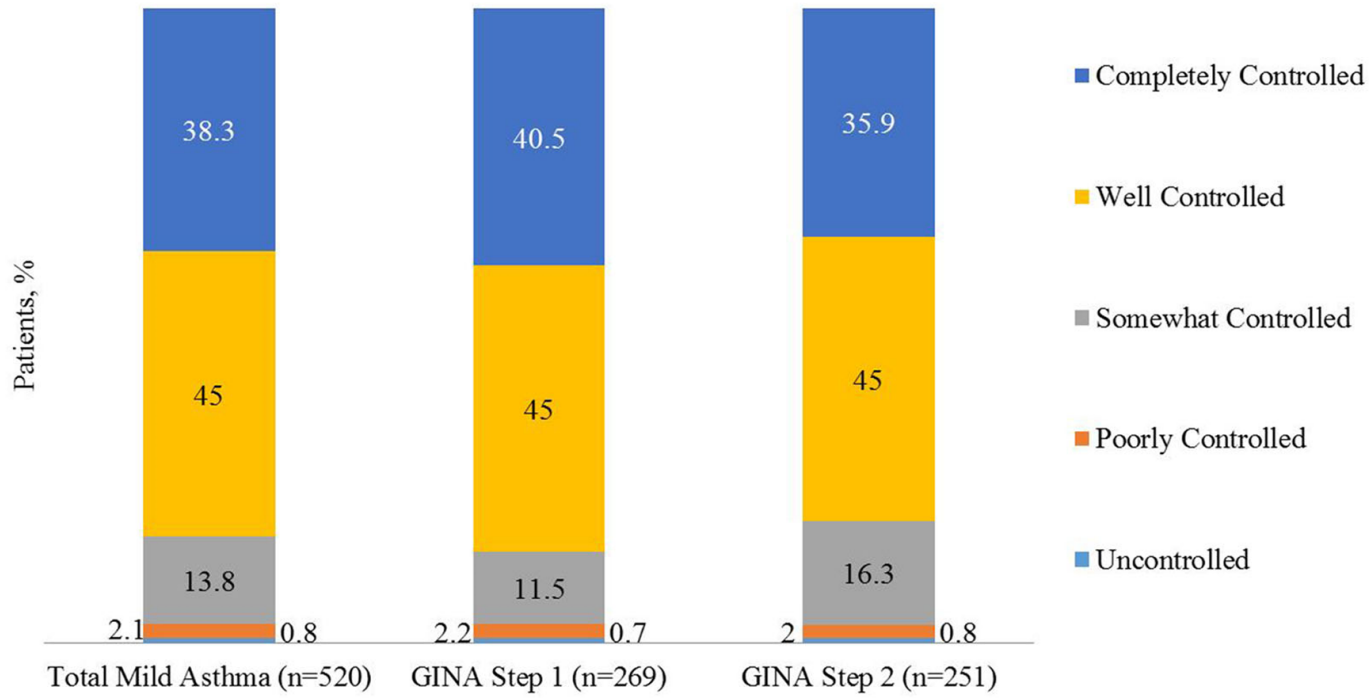
What patients perceive *vs.* ACT assessment in asthma



Respirology. 2021 Oct;26(10):917-919.

Symptom control in mild asthma

- A prospective cross-sectional multinational survey in mild asthma



Patient-reported perceptions of asthma control

The proportion of patients with

ACT<20 : 25.3% (n=129)

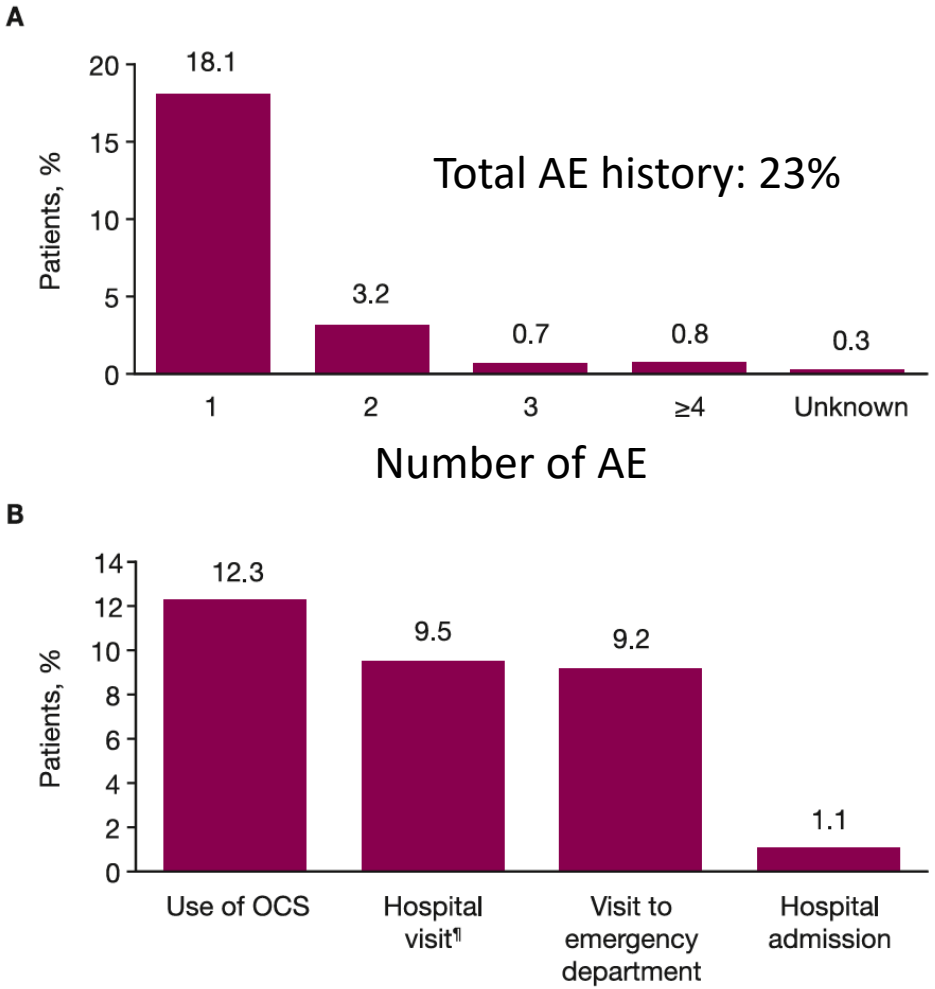
Adv Ther. 2017 Apr 8;34(5):1109–1127

Symptom control according to exacerbation history

Original Research

The burden of mild asthma: Clinical burden and healthcare resource utilisation in the NOVELTY study

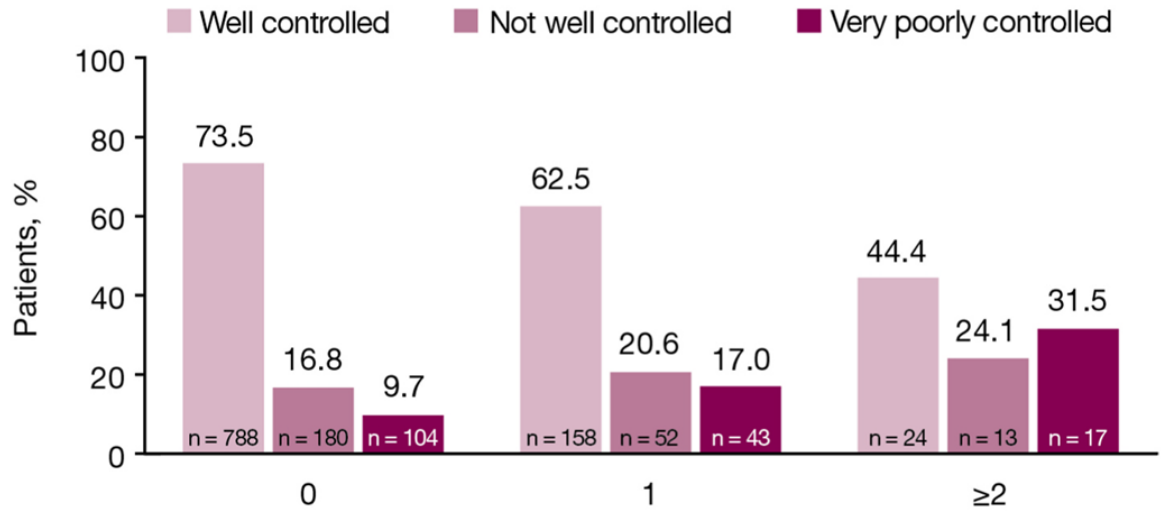
* NOVELTY study: 3-year prospective, multicenter observational cohort study,



Total AE history: 23%

Baseline mean ACT score: **20.8**

Proportion of patients with **ACT<20: 29.7%**



Respir Med. 2022 Aug-Sep:200:106863.

Lung function decline in mild asthma

- In newly diagnosed male asthmatics, FEV_1 decline was more accelerated compared to those without asthma during observation.

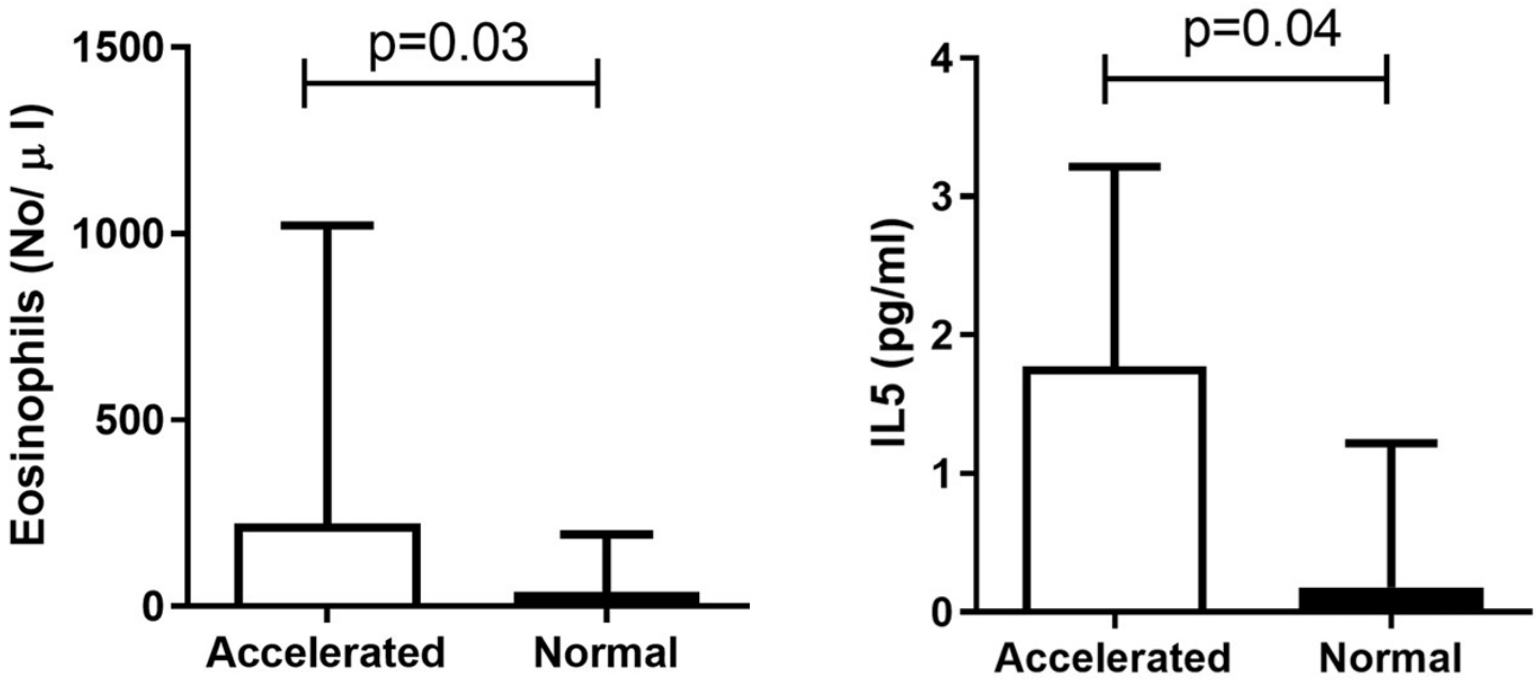
REGRESSION ANALYSIS OF ΔFEV_1 (mL/YR) ON AGE, SMOKING, AND ASTHMA GROUP
$[\Delta FEV_1 = k_1 + (k_2 \times age) + (k_3 \times height) + (k_4 \times smoking) + (k_{5\text{-}7} \times asthma\ group)]$

	Women (n = 5,877)			Men (n = 4,597)		
Independent Variable	Regression Coefficient	SE	p Value	Regression Coefficient	SE	p Value
Intercept	−66.0			−107.0		
Age, yr	0.99	0.12	< 0.001	0.79	0.17	< 0.001
Height, m	0.3	0.2	0.172	0.6	0.3	< 0.05
Smoking*	8.6	2.3	< 0.001	15.3	3.8	< 0.001
Asthma group†						
A-NA	−9.9	19.0	0.590	4.9	22.0	0.826
NA-A	11.0	8.9	0.216	39.0	12.8	0.002
A-A	3.0	9.1	0.742	1.7	15.0	0.915

Am J Respir Crit Care Med. 1994 Sep;150(3):629-34.

Biologic factors related with lung function decline

- In mild asthma, sputum eosinophil and sputum IL-5 was associated with accelerated lung function decline



* Accelerated means FEV1 decline >30mL/yr

Respir Med. 2020 Feb:162:105875.

Contents

Current treatment strategy in mild asthma

It is time to change the way we manage mild asthma : an update in GINA 2019

	Controller options	GINA 2018	GINA 2019
Step 1 *(Patients with symptoms <twice a month and no exacerbation risk factors)*	Preferred	• SABA as-needed and no controller.	• **As-needed low dose ICS-formoterol (off- label).**
	Other options	• Daily low dose ICS.	• **Low dose ICS taken whenever SABA is taken (off-label).** This may involve combination (ICS-SABA) in a single or separate (ICS inhaler + SABA inhaler) inhaler/s.
Step 2	Preferred	• Daily low dose ICS.	• Daily low dose ICS. • **As-needed low dose ICS-formoterol (off-label)**
	Other options	• Daily LTRA. • Daily low dose ICS-LABA.	• **Low dose ICS taken whenever SABA is taken (off-label)** • Daily LTRA. • Daily low dose ICS-LABA (better improvement in symptoms and FEV_1 than when ICS is used alone but more costly, and exacerbation rate is similar to the above option).

Respir Res. 2019 Aug 14;20(1):183.

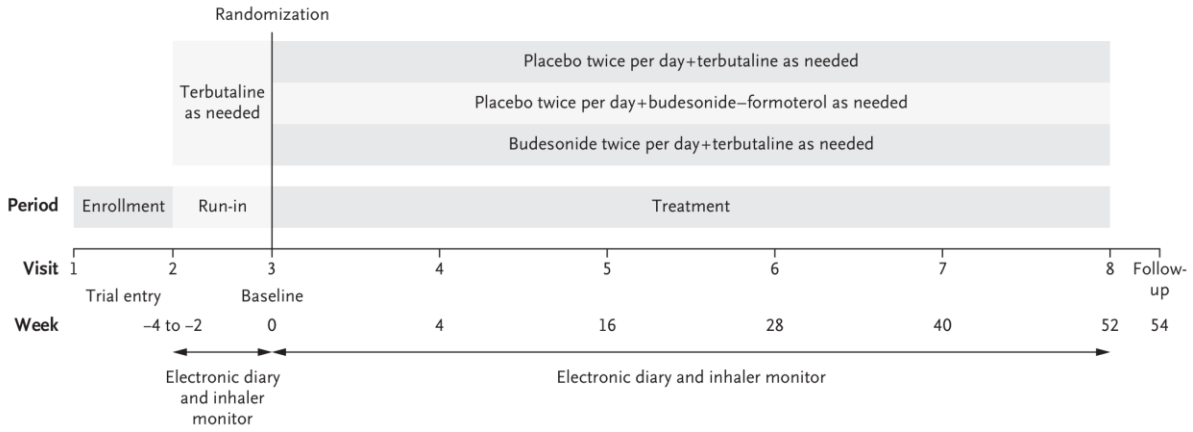
ICS containing regimen *vs.* SABA alone (SYGMA 1 trial)

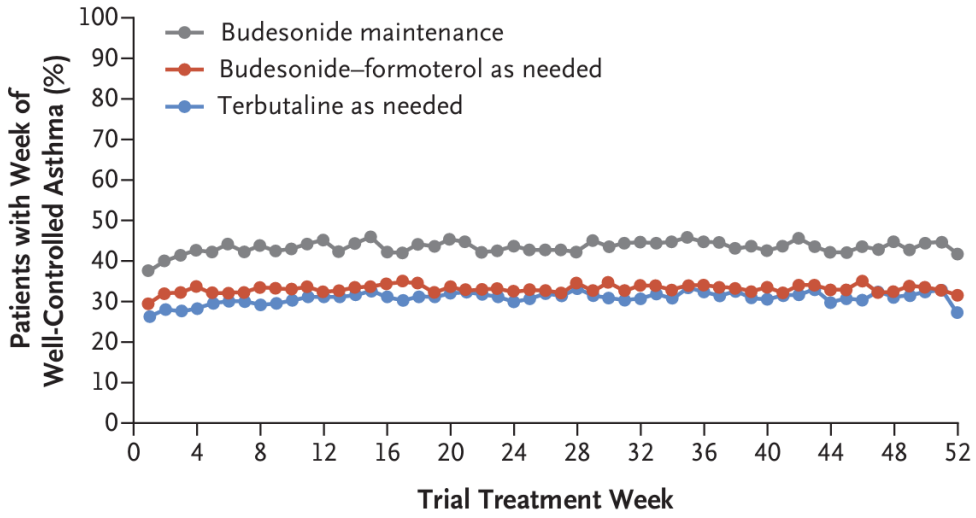
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.





Variable	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)
All severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	152 (11.9)	71 (5.6)	78 (6.1)
Total no. of exacerbations	188	77	89
Annualized exacerbation rate	0.20	0.07	0.09
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.36	—	0.83
95% CI	0.27–0.49	—	0.59–1.16
P value	<0.001	—	0.28

N Engl J Med. 2018 May 17;378(20):1865-1876.

ICS containing regimen *vs.* SABA alone (SYGMA 2 trial)

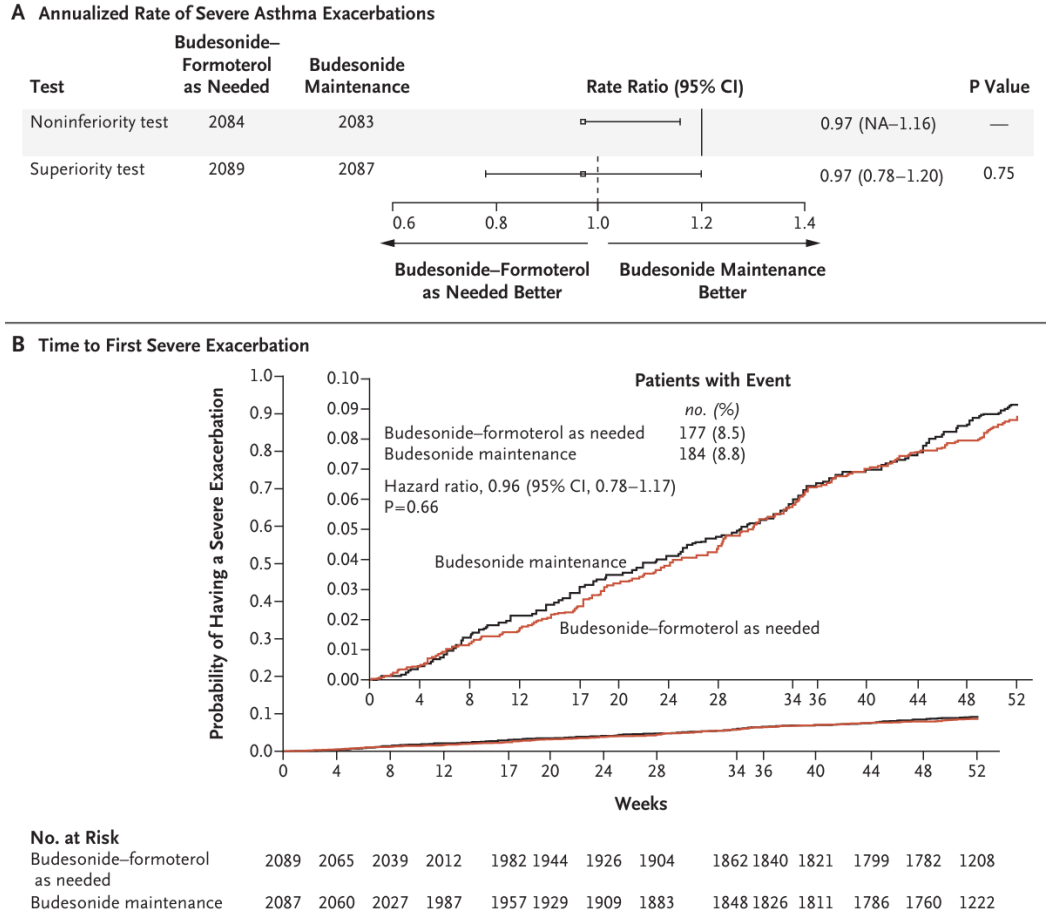
ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline, According to Treatment Group.*

Characteristic	Budesonide–Formoterol as Needed (N=2089)	Budesonide Maintenance Therapy (N=2087)	Total (N=4176)
Asthma control according to pretrial treatment — no. (%)§			
Uncontrolled with short-acting bronchodilator	959 (45.9)	975 (46.7)	1934 (46.3)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	1130 (54.1)	1112 (53.3)	2242 (53.7)
No. of severe exacerbations in previous 12 mo — no. (%)			
0	1630 (78.0)	1627 (78.0)	3257 (78.0)
1	365 (17.5)	362 (17.3)	727 (17.4)
≥2	94 (4.5)	98 (4.7)	192 (4.6)



N Engl J Med. 2018 May 17;378(20):1877-1887.

Budesonide maintenance in mild asthma

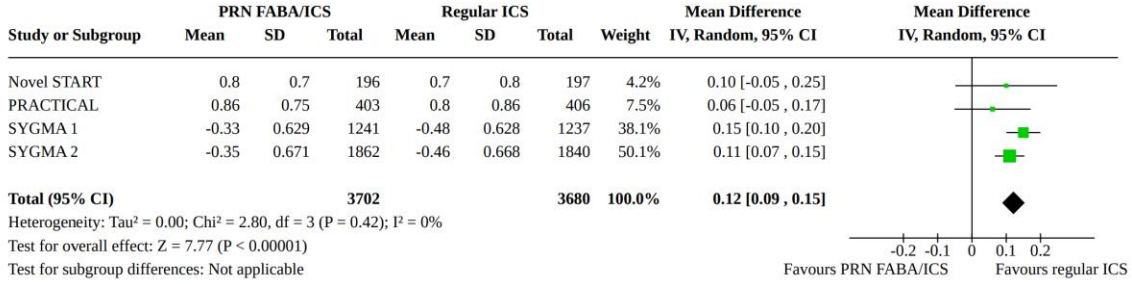
- **ACQ-5, FEV_1, FeNO**

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

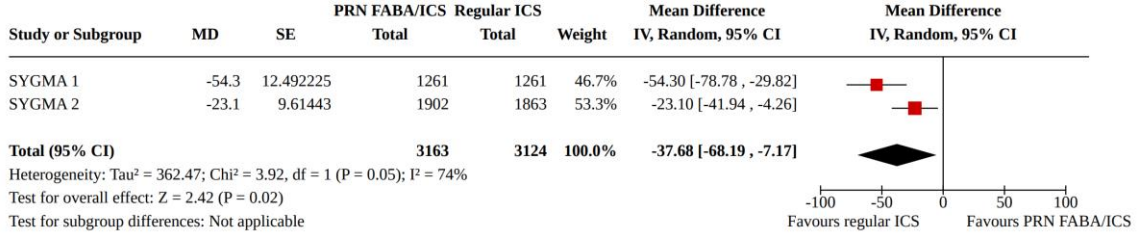
- Meta-analysis of all four RCTs, n=9,565
  - ✓ ACQ-5 mean difference 0.15 (MCID 0.5)
  - ✓ FEV_1 mean difference ~54 mL
  - ✓ FeNO mean difference ~10ppb

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

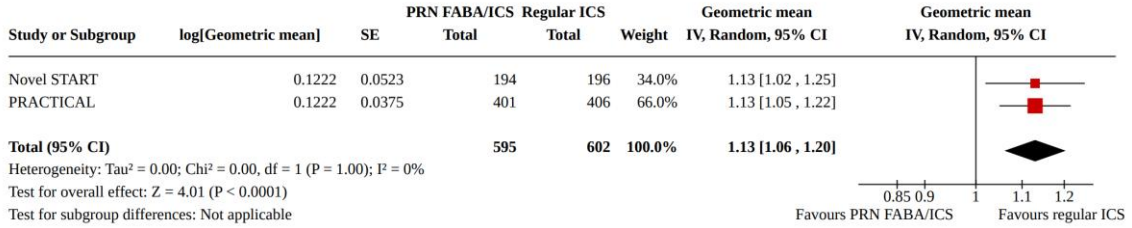
ACQ-5



FEV_1



FeNO



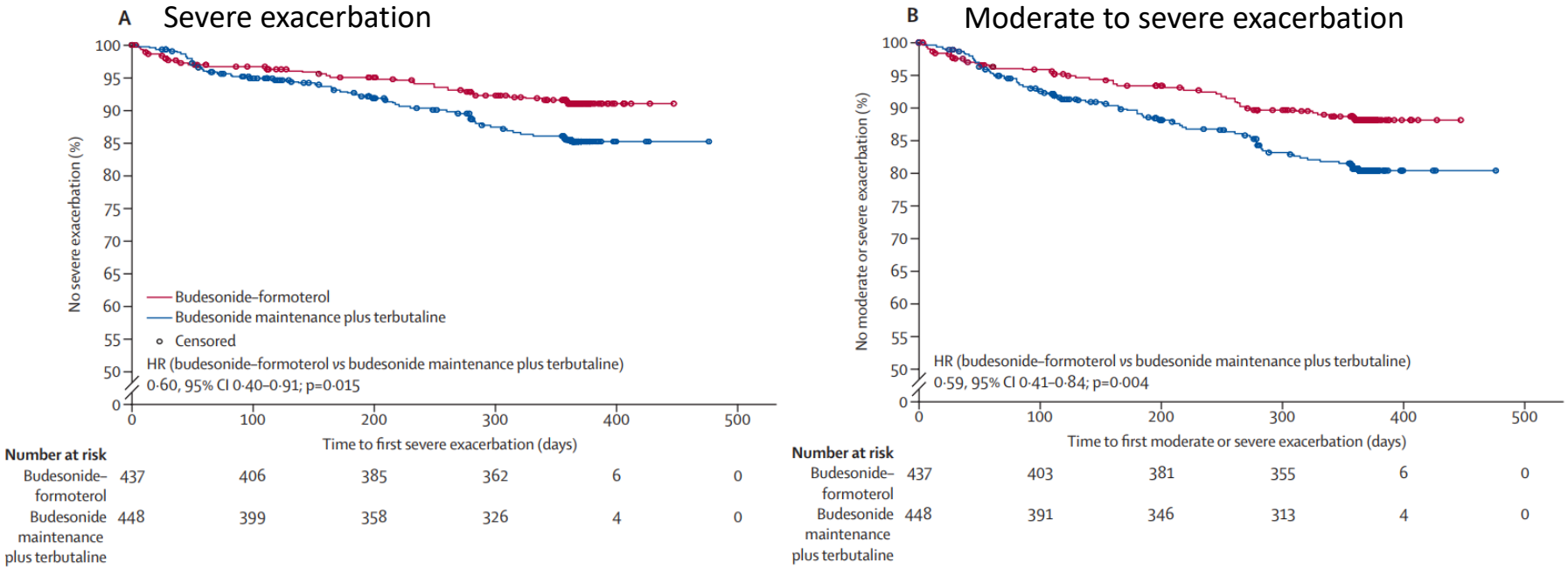
Cochrane Database Syst Rev. 2021 May 4;5(5):CD013518.

Severe exacerbation reduced by as needed ICS/formoterol

- **Severe exacerbation in mild asthma**

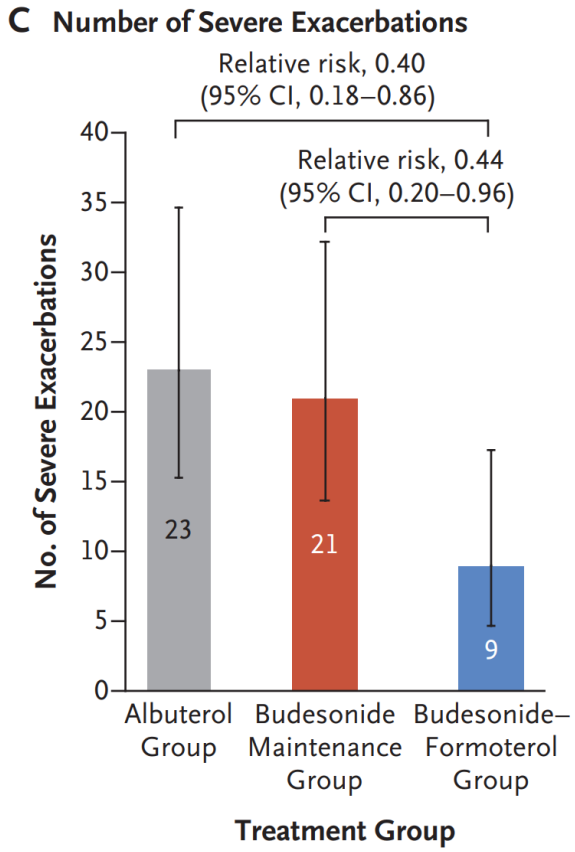
  : as needed Budesonide + Formoterol > Budesonide maintenance + as needed albuterol

PRACTICAL trial (mild to moderate asthma)



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

Novel START trial (mild asthma)



N Engl J Med 2019; 380:2020-2030

Severe exacerbation reduced by as needed ICS/formoterol

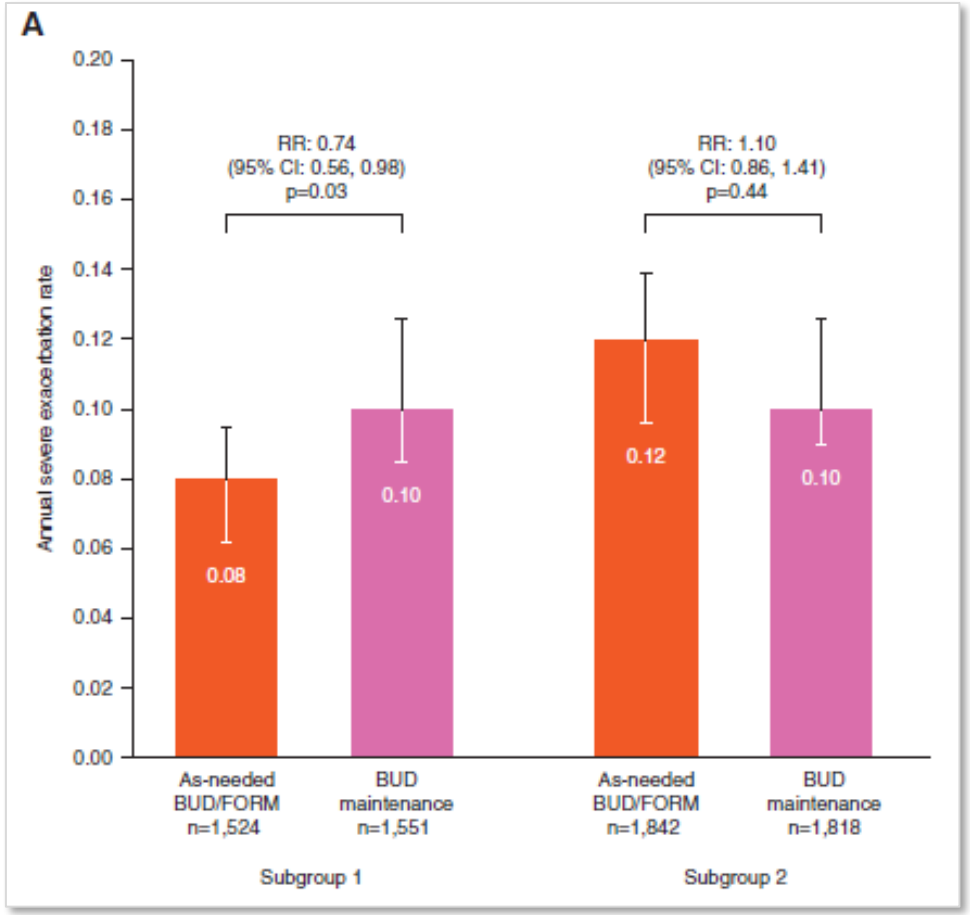
- **Severe exacerbation in mild asthma**

  : 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.



Severe exacerbation reduced by as needed ICS/formoterol

- **Reduced severe exacerbation in mild asthma**

  : As needed ICS + Formoterol or ICS maintenance + as needed SABA > SABA alone

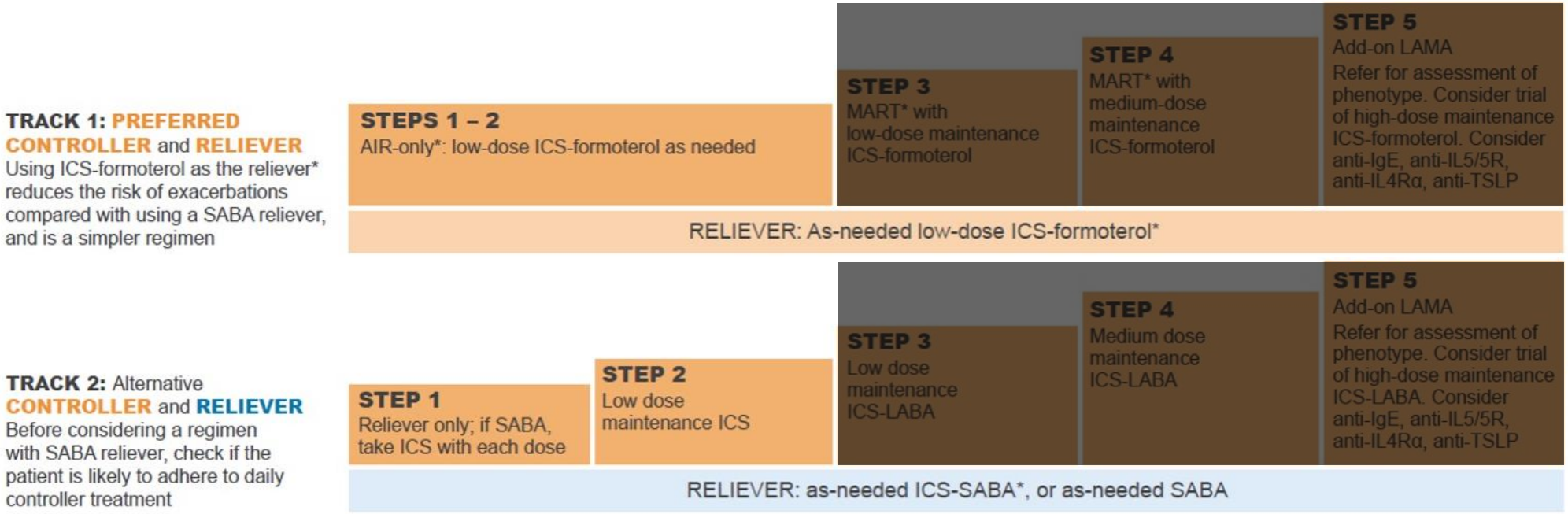
  : **As needed ICS + Formoterol > ICS maintenance + as needed SABA**

Group and comparison	No. of patients (No. of trials)	Patients in intervention group with outcome, %	Patients in comparator group with outcome, %	Certainty of evidence	Network risk difference (95% CI)	Favors intervention	Favors comparator
Severe exacerbations							
GINA step 1							
ICS-formoterol vs SABA	19 184 (13)	6.7	10.3	High	-3.6 (-4.1 to -2.9)		
ICS-SABA vs SABA	4852 (4)	8.7	10.3	High	-1.6 (-2.8 to -0.5)		
ICS-formoterol vs ICS-SABA	3949[b] (22)	6.8	8.7	Moderate	-1.9 (-3.0 to -0.7)		
GINA step 2							
ICS-formoterol vs SABA	19 184 (13)	11.2	17.2	High	-6.0 (-6.9 to -4.8)		
ICS-SABA vs SABA	4852 (4)	14.4	17.2	High	-2.8 (-4.6 to -0.9)		
ICS-formoterol vs ICS-SABA	3949[b] (22)	11.2	14.4	Moderate	-3.2 (-4.9 to -1.2)		

JAMA. 2025 Jan 14;333(2):143-152

GINA treatment options: Track 1 & Track 2

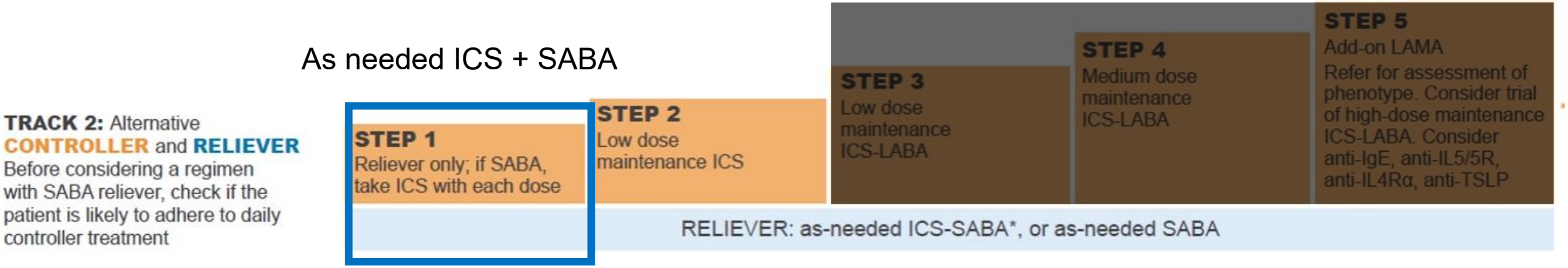
- **Track 1 is preferred** because ICS-formoterol as reliever (or AIR)
  - Reduces the risk of severe exacerbations compared with using a SABA reliever (Track 2)
  - Similar symptom control and lung function
  - Simpler regimen



GINA 2025 report

GINA treatment options: Track 2

- **Track 2, with SABA as the reliever, is an 'alternative' strategy**
  - Track 2 can be considered,
    - ✓ If Track 1 is not possible AND
    - ✓ If a patient is stable with good adherence and no exacerbations on their current therapy



GINA 2025 report

As needed ICS + SABA in Track 2 regimen

- **Papi et al [BEST study group] (N Engl J Med. 2007 May 17;356(20):2040-52.)** — For adults with mild asthma
- Martinez et al. [TREAXA trial] (Lancet. 2011 Feb 19;377(9766):650-7.)
- Sumino et al. (JACI in practice 2020;8: 176-185 e172)

For children with mild asthma

As needed ICS + SABA *vs.* Regular ICS

- Double-blind, Double-dummy, Randomized controlled trial
- **Mild persistent asthma** for ≥6 months, age of 18~65, FEV1 ≥ 75%, BDR positivity or MBPT positivity
- **Previous treatment: SABA or Low-dose ICS (<500ug /day of beclomethasone [standard particle])**
- Intervention: 4 groups (**As needed ICS/SABA vs. As needed SABA vs. Regular ICS vs. Regular ICS/SABA**)
- Primary outcome: Morning PEF at 6 months

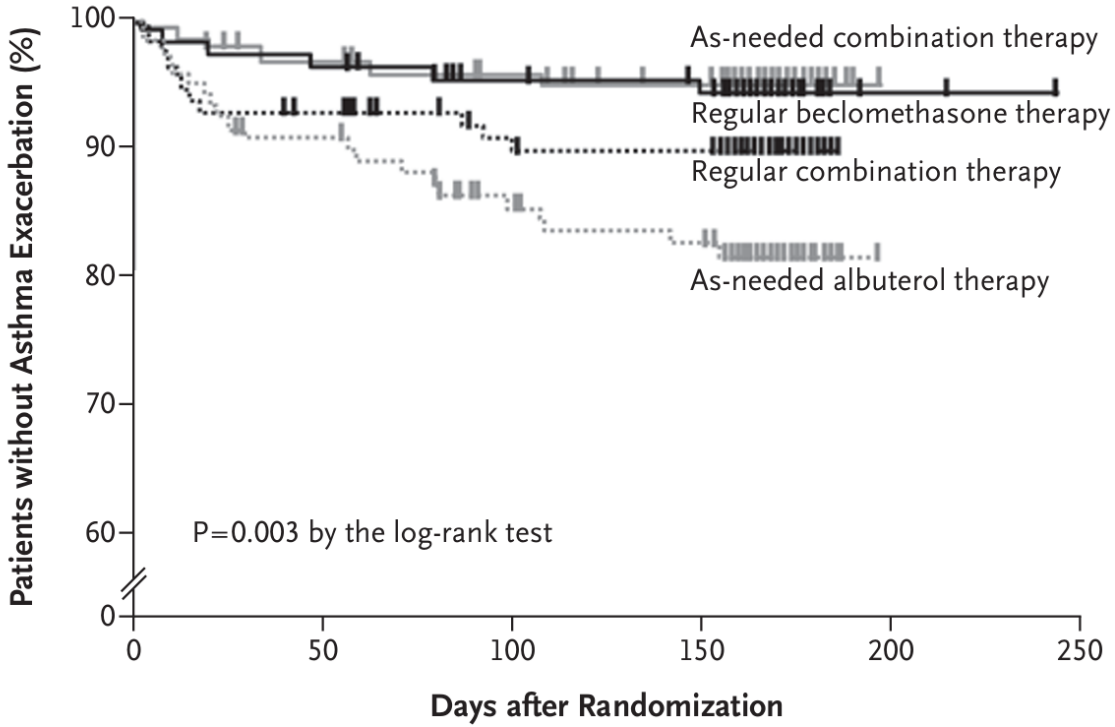
Table 1. Characteristics of Patients at Baseline.*

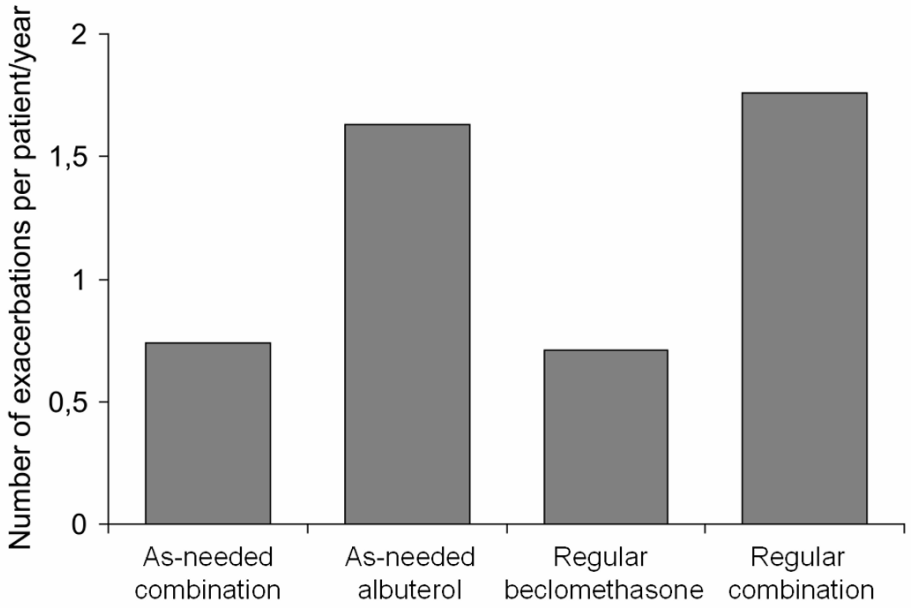
Characteristic	As-Needed Combination Therapy (N=122)	As-Needed Albuterol Therapy (N=118)	Regular Beclomethasone Therapy (N=106)	Regular Combination Therapy (N=109)
Male sex — no. (%)	50 (41.0)	49 (41.5)	45 (42.5)	43 (39.4)
Age — yr	36.8±13.1	40.6±13.8	37.9±13.5	39.9±14.4
Height — cm	168.6±10.5	168.4±9.1	168.6±8.3	167.3±8.8
Atopy — no. (%)	77 (63.1)	68 (57.6)	66 (62.3)	64 (58.7)
Weight — kg	69.0±13.3	71.9±14.7	67.1±12.2	69.5±13.3
Previous inhaled corticosteroids — no. (%)	36 (29.5)	36 (30.5)	33 (31.1)	39 (35.8)
Mean daily dose of inhaled corticosteroid (beclomethasone equivalent) at screening visit — μg†	458.8±163.7	468.6±155.8	472.7±122.7	439.7±168.3

N Engl J Med. 2007 May 17;356(20):2040-52.

As needed ICS + SABA *vs.* Regular ICS

Group	Missing Values Replaced by LOCF†			Missing Values Replaced by ML‡		
	Value	Difference (95% CI)	P Value	Value	Difference (95% CI)	P Value
Morning PEF (liters/min)						
As-needed combination	442.75±9.68	9.47 (0.83 to 18.11)	0.03	438.59±2.80	8.31 (0.58 to 16.04)	0.04
As-needed albuterol	428.52±10.49	−2.49 (−11.40 to 6.42)		430.29±2.84	−4.44 (−12.39 to 3.52)	
Regular beclomethasone	433.08±10.83	11.96 (2.96 to 20.97)	0.009	442.36±3.01	12.74 (4.74 to 20.74)	0.002
Regular combination	435.18±9.55	−1.36 (−10.13 to 7.42)		440.65±2.93	−2.05 (−9.89 to 5.78)	

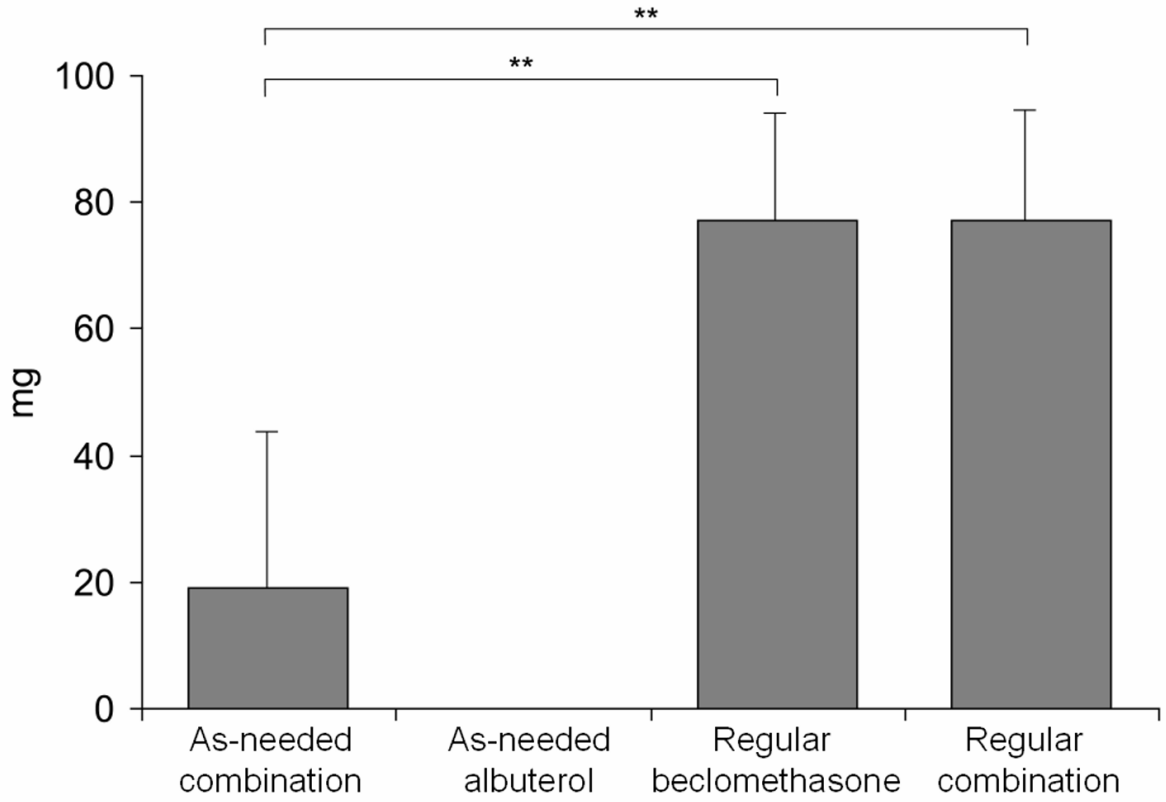




N Engl J Med. 2007 May 17;356(20):2040-52.

As needed ICS + SABA *vs.* Regular ICS

- As needed ICS+SABA group showed **a lower 6-month cumulative dose of the ICS** compared to regular ICS group



N Engl J Med. 2007 May 17;356(20):2040-52.

GINA treatment options: Track 2

- **Track 2, with SABA as the reliever, is an 'alternative' strategy**
  - Track 2 can be considered,
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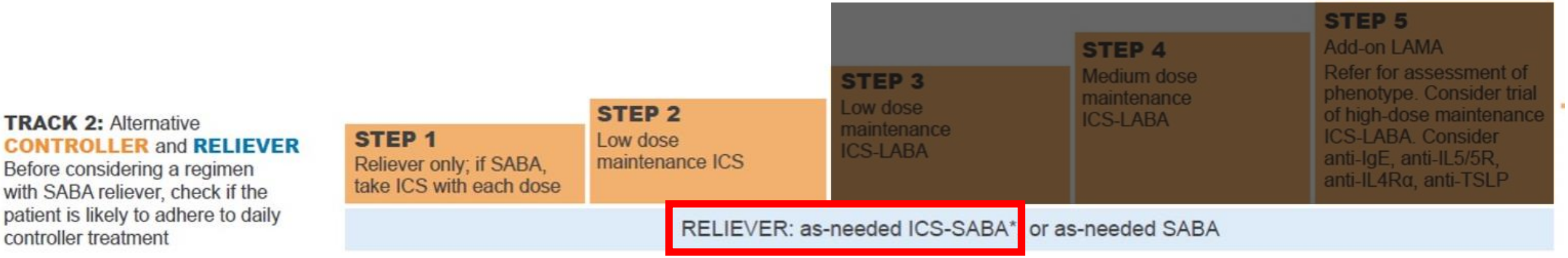
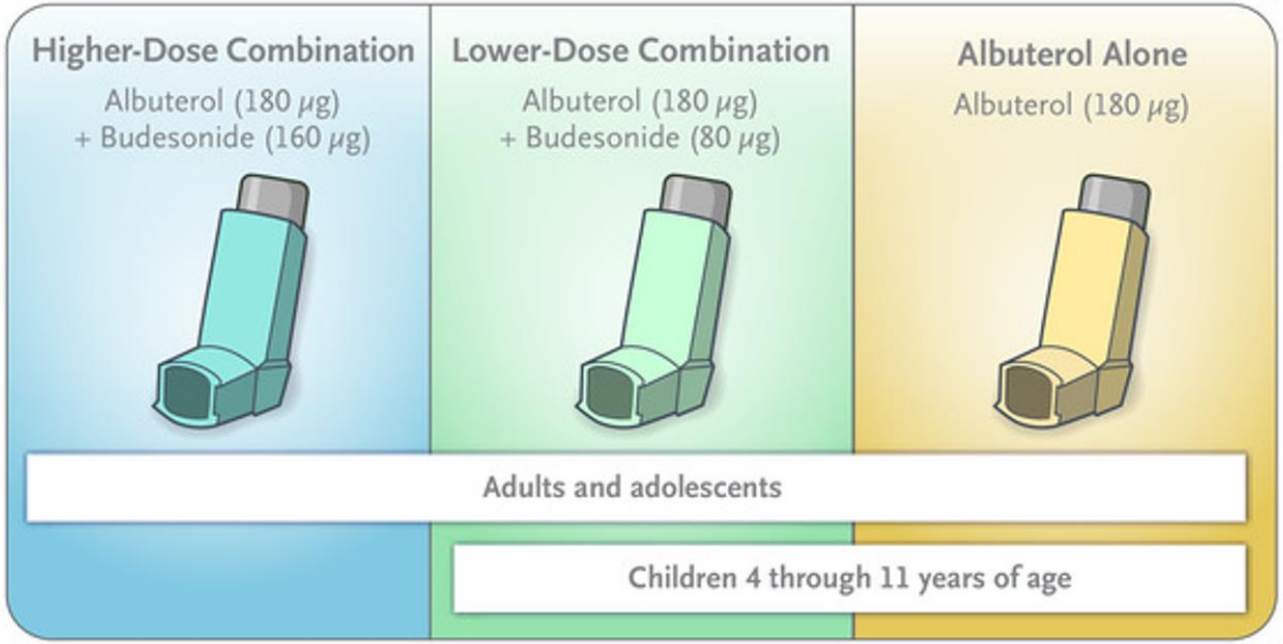


GINA 2025 report

As needed ICS + SABA in moderate-to-severe asthma

- 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)

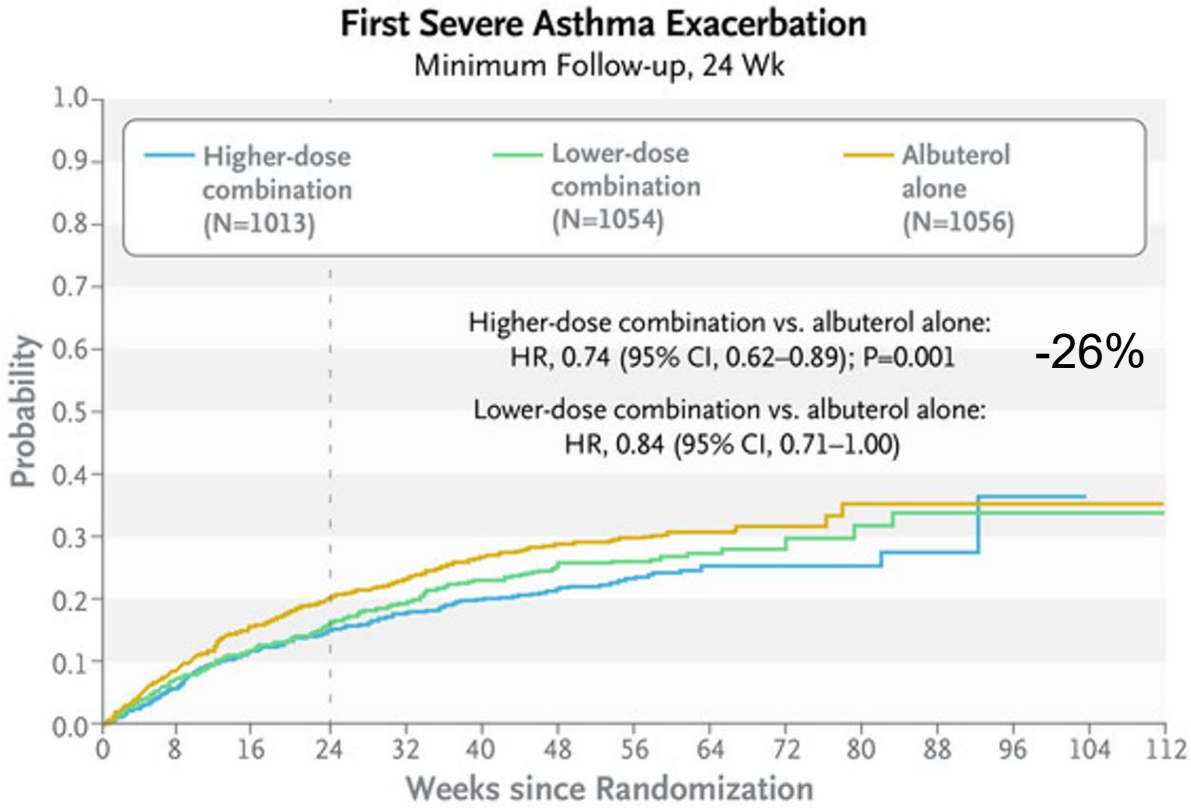


N Engl J Med. 2022 Jun 2;386(22):2071-2083.

As needed ICS + SABA > SABA alone

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

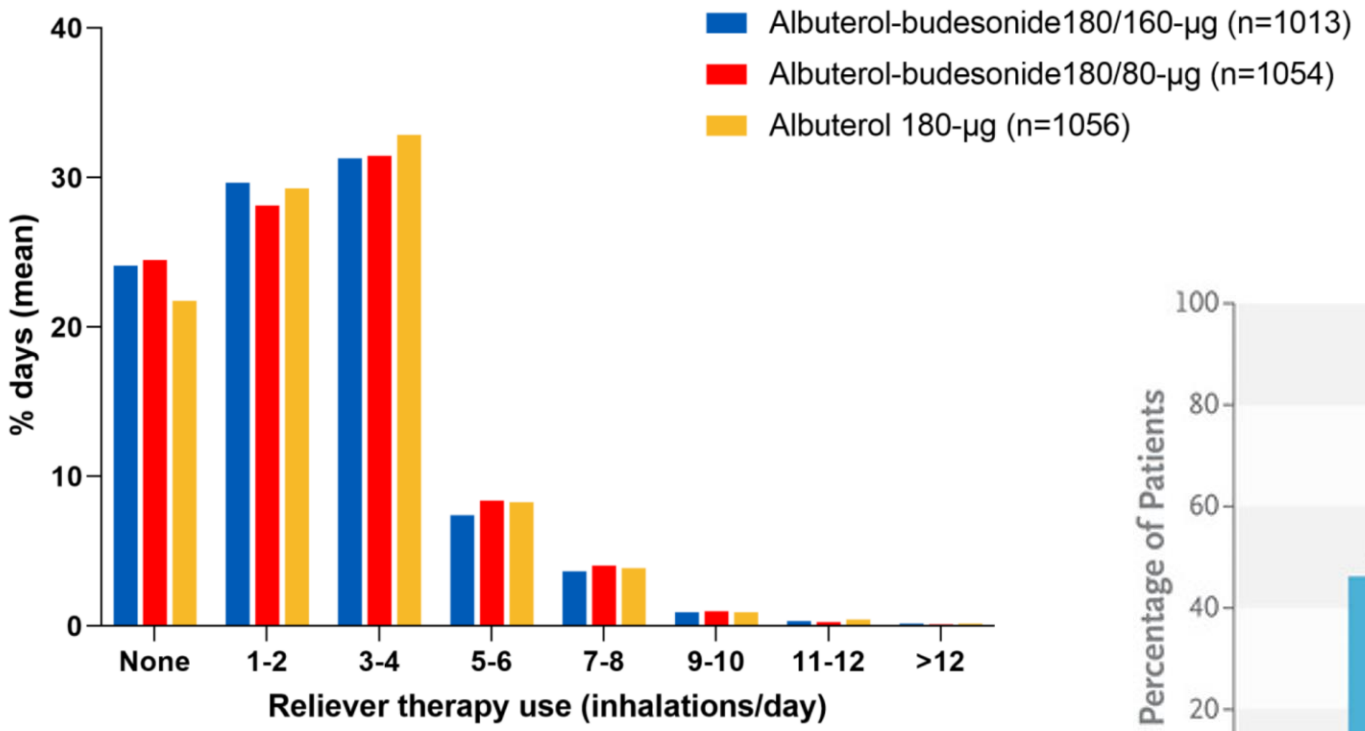
Characteristic	Albuterol (180 μg)–Budesonide (160 μg) (N=1013)	Albuterol (180 μg)–Budesonide (80 μg) (N=1054)	Albuterol (180 μg) (N=1056)	All Patients (N=3123)
Maintenance treatment — no. (%)				
Low-dose inhaled glucocorticoid–LABA or medium-dose inhaled glucocorticoid	314 (31.0)	334 (31.7)	308 (29.2)	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)

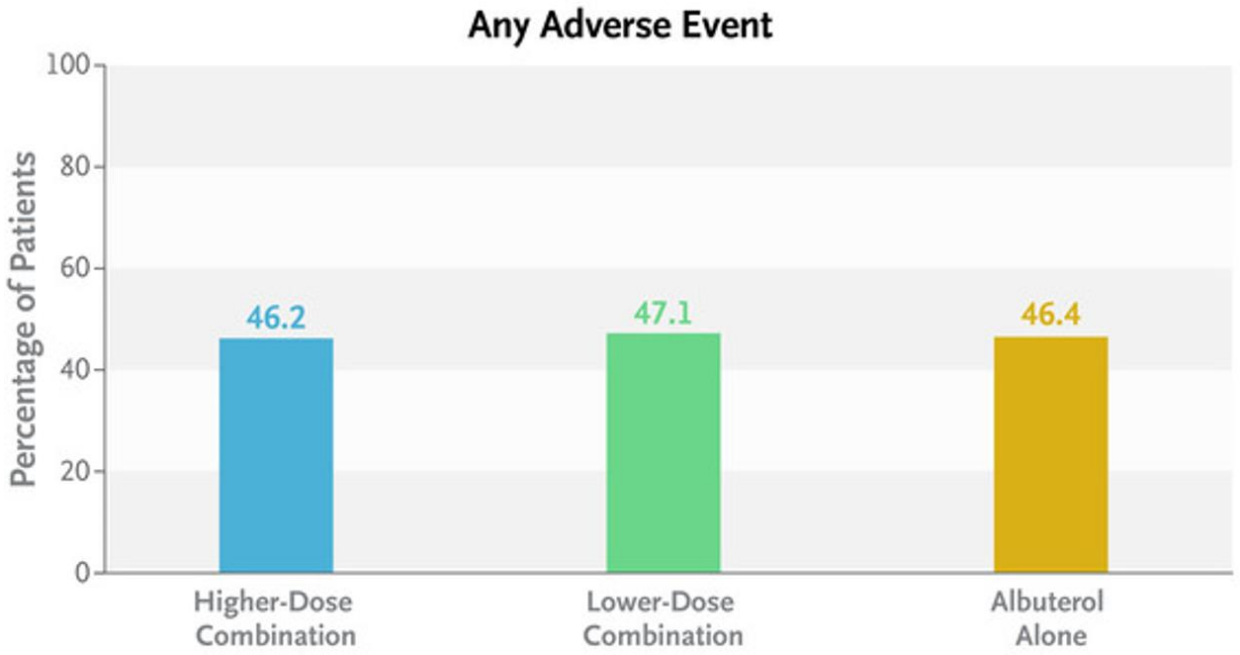


-26%

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.

As needed ICS + SABA in “mild” asthma

- BATURA trial
- Phase 3b, Multi-center Double-blind, RCT
- Uncontrolled mild asthma patients (NAEPP Step 1,2), ≥12 years old, AIRQ score ≥2 (not well controlled)
- **Pre-trial treatment**: SABA only or SABA+LD-ICS or SABA+LTRA
- **Intervention**: As needed-Albuterol (180ug)/**Budesonide (160ug)** vs. As needed-Albuterol (180ug)
- All visits were conducted remotely with the use of the telehealth platform Science 37

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Full Analysis Population).*

Characteristic	Albuterol–Budesonide (N = 1209)	Albuterol (N = 1212)	Total Population (N = 2421)
Pretrial asthma medication — no. (%)			
SABA only	900 (74.4)	901 (74.3)	1801 (74.4)
SABA plus low-dose inhaled glucocorticoid or LTRA	309 (25.6)	311 (25.7)	620 (25.6)

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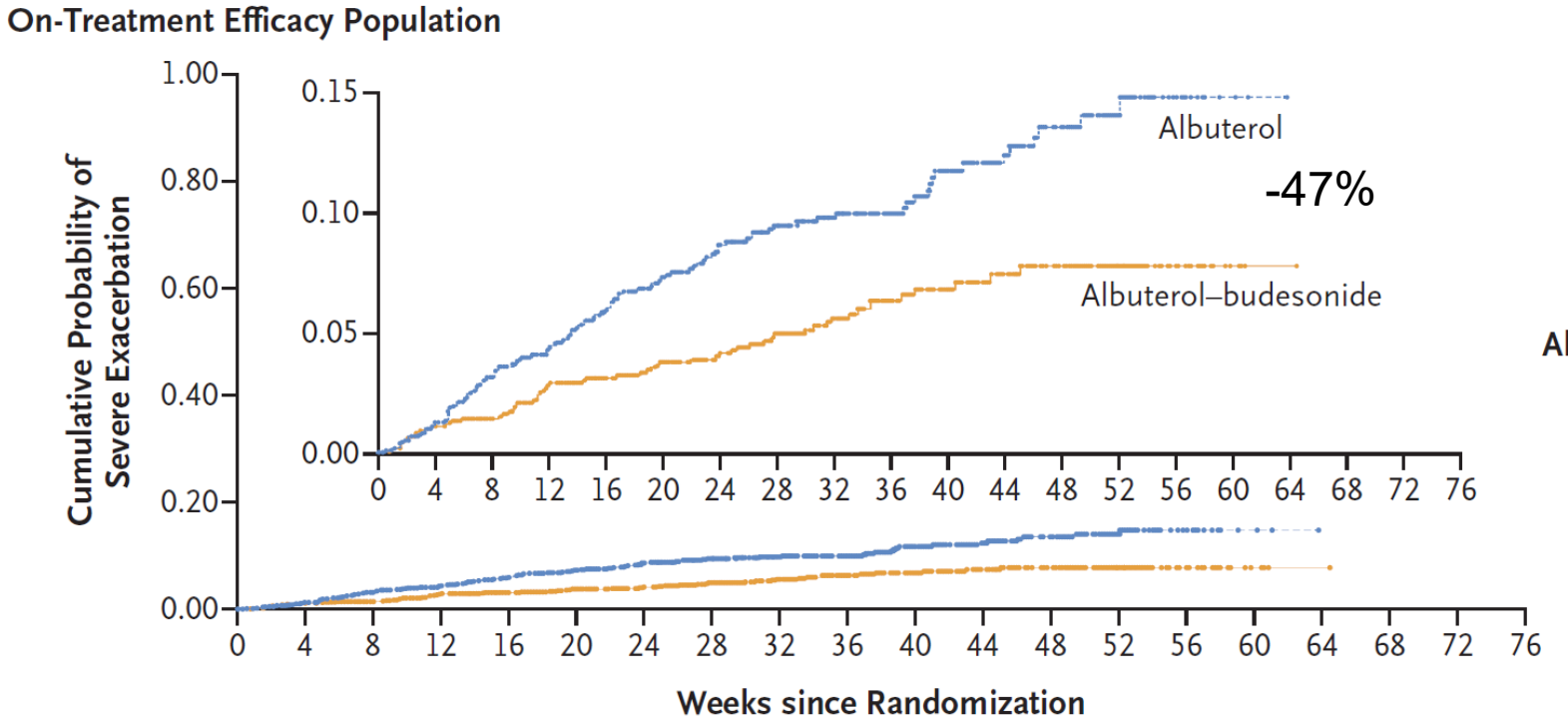
As needed Albuterol-Budesonide > Albuterol alone



No. of Participants with Event (%)

Albuterol	110 (9.1)
Albuterol–Budesonide	62 (5.1)

Hazard ratio with albuterol–budesonide, 0.53 (95% CI, 0.39–0.73)
P<0.001

No. at Risk

Albuterol	1212	1158	1035	939	863	799	712	619	512	418	309	250	198	119	15	3	0	0	0	0
Albuterol–budesonide	1209	1176	1070	961	909	837	763	663	553	445	328	268	215	121	19	5	1	0	0	0

A severe exacerbation was defined as a worsening of symptoms resulting in at least 3 days' use of a systemic glucocorticoid, an emergency department or urgent care visit for asthma warranting systemic glucocorticoids, hospitalization due to asthma, or death

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As needed Albuterol-Budesonide > Albuterol alone

Table 2. Annualized Rate of Severe Asthma Exacerbations and Annualized Total Exposure to Systemic Glucocorticoids.*

Variable	Full Analysis Population, ≥12 Yr of Age		Full Analysis Population, ≥18 Yr of Age	
	Albuterol–Budesonide (N=1209)	Albuterol (N=1212)	Albuterol–Budesonide (N=1180)	Albuterol (N=1173)
Annualized rate of severe exacerbations				
No. of participants evaluated	1209	1212	1180	1173
No. of first severe exacerbations	83	160	82	159
Time at risk — participant-yr	845.8	823.8	825.7	797.4
Estimated annualized rate (95% CI)	0.15 (0.11 to 0.20)	0.32 (0.25 to 0.41)	0.15 (0.12 to 0.20)	0.33 (0.26 to 0.43)
Rate ratio (95% CI)	0.47 (0.34 to 0.64)	—	0.46 (0.33 to 0.63)	—
P value	<0.001	—	<0.001	—
Annualized total exposure to systemic glucocorticoids†				
No. of participants evaluated	1204	1203	1175	1164
Mean total amount per participant of exposure to systemic glucocorticoids — mg/yr	23.2±142.9	61.9±662.1	23.0±142.4	63.0±672.3
Difference in arithmetic means — mg/yr	−38.7	—	−40.0	—
Percent difference in arithmetic means	−62.5	—	−63.5	—
P value‡	<0.001	—	<0.001	—

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Similar frequency of reliever and adverse events

- **Daily use of reliever**
  - ✓ Albuterol-budesdonide: 1.5 inhalations/day
  - ✓ Albuterol: 1.8 inhalations/day

- **Safety findings**
  - ✓ Two groups had similar safety profiles

Table 3. Adverse Events (Safety Analysis Population).*

Event	Albuterol–Budesonide (N = 1209)	Albuterol (N = 1212)
	no. of participants (%)	
Any adverse event	510 (42.2)	527 (43.5)
Events occurring in ≥2% of participants in either group		
Upper respiratory tract infection	65 (5.4)	73 (6.0)
Coronavirus disease 2019	63 (5.2)	67 (5.5)
Nasopharyngitis	45 (3.7)	32 (2.6)
Sinusitis	38 (3.1)	30 (2.5)
Bronchitis	29 (2.4)	32 (2.6)
Cough	30 (2.5)	29 (2.4)
Influenza	26 (2.2)	21 (1.7)
Asthma	17 (1.4)	25 (2.1)
Any serious adverse event	37 (3.1)	37 (3.1)
Any adverse event leading to treatment discontinuation	15 (1.2)	33 (2.7)
Any treatment-related adverse event†	50 (4.1)	48 (4.0)
Any adverse event with an outcome of death‡	1 (0.1)	1 (0.1)

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Maintenance therapy during study

Table S6. Change in maintenance therapy during the randomized treatment period (full analysis set; age ≥12 years; on-treatment efficacy population).

	Albuterol–budesonide 180/160 µg (N=1209)	**Albuterol 180 µg (N=1212)**
Participants that changed their maintenance therapy, n (%)	27 (2.2)	35 (2.9)
Participants that stepped down or stopped maintenance therapy, n (%)	6 (0.5)	7 (0.6)
Time from treatment initiation to a step down or stop in maintenance therapy, days, median (range)	83.0 (6–143)	54.0 (6–277)
Participants that stepped up maintenance therapy, n (%)	22 (1.8)	29 (2.4)
Time from treatment initiation to a step up in maintenance therapy, days, median (range)	107.0 (10–258)	88.0 (8–348)

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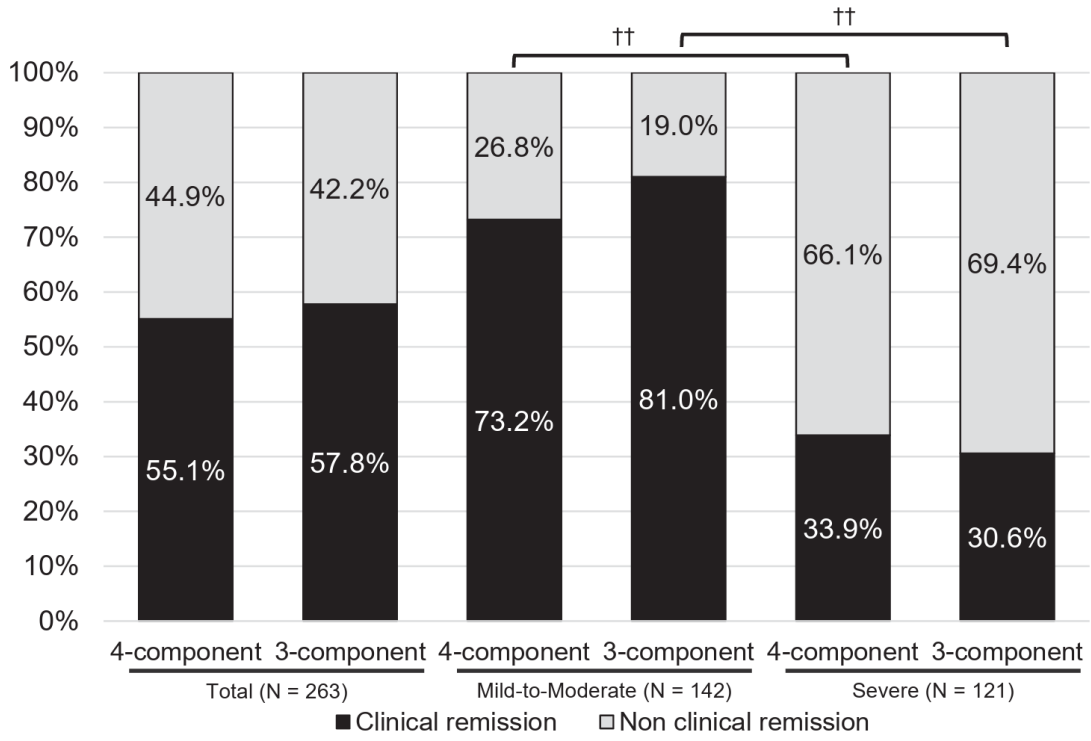
On treatment clinical remission in mild asthma

- **Clinical remission** is emerging as a realistic treatment goal

Biological remission (potential components)
- Plus low type 2 biomarkers (eg, FeNO <25 ppb and blood eosinophils <300 per µL)
- Plus normal airway responsiveness (negative AHR test)

Clinical remission (four components)
- Plus stable or normal lung function (eg, FEV_1 decline of ≤5% or FEV_1 ≥80% predicted)

Clinical remission (three components)
- Very mild or no asthma symptoms (eg, ACT ≥20 or ≥23, ACQ <1·5 or ≤0·75 for very mild or no symptoms, respectively)
- No asthma exacerbations (medical history)
- No systemic corticosteroid use (documented medication use)



Lancet Respir Med. 2025 Jan;13(1):2-3.

J Allergy Clin Immunol Glob. 2025 Jan 30;4(2):100431.

Summary

• Definition of mild asthma

- ✓ “Mild asthma” is not same with “Asthma not at risk” or “Asthma without need for treatment”
- ✓ “Mild asthma” means **“Asthma requires low-dose ICS treatment for well-controlled condition”**

• Airway inflammation and remodeling in mild asthma

- ✓ Mild asthma is a disease of **chronic airway inflammation**
- ✓ Even in mild asthma, **pathological changes are already present**
  - TGF-β–mediated airway remodeling
  - IL-13–induced smooth muscle hypertrophy

Summary

• Clinical course of mild asthma

- ✓ Even with infrequent symptoms, patients with mild asthma have a **3~33% risk of severe exacerbations**, and **3~15% of asthma-related deaths** occur in this population
- ✓ **Mild asthma may progress** over time, particularly in the absence of appropriate treatment (eg. ICS/LABA)
- ✓ Approximately **25~30%** of patients with mild asthma experience **poor symptom control**

• Treatment of mild asthma

- ✓ **SABA alone** without ICS is related with **increased risk of severe exacerbation**
- ✓ **Track 1 (as needed ICS/Formoterol**) is preferred over **Track 2 (as needed SABA)**
- ✓ Among reliever options **in Track 2, as needed ICS/SABA** may be more beneficial than as needed SABA

Thank you for your attention

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