Year in Review 2020

-Asthma-

김덕겸
서울의대, 서울특별시 보라매병원

Contents

- **Updates in GINA guideline (www.ginasthma.org)**
  - Recommendation in COVID-19 pandemic (2020)
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    - PRACTICAL (Lancet 2019; 394: 919–28)
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- **Considerations in treatment of asthma**
  - ICS in non-eosinophilic airway inflammation (Novel START & SIENA study, N Engl J Med 2019;380:2009-19)
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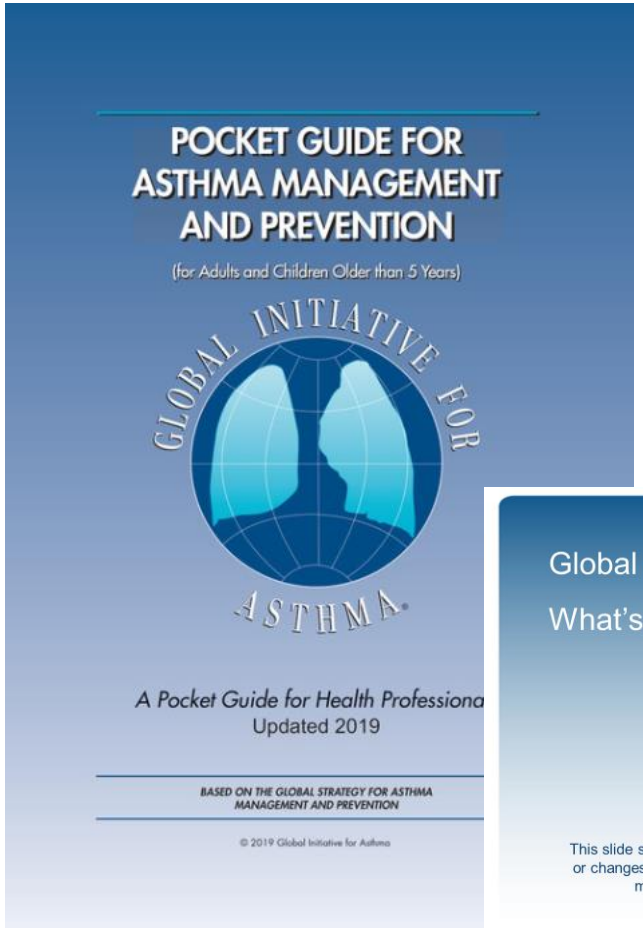
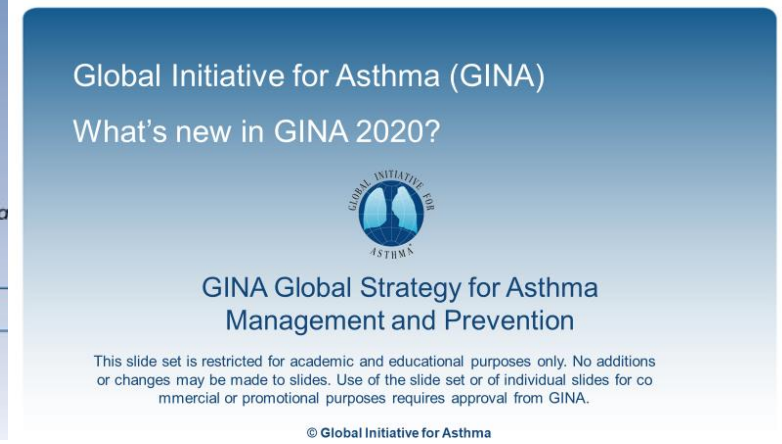
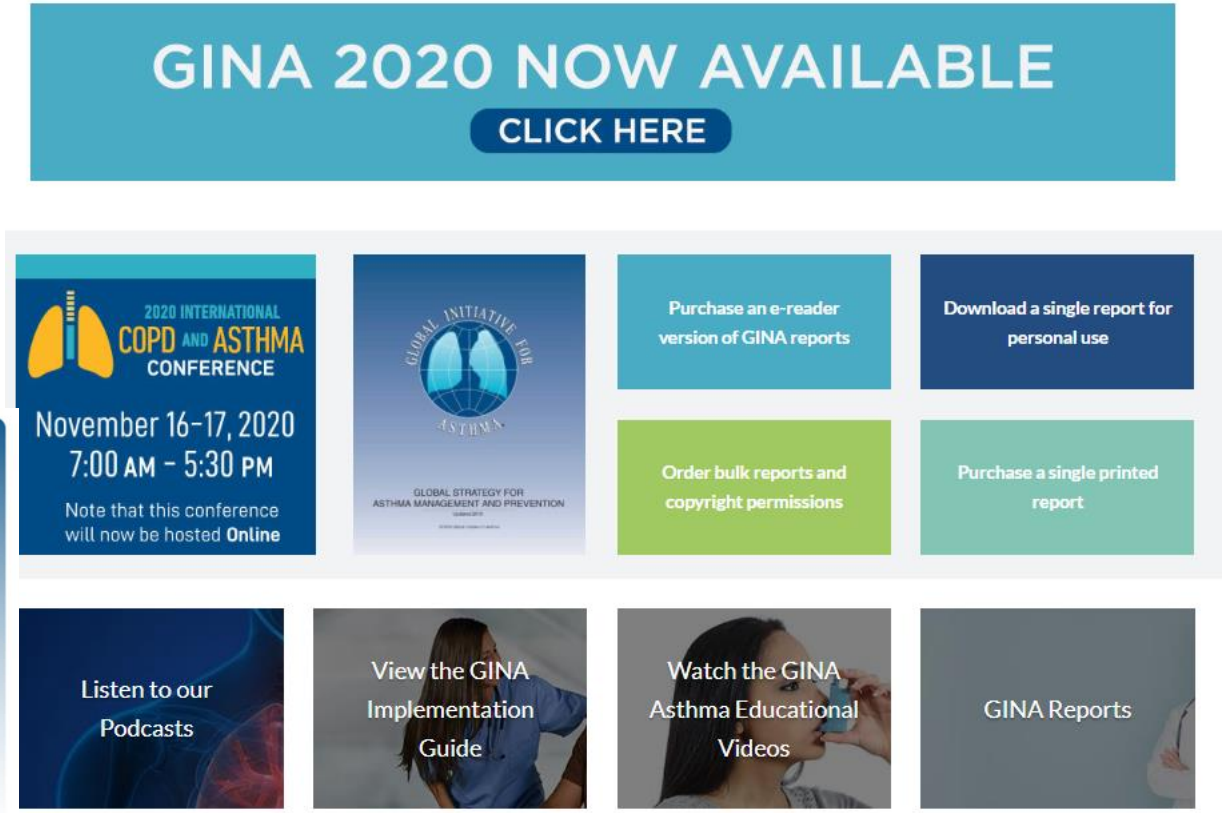
  - Biologics – reslizumab (SC) (www.thelancet.com/respiratory, e-pub)
  - Self-management support intervention in older patients with asthma (SAMBA study, *JAMA Intern Med*. 2019;179(8):1113-1121)

Updated GINA Guideline







COVID-19 and asthma *(as at April 3, 2020)*

- **Advise patients with asthma to continue taking their prescribed asthma medications, particularly *inhaled corticosteroids* (ICS), and oral corticosteroids (OCS) if prescribed**
  - Asthma medications should be continued as usual. Stopping ICS often leads to potentially dangerous worsening of asthma
  - For patients with severe asthma: continue biologic therapy, and do not suddenly stop OCS if prescribed
- **Make sure that all patients have a *written asthma action plan* with instructions about:**
  - Increasing controller and reliever medication when asthma worsens
  - Taking a short course of OCS for severe asthma exacerbations
- ***Avoid nebulizers* where possible**
  - Nebulizers increase the risk of disseminating virus to other patients AND to health care professionals
  - Pressurized metered dose inhaler via a spacer is the preferred treatment during severe exacerbations, with a mout hpiece or tightly fitting face mask if required

COVID-19 and asthma *(as at March 30, 2020)*

- ***Avoid spirometry*** **in patients with confirmed/suspected COVID-19**
  - Spirometry can disseminate viral particles and expose staff and patients to risk of infection
  - While community transmission of the virus is occurring in your region, postpone spirometry and peak flo w measurement within health care facilities unless there is an urgent need
  - Follow contact and droplet precautions

- ***Follow strict infection control procedures*** **if aerosol-generating procedures are needed**
  - For example: nebulization, oxygen therapy (including with nasal prongs), sputum induction, manual ventil ation, non-invasive ventilation and intubation

- ***Follow local health advice*** **about hygiene strategies and use of personal protective equipme nt, as new information becomes available in your country or region**

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

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@ERSpublications
GINA no longer recommends treating adults/adolescents with asthma with short-acting bronchodilators alone. Instead, they should receive symptom-driven (in mild asthma) or a daily corticosteroid-containing inhaler, to reduce risk of severe exacerbations. http://bit.ly/310LLzE

Cite this article as: Reddel HK, FitzGerald JM, Bateman ED, *et al*. GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019; 53: 1901046 [https://doi.org/10.1183/13993003.01046-2019].

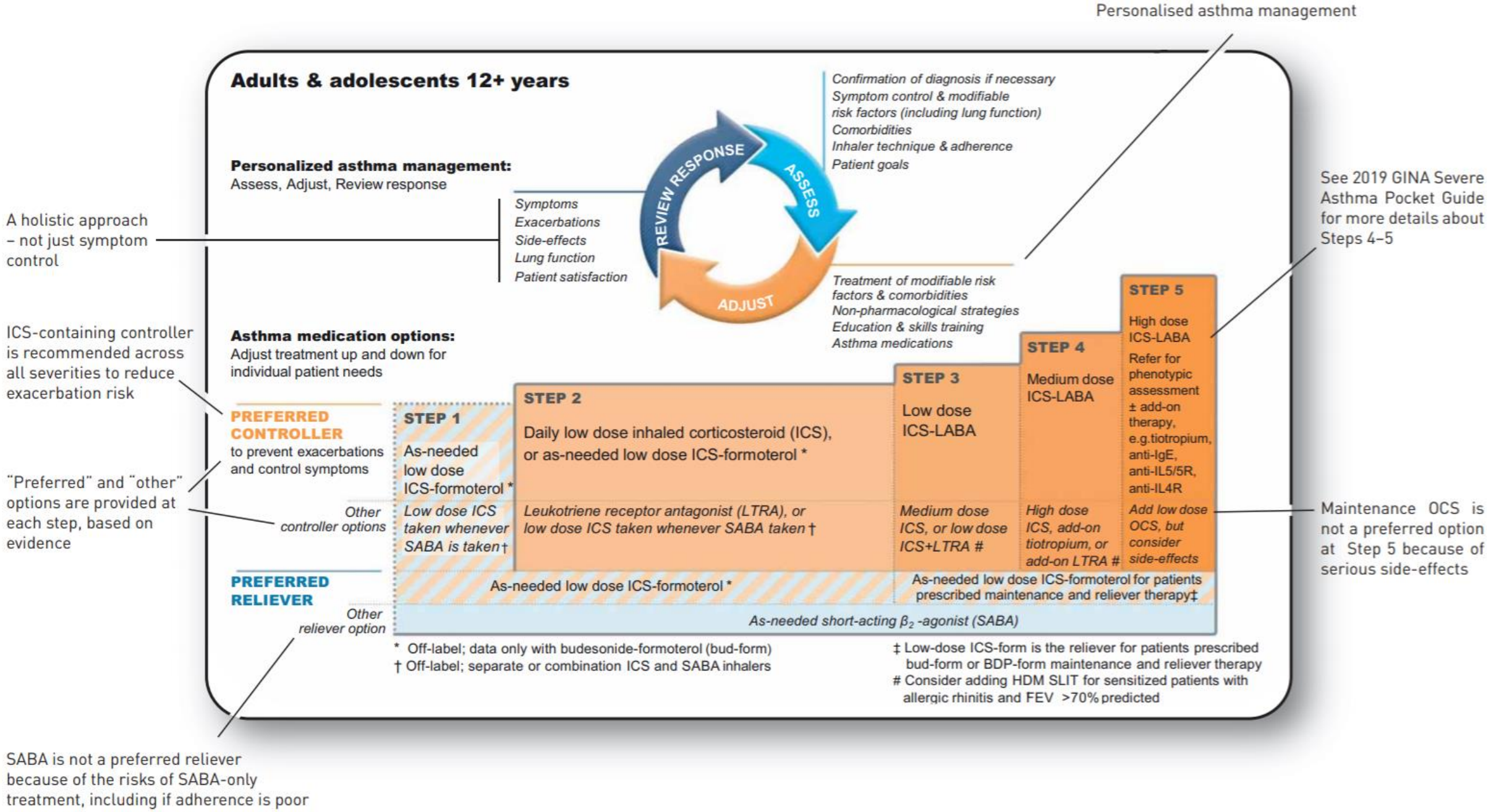
- Safety of SABA, LABA only
- Efficacy of ICS in mild asthma
- Paradox in step 1 & step 2
- ICS/formoterol

- Symbicort Given as Needed in Mild Asthma (SYGMA 1 & 2)

- Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults.
- To reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment.

Eur Resp J 2019;53:1901046

GINA 2019/2020



GINA 2019 RECOMMENDATIONS ABOUT RELIEVER MEDICATIONS IN STEPS 3-5

GINA Alert

FOR MEDIA WORLDWIDE
November 12, 2019

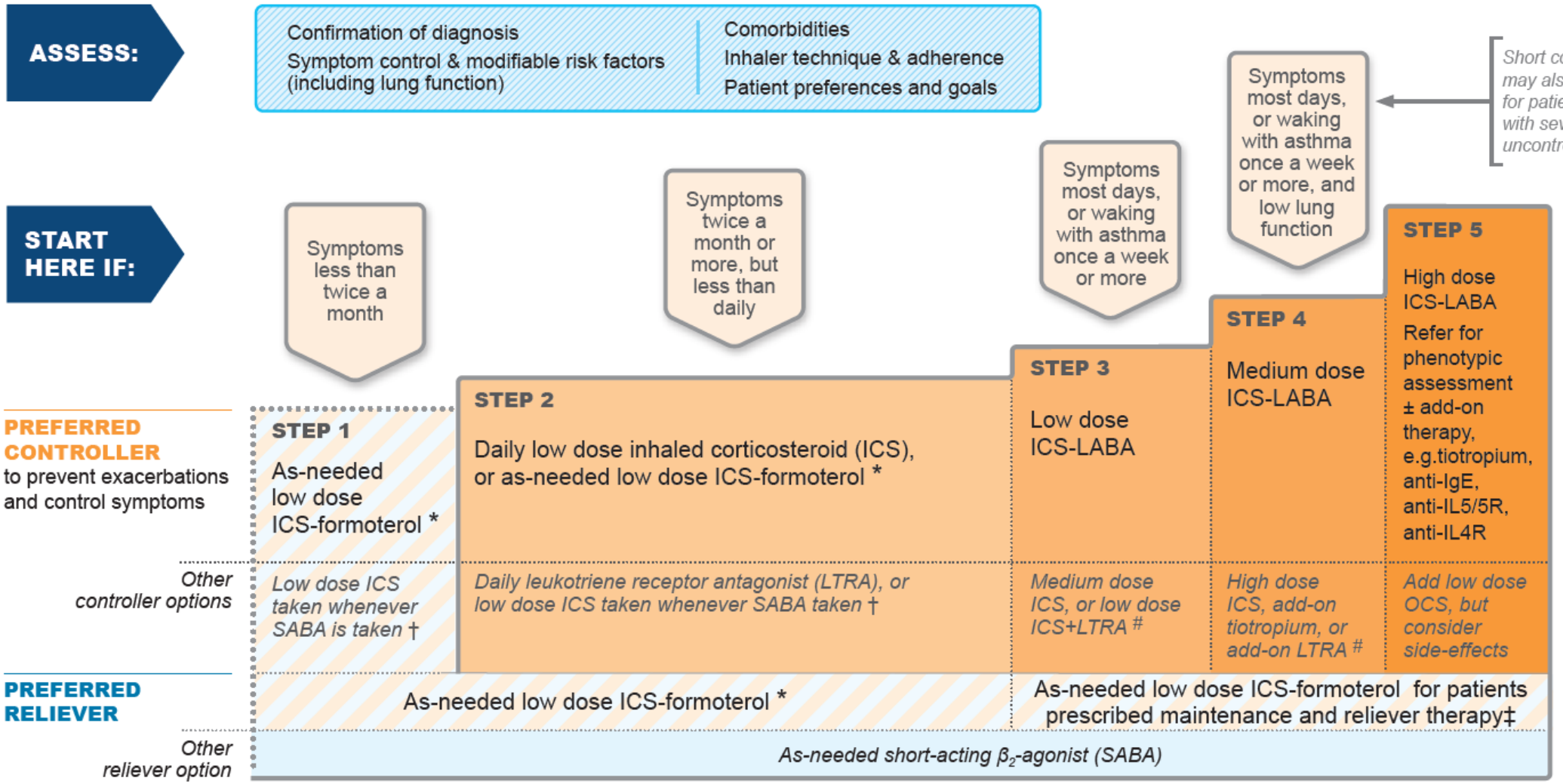
MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

We have become aware that the GINA 2019 recommendation for 'Preferred reliever' in Steps 3-5 is sometimes being misinterpreted. Please note the following important information.

In these patients, low-dose ICS-formoterol is the preferred reliever only for patients who are prescribed maintenance and reliever therapy with ICS-formoterol. GINA does not recommend use of ICS-formoterol as the reliever for patients taking combination ICS-LABA medications with a different LABA. For these patients, their as-needed reliever inhaler should be a SABA.

recommend use of ICS-formoterol as the reliever for patients taking combination ICS-LABA medications with a different LABA. For these patients,

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA



* Data only with budesonide-formoterol (bud-form)

† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA

FIRST ASSESS:

- Confirmation of diagnosis
- Symptom control & modifiable risk factors (including lung function)
- Comorbidities
- Inhaler technique & adherence
- Patient preferences & goals

IF: / **START WITH:**

Symptoms most days, waking at night ≥ once a week and low lung function? — YES → Medium dose ICS-LABA (MART or maintenance-only) — **STEP 4**

NO

Symptoms most days,or waking at night ≥ once a week? — YES → Low dose ICS-LABA (MART or maintenance-only) — **STEP 3**

NO

Symptoms twice a month or more? — YES → Daily low dose ICS or as-needed low dose ICS-formoterol — **STEP 2**

NO

As-needed low dose ICS-formoterol — **STEP 1**

Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

Limitations of SYGMA studies (double-blinded RCT)

- Limitation in reflecting real world practice

- High internal validity, limited external validity
  - Double blinding may remove the advantage of single inhaler for symptom relief
  - During a run-in phase, low dose ICS or LTRA should be withdrawn (*i.e*, allow for worsening)
  - Baseline eligibility (SABA ≥ 2 /week)

  →excluded patients with intermittent symptoms for whom regular ICS is recommended.

- Open-label clinical trials are necessary

Real-world clinical trials of Budesonide–Formoterol as Needed for Mild Asthma

	SYGMA 1	Novel START	SYGMA 2	PRACTICAL
Journal	NEJM 2018	NEJM 2019	NEJM 2018	Lancet 2019
Study type	RCT	**Real world**	RCT	**Real world**
Severity	Mild (Step 2)	Mild (**Step 1,2**)	Mild(Step 2)	Mild to Moderate(Step 1,2,3)
# of participants	3,836	668	4,176	885
Arm				
SABA Only	O	O	X	X
ICS maintenance + SABA	O	O	O	O
***As needed* ICS/FOR**	O	O	O	O
Primary outcome	Symptom control	Exacerbation rate	Severe exacerbation rate	Severe exacerbation rate

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

From the Medical Research Institute of New Zealand (R.B., M.H., I.B., S.E., C.H., K.O., M. Williams), the Capital and Coast District Health Board (R.B.), and the University of Otago Wellington (M. Weatherall), Wellington, the Department of Respiratory Medicine, Waikato Hospital, Hamilton (R.J.H.), and the Department of Preventive and Social Medicine, University of Otago, Dunedin (R.J.H.) — all in New Zealand; Woolcock Institute of Medical Research, University of Sydney, Sydney (H.K.R.); the Nottingham NIHR Biomedical Research Centre, University

ABSTRACT

BACKGROUND

In double-blind, placebo-controlled trials, budesonide–formoterol used on an as-needed basis resulted in a lower risk of severe exacerbation of asthma than as-needed use of a short-acting β_2-agonist (SABA); the risk was similar to that of budesonide maintenance therapy plus as-needed SABA. The availability of data from clinical trials designed to better reflect clinical practice would be beneficial.

METHODS

We conducted a 52-week, randomized, open-label, parallel-group, controlled trial involving adults with mild asthma. Patients were randomly assigned to one of three treatment groups: albuterol (100 μg, two inhalations from a pressurized metered-dose inhaler as needed for asthma symptoms) (albuterol group); budesonide (200 μg,

Novel START study

- 52-week RCT, open-label (1:1:1)
  - Albuterol group
  - Budesonide(BUD) maintenance group
  - BUD-FOR group (as needed)
- Adults with mild asthma who had been treated with only as-needed SABA
- Primary outcome
  - the annualized rate of asthma exacerbations per patient

N Engl J Med 2019;380:2020-30.

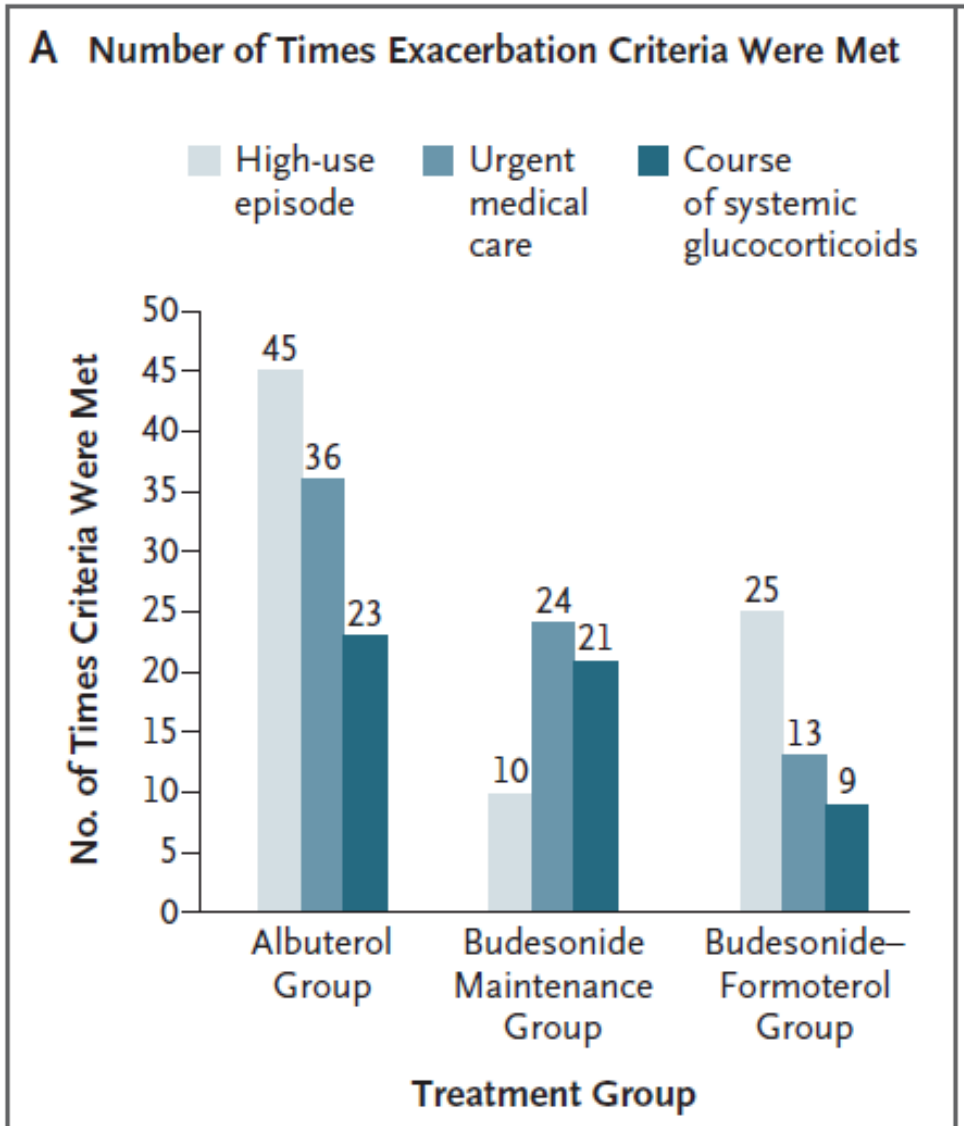
Table 1. Characteristics of the Patients at Baseline.*

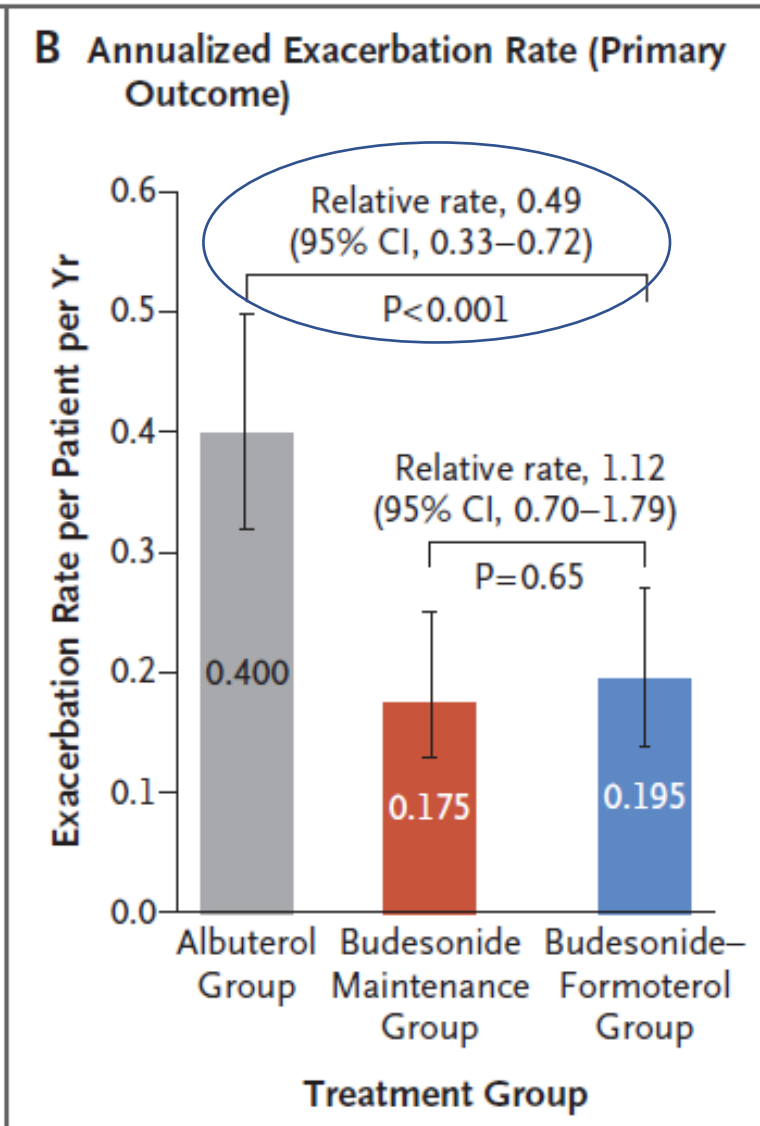
Characteristic	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Age — yr	35.8±14.0	34.9±14.3	36±14.1
Female sex — no. (%)	113 (50.7)	129 (57.3)	122 (55.5)
Current smoker — no. (%)	24 (10.8)	22 (9.8)	18 (8.2)
Patient-reported SABA use in the 4 weeks before enrollment			
No. of occasions per wk			
Mean	3.4±3.3	3.2±3.0	3.8±3.5
Median (IQR)	2 (1–4)	2 (1–4)	3 (1–5)
Range	0–14	0.5–14	0.5–14
Patients who had ≤2 occasions per wk — no. (%)	127 (57.0)	132 (58.7)	105 (47.7)
Puffs per wk			
Mean	6.52±7.83	5.82±5.25	6.98±6.91
Median (IQR)	4 (2–8)	4 (2–7)	4 (2–8)
Range	0–84	0.5–28	0.5–42
No. of hospital admissions for asthma at any time before enrollment — mean per patient	0.3±0.9	0.3±0.9	0.3±1.3
No. of severe exacerbations in the previous 12 mo. — no. (%)			
0	203 (91.0)	208 (92.4)	208 (94.5)
1	20 (9.0)	15 (6.7)	12 (5.5)
2	0	2 (0.9)	0
Any	20 (9.0)	17 (7.6)	12 (5.5)
ACQ-5 score†	1.1±0.7	1.1±0.7	1.1±0.7
On-treatment FEV_1 — % of predicted value‡	89.2±13.7	90.3±13.6	89.8±14.1
Median F_{ENO} (range) — ppb	40 (5–235)	38 (5–200)	37 (3–300)
Periostin — ng/ml	69.3±28.9	70.6±27.8	70.8±27.0
Blood eosinophil count — $\times 10^{-9}$ per liter	0.3±0.2	0.3±0.2	0.3±0.2

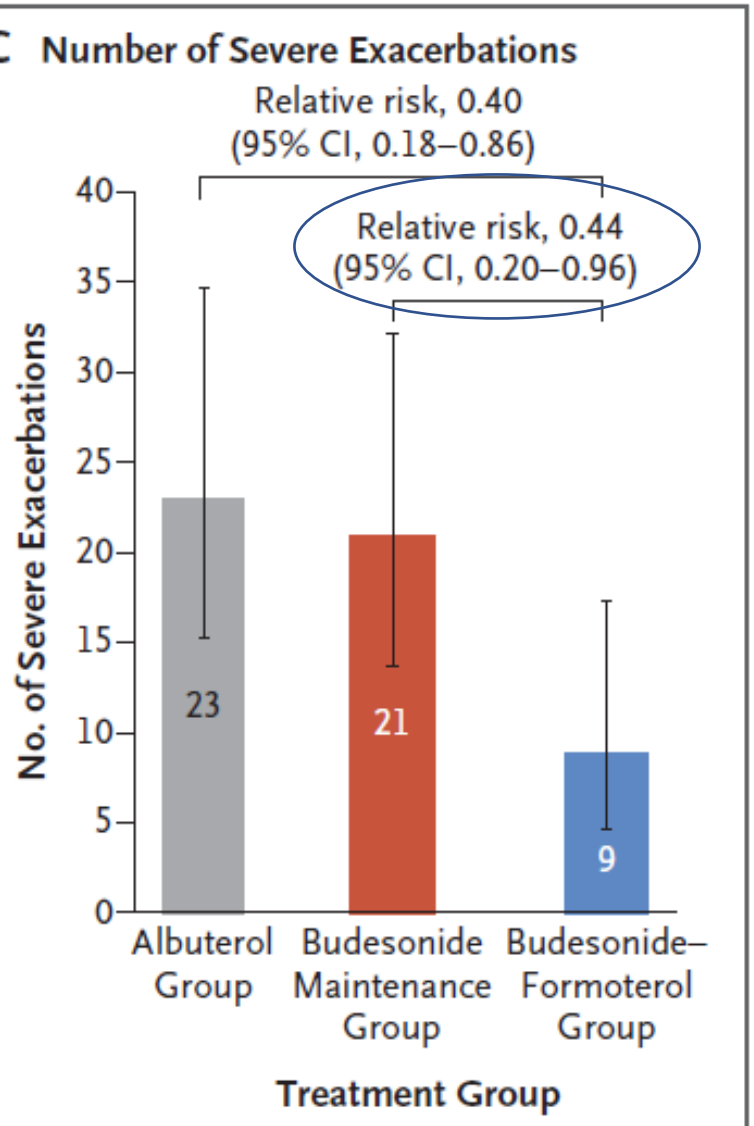
N Engl J Med 2019;380:2020-30.

Exacerbation Results

The open-label study reflecting clinical practice, showed that budesonide–formoterol used as needed was superior to albuterol used as needed for the prevention of exacerbations in adults with mild asthma







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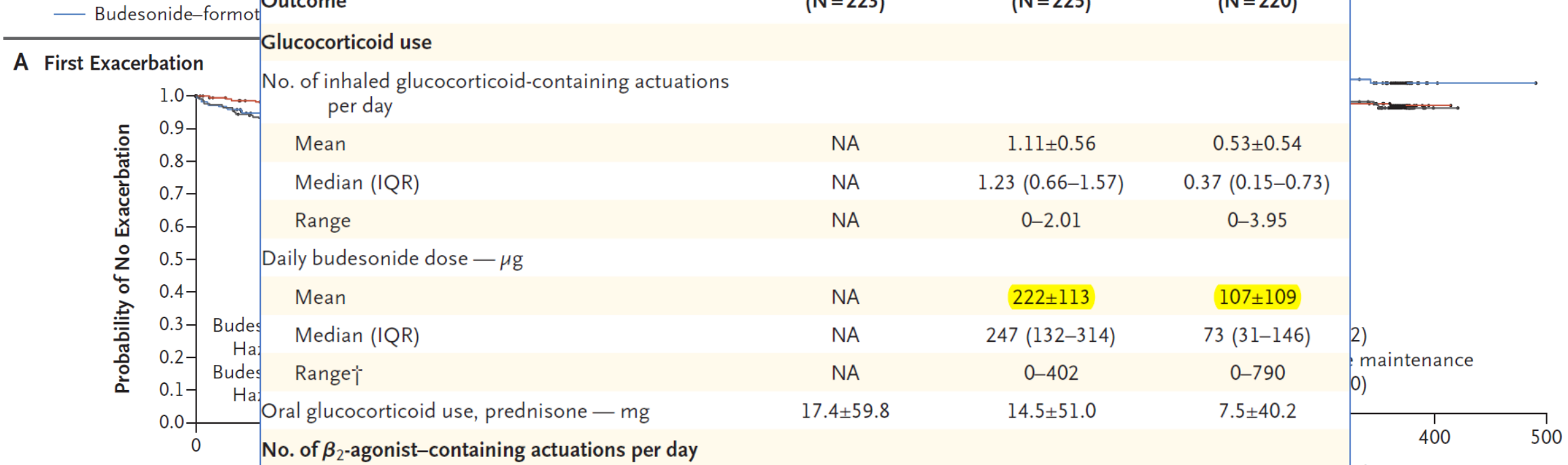


Table 2. Medication Outcomes.*

Outcome	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Glucocorticoid use			
No. of inhaled glucocorticoid-containing actuations per day			
Mean	NA	1.11±0.56	0.53±0.54
Median (IQR)	NA	1.23 (0.66–1.57)	0.37 (0.15–0.73)
Range	NA	0–2.01	0–3.95
Daily budesonide dose — μg			
Mean	NA	222±113	107±109
Median (IQR)	NA	247 (132–314)	73 (31–146)
Range†	NA	0–402	0–790
Oral glucocorticoid use, prednisone — mg	17.4±59.8	14.5±51.0	7.5±40.2
No. of β_2-agonist–containing actuations per day			
Mean	1.01±1.60	0.52±1.03	0.53±0.54
Median (IQR)	0.50 (0.18–1.18)	0.18 (0.06–0.46)	0.37 (0.15–0.73)
Range	0.0–16.3	0.0–8.7	0–3.95

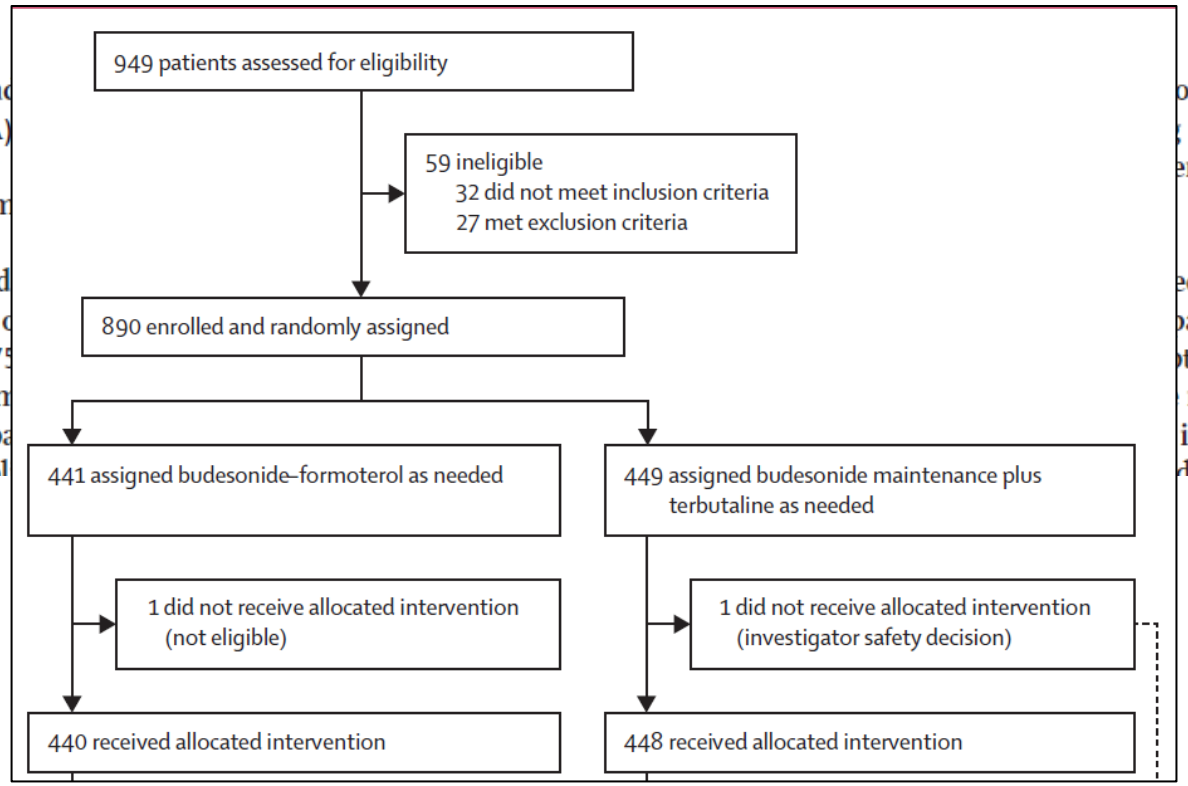
Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Jo Hardy, Christina Baggott*, James Fingleton, Helen K Reddel, Robert J Hancox, Matire Harwood, Andrew Corin, Jenny Sparks, Daniela Hall, Doñah Sabbagh, Saras Mane, Alexandra Vohlidkova, John Martindale, Mathew Williams, Philippa Shirtcliffe, Mark Holliday, Mark Weatherall, Richard Beasley, on behalf of the PRACTICAL study team†*

Summary

Background In ac… …ong-acting β-agonist (LABA) … β-agonist (SABA) reliever … er therapy compared with m…

Methods We did … ed trial at 15 primary care … pants were adults aged 18–75 … otom relief with or without m… randomly assigned participa… inhalation as needed for rel… daily) plus



Lancet 2019; 394: 919–28
Published Online August 23, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31948-8

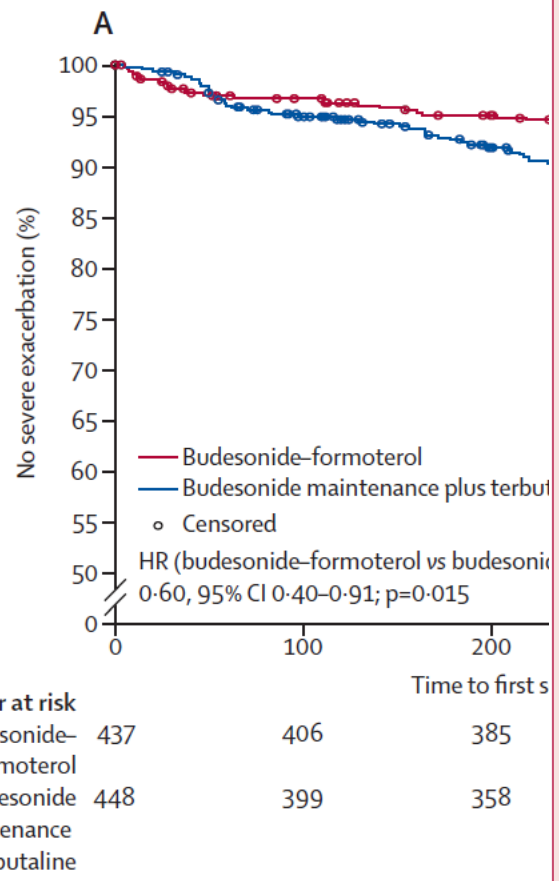
See Comment page 897

*Joint first authors
†PRACTICAL study investigators are listed in the appendix p 6
Medical Research Institute of New Zealand, Newtown, …

independently funded open-label study

Primary outcome : the number of severe asthma exacerbations per patient per year

Estimates of the occurrence of exacerbations



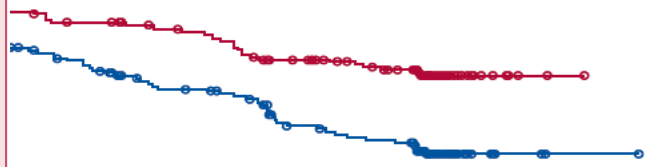
Number at risk

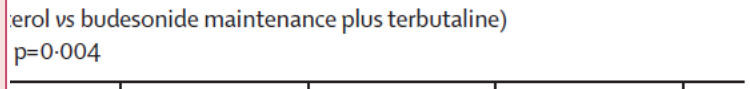
Budesonide–formoterol	437	406	385	
Budesonide maintenance plus terbutaline	448	399	358	

	Budesonide–formoterol as needed (n=55)	Budesonide maintenance plus terbutaline as needed (n=55)
Inhaled corticosteroid use		
Number of budesonide-containing actuations per day		
Mean (SD)	0·9 (0·7)	1·5 (0·4)
Median (IQR)	0·8 (0·4–1·3)	1·6 (1·2–1·8)
Range†	0·0–3·4	0·1–2·3
Daily budesonide dose (µg)		
Mean (SD)	176·0 (143·0)	302·5 (84·8)
Median (IQR)	164·3 (74·0–251·7)	328·3 (245·8–364)
Range‡	6·7–682·5	26·8–458·1
β_2-agonist use		
Number of β_2-agonist-containing actuations per day		
Mean (SD)	0·9 (0·7)	0·5 (0·6)
Median (IQR)	0·8 (0·4–1·3)	0·3 (0·1–0·6)
Range†	0·0–3·4	0·0–2·7

*Use of inhaled corticosteroids and β_2-agonists was determined with electronic monitoring of the trial inhalers in a subset of 110 participants. †Range refers to the minimum and maximum mean number of actuations per day. ‡Range refers to the minimum and maximum mean daily dose.

Table 2: Medication outcomes in electronic monitoring subgroups*





	381	355	6	0
	346	313	4	0

*** Time to first sev** … **moderate or severe exacerbation**

HR 0·60, 95% CI 0 … **59, 95% CI 0·41–0·84; p=0·004**

	SYGMA 1	Novel START	SYGMA 2	PRACTICAL
Journal	NEJM 2018	NEJM 2019	NEJM 2018	Lancet 2019
Study type	RCT	**Real world**	RCT	**Real world**
Severity	Mild (Step 2)	Mild (**Step 1,2**)	Mild(Step 2)	Mild to Moderate(Step 1,2,3)
# of participants	3,836	668	4,176	885
Arm				
SABA Only	O	O	X	X
ICS maintenance + SABA	O	O	O	O
***As needed* ICS/FOR**	O	O	O	O
Primary outcome	Symptom control	Exacerbation rate	Severe exacerbation rate	Severe exacerbation rate
Adherence (as needed ICS/FOR)	**79.1%**		**62.8%**	
ICS dose (day, median)	**57ug** vs 340ug	**73ug** vs 247ug	**66ug** vs 267ug	**164ug** vs 328ug
Severe exacerbation	**(annualized rate)**	**(frequency)**	**(annualized rate)**	**(annualized rate)**
SABA only	20%	23	X	X
ICS maintenance+ SABA	9%	21	12%	17.2%
***As needed* ICS/FOR**	7%	9	11%	11.9%

Single inhaler triple therapy in uncontrolled asthma (TRIMARAN & TRIGGER)

Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials

Johann Christian Virchow*, Piotr Kuna, Pierluigi Paggiaro, Alberto Papi, Dave Singh, Sandrine Corre, Florence Zuccaro, Andrea Vele, Maxim Kots, George Georges, Stefano Petruzzelli, Giorgio Walter Canonica*

Summary

Background To date, no studies have assessed the efficacy of single-inhaler triple therapy in asthma. Here we report on two studies that compared the single-inhaler extrafine combination of beclometasone dipropionate (BDP; inhaled corticosteroid), formoterol fumarate (FF; long-acting β_2 agonist), and glycopyrronium (G; long-acting muscarinic antagonist) with the combination of BDP with FF.

Methods Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials (Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA [TRIMARAN] and Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium [TRIGGER]) recruited patients from 171 sites across 16 countries (TRIMARAN), and from 221 sites across 17 countries (TRIGGER). The sites were a mixture of secondary and tertiary care centres and specialised investigation units. Eligible patients were adults (aged 18–75 years) with uncontrolled asthma, a history of one or more exacerbations in the previous year, and previously treated with inhaled corticosteroid (TRIMARAN: medium dose; TRIGGER: high dose) plus a long-acting β_2 agonist. Enrolled patients were initially treated with BDP/FF (TRIMARAN: 100 µg BDP and 6 µg FF; TRIGGER: 200 µg BDP and 6 µg FF) for 2 weeks, then randomly assigned to treatment using an interactive response technology system with a balanced block randomisation scheme stratified by country. Patients, investigators, site staff, and sponsor staff were masked to BDP/FF/G and BDP/FF assignment. In TRIMARAN, patients were randomly assigned (1:1) to 52 weeks of BDP/FF/G (100 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (100 µg BDP and 6 µg FF), two inhalations twice daily. In TRIGGER, patients were randomly assigned (2:2:1) to 52 weeks of BDP/FF/G (200 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (200 BDP and 6 µg FF), both two inhalations twice daily, or open-label BDP/FF (200 µg BDP and 6 µg FF) two inhalations twice daily plus tiotropium 2·5 µg two inhalations once daily. Coprimary endpoints for both trials (BDP/FF/G *vs* BDP/FF) were pre-dose forced expiratory volume in 1 s (FEV_1) at week 26 and rate of moderate and severe exacerbations over 52 weeks. Safety was assessed in all patients who received at least one dose of study treatment. These trials were registered with ClinicalTrials.gov, NCT02676076 (TRIMARAN), NCT02676089 (TRIGGER).

Findings Between Feb 17, 2016, and May 17, 2018, 1155 patients in TRIMARAN were given BDP/FF/G (n=579) or BDP/FF (n=576). Between April 6, 2016, and May 28, 2018, 1437 patients in TRIGGER were given BDP/FF/G (n=573), BDP/FF (n=576), or BDP/FF plus tiotropium (n=288). Compared with the BDP/FF group, week 26 predose FEV_1 improved in the BDP/FF/G group by 57 mL (95% CI 15–99; p=0·0080) in TRIMARAN and by 73 mL (26–120; p=0·0025) in TRIGGER, with reductions in the rate of moderate and severe exacerbations of 15% (rate ratio 0·85, 95% CI 0·73–0·99; p=0·033) in TRIMARAN and 12% (0·88, 0·75–1·03; p=0·11) in TRIGGER. Four patients had treatment-related serious adverse events, one in TRIMARAN in the BDP/FF/G group and three in TRIGGER—one in the BDP/FF/G and two in the BDP/FF group. Three patients in the BDP/FF/G group in TRIMARAN and two patients in TRIGGER—one in the BDP/FF/G group and one in the BDP/FF group—had adverse events leading to death. None of the deaths were considered as related to treatment.

Interpretation In uncontrolled asthma, addition of a long-acting muscarinic antagonist to inhaled corticosteroid plus long-acting β_2-agonist therapy improves lung function and reduces exacerbations.

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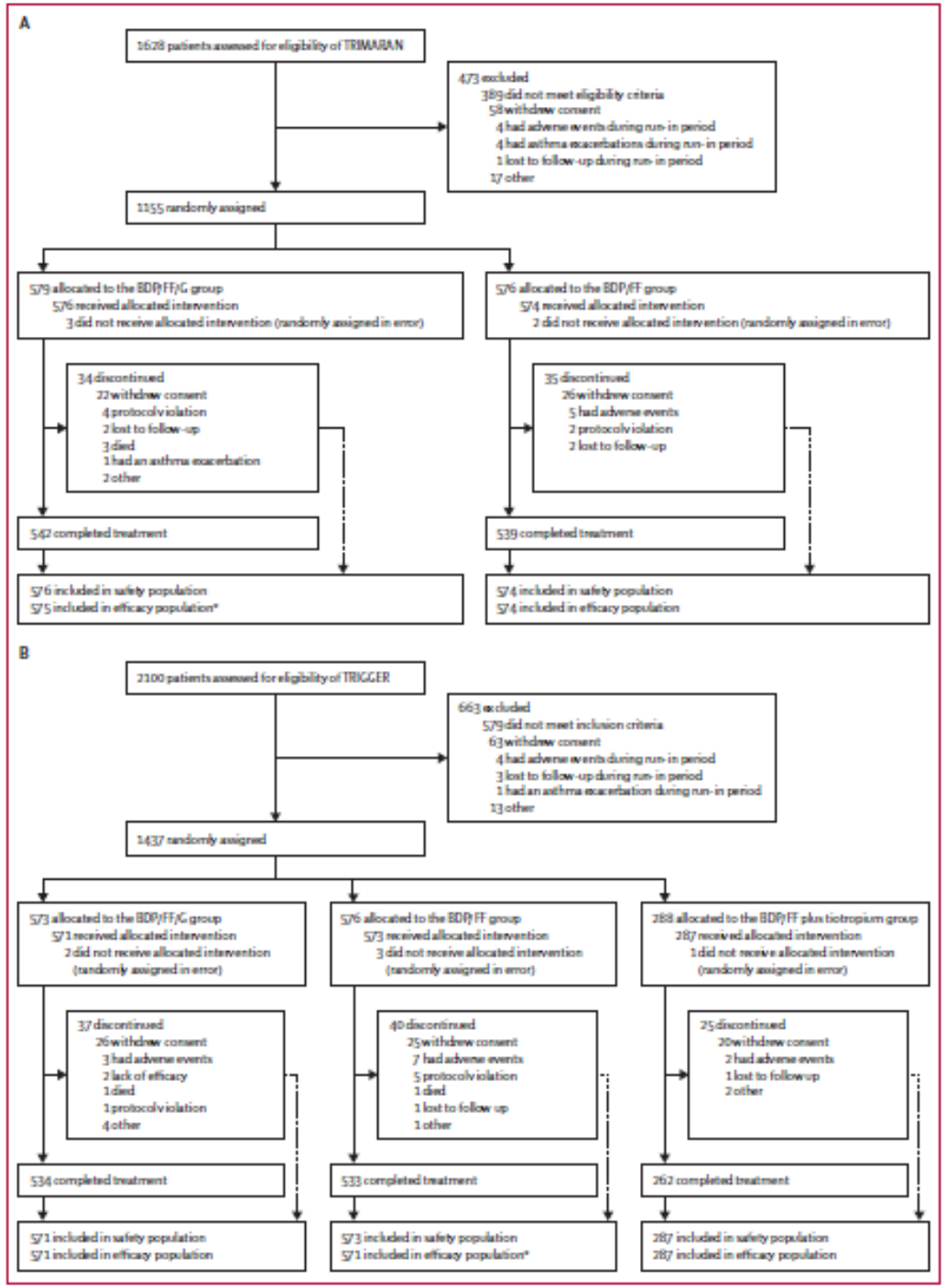
Introduction

Goals of asthma management are to achieve symptom control and avoid future risks, especially risks of exacerbations.[1] Asthma is characterised by the presence of chronic airway inflammation; hence inhaled corticosteroids are the mainstay of therapy.[2] Many patients are able to achieve good disease control, especially from an inhaled corticosteroid plus long-acting β_2 agonist

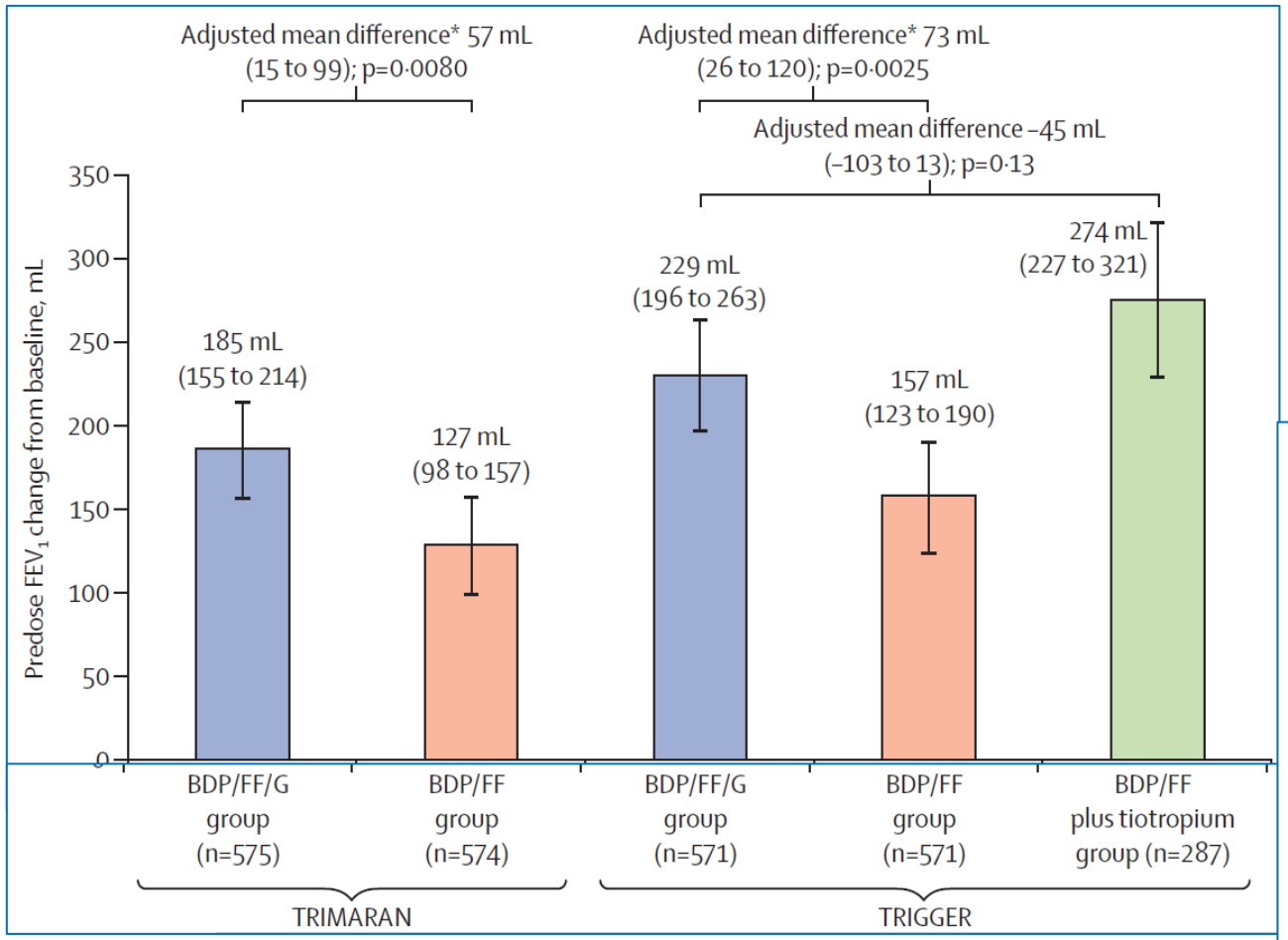
- Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials
- Triple in asthma with uncontrolled patients on medium strength of ICS/LABA [TRIMARAN]
- Triple in asthma high strength vs. ICS/LABA and Tiotropium [TRIGGER]
- adults (aged 18–75 years) with uncontrolled asthma, ≥1 exacerbations/year, and previously treated with ICS/LABA
- Pre-dose FEV1 at 26wks
- Rate of mod/severe exacerbation

JC Virchow, P Kuna, P Paggiaro, A Papi, D Singh et al. Lancet 2019; 394: 1737–49*

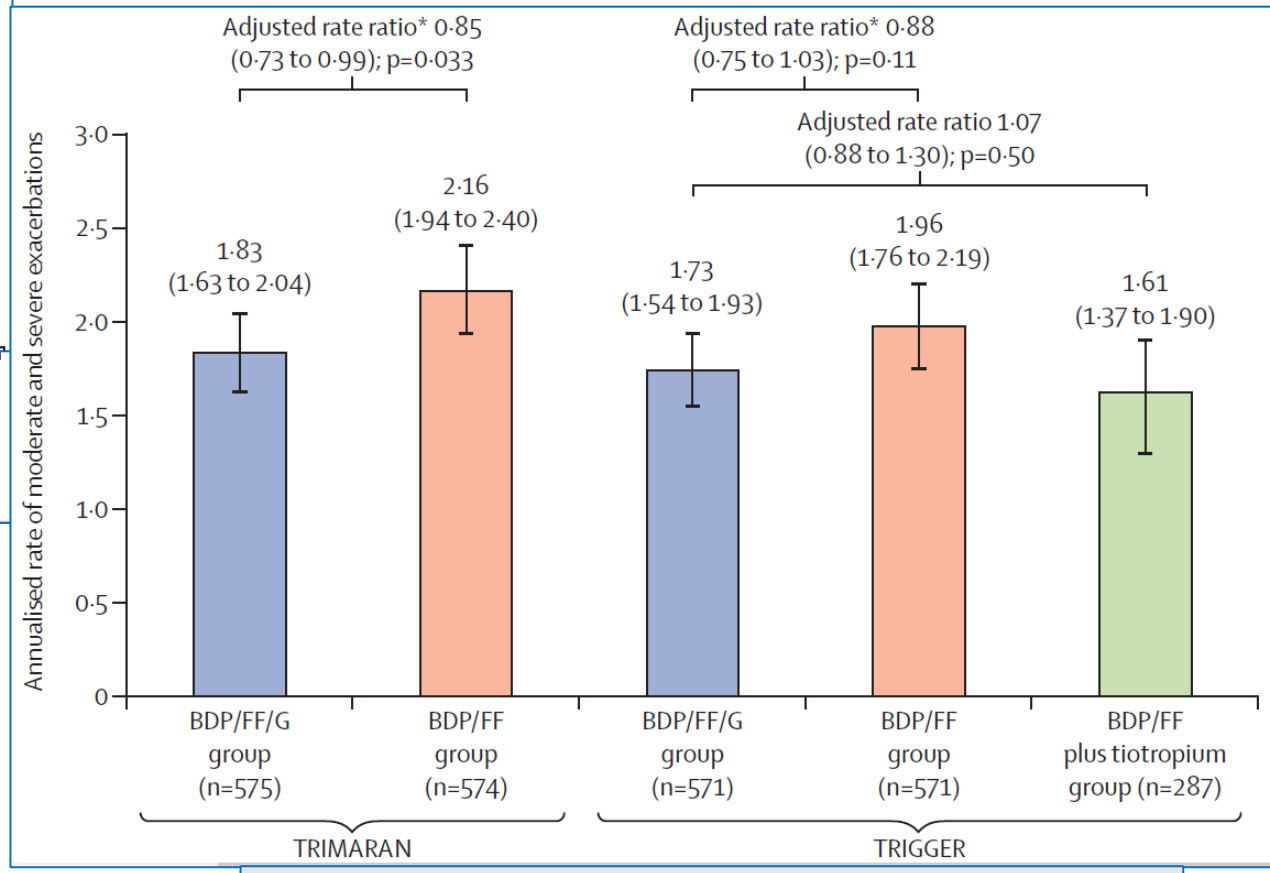
	TRIMARAN	TRIGGER
Recruitment sites	171 sites across 16 countries	221 sites across 17 countries
Enrolled criteria	Adults (18-75 years) with uncontrolled asthma (AE ≥ 1/previous year, ICS+LABA treatment)	
Study design & randomization	Double-blind, randomized, 52wks	
# of participants	1,155	1,437
Study arm	1:1	2:2:1
BDP/FF/G	**100 µg BDP**, 6 µg FF, 10 µg G	**200 µg BDP**, 6 µg FF, 10 µg G
BDP/FF	100 µg BDP, 6 µg FF	200 BDP, 6 µg FF
Open labeled Tiotropium	X	tiotropium 2.5 µg x 2/day
Coprimary outcome	• pre-dose FEV1 at week 26 • rate of moderate and severe exacerbations over 52 weeks	
pre-dose FEV_1 at 26wks	**57 mL (95% CI 15–99; p=0·0080)**	**73 mL (26–120; p=0·0025)**
▲ rate of moderate/severe exacerbation	**15% (rate ratio 0·85, 95% CI 0·73–0·99; p=0·033)**	12% (0·88, 0·75–1·03; p=0·11)



	TRIMARAN		TRIGGER		
	BDP/FF/G group (n=576)	BDP/FF group (n=574)	BDP/FF/G group (n=571)	BDP/FF group (n=573)	BDP/FF plus tiotropium group (n=287)
Sex					
Male	221 (38%)	221 (39%)	212 (37%)	245 (43%)	103 (36%)
Female	355 (62%)	353 (61%)	359 (63%)	328 (57%)	184 (64%)
Race					
Asian	0	0	2 (<1%)	0	0
White	575 (100%)	574 (100%)	569 (>99%)	573 (100%)	286 (>99%)
Other	1 (<1%)	0	0	0	1 (<1%)
Age, years	52·6 (12·4)	52·5 (12·2)	53·1 (12·2)	54·0 (11·9)	51·6 (12·3)
Body-mass index, kg/m²	28·0 (4·81)	27·9 (5·07)	28·4 (5·14)	28·7 (5·87)	28·5 (5·21)
≥30	173 (30%)	170 (30%)	204 (36%)	205 (36%)	102 (36%)
Smoking status					
Former smoker	92 (16%)	76 (13%)	83 (15%)	80 (14%)	42 (15%)
Non-smoker	484 (84%)	498 (87%)	488 (85%)	493 (86%)	245 (85%)
Smoking history (pack-years)*	4·1 (2·4)	4·8 (2·5)	4·9 (2·4)	4·8 (2·3)	5·6 (2·6)
Duration of asthma, years	24·8 (12·9)	25·2 (12·8)	24·8 (12·2)	26·2 (12·6)	24·5 (12·4)
Exacerbations in the previous year					
1	474 (82%)	473 (82%)	439 (77%)	452 (79%)	229 (80%)
>1	102 (18%)	101 (18%)	132 (23%)	121 (21%)	58 (20%)
Before-salbutamol FEV_1, L†	1·7 (0·56)	1·7 (0·56)	1·6 (0·56)	1·6 (0·57)	1·6 (0·59)
Before-salbutamol FEV_1, % of predicted normal value†	55·2 (12·3)	55·7 (12·0)	51·9 (13·5)	51·8 (13·5)	52·1 (13·2)
Range	17–79	20–79	15–79	16–79	22–79
Reversibility, %	32·5 (24·72)	30·8 (20·53)	33·2 (20·21)	33·9 (21·87)	34·9 (26·99)
Range	12·1–419·2	12·1–163·0	12·1–147·9	12·0–152·5	12·2–234·5
Before-salbutamol FEV_1/FVC ratio†	0·60 (0·12)	0·61 (0·12)	0·59 (0·12)	0·59 (0·13)	0·59 (0·12)
Range	0·26–0·96	0·27–0·94	0·23–0·95	0·27–0·94	0·29–0·88
After-salbutamol FEV_1/FVC ratio‡	0·65 (0·11)	0·65 (0·11)	0·63 (0·12)§	0·63 (0·12)	0·63 (0·12)
Range	0·31–0·97	0·32–0·91	0·27–0·93	0·26–0·92	0·34–0·96
Previous inhaled corticosteroid or long-acting β_2-agonist therapy¶					
Inhaled corticosteroid	61 (11%)	72 (13%)	153 (27%)	144 (25%)	67 (23%)
Inhaled corticosteroid plus long-acting β_2 agonist	531 (92%)	515 (90%)	525 (92%)	520 (91%)	267 (93%)
Long-acting β_2 agonist	55 (10%)	66 (11%)	74 (13%)	71 (12%)	35 (12%)
ACQ-7 score‖	2·3 (0·52)	2·3 (0·53)	2·5 (0·53)§	2·4 (0·54)**	2·4 (0·53)
Peak expiratory flow, L/min††					
Morning	297 (107·5)‡‡	299 (106·0)‡‡	279 (104·2)§§	275 (101·2)¶¶	287 (106·4)
Evening	310 (108·2)‖‖	314 (107·6)‡‡	292 (104·7)¶¶	287 (103·1)‖‖	299 (107·6)
Daily asthma symptom scores††	0·76 (0·49)	0·77 (0·50)	0·81 (0·52)	0·83 (0·51)	0·84 (0·50)
Percentage of asthma symptom-free days††	9·9% (22·78)	11·0% (24·19)	10·2% (23·09)	9·5% (23·14)	10·8% (26·58)
Percentage of asthma control days††	9·1% (21·45)	10·4% (23·48)	9·9% (22·66)	8·9% (22·24)	10·1% (26·22)



Pre-dose FEV_1 at week 26

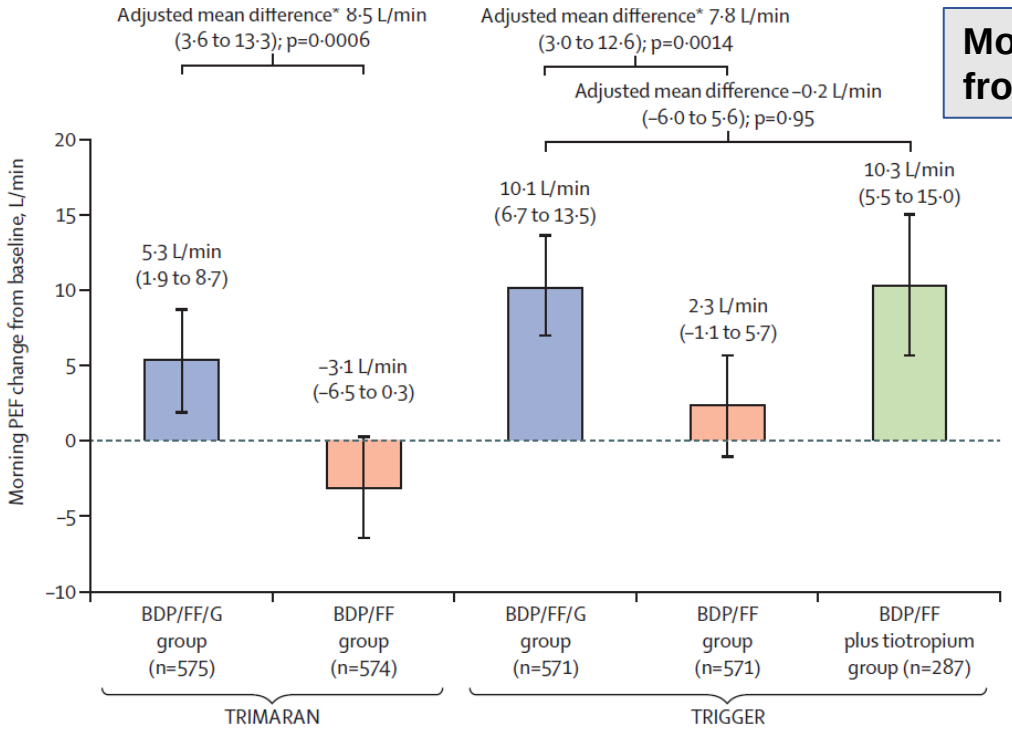


Annualized rate of mod/severe AE

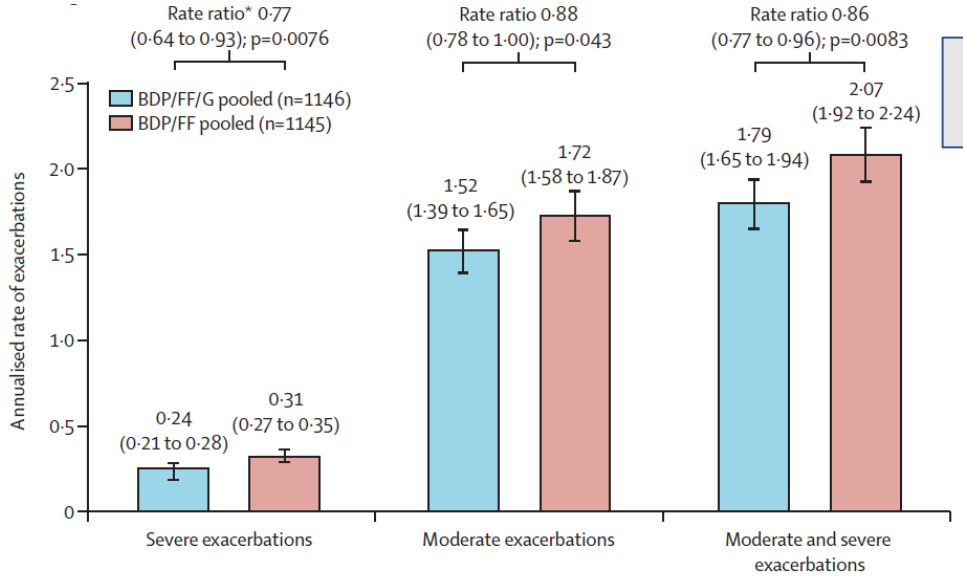
Peak FEV1 change from baseline (Triple vs BDP/FF)

- adj. mean difference in TRIMARAN
  84 mL (40 to 129); p=0·0002
- adj. mean difference in TRIGGER
  105 mL (57 to 153); p<0·0001

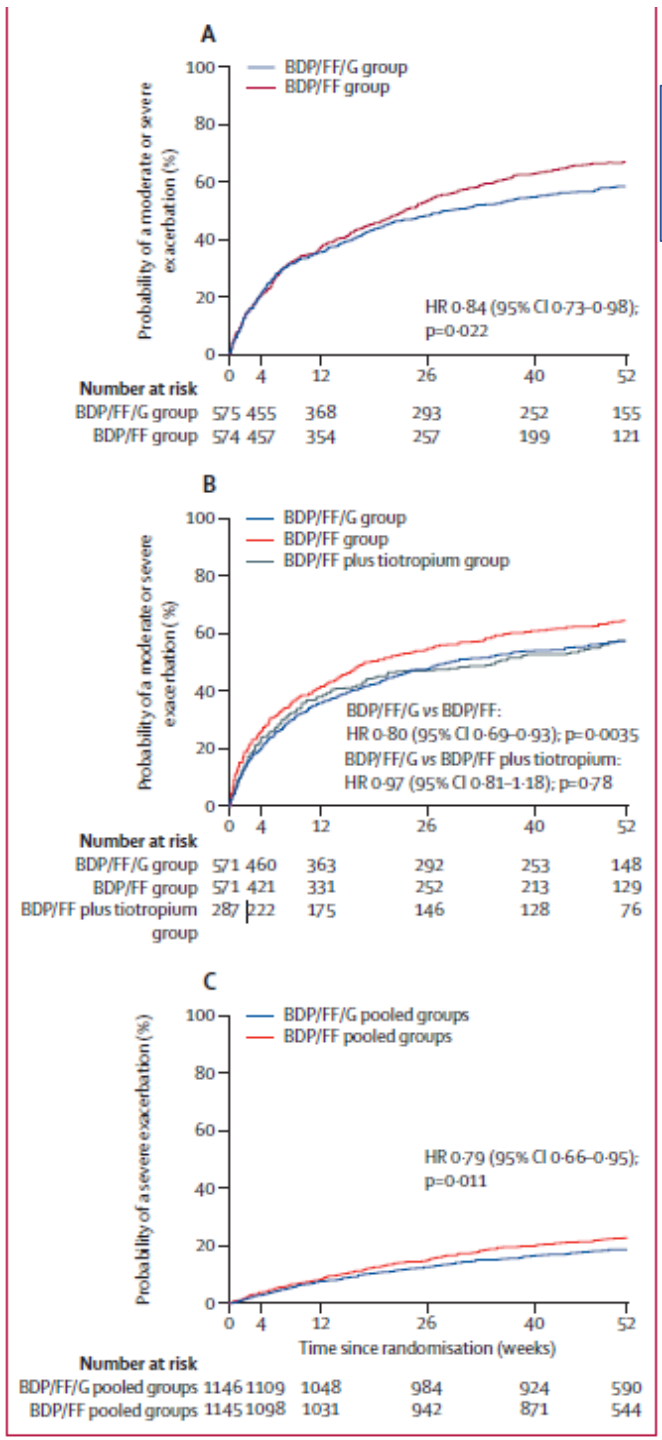
Morning PEF change from baseline, L/min



Annualized rate of exacerbations



Time to first moderate or severe exacerbation



Summary: TRIMARAN and TRIGGER

- Compared with the BDP/FF group, week 26 pre-dose FEV_1 improved in the BDP/FF/G group

  (57 mL, p=0·0080 in TRIMARAN , 73 mL, p=0·0025 in TRIGGER).

- BDP/FF/G (a single-inhaler triple therapy) prevents exacerbation data to a greater degree than BDP/FF in uncontrolled asthma
  - Reduction in rate of moderate exacerbations by 12% & combined moderate and severe exacerbations by 14% and the time to first moderate or severe exacerbation
  - Rate of the more clinically relevant severe exacerbations ▼ 23% in pooled analysis
  - Time to first severe exacerbation ▼ 21% (HR 0·79)

- Single inhaler BDP/FF/G triple therapy showed some benefits in terms of asthma symptoms and control in adults with uncontrolled asthma treated with a medium-to-high dose ICS/LABA

Characteristics of prominent response to triple therapy in patients with asthma uncontrolled on ICS/LABA: A stratified analysis of the TRIMARAN and TRIGGER studies

- **pre-specified pooled analysis of TRIMARAN & TRIGGER.**

- **Six easily identifiable traits are associated with the most prominent response to triple therapy (BDP/FF/GB)**
  - Differences in adjusted rate ratios (RR) ($p < 0.024$).

  - BMI < 25 kg/m^2 (0.57)
  - males (0.65)
  - 1 exacerbation in the previous year (0.73)
  - non-smokers (0.76)
  - age < 65 years (0.77)
  - reversibility > 400 mL following salbutamol 400 µg (0.73)

Dave Singh, J. Christian Virchow, et al. European Respiratory Journal 2019 54: RCT3779

Contents

- **Updates in GINA guideline (www.ginasthma.org)**
  - Recommendation in COVID-19 pandemic (2020)
  - Anti-inflammatory reliever in mild asthma (2019)

- **Updated data of ICS/FOR in asthma**
  - Real-world data of ICS/FOR in mild asthma
    - Novel START (N Engl J Med 2019;380:2020-30)
    - PRACTICAL (Lancet 2019; 394: 919–28)
  - Triple therapy with a single inhaler (TRIMARAN, TRIGGER, *Lancet 2019; 394: 1737–49)*

- **Considerations in treatment of asthma**
  - ICS in non-eosinophilic airway inflammation (Novel START & SIENA study, N Engl J Med 2019;380:2009-19)
  - Montelukast: black box-warning
  - Biologics – reslizumab (SC) (www.thelancet.com/respiratory, e-pub)
  - Self-management support intervention in older patients with asthma (SAMBA study, *JAMA Intern Med*. 2019;179(8):1113-1121)

Predictive value of blood eosinophils & FeNO in mild asthma

Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial

Ian D Pavord, Mark Holliday, Helen K Reddel, Irene Braithwaite, Stefan Ebmeier, Robert J Hancox, Tim Harrison, Claire Houghton, Karen Oldfield, Alberto Papi, Mathew Williams, Mark Weatherall, Richard Beasley, on behalf of the Novel START Study Team

- **A prespecified subgroup analysis of Novel STRAT study**
  - to assess the difference of annual rates of asthma exacerbations per patient depending on levels of blood eosinophil count, FeNO, or a composite score of both
    - **As needed SABA**
    - **BUD maintenance + as needed SABA**
    - **As needed BUD/FOR**

needed salbutamol (two inhalations of 100 µg in a pressurised metered dose inhaler), maintenance budesonide (200 µg twice per day by inhaler) plus as-needed salbutamol (two inhalations of 100 µg), or as-needed budesonide–formoterol (one inhalation of 200 µg budesonide and 6µg formoterol by inhaler). The primary outcome was the

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Pavord ID[1], Holliday M[2], Reddel HK et al. ***Lancet Respir Med* 2020** Published **Online** March 11, 2020

Baseline characteristics by baseline biomarker group

	Blood eosinophil count (×10⁹/L)			FeNO (ppb)			Composite score		
	<0·15 (n=184)	0·15 to <0·30 (n=256)	≥0·30 (n=216)	<20 (n=159)	20 to 50 (n=249)	>50 (n=260)	1: blood eosinophils <0·15×10⁹/L and FeNO <20 ppb (n=78)	2: any pattern other than scores 1 or 3 (n=432)	3: blood eosinophils ≥0·3×10⁹/L and FeNO >50 ppb (n=146)
Sex									
Female	114 (62%)	132 (52%)	111 (51%)	117 (74%)	130 (52%)	117 (45%)	61 (78%)	223 (52%)	73 (50%)
Male	70 (38%)	124 (48%)	105 (49%)	42 (26%)	119 (48%)	143 (55%)	17 (22%)	211 (48%)	73 (50%)
Current smoker	19 (10%)	24 (9%)	21 (10%)	31 (19%)	17 (7%)	16 (6%)	12 (15%)	42 (10%)	10 (7%)
≥1 exacerbation in past year	16 (9%)	14 (5%)	18 (8%)	9 (6%)	23 (9%)	17 (7%)	6 (8%)	30 (7%)	12 (8%)
Hospitalisation with asthma ever	10 (5%)	41 (16%)	44 (20%)	15 (9%)	44 (18%)	48 (18%)	5 (6%)	69 (16%)	30 (21%)
Age, years	36·0 (14·9)	38·1 (14·4)	31·9 (12·3)	36·1 (14·2)	38·0 (14·9)	33·0 (12·9)	36·2 (15·1)	36·7 (14·3)	31·2 (12·1)
Age at onset of asthma, years	16·0 (12·9)	15·0 (14·9)	12·3 (11·9)	18·3 (13·9)	14·6 (14·0)	12·0 (12·5)	19·2 (14·1)	14·4 (13·8)	11·7 (11·5)
Body-mass index	27·3 (7·0)	28·1 (6·5)	26·6 (5·8)	28·7 (7·6)	28·0 (6·5)	26·0 (5·2)	27·7 (7·8)	27·9 (6·5)	25·7 (5·2)
SABA puffs per week	3·5 (3·3)	3·4 (3·3)	3·6 (3·3)	3·8 (3·7)	3·2 (2·9)	3·6 (3·3)	3·9 (3·5)	3·4 (3·3)	3·6 (3·2)
ACQ-5	1·0 (0·7)	1·1 (0·7)	1·2 (0·7)	1·2 (0·8)	1·0 (0·7)	1·1 (0·7)	1·1 (0·7)	1·1 (0·7)	1·2 (0·7)
FEV_1 % predicted	92·6 (14·3)	89·2 (13·9)	88·0 (13·0)	92·3 (14·3)	89·1 (13·8)	88·9 (13·4)	95·3 (14·0)	89·5 (13·8)	87·5 (13·0)
FeNO (ppb)	30·4 (24·8)	45·9 (38·8)	82·9 (50·7)	12·9 (4·0)	33·2 (8·2)	97·7 (42·1)	12·9 (3·9)	42·8 (33·2)	107·3 (42·8)
Blood eosinophil count (×10⁹/L)	0·10 (0·03)	0·22 (0·04)	0·51 (0·22)	0·18 (0·15)	0·24 (0·17)	0·38 (0·24)	0·09 (0·03)	0·23 (0·15)	0·52 (0·22)

Data are n (%) or mean (SD), unless otherwise stated. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion. SABA=short-acting β agonist. ACQ-5=Asthma Control Questionnaire 5-item version.

- Blood eosinophil count is an independent prognostic marker of risk for exacerbation independent of baseline ACQ-5 score or FEV_1

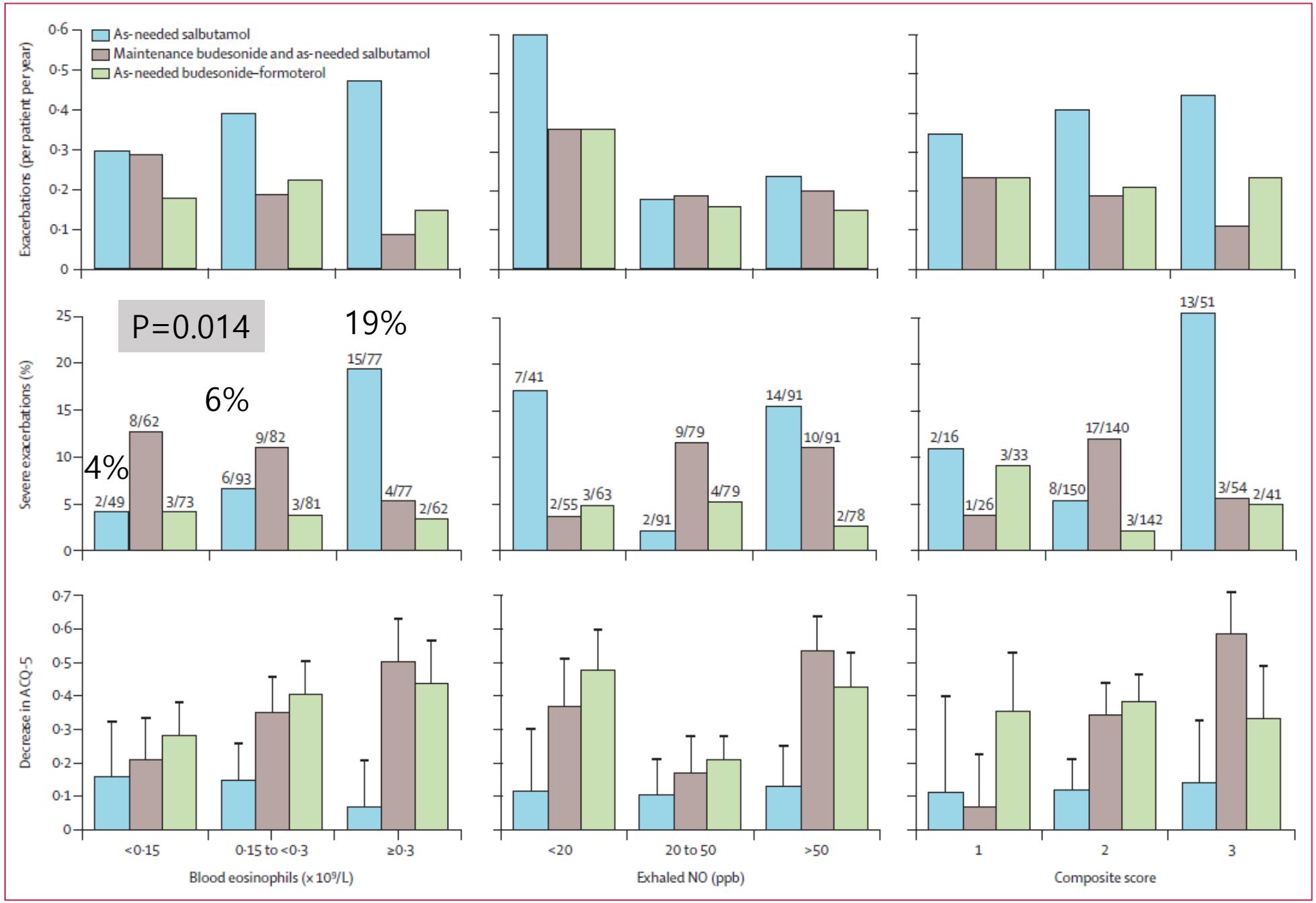

Figure: **Exacerbations, severe exacerbation, and mean decrease in ACQ-5 by treatment and biomarker category**

Exacerbation and severe exacerbation interaction analysis for the change in treatment effect

	Exacerbation rate ratios (95% CI)			Severe exacerbation risk odds ratios (95% CI)		
	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$
FeNO	..	..	0·28	..	..	0·009
High (>50 ppb)	0·53 (0·24–1·15)	0·72 (0·35–1·50)	..	0·32 (0·06–1·75)	1·93 (0·62–5·92)	..
Low (<20 ppb)	0·36 (0·17–0·76)	0·19 (0·08–0·47)	..	0·18 (0·04–0·84)	0·09 (0·02–0·50)	..
p value (high *vs* low)	0·51	0·028	..	0·65	0·0040	..
Blood eosinophils count	..	..	0·014	..	..	0·009
High (≥0·3 × 10⁹/L)	0·28 (0·12–0·63)	0·13 (0·05–0·33)	..	0·15 (0·03–0·79)	0·11 (0·03–0·45)	..
Low (<0·15 × 10⁹/L)	0·63 (0·27–1·44)	1·15 (0·51–1·28)	..	1·42 (0·19–10·50)	5·72 (0·97–33·60)	..
p value (high *vs* low)	0·18	0·0006	..	0·10	0·0007	..
Composite score	..	..	0·54	..	..	0·005
High (FeNO >50 ppb and eosinophils ≥0·3 × 10⁹/L)	0·52 (0·23–1·22)	0·24 (0·90–0·65)	..	0·15 (0·03–0·71)	0·17 (0·05–0·65)	..
Low (FeNO <20 ppb and eosinophils <0·15 × 10⁹/L)	0·68 (0·22–2·14)	0·68 (0·20–2·35)	..	0·17 (0·05–0·65)	0·31 (0·03–3·67)	..
p value (high *vs* low)	0·73	0·20	..	0·18	0·68	..

$p_{interaction}$ refers to the interaction between any treatment effect and the biomarker status. p values between treatment comparisons were only considered further if this interaction was significant. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

Table 3: Exacerbation and severe exacerbation interaction analysis for the change in treatment effect for treatments containing budesonide compared with as-needed salbutamol

Summary: predictive value of blood eosinophils & FeNO in mild asthma

- The relationship between the blood eosinophil count and exacerbations is very different for as-needed SABA, as-needed BUD/FOR, and maintenance BUD plus as-needed SABA.

- The benefits for preventing exacerbations of maintenance BUD plus as-needed SABA over as-needed SABA alone increased progressively with increasing blood eosinophil count category.

- The benefits for preventing exacerbations of as-needed BUD/FOR over as needed SABA for preventing exacerbations were independent of baseline biomarkers.

Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

S.C. Lazarus, J.A. Krishnan, T.S. King, J.E. Lang, K.V. Blake, R. Covar, N. Lugogo, S. Wenzel, V.M. Chinchilli, D.T. Mauger, A.-M. Dyer, H.A. Boushey, J.V. Fahy, P.G. Woodruff, L.B. Bacharier, M.D. Cabana, J.C. Cardet, M. Castro, J. Chmiel, L. Denlinger, E. DiMango, A.M. Fitzpatrick, D. Gentile, A. Hastie, F. Holguin, E. Israel, D. Jackson, M. Kraft, C. LaForce, R.F. Lemanske, Jr., F.D. Martinez, W. Moore, W.J. Morgan, J.N. Moy, R. Myers, S.P. Peters, W. Phipatanakul, J.A. Pongracic, L. Que, K. Ross, L. Smith, S.J. Szefler, M.E. Wechsler, and C.A. Sorkness, for the National Heart, Lung, and Blood Institute AsthmaNet*

ABSTRACT

BACKGROUND

In many patients with mild, persistent asthma, the percentage of eosinophils in sputum is less than 2% (low eosinophil level). The appropriate treatment for these patients is unknown.

METHODS

In this 42-week, double-blind, crossover trial, we assigned 295 patients who were at least 12 years of age and who had mild, persistent asthma to receive mometasone (an inhaled glucocorticoid), tiotropium (a long-acting muscarinic antagonist), or placebo. The patients were categorized according to the sputum eosinophil level (<2% or ≥2%). The primary outcome was the response to mometasone as compared with placebo and to tiotropium as compared with placebo among patients with a low sputum eosinophil level who had a prespecified differential response to one of the trial agents. The response was determined according to a hierarchical composite outcome that incorporated treatment failure, asthma control days, and the forced expiratory volume in 1 second; a two-sided P value of less than 0.025 denoted statistical significance. A secondary outcome was a comparison of results in patients with a high sputum eosinophil level and those with a low level.

RESULTS

A total of 73% of the patients had a low eosinophil level; of these patients, 59% had a differential response to a trial agent. However, there was no significant difference in the response to mometasone or tiotropium, as compared with placebo. Among the patients with a low eosinophil level who had a differential treatment response, 57% (95% confidence interval [CI], 48 to 66) had a better response to mometasone, and 43% (95% CI, 34 to 52) had a better response to placebo (P=0.14). In contrast 60% (95% CI, 51 to 68) had a better response to tiotropium, whereas 40% (95% CI, 32 to 49) had a better response to placebo (P=0.029). Among patients with a high eosinophil level, the response to mometasone was significantly better than the response to placebo (74% vs. 26%) but the response to tiotropium was not (57% vs. 43%).

CONCLUSIONS

The majority of patients with mild, persistent asthma had a low sputum eosinophil level and had no significant difference in their response to either mometasone or tiotropium as compared with placebo. These data provide equipoise for a clinically directive trial to compare an inhaled glucocorticoid with other treatments in patients with a low eosinophil level. (Funded by the National Heart, Lung, and Blood Institute; SIENA ClinicalTrials.gov number, NCT02066298.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Lazarus at the Division of Pulmonary and Critical Care Medicine and the Cardiovascular Research Institute, University of California, San Francisco, M-1336, 505 Parnassus Ave., San Francisco, CA 94143, or at lazma@ucsf.edu.

*A complete list of the investigators in the National Heart, Lung, and Blood Institute AsthmaNet is provided in the Supplementary Appendix, available at NEJM.org.

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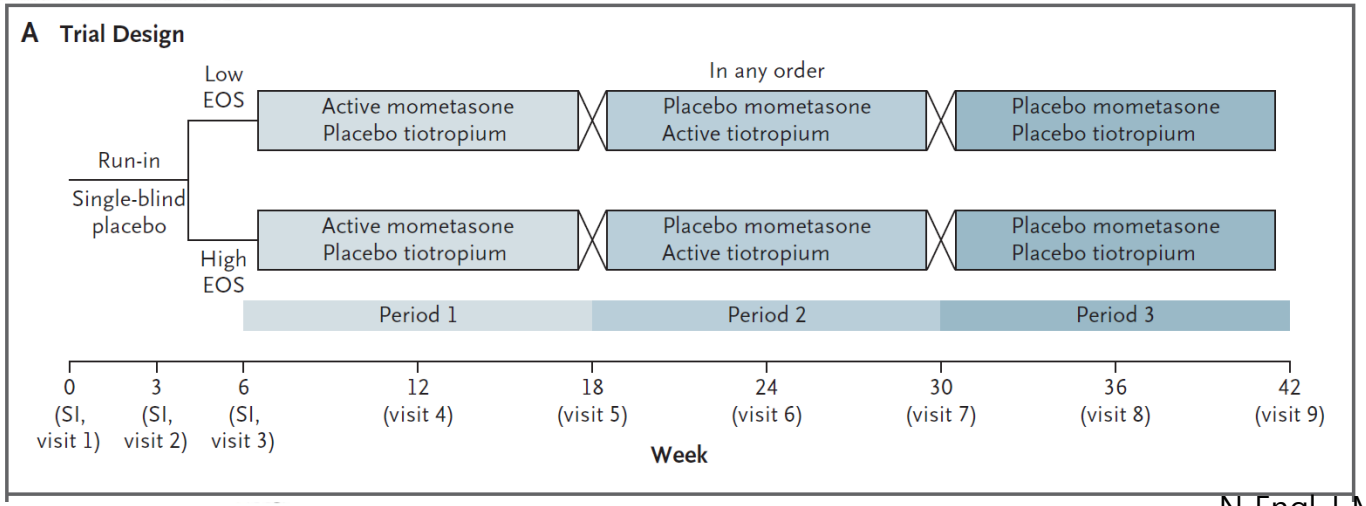
DOI: 10.1056/NEJMoa1814917

Steroids in Eosinophil-Negative Asthma (SIENA)

Q: Will patients with mild asthma who do not have eosinophilic airway inflammation have a similar response to inhaled glucocorticoid therapy?

- 42-week, double-blind, crossover trial
- N=295 (>12years old, mild, persistent asthma)
- Mometasone vs Tiotropium vs. Placebo
- Sputum eosinophil < 2% vs ≥ 2%
- Composite outcome; treatment failure, asthma control days, and FEV_1
- a power of 90% at a two-sided significance of **0.025** (Bonferroni correction) to detect a difference in probabilities of 0.20



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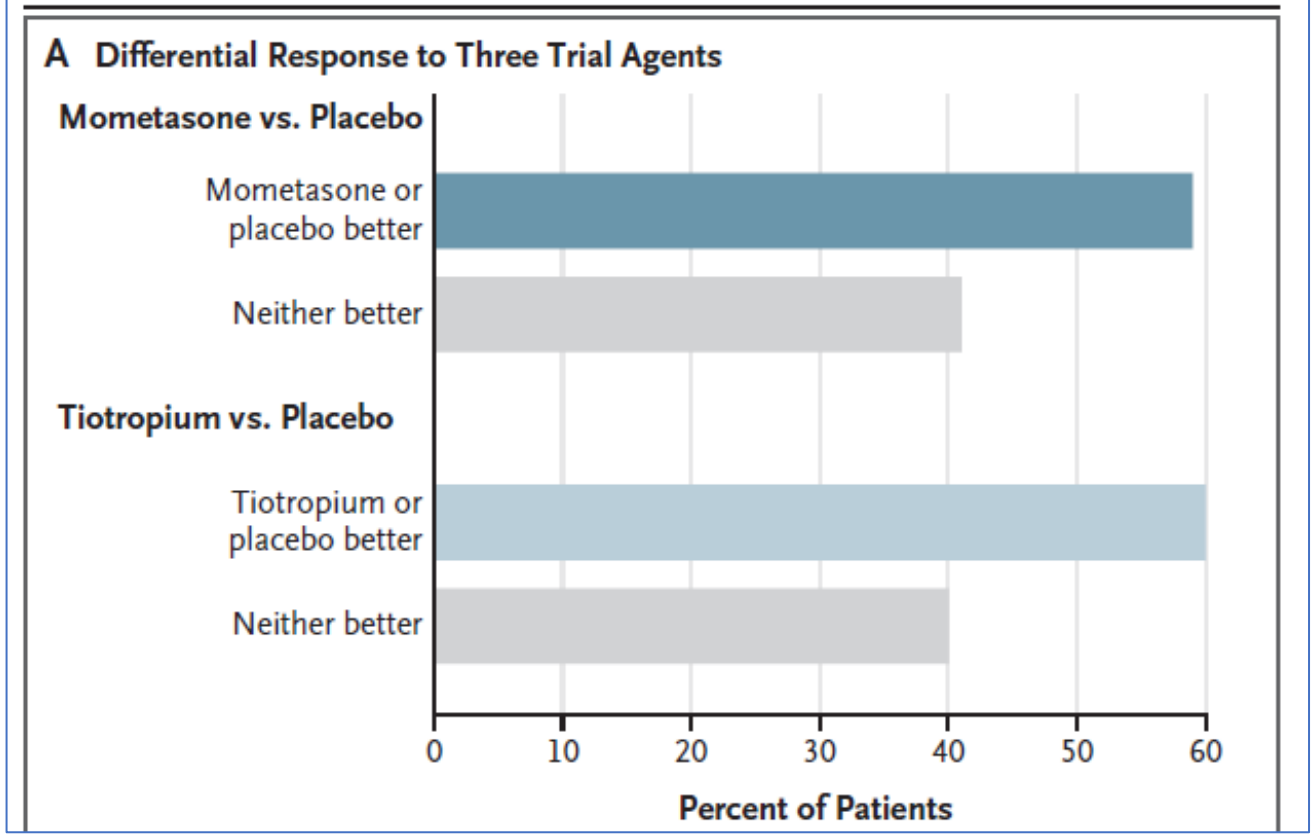
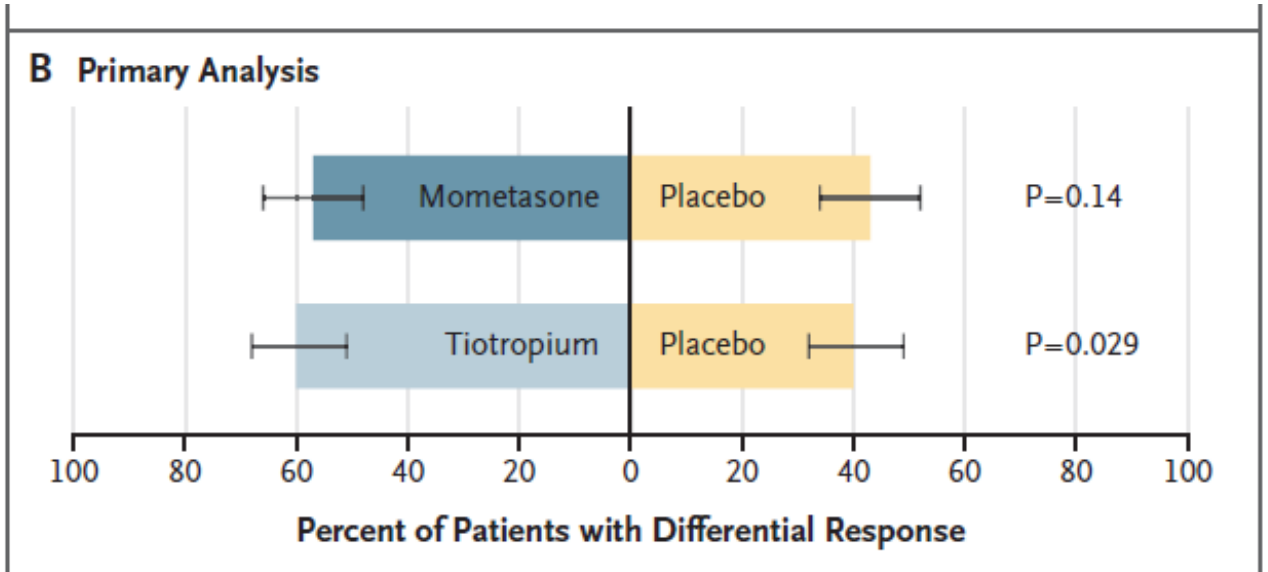


268 (73%) were classified as having a low eosinophil level and 98 (27%) as having a high eosinophil level.

Defined differential response to a trial agent

- No treatment failure in one period or one failure during 3 trial period,
- ▲ Annualized asthma control days >31days;
- ▲ FEV1 > 5%

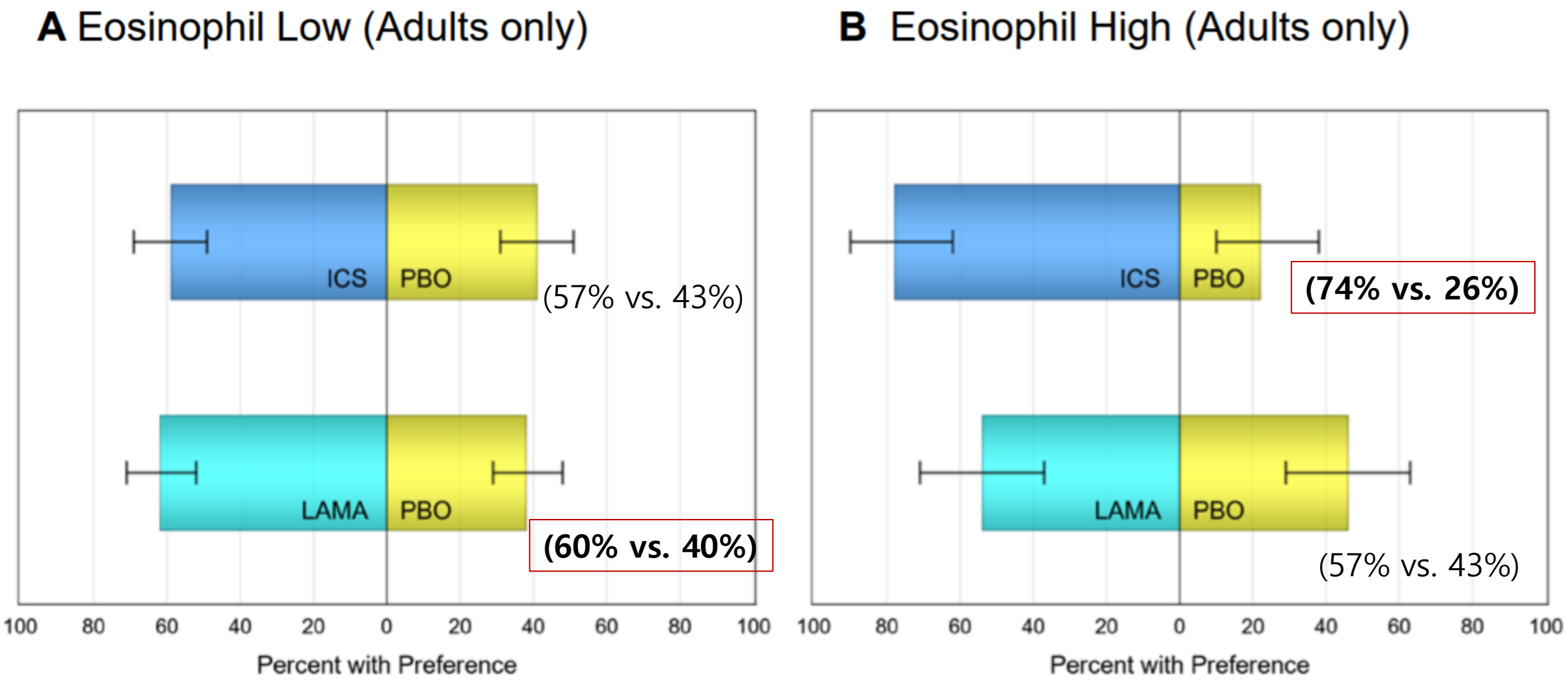


Pairwise Comparisons of Active Treatments and Placebo in the Low-Eosinophil Stratum.

- 57%; 95% CI (48-66) vs. 43%; 95% CI (34-52) p = 0.14
- 60%; 95% CI (51-56) vs. 40%; 95% CI (32-49) p = 0.029

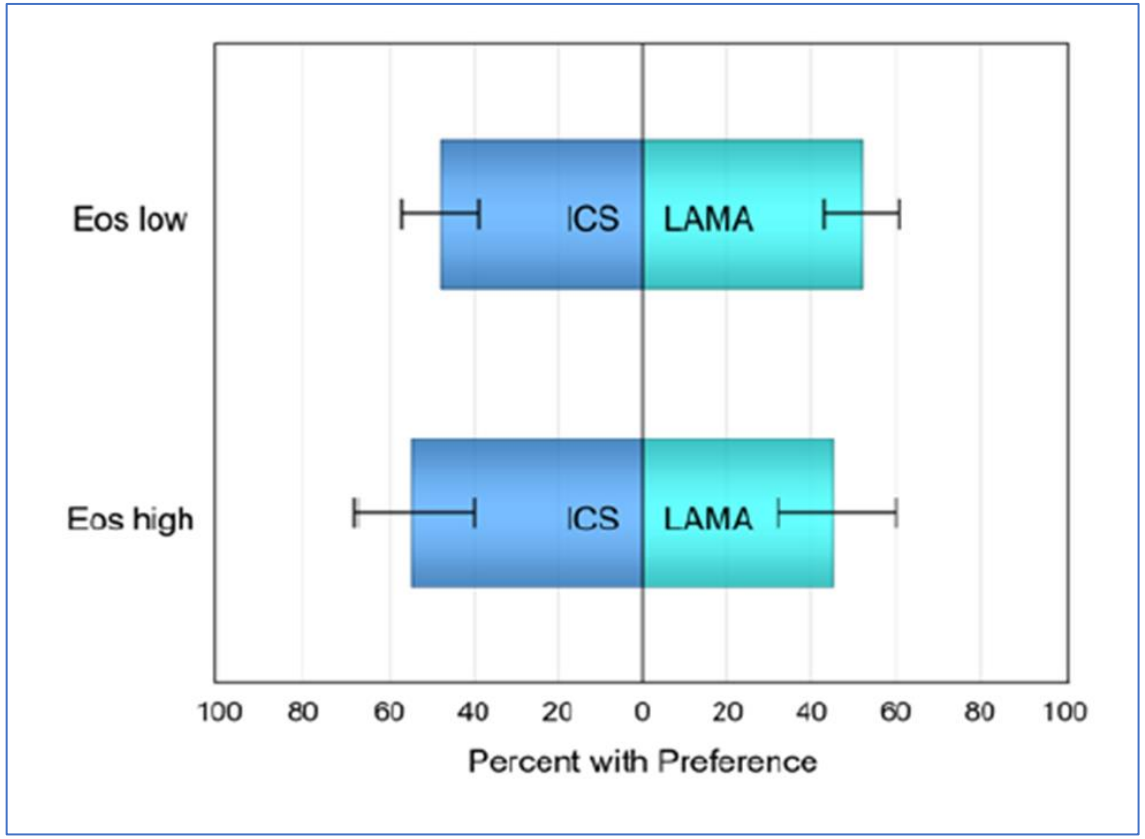
N Engl J Med 2019;380:2009-19

Pairwise comparison of ICS vs LAMA in the Eosinophil low and eosinophil high strata



N Engl J Med 2019;380:2009-19

ICS vs LAMA in non-eosinophilic airway inflammation in mild persistent asthma



- **The majority of patients with mild, persistent asthma had a low sputum eosinophil level and had no significant difference in their response to either mometasone or tiotropium as compared with placebo.**

Adverse effects with montelukast

Other Step 2 controller options for adults and adolescents

If as-needed ICS-formoterol is not available, another option is for low dose ICS to be taken whenever SABA is taken. The evidence is from studies with separate or combination ICS and SABA inhalers,[184-186,201] showing no difference in exacerbations compared with daily ICS.

Leukotriene receptor antagonists (LTRA) are less effective than ICS,[202] particularly for exacerbations (Evidence A). They may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS; for patients who experience intolerable side-effects from ICS; or for patients with concomitant allergic rhinitis[203,204] (Evidence B). Before prescribing montelukast, health professionals should consider its benefits and risks, and patients should be counselled about the risk of neuropsychiatric events. The US Food and Drug Administration (FDA) recently required a boxed warning to be provided about the risk of serious mental health adverse effects with montelukast.[205]

For adult or adolescent patients not previously using controller treatment, regular daily combination low dose ICS-LABA as the initial maintenance controller treatment reduces symptoms and improves lung function compared with low dose ICS alone.[206] However, it is more expensive and does not further reduce the risk of exacerbations compared with ICS alone[206] (Evidence A).

For patients with purely seasonal allergic asthma, e.g. with birch pollen, with no interval asthma symptoms, regular daily ICS or as-needed ICS-formoterol should be started immediately symptoms commence, and be continued for four weeks after the relevant pollen season ends (Evidence D).

Warning for risk of serious neuropsychiatric events for montelukast

FDA NEWS RELEASE

FDA Requires Stronger Warning About Risk of Neuropsychiatric Events Associated with Asthma and Allergy Medication Singulair and Generic Montelukast

Share Tweet LinkedIn Email Print

For Immediate Release: March 04, 2020

Español

The U.S. Food and Drug Administration today announced that it is requiring a boxed

Concise, one-half page summary of information in the Full Prescribing Information

- Limitations Statement
- Product Names and Date of Initial U.S. Approval
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage & Administration
- Dosage Forms & Strengths
- Contraindications
- Warnings & Precautions
- Adverse Reactions (listing of most common ARs)
- Drug Interactions
- Use in Specific Populations
- Patient Counseling Information Statement

safety, such that many products are available over the counter without a prescription."

The FDA updated the product labeling in 2008 to include information about

22

Drugs

Home › Drugs › Drug Safety and Availability › Postmarket Drug Safety Information for Patients and Providers
› Drug Safety Information for Heathcare Professionals

Drug Safety and Availability

- Postmarket Drug Safety Information for Patients and Providers
- Drug Safety Information for Heathcare Professionals
- Healthcare Professional Sheets

Early Communication About an Ongoing Safety Review of Montelukast (Singulair)

[See 8/28/2009 Update for current information on this safety issue]

3/23/2008

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing this product. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

FDA is investigating a possible association between the use of Singulair and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide. Singulair is a medicine in the drug class known as leukotriene receptor antagonists. Singulair is used to treat asthma and the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose) and to prevent exercise-induced asthma.

Over the past year, the maker of Singulair, Merck & Co, Inc., has updated the prescribing information and patient information for Singulair to include the following post-marketing adverse events: tremor (March 2007), depression (April 2007), suicidality (suicidal thinking and behavior) (October 2007), and anxiousness (February 2008).

In February 2008, FDA and Merck discussed how best to communicate these labeling changes to prescribers and patients. Merck plans to highlight the recent changes in the prescribing information in face-to-face interactions with prescribers and provide prescribers with patient information leaflets about Singulair. The Singulair website includes the most current prescribing information and patient information for Singulair (www.singulair.com).

FDA is working with Merck to further evaluate a possible link between the use of Singulair and behavior/mood changes, suicidality and suicide in response to inquiries received by FDA. FDA has requested that Merck evaluate Singulair study data for more information about suicidality and suicide. FDA is reviewing the postmarketing reports it has received of behavior/mood changes, suicidality and suicide in patients who took Singulair.

Due to the complexity of the analyses, FDA anticipates that it may take up to 9 months to complete the ongoing evaluations. As soon as this review is complete, FDA will communicate the conclusions and recommendations to the public.

Singulair is an effective medicine that is indicated for the treatment of asthma and symptoms of allergic rhinitis. Patients should not stop taking Singulair before talking to their doctor if they have questions about this new information. Until further information is available, healthcare professionals and caregivers should monitor patients

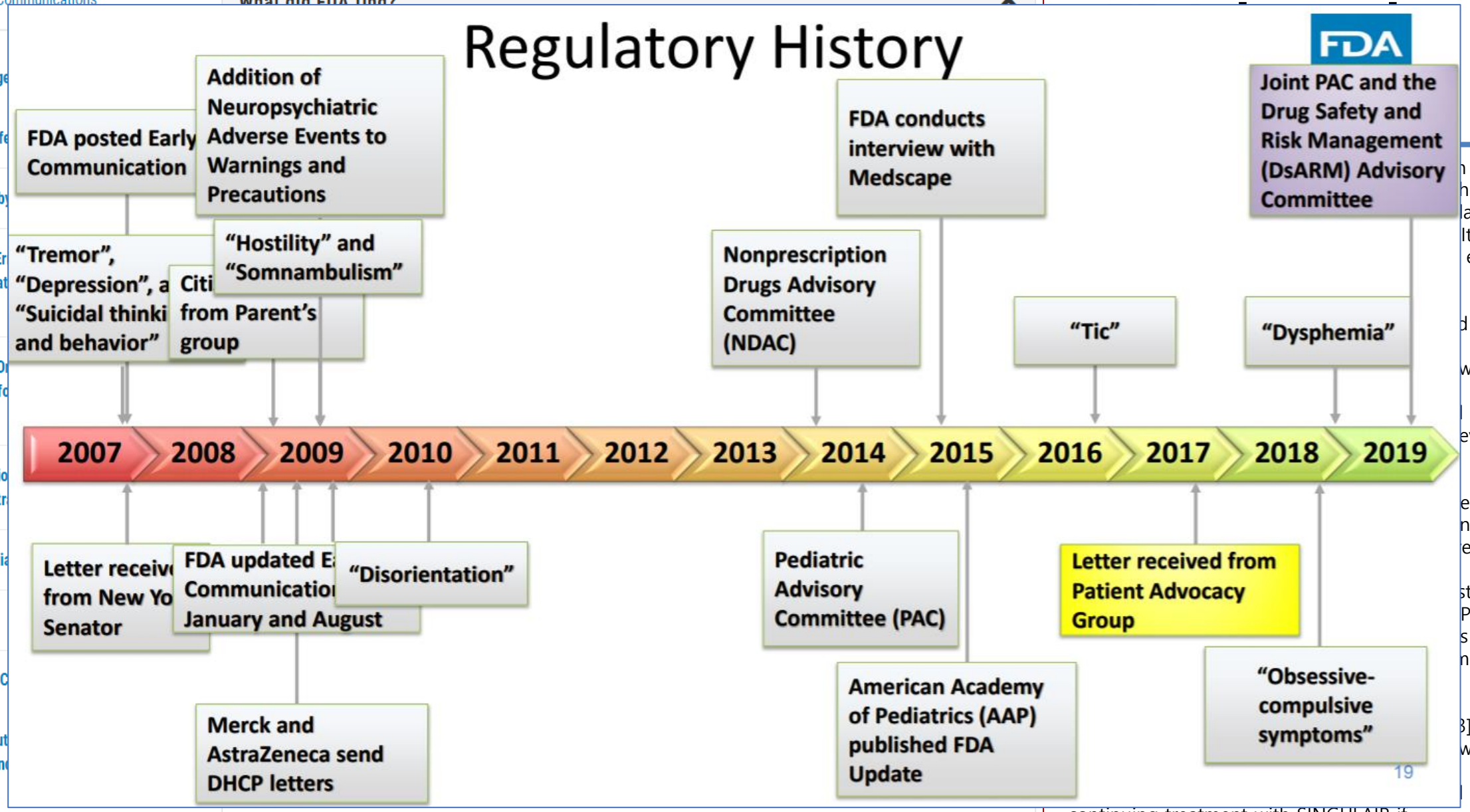
Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice

Table 3. Most common adverse drug reactions (ADRs) after montelukast reported to the Netherlands Pharmacovigilance Centre Lareb and the WHO Global ICSR database VigiBase®.

Adverse drug reaction	Total number of reports at VigiBase®	ROR[1] VigiBase® (95% CI)	Number of reports in children <19 year at VigiBase®	ROR[1] VigiBase® in children <19y (95% CI)	Total number of reports at Lareb	ROR[1] Lareb (95% CI)	Number of reports in children <19 year at Lareb	ROR[1] Lareb in children <19 year (95% CI)
Depression	1188	6.93 (6.54–7.36)	493	20.52 (18.65–22.58)	5	1.91 (0.79–4.62)	–	–
Headache	1128	1.85 (1.75–1.97)	371	1.91 (1.72–2.12)	37	2.26 (1.61–3.19)	17	3.18 (2.66–3.70)
Aggression	1101	24.99 (23.49–26.59)	808	29.77 (27.54–32.18)	11	9.27 (5.06–16.99)	7	12.02 (11.24–12.80)
Suicidal ideation	1047	20.43 (19.18–21.76)	495	38.27 (34.68–42.22)	1	–	–	–
Insomnia	1020	5.08 (4.77–5.41)	417	11.15 (10.07–12.35)	15	3.45 (2.05–5.81)	7	4.60 (3.83–5.38)
Anxiety	948	5.11 (4.79–5.46)	468	16.99 (15.41–18.72)	6	2.79 (1.24–6.26)	2	–
Abnormal behavior	892	34.05 (31.79–36.46)	643	17.64 (15.99–19.46)	7	12.02 (5.64–25.61)	7	8.56 (7.79–9.34)
Nightmares	749	22.48 (20.87–24.21)	448	78.04 (69.95–87.07)	25	19.29 (12.75–29.17)	13	56.72 (56.09–57.35)
Dyspnea	649	1.30 (1.20–1.41)	120	1.14 (0.95–1.36)	13	1.47 (0.84–2.56)	–	—
Rash	540	0.65 (0.59–0.71)	161	0.31 (0.26–0.36)	17	1.77 (1.09–2.89)	7	1.28 (0.51–2.05)
Abdominal pain	511	1.81 (1.66–1.98)	222	2.24 (1.95–2.56)	15	2.24 (1.33–3.77)	8	3.67 (2.95–4.40)
Dizziness	541	0.89 (0.82–0.97)	97	0.72 (0.59–0.88)	12	0.94 (0.53–1.68)	–	–
Myalgia	352	1.66 (1.49–1.84)	58	1.57 (1.21–2.03)	12	1.26 (0.71–2.25)	–	–
Muscle spasms	291	2.44 (2.17–2.74)	57	3.98 (3.06–5.17)	10	2.87 (1.53–5.40)	–	–
Nausea	557	0.61 (0.56–0.66)	104	0.56 (0.46–0.68)	10	0.65 (0.35–1.23)	4	1.17 (0.16–2.17)

Disclaimer: This publication contains information obtained from UMC through https://vigilyze.who-umc.org (restricted access), accessed at 03-11-2016. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases, The information shown in this article does not represent the opinion of the World Health Organization. For more information see http://www.who-umc.org/graphics/25300.pdf

Pharma Res Per, 5(5), 2017, e00341



Drug Safety Communications

What did FDA find?

Drug Shortage

FDA Drug Safe

Information by

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We previously communicated about mental health side effects with montelukast in March 2008, January 2009, June 2009, and August 2009.

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What should health care professionals do?

- Health care professionals should consider the risks and benefits of montelukast when deciding to prescribe or continue patients on the medicine.
- Ask patients about any history of psychiatric illness prior to initiating treatment.
- Advise all patients of the risk of neuropsychiatric events when prescribing montelukast.
- Monitor all patients treated with montelukast for neuropsychiatric symptoms.
- Most reported cases of neuropsychiatric events occurred during montelukast treatment, but some occurred after discontinuation.
- Only prescribe montelukast for allergic rhinitis in patients who have an inadequate response or intolerance to alternative therapies.

https://www.fda.gov/drugs/drug-safety-and-availability/

Biologics for treatment of severe asthma

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider ***add-on biologic Type 2*** targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*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*

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

Anti-IL5 / Anti-IL5R

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

- Exacerbations in last year
- Blood eosinophils ≥300/µl

no / *no*

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

... for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

... or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Choose one if eligible; trial for at least 4 months and assess response

Good asthma response?

yes — Good response to T2-targeted therapy

no — **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

no — Little/no response to T2-targeted therapy

unclear — Extend trial to 6-12 months

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Type 2 biologic medications for severe asthma

	Target	Dose	Primary treatment group	Primary benefits	Stage of development
Mepolizumab (GlaxoSmithKline, Brentford, UK)	IL-5	Subcutaneous, 100 mg, Q4 weeks	Severe eosinophilic asthma (≥150 cells per µL at screening or ≥300 cells per µL in past year)	Considerable improvement in asthma exacerbations and symptoms; mild improvement in FEV_1 and steroid sparing	FDA approved for severe eosinophilic asthma
Reslizumab (Teva Pharmaceuticals, Petah Tikva, Israel)	IL-5	Intravenous, 3·0 mg/kg, Q4 weeks	Moderate to severe eosinophilic asthma (≥400 cells per µL)	Considerable improvement in asthma exacerbations; mild improvement in FEV_1 and symptoms	FDA approved for severe eosinophilic asthma
Benralizumab (MedImmune, Gaithersburgh, USA; and AstraZeneca, Cambridge, UK)	IL-5RA	Subcutaneous, 30 mg, Q8 weeks	Severe eosinophilic asthma (≥300 cells per µL)	Considerable improvement in asthma exacerbations; mild improvement in FEV_1 and steroid sparing	FDA approved for severe eosinophilic asthma
Lebrikizumab (Genentech, San Francisco, USA; and Roche, Basel, Switzerland)	IL-13	Subcutaneous, 38–125 mg, Q4 weeks	Severe asthma with periostin concentrations ≥50 ng/mL or blood eosinophils ≥300 cells per µL	Mild improvement in asthma exacerbations	No longer in development for asthma
Pitrakinra (Amgen, Thousand Oaks, USA)	IL-4RA	Subcutaneous, 25 mg once a day or 60 mg nebulised twice a day	Atopic asthma	Modest efficacy in allergen challenge model	No longer in development for asthma
Dupilumab (Regeneron, Tarrytown, USA; and Sanofi, Paris, France)	IL-4RA	Subcutaneous, 200 or 300 mg, Q4 weeks	Moderate to severe eosinophilic asthma (>300 cells per µL)	Considerable improvement in asthma exacerbations, FEV_1, and symptoms; mild improvement in steroid sparing	FDA approved for moderate to severe eosinophil asthma or oral corticosteroid-dependent asthma
Tezepelumab (Amgen; and MedImmune)	TSLP	Subcutaneous, 70 mg Q4 weeks, 210 mg Q4 weeks, or 280 mg Q2 weeks	Moderate to severe asthma	Considerable improvement in asthma exacerbations; mild improvement in FEV_1 and symptoms	Ongoing phase 3 trial
REGN3500 (Regeneron)	IL-33	Subcutaneous, dose to be determined	Moderate to severe eosinophilic asthma (≥300 cells per µL)	Mild improvement in loss of asthma control and FEV_1	Recently completed phase 2B trial

FEV_1=forced expiratory volumes in 1 s. FDA=US Food and Drug Administration. Q2=every 2 weeks. Q4=every 4 weeks. Q8=every 8 weeks.

Lancet 2020; 395: 371–83

Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials

Jonathan A Bernstein*, J Christian Virchow*, Kevin Murphy, Jorge Fernando Maspero, Joshua Jacobs, Yochai Adir, Marc Humbert, Mario Castro, Douglas A Marsteller, Jennifer McElhattan, Lisa Hickey, Margaret Garin, Rebecca Vanlandingham, Guy Brusselle

Summary

Background Reslizumab 3 mg/kg administered intravenously is approved for the treatment of severe eosinophilic asthma. We assessed the safety and efficacy of subcutaneous reslizumab 110 mg in two trials in patients with uncontrolled severe asthma and increased blood eosinophils. The aim was to establish whether subcutaneous reslizumab 110 mg can reduce exacerbation rates in these patients (study 1) or reduce maintenance oral corticosteroid dose in patients with corticosteroid-dependent asthma (study 2).

Methods Both studies were randomised, double-blind, placebo-controlled, phase 3 studies. Entry criteria for study 1 were uncontrolled severe asthma, two or more asthma exacerbations in the previous year, a blood eosinophil count of 300 cells per µL or more (including no more than 30% patients with an eosinophil count <400 cells/µL), and at least a medium dose of inhaled corticosteroids with one or more additional asthma controllers. Patients in study 2 had severe asthma, a blood eosinophil count of 300 cells per µL or more, daily maintenance oral corticosteroid (prednisone 5–40 mg, or equivalent), and high-dose inhaled corticosteroids plus another controller. Patients were randomly assigned (1:1) to subcutaneous reslizumab (110 mg) or placebo once every 4 weeks for 52 weeks in study 1 and 24 weeks in study 2. Patients and investigators were masked to treatment assignment. Primary efficacy outcomes were frequency of exacerbations during 52 weeks in study 1 and categorised percentage reduction in daily oral corticosteroid dose from baseline to weeks 20–24 in study 2. Primary efficacy analyses were by intention to treat, and safety analyses included all patients who received at least one dose of study treatment. These studies are registered with ClinicalTrials.gov, NCT02452190 (study 1) and NCT02501629 (study 2).

Findings Between Aug 12, 2015, and Jan 31, 2018, 468 patients in study 1 were randomly assigned to placebo (n=232) or subcutaneous reslizumab (n=236), and 177 in study 2 to placebo (n=89) or subcutaneous reslizumab (n=88). In study 1, we found no significant difference in the exacerbation rate between reslizumab and placebo in the intention-to-treat population (rate ratio 0·79, 95% CI 0·56–1·12; p=0·19). Subcutaneous reslizumab reduced exacerbation frequency compared with placebo in the subgroup of patients with blood eosinophil counts of 400 cells per µL or more (0·64, 95% CI 0·43–0·95). Greater reductions in annual exacerbation risk (p=0·0035) and longer time to first exacerbation were observed for patients with higher trough serum reslizumab concentrations. In study 2, we found no difference between placebo and fixed-dose subcutaneous reslizumab in categorised percentage reduction in daily oral corticosteroid dose (odds ratio for a lower category of oral corticosteroid use in the reslizumab group *vs* the placebo group, 1·23, 95% CI 0·70–2·16; p=0·47). The frequency of adverse events and serious adverse events with reslizumab were similar to those with placebo in both studies.

Interpretation Fixed-dose (110 mg) subcutaneous reslizumab was not effective in reducing exacerbation frequency in patients with uncontrolled asthma and increased blood eosinophils (≥300 cells/µL), or in reducing the daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe eosinophilic asthma. Higher

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See Online/Comment
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Subcutaneous Reslizumab in Severe Asthma

Entry criteria for study 1 (exacerbation study) uncontrolled severe asthma,

- ≥ 2 exacerbations in the previous year,
- a blood eosinophil count ≥ 300 cells/µL (including no more than 30% patients with Eos <400 cells/µL),
- at least a medium dose of ICS with ≥ 1 additional asthma controllers

Entry criteria for study 2 (steroids sparing study) severe asthma

- a blood eosinophil count ≥ 300 cells/µL,
- daily maintenance oral corticosteroid (prednisone 5–40 mg, or equivalent),
- high-dose ICS plus another controller

	Asthma exacerbation study (study 1)		Oral corticosteroid-sparing study (study 2)	
	Placebo (n=230)*	Subcutaneous reslizumab (n=234)*	Placebo (n=89)	Subcutaneous reslizumab (n=88)
Age, years	44·8 (17·7)	46·9 (17·6)	53·1 (12·0)	55·5 (12·7)
Sex, n (%)				
Men	102 (44%)	90 (38%)	32 (36%)	28 (32%)
Women	128 (56%)	144 (62%)	57 (64%)	60 (68%)
Weight, kg				
Mean (SD)	76·9 (18·3)	78·3 (19·4)	82·7 (18·9)	79·6 (21·4)
Median (IQR)	75·0 (23·6)	77·5 (25·2)	82·0 (20·7)	75·6 (26·2)
BMI, kg/m²	27·4 (6·1)	28·3 (6·2)	29·9 (6·3)	29·4 (8·0)
FEV_1 reversibility, %	24·6% (21·3)	22·8% (17·1)	24·6% (20·5)	26·0% (25·9)
Pre-bronchodilator FEV_1, L	2·1 (0·9)	2·0 (0·8)	1·7 (0·7)	1·6 (0·7)
FEV_1, % predicted	65·0% (19·7)	64·4% (18·3)	58·7% (19·8)	55·2% (16·7)
ACQ-6 score	2·6 (0·8)	2·6 (0·8)	2·4 (1·2)	2·3 (1·1)
AQLQ score	4·4 (1·0)	4·3 (1·0)	4·4 (1·2)	4·4 (1·1)
Blood eosinophil count, cells/μL†	737 (484)	787 (538)	521 (491)	479 (388)
Eosinophil count				
<300 cells/μL	0	1 (<1%)	33 (37%)	28 (32%)
≥300 to <400 cells/μL	42 (18%)	48 (21%)	13 (15%)	19 (22%)
≥400 cells/μL	188 (82%)	185 (79%)	43 (48%)	41 (47%)
Phadiatop test				
Positive	154 (67%)	159 (68%)	47 (53%)	47 (53%)
Missing	12 (5%)	4 (2%)	3 (3%)	1 (1%)
Former smoker	28 (12%)	31 (13%)	13 (15%)	12 (14%)
Age at asthma onset, years	27·5 (19·2)	29·0 (19·9)	32·9 (17·9)	32·8 (17·7)
Time since diagnosis, years	17·5 (13·5)	18·0 (14·0)	20·1 (14·2)	22·3 (16·0)
Asthma exacerbations requiring systemic corticosteroids in the past 12 months	2·3 (0·8)	2·4 (1·0)	1·85 (1·2)	2·1 (1·6)
Inhaled corticosteroid	229 (>99%)‡	232 (>99%)‡	89 (100%)	88 (100%)
High-dose§	98 (43%)	99 (42%)	70 (79%)¶	70 (80%)¶
Medium-dose§	122 (53%)	128 (55%)	17 (19%)	18 (20%)
Long-acting β agonist	218 (95%)	224 (96%)	84 (94%)	87 (99%)
Oral corticosteroid	15 (7%)	15 (6%)	89 (100%)	88 (100%)
Aspirin sensitivity‖	23 (10%)	26 (11%)	7 (8%)	5 (6%)
Chronic rhinosinusitis with nasal polyps‖	38 (17%)	37 (16%)	13 (15%)	10 (11%)

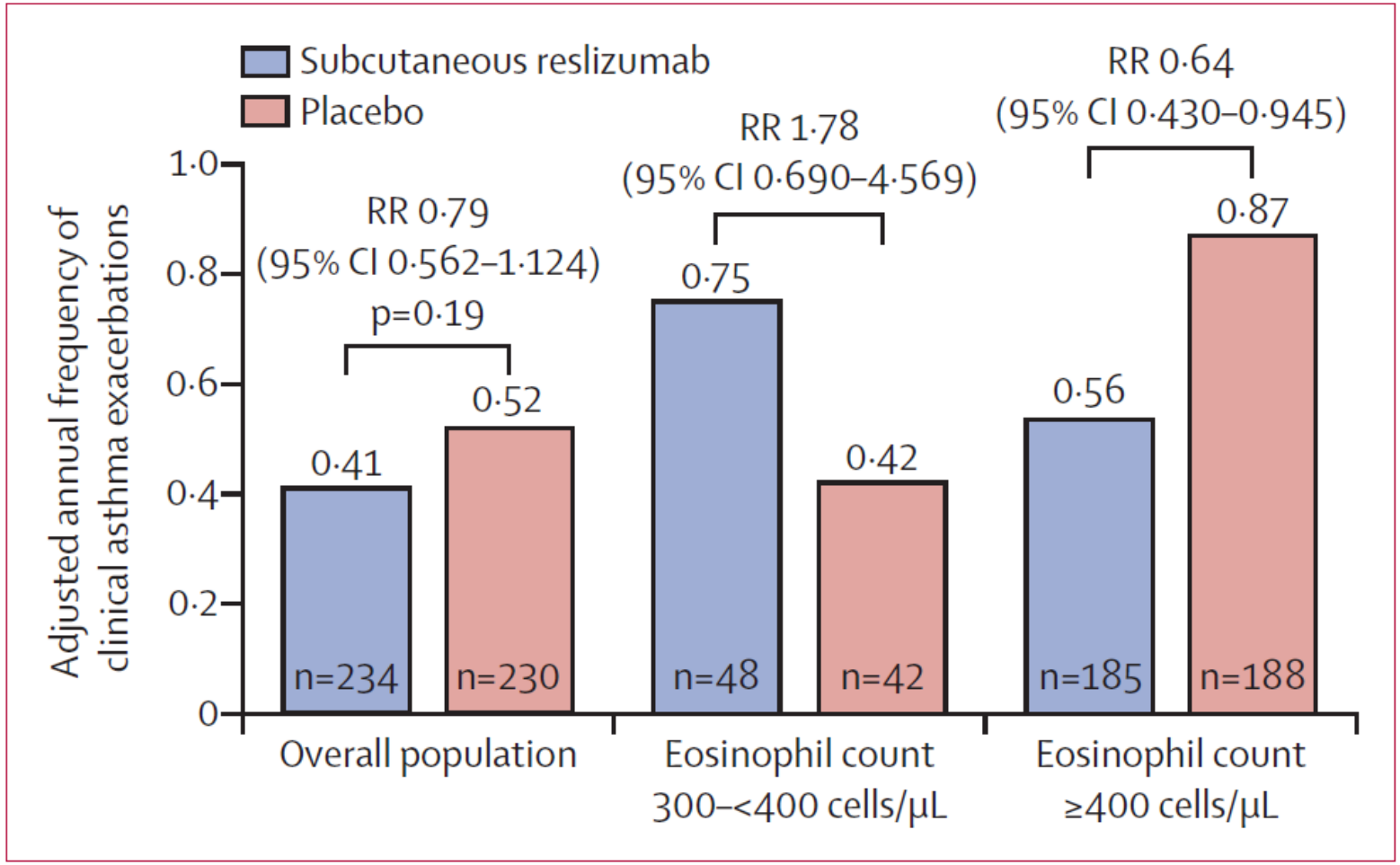


Figure 2: **Adjusted frequency of clinical asthma exacerbations during 52 weeks in the intention-to-treat population and in subgroups of patients based on baseline eosinophil counts in study 1**

Primary and key secondary efficacy outcomes in study 1

	ITT population		Eosinophil count 300 to <400 cells/μL		Eosinophil count ≥400 cells/μL	
	Placebo (n=230)	Subcutaneous reslizumab (n=234)	Placebo (n=42)	Subcutaneous reslizumab (n=48)	Placebo (n=188)	Subcutaneous reslizumab (n=185)
Adjusted CAEs excluding exacerbation duration from the offset*	0·52	0·41	0·42	0·75	0·87	0·56
RR (95% CI) for reslizumab *vs* placebo	..	0·79 (0·56 to 1·12)	..	1·78 (0·69 to 4·57)	..	0·64 (0·43 to 0·95)
p value	..	0·19	..	..	..	..
Change in pre-bronchodilator FEV_1 at 52 weeks, L, LSM (SE)†	0·23 (0·040)	0·37 (0·039)	0·25 (0.093)	0·38 (0.092)	0·26 (0.042)	0·41 (0.041)
Absolute increase (95% CI) *vs* placebo	..	0·14 (0·057 to 0·23)	..	0·13 (–0·053 to 0·31)	..	0·15 (0·054 to 0·25)
Change in ACQ-6 at 52 weeks, LSM (SE)‡	–1·14 (0·080)	–1·22 (0·078)	–1·36 (0.19)	–1·27 (0.19)	–1·05 (0.084)	–1·18 (0.081)
Absolute change (95% CI) *vs* placebo	..	–0·09 (–0·27 to 0·10)	..	0·09 (–0·31 to 0·48)	..	–0·12 (–0·32 to 0·083)
Change in AQLQ+12 at 52 weeks, LSM (SE)*§	1·06 (0·089)	1·14 (0·087)	1·25 (0·20)	1·30 (0·20)	1·02 (0.093)	1·11 (0.091)
Absolute increase (95% CI) *vs* placebo	..	0·08 (–0·11 to 0·27)	..	0·05 (–0·38 to 0·49)	..	0·08 (–0·14 to 0·30)

ACQ-6=Asthma Control Questionnaire-6. AQLQ+12=Asthma Quality of Life Questionnaire for patients aged ≥12 years. CAE=clinical asthma exacerbation. ITT=intention-to-treat. LSM=least squares mean. RR=rate ratio. *For this analysis, the offset variable was calculated as the logarithm of treatment duration minus the summed duration of exacerbations during the treatment period. †Minimal clinically important difference was a change of 0·1 L. ‡Minimal clinically important difference was change in score of –0·5. §Minimal clinically important difference was change in score of 0·5.

Oral corticosteroid outcomes in the intention-to-treat population in study 2

Categorised percentage oral corticosteroid dose reduction (5-level response) at weeks 20–24*		
90 to 100%	20 (22%)	18 (20%)
75 to <90%	4 (4%)	8 (9%)
50 to <75%	8 (9%)	13 (15%)
>0 to <50%	9 (10%)	7 (8%)
No decrease†	48 (54%)	42 (48%)
Reslizumab *vs* placebo	..	1·23 (0·70–2·16)
p value	..	0·47
Categorised oral corticosteroid dose reduction (responder analyses) at weeks 20–24		
At least 50% reduction from baseline	32 (36%)	39 (44%)
Reslizumab *vs* placebo	..	1·45 (0·79–2·68)
Oral corticosteroid dose ≤5 mg	34 (38%)	37 (42%)
Reslizumab *vs* placebo	..	1·19 (0·63–2·23)
Oral corticosteroid dose 0 mg	20 (22%)	18 (20%)
Reslizumab *vs* placebo	..	0·82 (0·37–1·82)
At least 5 mg reduction from baseline	31 (35%)	36 (41%)
Reslizumab *vs* placebo	..	1·36 (0·72–2·56)

Data are n (%) or OR (95% CI), unless otherwise indicated. OR=odds ratio. *All data were included; missing data were included as non-responders. †No decrease in oral corticosteroid dose, loss of baseline asthma control during weeks 20–24, or discontinuation from study drug.

Reslizumab given as a fixed-dose (110 mg) subcutaneous injection was not effective in reducing exacerbation rates in patients with uncontrolled asthma and an increased blood eosinophil count (≥300 cells/μL), or in reducing the daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe eosinophilic asthma.

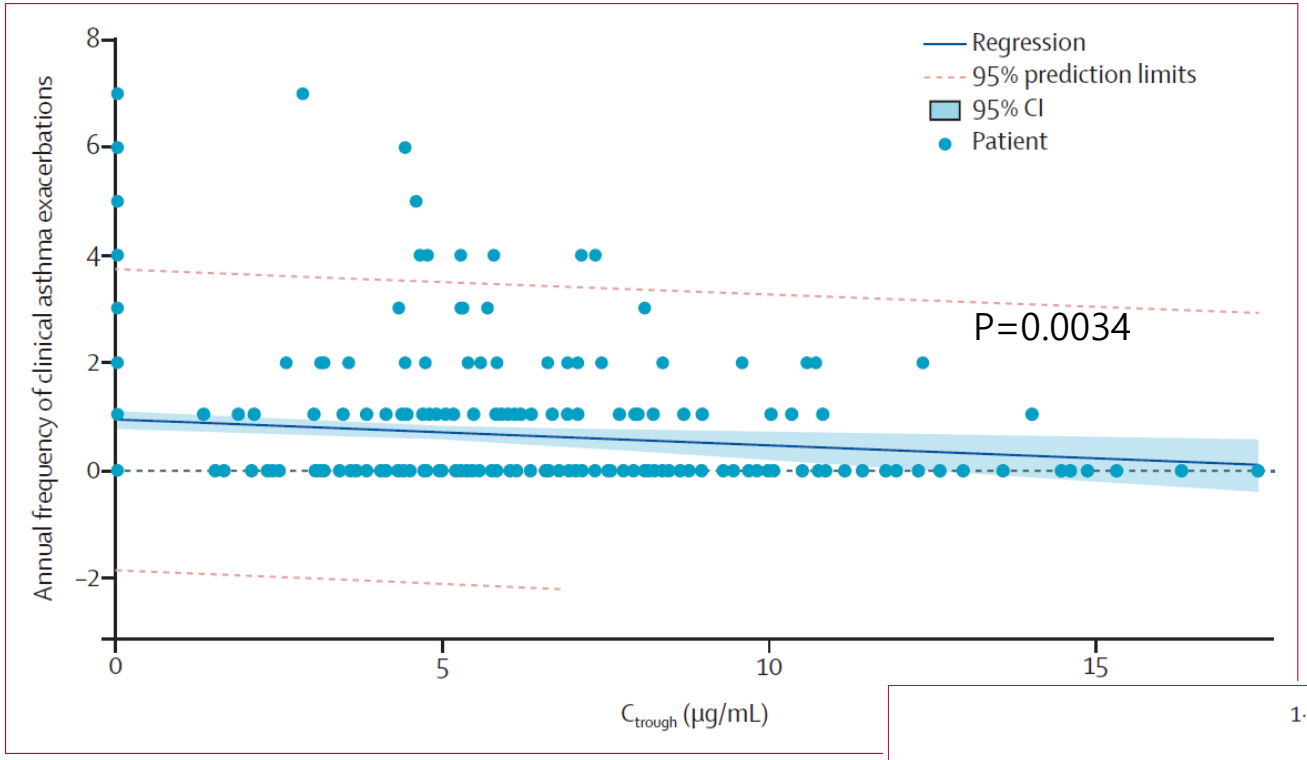
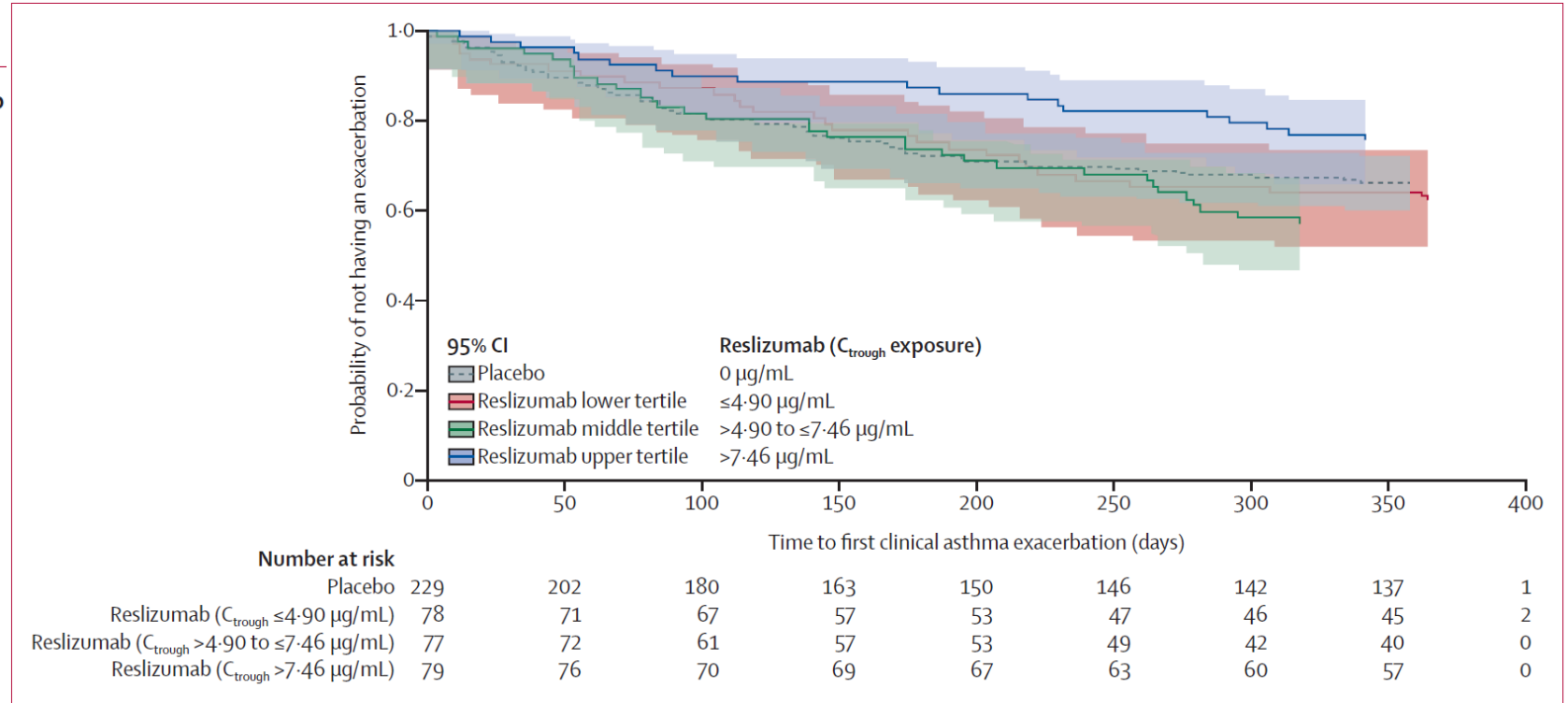


Figure 5: Relationship between trough serum concentration of reslizumab asthma exacerbations in study 1

the magnitude of effect of fixed-dose subcutaneous reslizumab on rates of clinical asthma exacerbations was lower than the 50–59% reduction observed with the higher reslizumab exposures associated with weight-based dosing of intravenous reslizumab.



JAMA Internal Medicine | Original Investigation

Effect of a Self-management Support Intervention on Asthma Outcomes in Older Adults
The SAMBA Study Randomized Clinical Trial

Alex D. Federman, MD, MPH; Rachel O'Conor, PhD; Irina Mindlis, MPH; Jamillah Hoy-Rosas, MPH, RD; Diane Hauser, MPA; Joseph Lurio, MD; Nandini Shroff, MPH; Ray Lopez, BA; Joel Erblich, PhD; Michael S. Wolf, PhD, MPH; Juan P. Wisnivesky, MD, DrPH

Supplemental content

IMPORTANCE Older adults with asthma have worse control and outcomes than younger adults. Interventions to address suboptimal self-management among older adults with asthma are typically not tailored to the specific needs of the patient.

to participate, and were randomized to 1 of 3 groups: home-based intervention, clinic-based intervention, or control (usual care). A total of 391 patients received the allocated treatment

INTERVENTIONS Screening for psychosocial, physical, cognitive, and environmental barriers to asthma control and self-management with actions to address identified barriers. The intervention was delivered in the home or primary care practices by asthma care coaches.

MAIN OUTCOMES AND MEASURES Primary outcomes were the Asthma Control Test, Mini Asthma Quality of Life Questionnaire, Medication Adherence Rating Scale, metered dose inhaler technique, and emergency department visits for asthma care. Primary analyses compared intervention (home or clinic based) with usual care.

RESULTS Of the 391 patients who received treatment, 58 (15.1%) were men, and the mean (SD) age was 67.8 (7.4) years. After accounting for baseline scores, scores on the asthma control test were better in the intervention groups vs the control group (difference-in-differences at 3 months, 1.2; 95% CI, 0.2-2.2; $P = .02$; 6 months, 1.0; 95% CI, 0.0-2.1; $P = .049$; 12 months, 0.6; 95% CI, −0.5 to 1.8; $P = .28$; and overall, $\chi^2 = 13.4$, with 4 degrees of freedom; $P = .01$). Emergency department visits were lower at 12 months for the intervention groups vs the control group (16 [6.2%] vs 17 [12.7%]; $P = .03$; adjusted odds ratio, 0.8; 95% CI, 0.6-0.99; $P = .03$). Statistically significant improvements were observed for the intervention vs control patients in quality of life (overall effect: $\chi^2 = 10.5$, with 4 degrees of freedom; $P = .01$), medication adherence (overall effect: $\chi^2 = 9.5$, with 4 degrees of freedom; $P = .049$), and inhaler technique (metered-dose inhaler technique, correctly completed steps at 12 months, median [range]: 75% [0%-100%] vs 58% [0%-100%]). No significant differences in outcomes were observed between patients receiving the intervention in home vs practice settings.

CONCLUSIONS AND RELEVANCE An intervention directed by patients' needs and barriers improved asthma outcomes and self-management behaviors among older adults.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02316223

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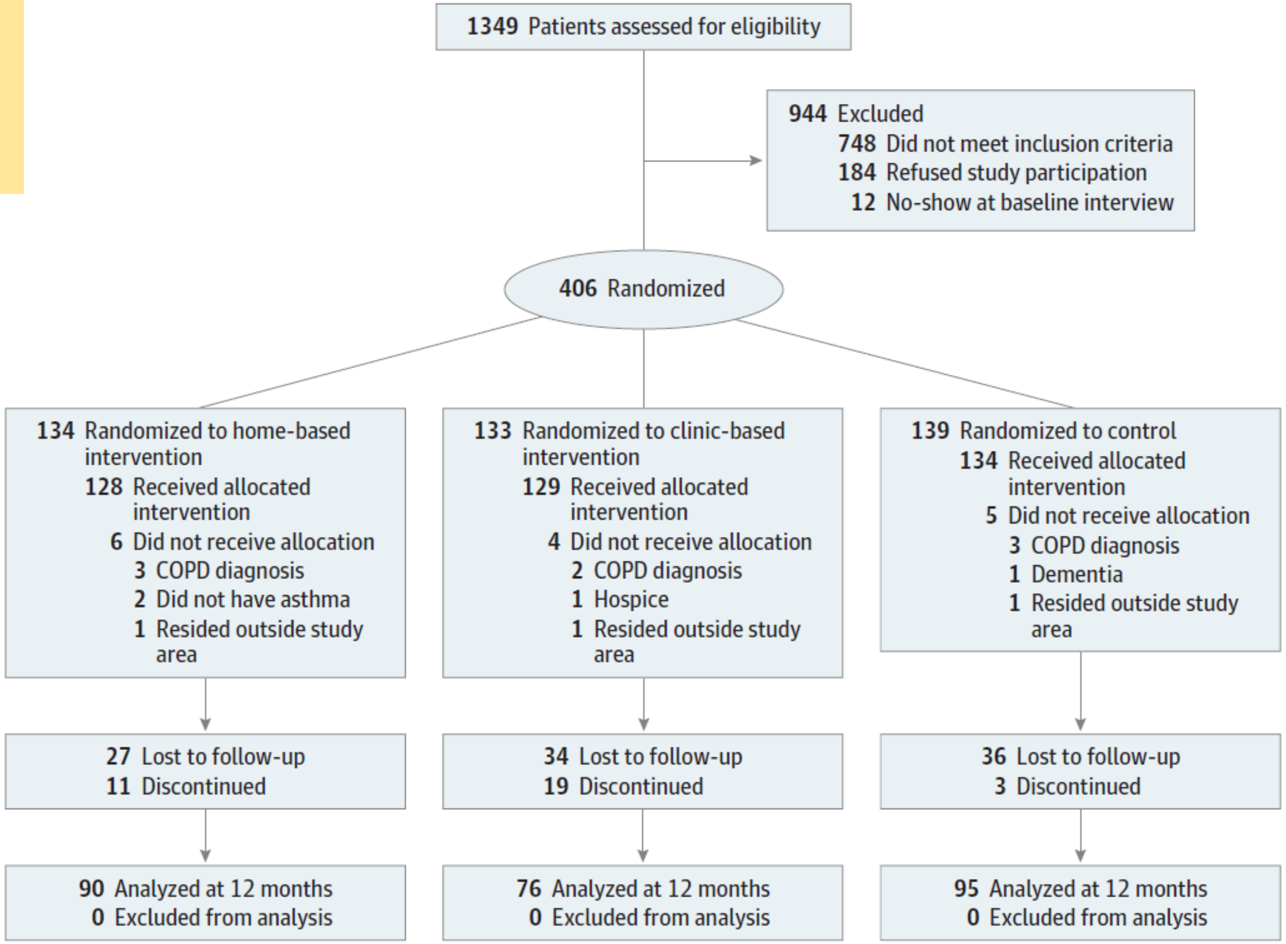
To test the effect of a comprehensive, patient-tailored asthma self-management support intervention for older adults on clinical and self-management outcomes.

The SAMBA Study RCT

- Three-arm randomized clinical trial
-
-
-



JAMA Intern Med. 2019;179(8):1113-1121

SAMBA (Supporting Asthma Management Behaviors in Adults)

COMPREHENSIVENESS

SAMBA embraces the enormous research literature demonstrating that socioeconomic, psychosocial, cognitive, environmental, and health status-related factors influence chronic illness self-care and health outcomes in adults. Improvements in self-care behaviors and health outcomes can only be achieved by addressing an individual's multiple barriers to achieving good outcomes.

EFFICIENCY

The attention of individuals we seek to support and the resources needed to support them are limited. Identification of barriers and steps taken to address them can be performed systematically and in a targeted fashion to achieve greater efficiency than that achieved by typical social work or care coach interventions.

SUSTAINABILITY

To succeed, care management/ coaching models must be flexible to operate smoothly within environments with varying workflows and cultures and support new models of healthcare that strive for value over volume. Achieving these goals requires the collaboration of the key stakeholders: patients, clinicians, academics, administrators, community and hospital-based institutions.

ENGAGEMENT

Engagement is the cornerstone of success for care management/care coaching programs. Soliciting the patient's wishes and acting on them is of paramount importance.

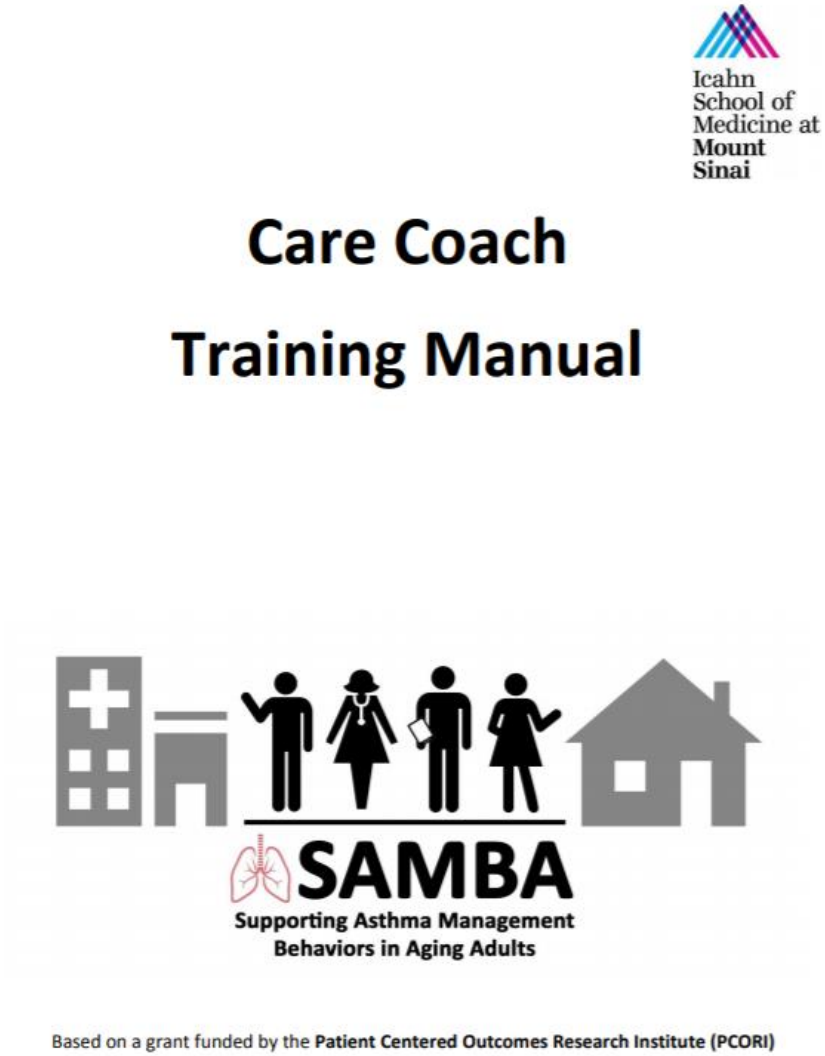
https://sambaforasthma.com/

Example of the SAMBA Intervention

(1) screening to identify barriers to asthma self-management

(2) targeted actions to address the barriers, and

(3) Reinforcement over time



Screening

During the initial encounter, the Asthma Care Coach (ACC) administers the screening assessment and identifies the following barriers to asthma control: poor inhaler technique, intermittent use of fluticasone propionate, and evidence of cockroach infestation in the home. Reasons for intermittent medication use identified through screening are patient's belief that asthma is an intermittent (vs chronic) disease and the cost of the medication.

Targeted Actions

Following screening during the initial and subsequent encounters, the ACC trains the patient on proper inhaler technique, provides brief asthma education focused exclusively on the chronic nature of asthma and the different roles and use of controller (eg, fluticasone) and rescue (albuterol) medications, advises the patient to discuss cost problems with her physician, and makes a referral for the New York City–sponsored pest remediation service available for residents of low-income households. The ACC faxes a summary of identified issues and actions to the patient's primary care physician.

Reinforcement

During subsequent encounters over 12 months, the ACC observes the patient's inhaler technique and corrects it if needed, reassesses medication adherence and the underlying contributing factors, and addresses new problems as they arise.

SAMBA indicates Supporting Asthma Self-Management Behaviors in Older Adults.

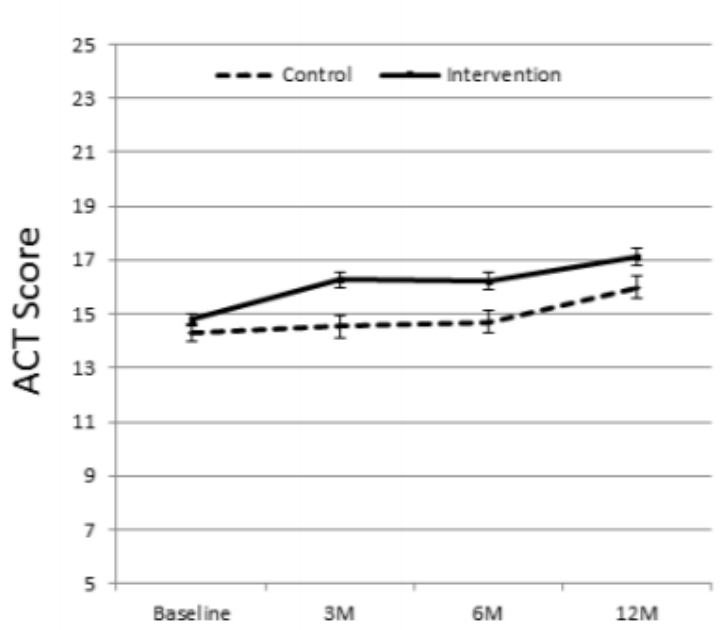
Table 2. Primary Outcomes: Intervention vs Control Group

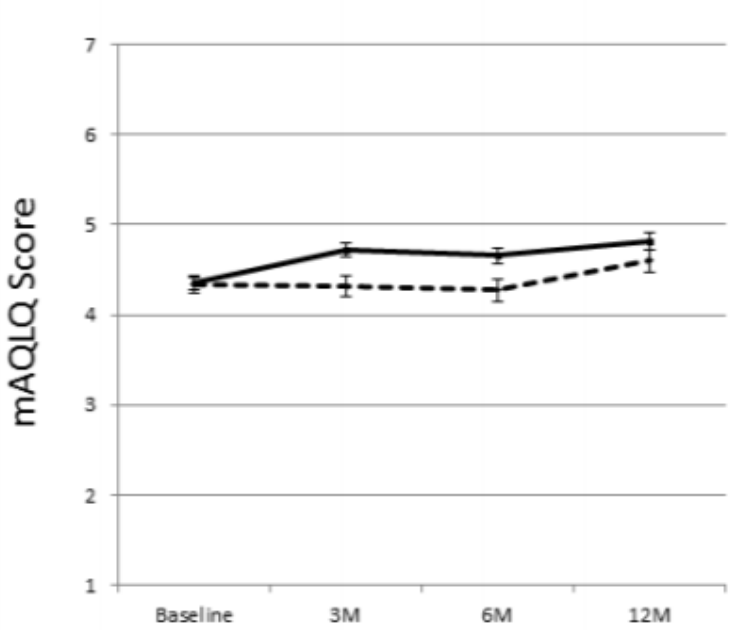
Characteristic	Intervention Value, Mean (SD)	Δ (95% CI)[a]	*P* Value[a]
Asthma Control Test score			
Baseline	14.8 (3.9)		
3 mo	16.2 (4.4)	1.4 (0.8 to 2.0)	<.001
6 mo	16.2 (4.4)	1.4 (0.8 to 2.1)	<.001
12 mo	17.1 (4.7)	2.2 (1.5 to 2.9)	<.001
Overall effect[b]			
Mini Asthma Quality of Life score			
Baseline	4.3 (1.2)		
3 mo	4.7 (1.2)	0.4 (0.2 to 0.5)	<.001
6 mo	4.7 (1.3)	0.3 (0.1 to 0.5)	<.001
12 mo	4.8 (1.3)	0.5 (0.3 to 0.7)	<.001
Overall effect[b]			
Medication Adherence Rating scale score			
Baseline			
3 mo			
6 mo			
12 mo			
Overall e			
MDI tech complete (range)			
Baseline			
12 mo			
Patients departm			
Baseli			
12 mo	6.2	0.9 (0.7 to 1.0)[c]	.02

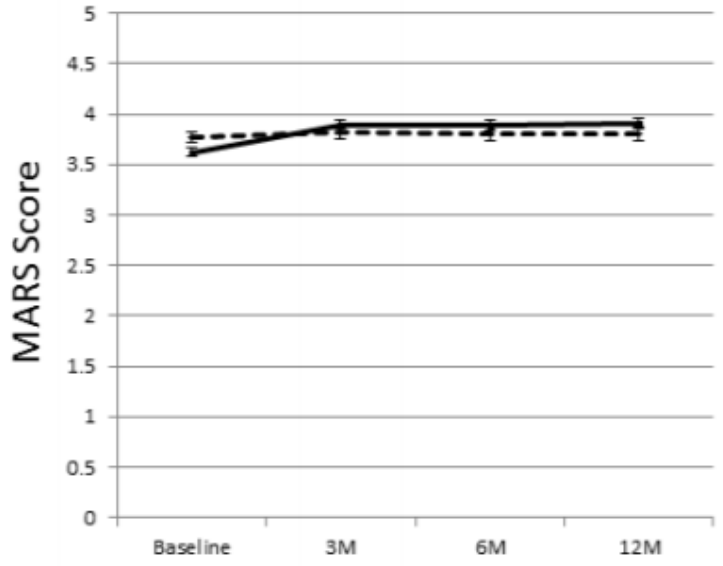
Table 3. Intervention Effect Sizes

Characteristic	Effe 3 mo
Control and quality of life	
Asthma Control Test	0.47
Mini Asthma Quality of Life Questionnaire	0.34
Self-management	
Medication Adherence Rating scale	0.11
Metered-dose inhaler technique	NA

ACT, Asthma Control Test; mAQLQ, mini-Asthma Quality of Life Questionnaire; MARS, Medication Adherence Rating Scale.







Overall effect

(intervention vs. control)

- **ACT, p=.01**
- **mAQLQ, p=.03**
- **MARS, p=.049**

Home-based vs. Clinic-based Intervention

	Home-based Intervention			Clinic-based Intervention			Home Effect	
	Value	Δ (95% CI)*	P*	Value	Δ (95% CI)*	P*	DiD (95% CI)*	P*
Asthma Control Test score, *mean (sd)*								
Baseline	15.0 (3.8)	-	-	14.6 (4.0)	-	-	-	-
3 months	16.6 (4.4)	1.6 (0.8, 2.4)	<.001	15.7 (4.4)	1.2 (0.3, 2.1)	.003	0.5 (-1.6, 0.5)	.35
6 months	16.8 (4.3)	1.6 (0.7, 2.5)	<.001	15.8 (4.4)	1.2 (0.3, 2.1)	.02	0.1 (-1.2, 1.0)	.87
12 months	17.4 (4.8)	2.5 (1.5, 3.4)	<.001	16.9 (4.7)	1.9 (0.8, 3.0)	<.001	0.3 (-1.5, 1.0)	.68
Overall effect†							$\chi^2(4)=3.2$	.52
Mini-Asthma Quality of Life score, *mean (sd)*								
Baseline	4.4 (1.2)	-	-	4.4 (1.2)	-	-	-	-
3 months	4.8 (1.8)	0.5 (0.3, 0.7)	<.001	4.6 (1.2)	0.3 (0.0, 0.5)	.03	0.2 (-0.2, 0.6)	.31
6 months	4.9 (1.2)	0.5 (0.2, 0.7)	<.001	4.5 (1.4)	0.1 (-0.1, 0.4)	.66	0.4 (0.1, 0.8)	.02
12 months	4.9 (1.3)	0.6 (0.4, 0.8)	<.001	4.8 (1.4)	0.3 (0.1, 0.6)	.01	0.2 (-0.2, 0.5)	.29
Overall effect†							$\chi^2(4)=6.7$	.15
Medication Adherence Rating Scale score, *mean (sd)*								
Baseline	3.6 (0.7)	-	-	3.7 (0.6)	-	-	-	-
3 months	3.9 (0.6)	0.3 (0.2, 0.5)	<.001	3.9 (0.6)	0.2 (0.0, 0.4)	.003	0.1 (-0.2, 0.3)	.58
6 months	3.9 (0.7)	0.3 (0.1, 0.5)	.003	4.0 (0.7)	0.3 (0.1, 0.4)	<.001	-0.1 (-0.3, 0.2)	.51
12 months	3.8 (0.8)	0.2 (0.0, 0.4)	.01	4.0 (0.7)	0.4 (0.2, 0.5)	<.001	-0.1 (-0.4, 0.2)	.44
Overall effect†							$\chi^2(4)=2.7$	.62
MDI technique, %								
12 months	7.7%	0.7 (0.5, 1.0)‡	.03	6.2%	0.9 (0.7, 1.2)‡	.70	1.3 (0.8, 20)§	.31

- No significant interactions of assignment to the home-based arm and physical impairment, cognitive impairment, or depression
- However, this study was not powered to test noninferiority of the 2 intervention arms

Summary: the SAMBA Study

- Identification of barriers to asthma self-management with targeted support is an effective method for improving proper asthma self-care, control, and quality of life among older adults.

- This study demonstrated that the value of patient centeredness and care coaching in supporting older adults with asthma and for ongoing efforts to engage patients in care delivery design and personalization.

Summary

- **Updates in GINA guideline (www.ginasthma.org)**
  - Recommendation in COVID-19 pandemic
  - Anti-inflammatory reliever in mild asthma

- **Updated data of ICS/FOR in asthma**
  - Real-world data of ICS/FOR in mild asthma
    - Novel START
    - PRACTICAL
  - Triple therapy with a single inhaler (TRIMARAN, TRIGGER)

- **Considerations in treatment of asthma**
  - ICS in non-eosinophilic airway inflammation (Novel START & SIENA study)
  - Montelukast: black box-warning
  - Biologics – reslizumab (SC)
  - Self-management support intervention in older patients with asthma (SAMBA study)

Thanks for your attention

CONCISE CLINICAL REVIEW

Inhaled Corticosteroid Therapy in Adult Asthma

Time for a New Therapeutic Dose Terminology

Richard Beasley[1,2,3], James Harper[1], Grace Bird[1], Ingrid Maijers[1], Mark Weatherall[3,4], and Ian D. Pavord[5]

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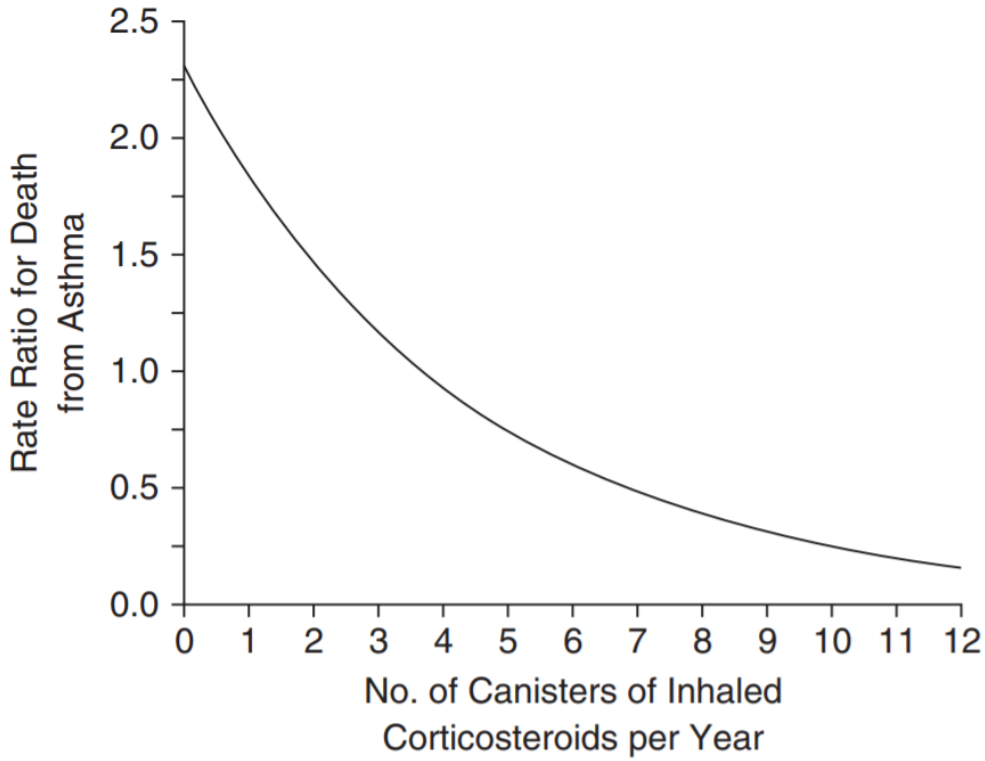
Table 1. Low, Medium, and High Doses of Inhaled Corticosteroids in Adults and Adolescents, Defined by Global Initiative for Asthma Guidelines

Inhaled Corticosteroid	Dose (μg/d)			Bioequivalence*
	Low	Medium	High	
Beclomethasone dipropionate (CFC)	200–500	>500–1,000	>1,000	1.0
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400	2.5
Budesonide (DPI)	200–400	>400–800	>800	1.25
Ciclesonide (HFA)	80–160	>160–320	>320	3.125
Fluticasone propionate (HFA)	100–250	>250–500	>500	2.0
Fluticasone furoate (DPI)	100	NA	200	5.0
Mometasone furoate	110–220	>220–440	>440	2.25

Definition of abbreviations: CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; NA = not applicable.
*Bioequivalence compared with beclomethasone dipropionate, derived from the stated "high dose."

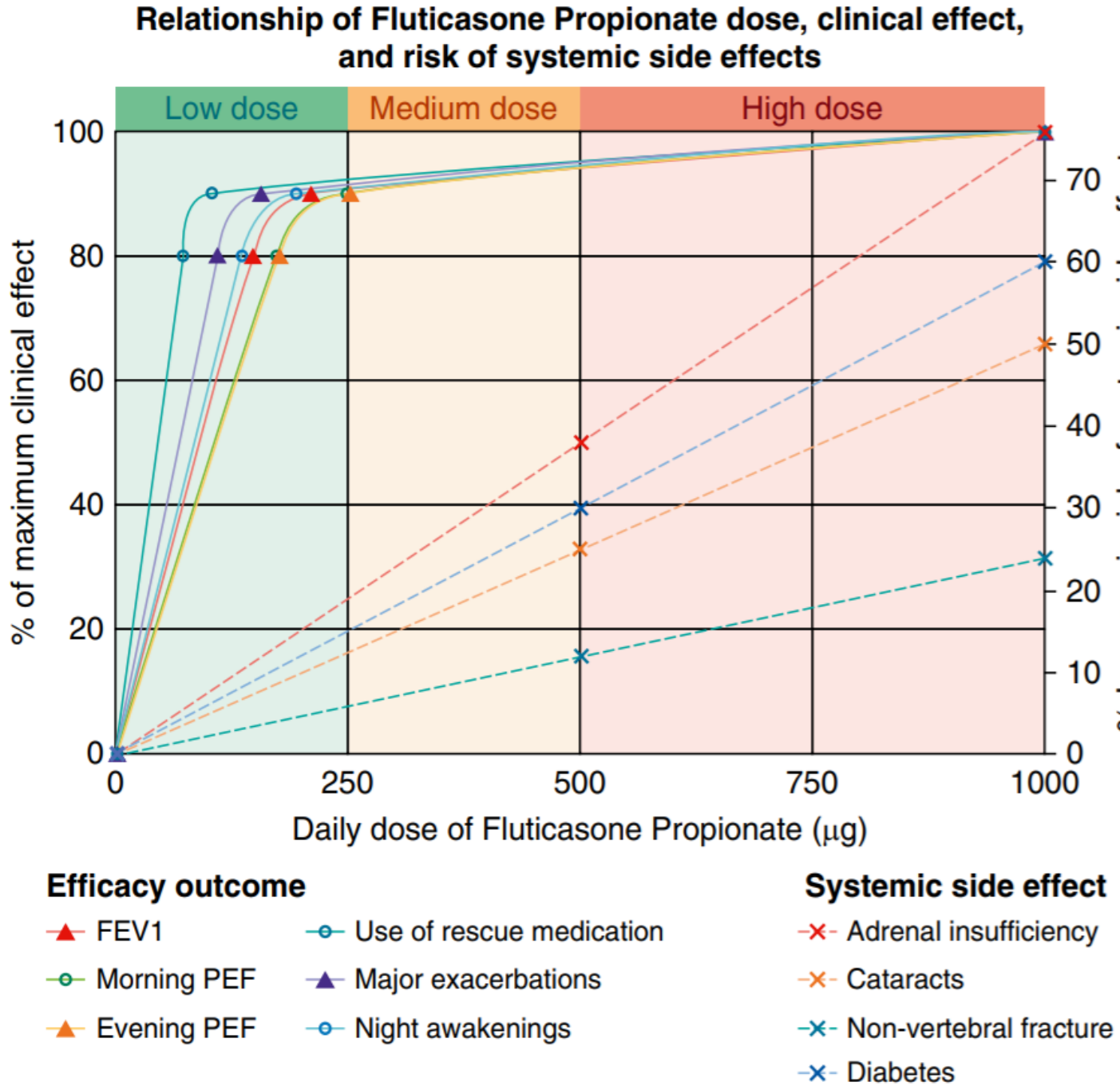


Am J Respir Crit Care Med Vol 199, Iss 12, pp 1471–1477, Jun 15, 2019

Table 5. Risk of Systemic Side Effects of Inhaled Corticosteroids

	Adrenal Insufficiency*	Cataracts	Nonvertebral Fracture	Diabetes†
500 μg/d increase in dose of FP or equivalent	1.38 (1.01–1.59)	1.25 (1.14–1.37)	1.12 (1.00–1.26)	1.30 (1.25–1.35)

Definition of abbreviation: FP = fluticasone propionate.
Derived from References 42–45. Data are shown as odds ratio (95% confidence interval) unless otherwise indicated.
*Adrenal function below the lower limit of the normal range.
†Adjusted rate ratio (95% confidence interval) determined for medium/moderate doses of 500–999 μg/d of FP.



Standard daily dose of ICS ?

- The classification of ICS by dose level using the current terminology of “low,” “medium,” and “high” is not evidence based, and clinical practice based on this terminology may lead to the prescription of inappropriately excessive doses of ICS, resulting in unnecessary systemic adverse effects.

- “standard daily dose,” which is defined as 200–250 mg of FP or equivalent, representing the dose at which about 80–90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity

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Balancing the Effect of Leukotrienes in Asthma

- Inflammation vs. its timely resolution
  - Distortion equilibrium between pro-inflammatory mediators vs SPM (specialized pro-resolving mediators)
  - SPM
    - Eicosanoid derived-lipoxins
    - omega-3–derived resolvins,
    - Protectins
    - Maresins
  - Lower lipoxins in severe asthma
    - Synthetomimetics of SPMs in resolution of inflammation and fibrosis
  - Maresin conjugates in tissue regeneration (MCTRs)
    - SPM sulfido-conjugates/CysLTs ratio in healthy lung (10:3) vs. diseased lung tissue (1:10)

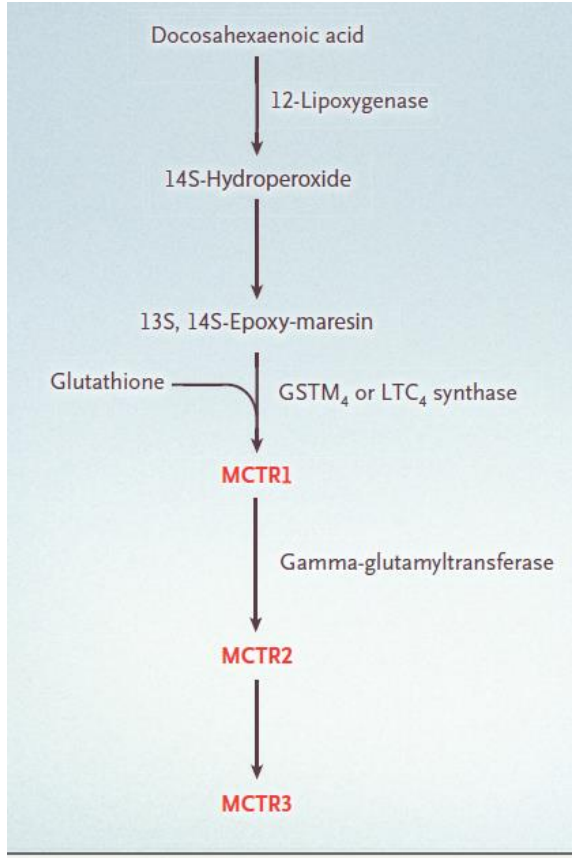
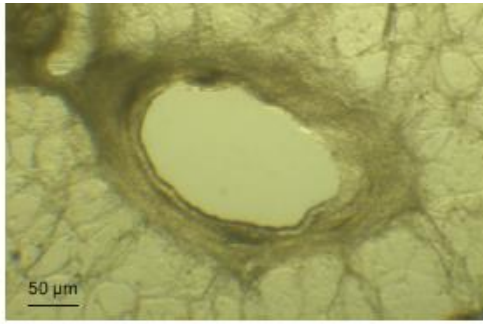
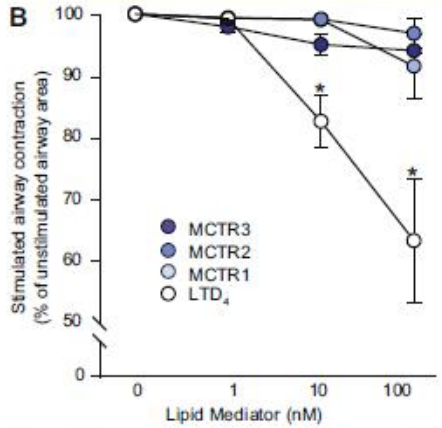
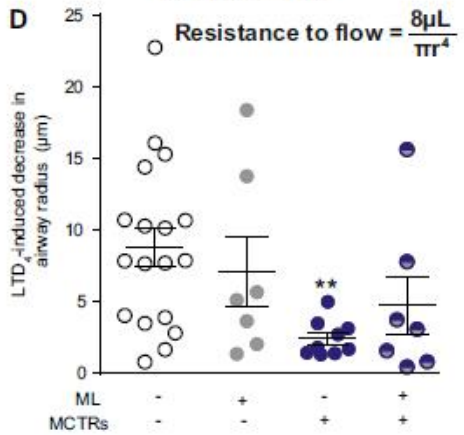


Figure 1. MCTR Biosynthesis.

(J Allergy Clin Immunol 2020;145:335-44.)







MCTRs Reduce Leukotrienes' Pro-phlogistic Lung Responses

DHA

↓ LOX (14S-lipoxygenation)

14S-hydroperoxy-intermediate

↓

13S,14S-epoxy-maresin

↓ GSTM4 or LTC4S

MCTR1

↓ GGT

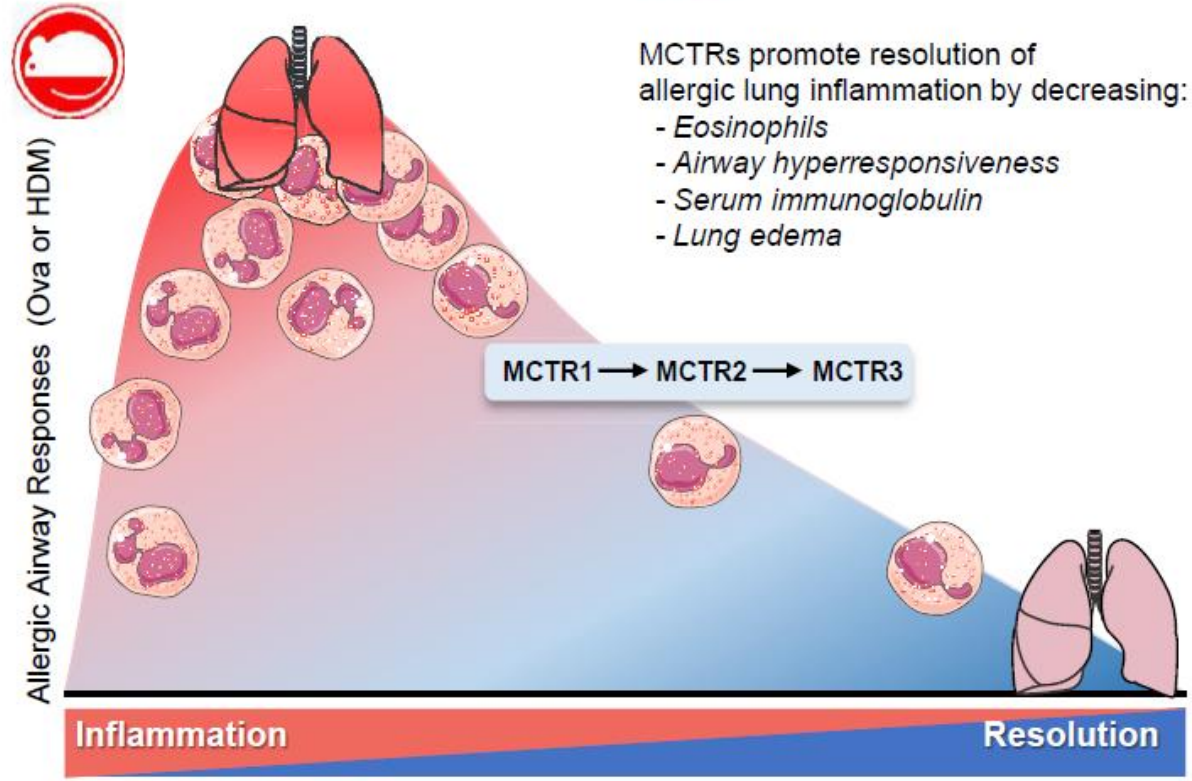
MCTR2

↓ DPEP

MCTR3

MCTR biosynthetic pathway

Human airways in precision cut lung sections



MCTRs promote resolution of allergic lung inflammation by decreasing:
- *Eosinophils*
- *Airway hyperresponsiveness*
- *Serum immunoglobulin*
- *Lung edema*

MCTR, maresin conjugate in tissue regeneration, LTD_4, leukotriene D_4; Ova, ovalbumin; HDM, house dust mite

(J Allergy Clin Immunol 2020;145:335-44.)

Balancing the Effect of Leukotrienes in Asthma

- MCTRs are abundant cysteinyl LMs in healthy human lung tissue.
- MCTRs block LTD_4-initiated airway contraction in lung sections.
- MCTRs selectively promoted the resolution of several airway responses, including hyperreactivity to methacholine, inflammation, and mucosal barrier permeability.
- It highlights, as an experimental therapeutic strategy, agonism of resolution as an alternative to antagonism of inflammation.

J Allergy Clin Immunol 2020;145:335-44