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Asthma School

Management of Mild Asthma

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Contents

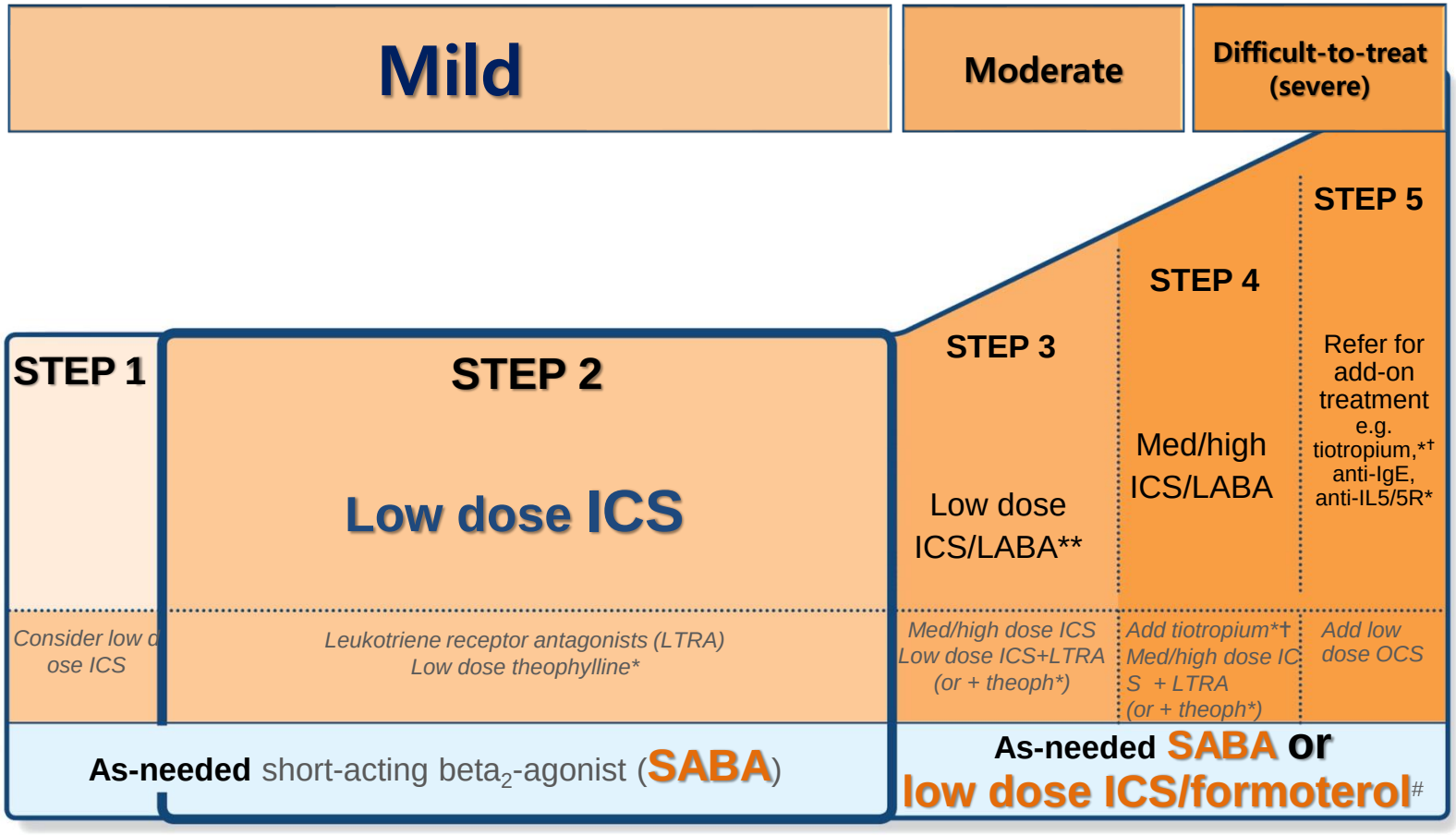
Definition of Mild Asthma

- Definition in the **GINA** document
  - "Asthma that is well controlled with **Step 1 or Step 2** treatment (Box 3-5, p.44), i.e. with as-needed reliever medication alone, or with **low-intensity controller** treatment such as low dose ICS, leukotriene receptor antagonists or chromones"
- Expert Panel Report 3 (**EPR-3**)
  - **Mild Intermittent**
    - Symptom **0-2/week** or **Step 1** treatment
  - **Mild Persistent**
    - Symptom **>2/week (not daily)** or **Step 2** treatment

GINA 2019

National Asthma Education Prevention Program, J Allergy Clin Immunol 2007;120:S94-138.

Asthma Severity & Treatment in GINA 2018



*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

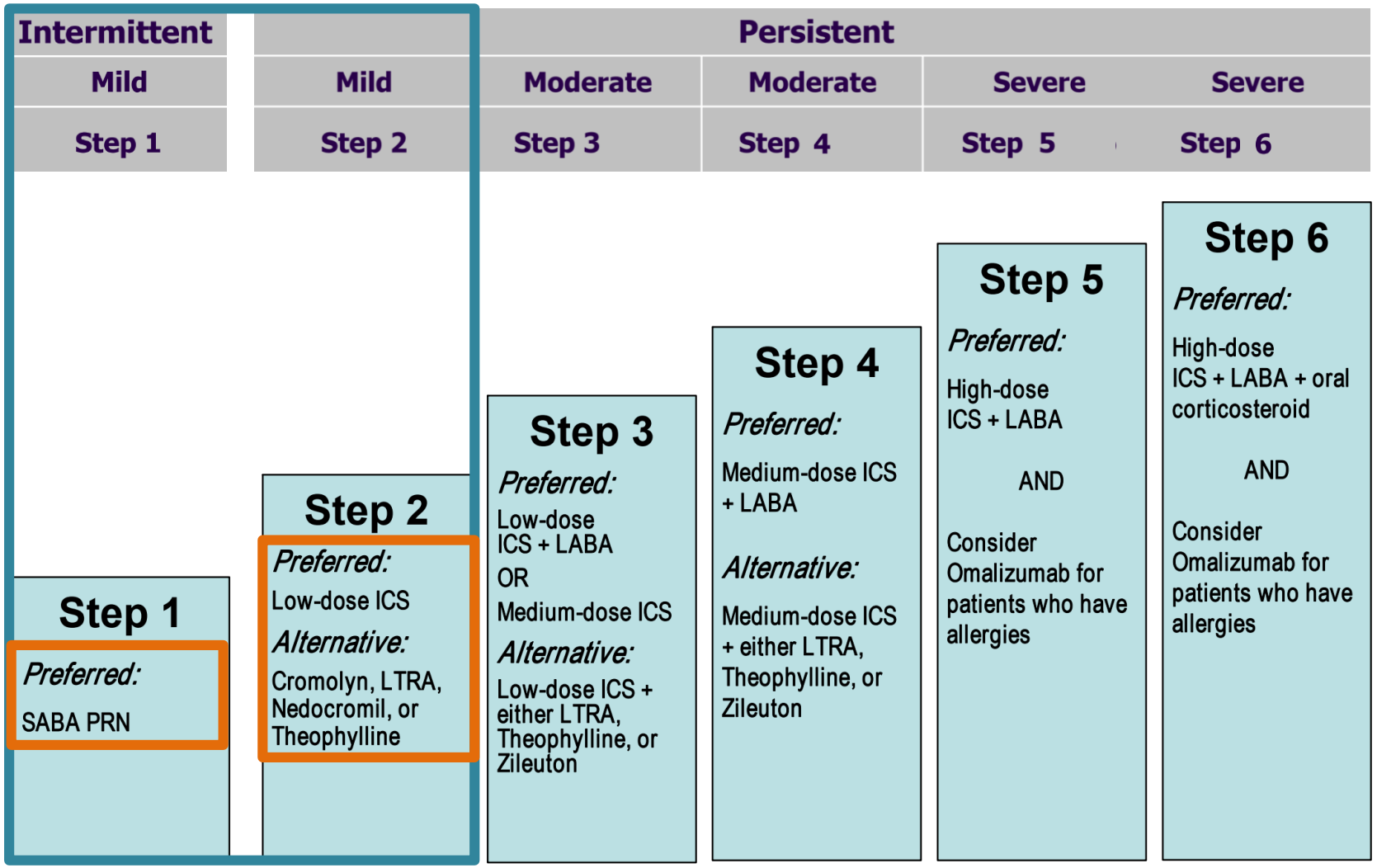
GINA 2018, Box 3-5

Classifying Severity For Patients Who Are Not Currently Taking Long-term Control Medications

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
				Persistent	
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20 –39 yr 80%** **40 –59 yr 75%** **60 –80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

Expert Panel Report 3 (EPR 3) J Allergy Clin Immunol 2007:120;S94-138

Classifying Severity In Patients After Asthma Becomes Well Controlled, by Lowest Level Of Treatment Required To Maintain Control



Expert Panel Report 3 (EPR 3) J Allergy Clin Immunol 2007:120;S94-138

Why asthma still kills
The National Review of Asthma Deaths (NRAD)

Confidential Enquiry report
May 2014

- Asthma deaths occurring between February 2012 and January 2013
- Analysis on **195** people who were thought to have died from asthma

- Of 155 patients for whom severity could be estimated, 61 (39%) appeared to have severe asthma.
- Fourteen (**9%**) were being treated for **mild asthma** and 76 (49%) for moderate asthma.
- It is likely that many patients who were treated as having mild or moderate asthma had poorly controlled undertreated asthma, rather than truly mild or moderate disease

The National Review of Asthma Deaths (NRAD) 2015

ORIGINAL ARTICLE

Exacerbation risk and characterisation of the UK's asthma population from infants to old age

Chloe I Bloom,[1] Francis Nissen,[2] Ian J Douglas,[2] Liam Smeeth,[2] Paul Cullinan,[1]

	18 to 54s		55+		
	N (% of BTS)	Rate (95% CI)	N (% of BTS)	Rate (95% CI)	Mean population rate per BTS step
BTS 1	26 607 (30.8)	1.82 (1.78 to 1.86)	11 805 (47.3)	5.01 (4.84 to 5.20)	2.39 (2.30–2.49)
BTS 2	19 704 (36.0)	2.79 (2.74 to 2.85)	14 041 (57.2)	6.60 (6.41 to 6.80)	3.73 (3.62–3.85)
BTS 3	8003 (42.9)	3.88 (3.75 to 4.01)	8155 (66.2)	8.53 (8.26 to 8.82)	5.87 (5.58–6.19)
BTS 4	15 362 (46.8)	5.16 (5.03 to 5.29)	17 638 (68.6)	10.83 (10.59 to 11.08)	6.51 (6.30–6.74)
BTS 5	8494 (57.9)	8.07 (7.84 to 8.31)	14 575 (75.0)	13.27 (13.00 to 13.55)	9.28 (8.50–10.20)
BTS 6	547 (87.8)	42.1 (39.2 to 45.4)	1531 (94.0)	60.19 (57.97 to 62.52)	47.64 (38.21–65.43)
Non-BTS	1211 (47.6)	6.90 (6.32 to 7.55)	2986 (64.7)	12.07 (11.43 to 12.75)	6.92 (6.37–7.53)

Bloom CI, Thorax 2018;73:313-20.

Official Journal of the Asian Pacific Society of Respirology
Respirology

Disease burden of mild asthma in China

- The Respiratory Disease Specific Program 2015, a cross-sectional survey
- From a total sample of 988 patients, 229 patients met the criteria for mild asthma,

	Overall (*n* = 229)	GINA Step	
		Step 1 (*n* = 58)	Step 2 (*n* = 171)
Physician, *n* (%)			
Chief Doctor	41 (18.6)	10 (17.5)	31 (18.9)
Vice Chief Doctor	90 (40.7)	22 (38.6)	68 (41.5)
Doctor in Charge	90 (40.7)	25 (43.9)	65 (39.6)
Missing, *n*	8	1	7
Currently prescribed treatment, *n* (%)			
SABA or SAMA monotherapy	58 (25.3)	58 (100.0)	0 (0.0)
Low-dose ICS monotherapy	37 (16.2)	0 (0.0)	37 (21.6)
LTRA monotherapy	87 (38.0)	0 (0.0)	87 (50.9)
Xanthine monotherapy	47 (20.5)	0 (0.0)	37 (21.6)
Treatment adherence	Not applicable	Not applicable	
Low			68 (46.9)
Medium			57 (39.3)
High			20 (13.8)
Missing, *n*			26

Ding B, Respirology 2018;23:369-77.

	Overall (*n* = 229)	GINA Step	
		Step 1 (*n* = 58)	Step 2 (*n* = 171)
ACT			
Mean (SD)	22.1 (1.8)	22.1 (1.2)	22.1 (2.1)
Missing, *n*	180	42	138
Physician visits for asthma, mean (SD)	4.7 (3.6)	6.0 (3.9)	4.3 (3.4)
Exacerbation history, *n* (%)			
No	183 (79.9)	51 (87.9)	132 (77.2)
Yes	46 (20.1)	7 (12.1)	39 (22.8)
Frequency of exacerbations in last 12 months			
Mean (SD)	0.2 (0.6)	0.2 (0.5)	0.3 (0.6)
Median	0	0	0
Missing, *n*	4	1	3
Number of exacerbations in last 12 months, *n* (%)			
0	185 (82.2)	51 (89.5)	134 (79.8)
1	30 (13.3)	2 (3.5)	28 (16.7)
2	8 (3.6)	4 (7.0)	4 (2.4)
3	2 (0.9)	0 (0.0)	2 (1.2)

Ding B, Respirology 2018;23:369-77.

Original Article

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*

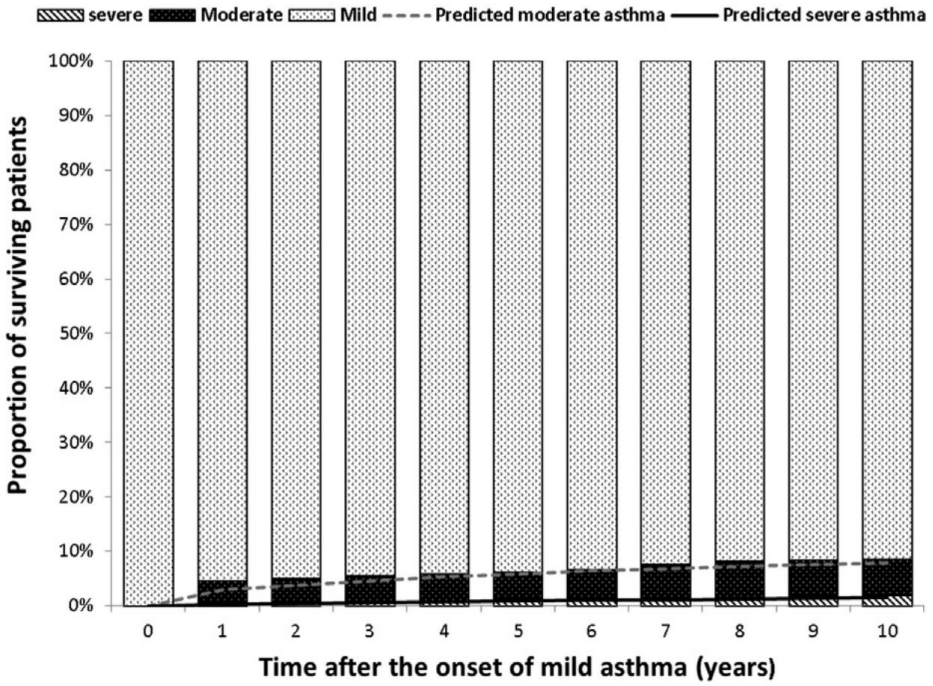
- the administrative health data of British Columbia, Canada
- **aged 14 to 45** years with newly diagnosed mild asthma between January 1997 and December 2012
- 70,829 patients with incident mild asthma (62% women; mean age, 31 years)

- Objective: To examine the long-term trajectories of mild asthma and the effects of early-stage 47 **risk factors** on the **subsequent disease course**.

Chen W, J Allergy Clin Immunol Pract 2018;6:2024-32 e5.

TABLE I. Characteristics of the study sample in the index year

Characteristic	Patients with mild asthma (N = 70,829)
Age (y), mean ± SD	30.5 ± 9.7
Sex, n (%)	
Female	43,891 (62)
Male	26,938 (38)
Socioeconomic status, n (%)	
Low	29,993 (42)
Middle	14,430 (20)
High	26,406 (37)
Comorbidity, n (%)	
None (CCI score = 0)	62,342 (88)
Mild (CCI score = 1)	7,266 (10)
Moderate (CCI score = 2)	873 (1)
High (CCI score ≥ 3)	348 (0.5)
Allergic rhinitis, n (%)	9,398 (13)
Inappropriate SABA use,* n (%)	
No	42,186 (59)
Yes	8,399 (12)
No ICS or SABA use	20,244 (29)
ICS vs ICS + LABA use, n (%)	
ICS	24,522 (35)
ICS + LABA	8,253 (12)
Both	906 (1)
No ICS use	37,148 (52)
ICS-adjusted daily dose,† mean ± SD	82.9 ± 115.4
No. of other controllers/wk,‡ mean ± SD	0.0 ± 0.0
No. of SABA doses/wk,§ mean ± SD	2.3 ± 2.4
Moderate-to-severe exacerbations,‖ mean ± SD	0.1 ± 0.3
No. of nonasthma hospitalizations, mean ± SD	1.2 ± 4.6
No. of nonasthma physician visits, mean ± SD	12.8 ± 13.9
No. of nonasthma medications, mean ± SD	71.3 ± 256.4



Chen W, J Allergy Clin Immunol Pract 2018;6:2024-32 e5.

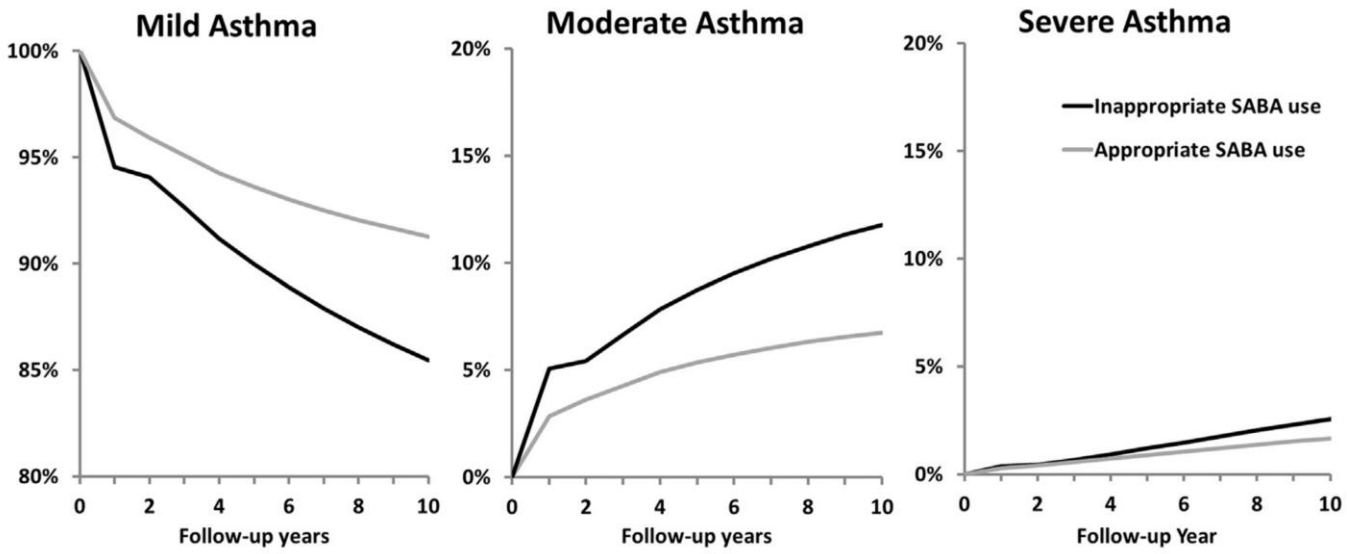
TABLE II. Effects of selected baseline risk factors on future severity of asthma

	OR of transitioning to a severity state in any future year			
	Transition to moderate/severe/dead (relative to mild)		Transition to severe/dead (relative to mild/moderate)	
Risk factors in the index year	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (per 10- y increase)	1.24 (1.22-1.27)	<.0001	1.24 (1.19-1.29)	<.0001
Sex (male vs female)	1.05 (1.01-1.08)	.006	1.05 (1.01-1.08)	0.006
SES				
Low	Reference			
Middle	0.93 (0.89-0.98)	.003	0.90 (0.82-1.00)	.047
High	0.95 (0.92-0.99)	.011	0.83 (0.76-0.90)	<.0001
Comorbidity				
CCI score = 0	Reference			
CCI score = 1	1.07 (1.02-1.13)	.010	1.06 (0.95-1.19)	.30
CCI score = 2	1.11 (0.97-1.27)	.122	1.45 (1.12-1.89)	.005
CCI score ≥ 3	1.25 (1.01-1.54)	.039	1.25 (1.01-1.54)	.018
Allergic rhinitis (yes vs no)	0.95 (0.91-1.00)	.063	0.95 (0.91-1.00)	.063
Inappropriate SABA use*				
No	Reference			
Yes	1.79 (1.68-1.90)	<.0001	1.29 (1.16-1.44)	<.0001
No ICS or SABA use	0.63 (0.59-0.68)	<.0001	1.00 (0.89-1.13)	0.98
ICS therapy				
ICS only	Reference			
ICS-LABA	0.92 (0.87-0.97)	.004	0.92 (0.87-0.97)	<.0001
Both	0.96 (0.84-1.10)	.56	0.96 (0.84-1.10)	.56
None	0.73 (0.69-0.78)	<.0001	0.73 (0.69-0.78)	<.0001

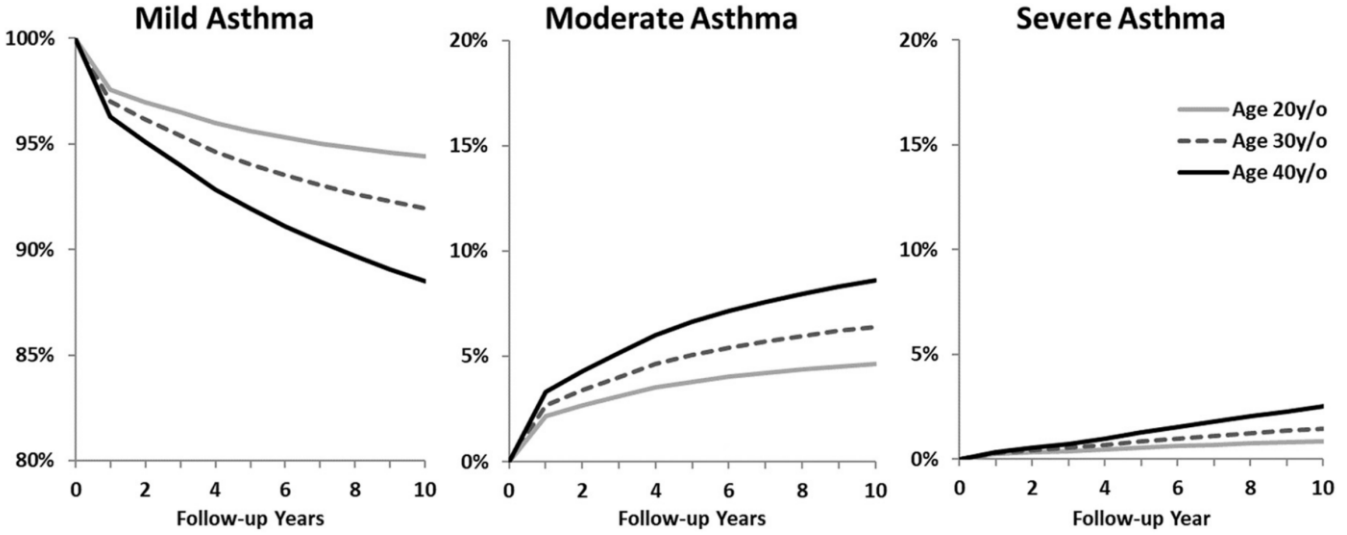
Defined as **high dose of SABA** and **low dose of ICS**:
using 2 or more puffs of SABA per week in the absence of ICS use,
or 9 or more canisters of SABA and less than 100 mg of ICS daily doses

Chen W, J Allergy Clin Immunol Pract 2018;6:2024-32 e5.

The Influences Of Rescue Medication Use In The Index Year On The Long-term Trajectory



The influence of baseline age on long-term trajectory



Chen W, J Allergy Clin Immunol Pract 2018;6:2024-32 e5.

Asthma admission rates and patterns of salbutamol and inhaled corticosteroid prescribing in England from 2013 to 2017

- English Clinical Commissioning Group (CCG) regions

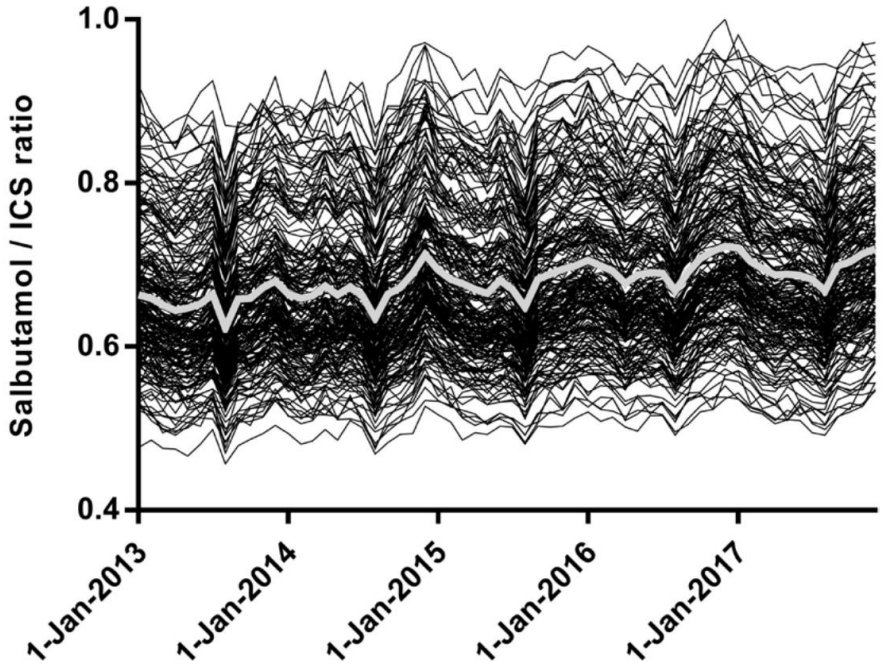


Figure 1 Salbutamol to ICS ratio in English CCGs

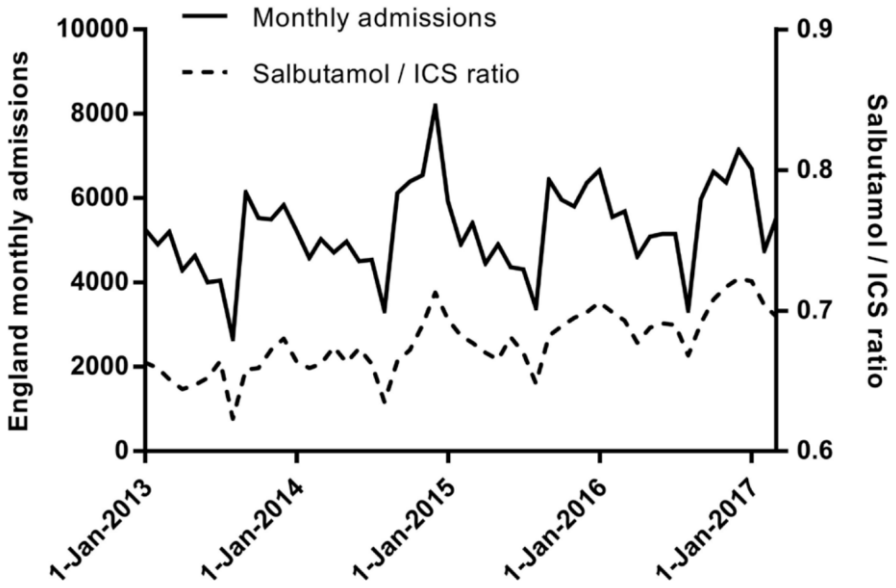
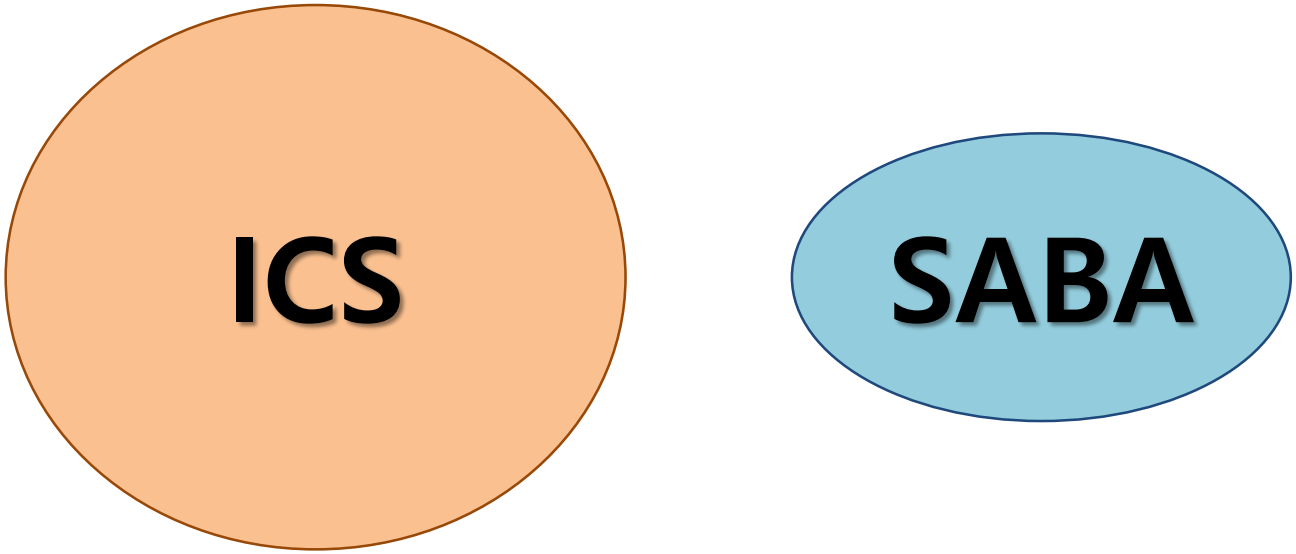


Figure 2 Temporal relationship between monthly asthma admission rates and the ratio of salbutamol to ICS prescribing in England. ICS, inhaled corticosteroid.

- **the ratio of salbutamol to ICS** prescriptions is positively associated with asthma **admission rates**, after accounting for median age, asthma prevalence and socioeconomic deprivation

Gonem S, Thorax 2019;74:705-6.

The Dilemma in the Management of Mild Asthma



underuse of ICSs and overuse of SABAs

- START -

Steroid Treatment As Regular Therapy

Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial

*Romain A Pauwels, Søren Pedersen, William W Busse, Wan C Tan, Yu-Zhi Chen, Stefan V Ohlsson, Anders Ullman, Carl Johan Lamm, Paul M O'Byrne on behalf of the START Investigators Group**

- a randomised, double-blind clinical trial in 7241 patients in 32 countries
- to assess the effects of **budesonide** in patients who had had **mild persistent asthma** for less than 2 years and who had **not had previous regular treatment with glucocort icosteroids**
- Patients aged 5–66 years received either budesonide or placebo once daily for 3 years in addition to their usual asthma medications
- The daily **budesonide** dose was **400 µg** (delivered by one inhalation from a **dry powde r** inhaler), or 200 µg for children younger than 11 years.

- Primary outcome : **time to first severe asthma-related event** (**SARE**; hospital admission, emergency treatment, or death)

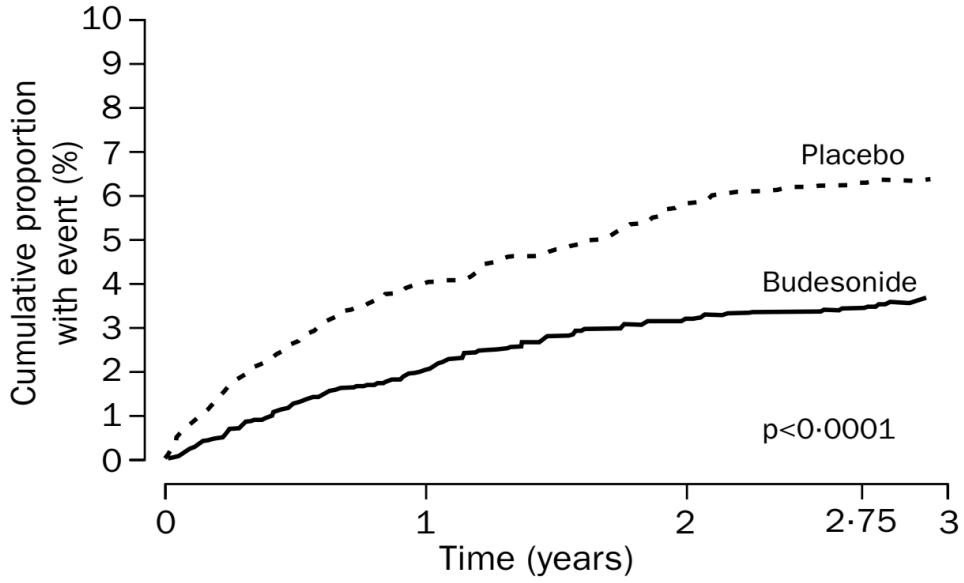
Pauwels RA, Lancet 2003;361:1071-6.

	Budesonide (n=3597)	Placebo (n=3568)
Mean age (SD) (years)	24 (15)	24 (15)
Age distribution (years)		
5–10	1000 (27·8%)	974 (27·3%)
11–17	640 (17·8%)	581 (16·3%)
18–66	1957 (54·4%)	2013 (56·4%)
Ethnic origin		
White	2351 (65·4%)	2310 (64·7%)
Black	50 (1·4%)	62 (1·7%)
Oriental	996 (27·7%)	997 (27·9%)
Other	198 (5·5%)	199 (5·6%)
Female sex	1949 (54·2%)	1925 (54·0%)
Duration of asthma before study entry		
< 3 months	1321 (36·8%)	1275 (35·7%)
⩾3–<6 months	517 (14·4%)	473 (13·3%)
⩾6 months–<1 year	558 (15·5%)	603 (16·9%)
⩾1 year	1199 (33·3%)	1216 (34·1%)
Symptomatic days in 2 weeks before study		
None	307 (8·6%)	313 (8·8%)
1–3 days	1299 (36·3%)	1233 (34·6%)
4–7 days	1199 (33·5%)	1274 (35·8%)
>7 days	772 (21·6%)	741 (20·8%)
Smoking status		
Current smoker	438 (12·2%)	392 (11·0%)
Ex-smoker	300 (8·3%)	334 (9·3%)
Passive smoker	1006 (28·0%)	1073 (30·1%)
Non-smoker	1849 (51·5%)	1769 (49·6%)
Prebronchodilator FEV_1 (% predicted, mean [SD])	86·3 (13·9)	86·6 (13·9)
Postbronchodilator FEV_1 (% predicted, mean [SD])	96·2 (13·1)	96·4 (13·3)

Data are number (%) unless otherwise indicated. Data missing for some variables.

Pauwels RA, Lancet 2003;361:1071-6.

Kaplan-meier Curve of Time to First Severe Asthma Related Event

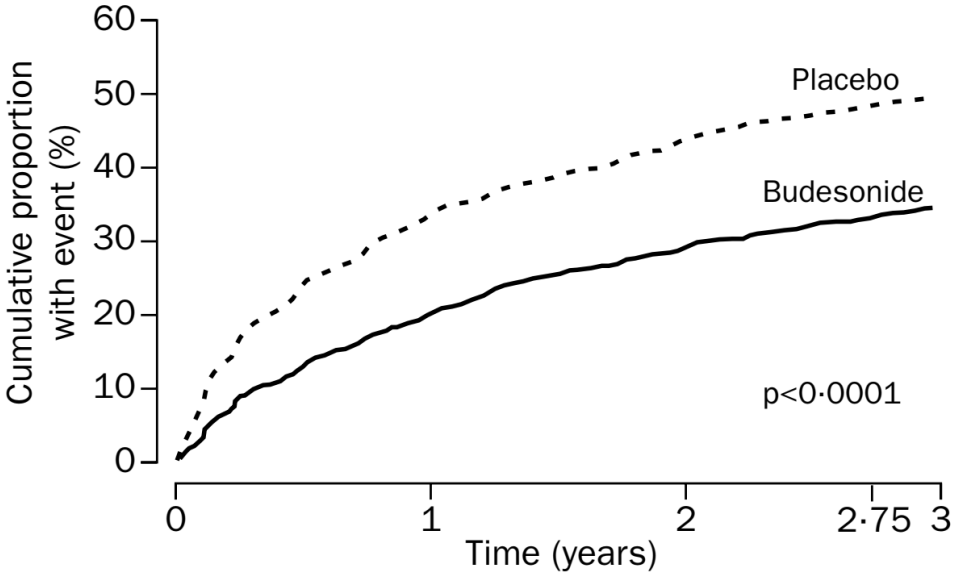


hazard ratio [HR] 0·56

95% CI: 0·45–0·71

(p<0·0001)

Kaplan-meier Curve of Time to First Non-study Glucocorticosteroid Tx



inhaled, oral, or systemic

glucocorticosteroids

- Placebo: 1599 (45%)
- Budesonide: 1121 (31%)

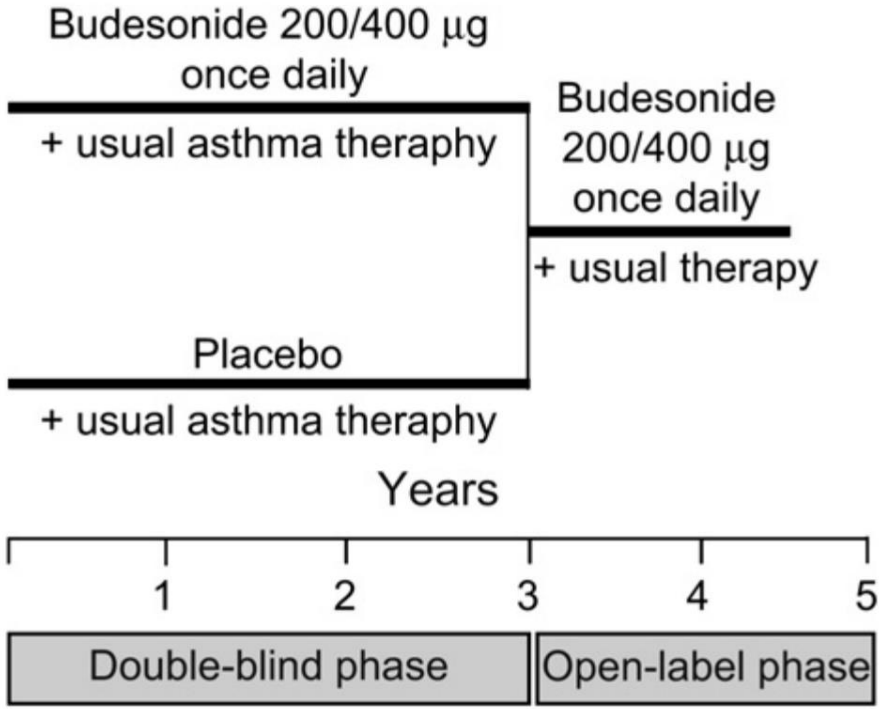
(p<0·0001)

Pauwels RA, Lancet 2003;361:1071-6.

The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: Effectiveness of early intervention with budesonide in mild persistent asthma

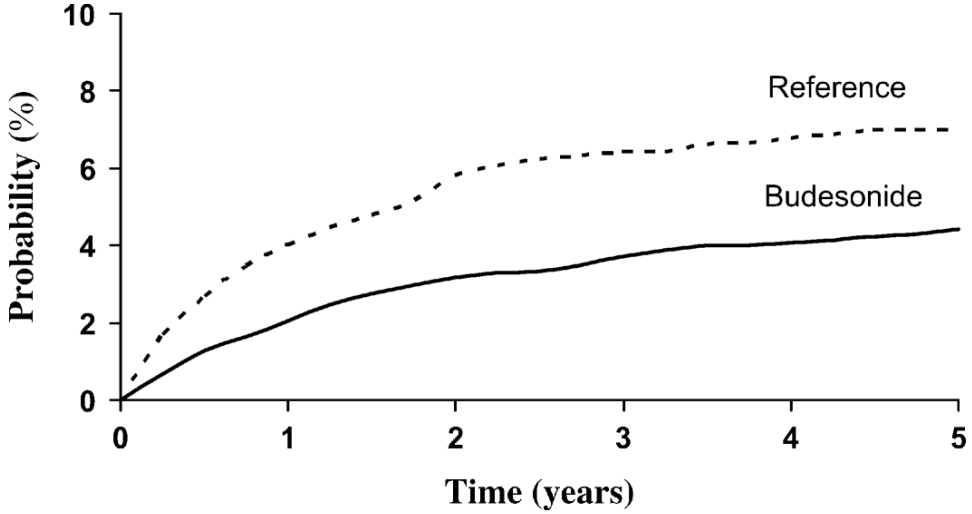
William W. Busse, MD,[a] Søren Pedersen, MD,[b] Romain A. Pauwels, MD,[c,†] Wan C. Tan, MD,[d] Yu-Zhi Chen, MD,[e] Carl Johan Lamm, PhD,[f] and Paul M. O'Byrne, MD,[g] on behalf of the START Investigators Group *Madison, Wis, Kolding, Denmark, Ghent, Belgium, Queenstown, Singapore, Vancouver, British Columbia, Canada, Beijing, China, Lund, Sweden, and Hamilton, Ontario, Canada*

- After 3 years of the START study, all patients received 2 years of open-label treatment with budesonide once daily



Busse WW, J Allergy Clin Immunol 2008;121:1167-74.

Cumulative Probability of Having a First SARE



odds ratio: 0.61

P <.001

Percentage of Patients Using Additional Asthma Medications

	Budesonide (n = 2604)		Reference (n = 2542)		
	Year 4	Year 5	Year 4	Year 5	*P* value*
Inhaled corticosteroids†	11.1	10.4	16.3	14.6	<.001
Oral/systemic corticosteroids	1.5	0.9	1.5	0.7	.79
Short-acting β_2-adrenergic agonists	61.8	60.3	63.8	62.2	.17
Long-acting β_2-adrenergic agonists	5.4	6.3	8.5	9.3	<.001
Xanthines	2.9	2.5	3.3	2.2	1.00
Cromones	1.5	0.9	2.6	2.1	.003
Leukotriene modifiers	1.3	1.4	1.5	1.4	.90
Other	5.2	5.3	5.4	5.2	1.00

patients in the **reference group** used **more additional asthma medications** during both th e open-label and double-blind phases.

Busse WW, J Allergy Clin Immunol 2008;121:1167-74.

Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne

- **A post-hoc analysis** of the Steroid Treatment As Regular Therapy (**START**) Study
- Of 7138 patients (n=3577 budesonide; n=3561 placebo), baseline symptom frequency
  - **0–1 days per week : 2184 (31%)**,
  - **more than 1 and less than or equal to 2 symptom days per week : 1914 (27%)**,
  - **more than 2 symptom days per week : 3040 (43%)**.

- Primary outcome: **time to first** severe asthma-related event (**SARE**; hospital admission, emergency treatment, or death) and change from baseline in lung function after bronc hodilator

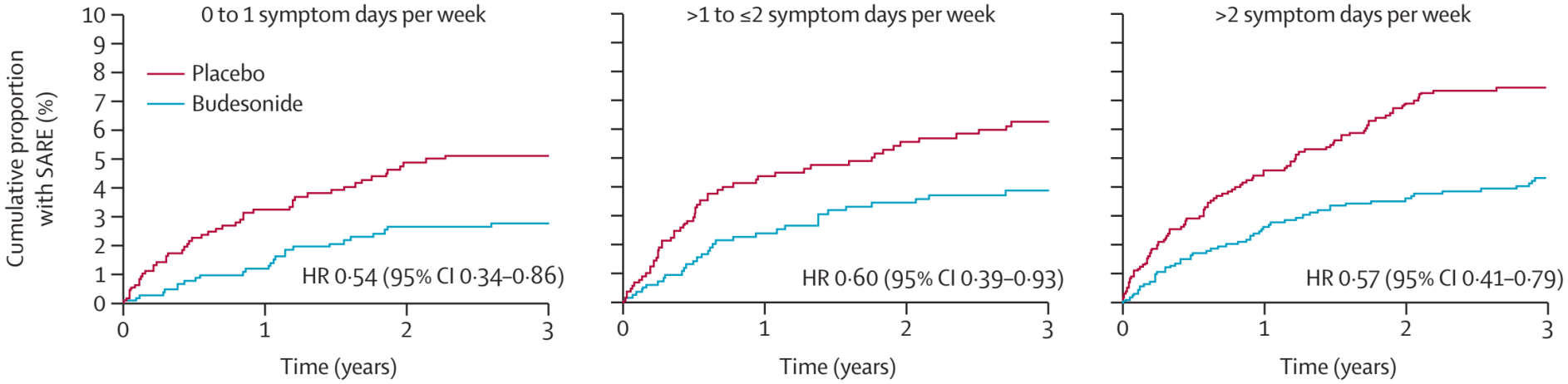
Reddel HK, Lancet 2017;389:157-66.

Baseline Characteristics

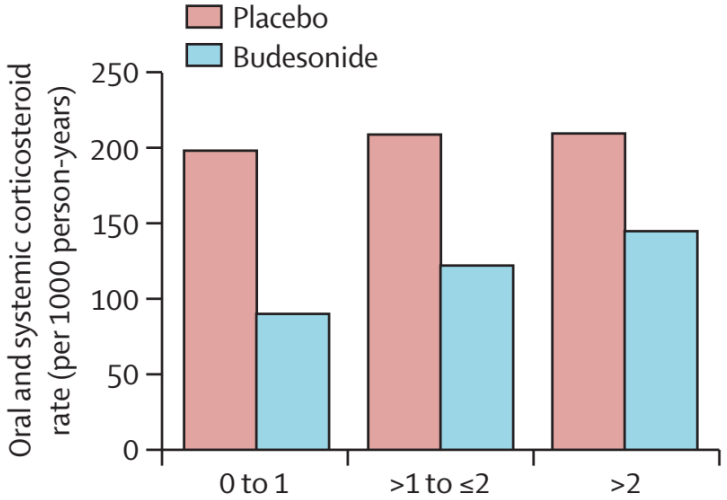
	Budesonide (symptom days a week)			Placebo (symptom days a week)		
	0 to 1 (n=1102)	>1 to ≤2 (n=951)	>2 (n=1524)	0 to 1 (n=1082)	>1 to ≤2 (n=963)	>2 (n=1516)
Age						
Mean age, years	22 (14)	24 (15)	24 (15)	22 (14)	25 (15)	26 (15)
Sex						
Female	587 (53%)	523 (55%)	829 (54%)	566 (52%)	501 (52%)	853 (56%)
Male	515 (47%)	428 (45%)	695 (46%)	516 (48%)	462 (48%)	663 (44%)
Race						
White	618 (56%)	588 (62%)	1126 (74%)	589 (54%)	610 (63%)	1104 (73%)
Black	11 (1%)	16 (2%)	22 (1%)	15 (1%)	22 (2%)	25 (2%)
Oriental	408 (37%)	284 (30%)	306 (20%)	431 (40%)	263 (27%)	303 (20%)
Other	65 (6%)	63 (7%)	70 (5%)	47 (4%)	68 (7%)	84 (6%)
Smoking status						
Non-smoker	609 (55%)	492 (52%)	740 (49%)	570 (53%)	481 (50%)	714 (47%)
Passive smoker	311 (28%)	268 (28%)	422 (28%)	341 (32%)	298 (31%)	434 (29%)
Ex-smoker	77 (7%)	78 (8%)	143 (9%)	88 (8%)	79 (8%)	166 (11%)
Current smoker	104 (9%)	113 (12%)	217 (14%)	83 (8%)	105 (11%)	202 (13%)
FEV_1						
Prebronchodilator FEV_1 (% predicted)	86% (14)	86% (13)	86% (14)	86% (14)	87% (14)	86% (14)
Postbronchodilator FEV_1 (% predicted)	96% (13)	96% (13)	96% (14)	96% (13)	97% (13)	96% (14)
Controller treatment before entry*						
Inhaled corticosteroid	49 (4%)	42 (4%)	84 (6%)	52 (5%)	41 (4%)	90 (6%)
Oral or other systemic corticosteroid	42 (4%)	39 (4%)	64 (4%)	45 (4%)	38 (4%)	76 (5%)
Xanthine	136 (12%)	113 (12%)	160 (11%)	140 (13%)	108 (11%)	160 (11%)
Cromoglicate	69 (6%)	73 (8%)	141 (9%)	69 (6%)	67 (7%)	131 (9%)
Leukotriene modifier	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)

Reddel HK, Lancet 2017;389:157-66.

Time to First Severe Asthma-related Event



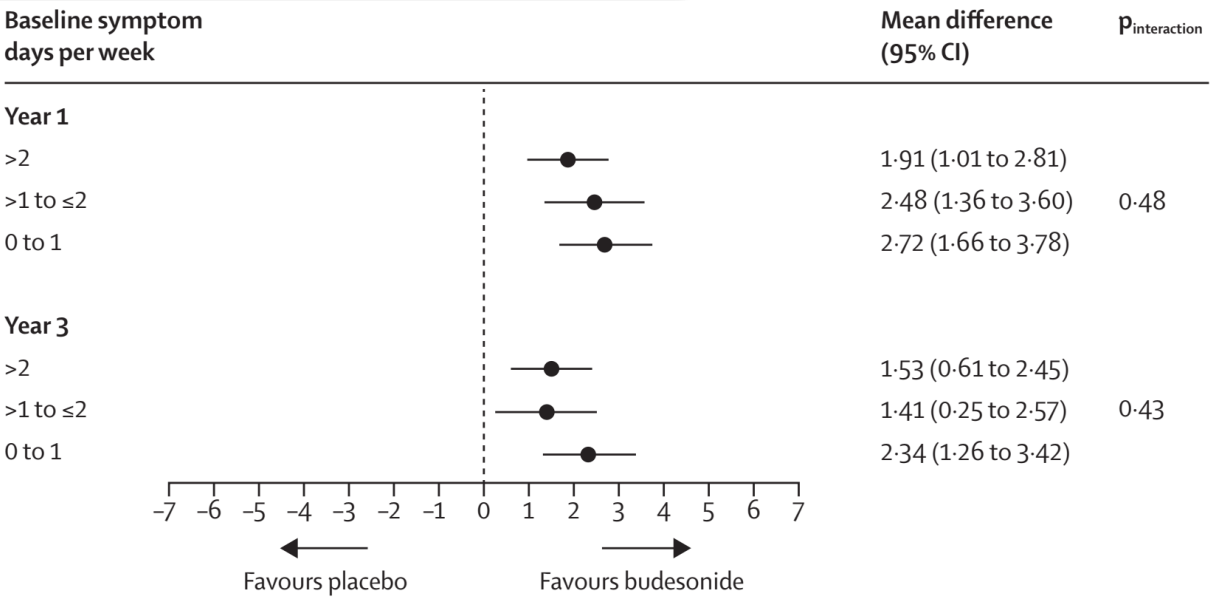
Rates and Rate Ratios for Severe Exacerbations



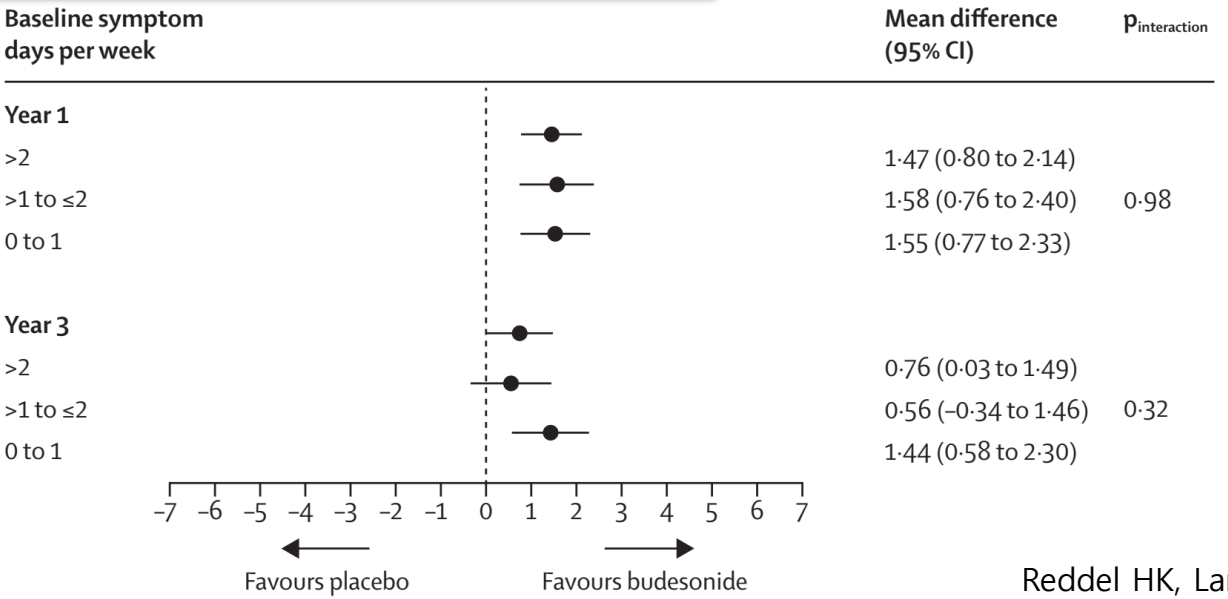
Rate ratio (95 % CI)	0·48 (0·38–0·61)	0·56 (0·44–0·71)	0·66 (0·55–0·80)

Reddel HK, Lancet 2017;389:157-66.

Prebronchodilator FEV1 (% predicted)

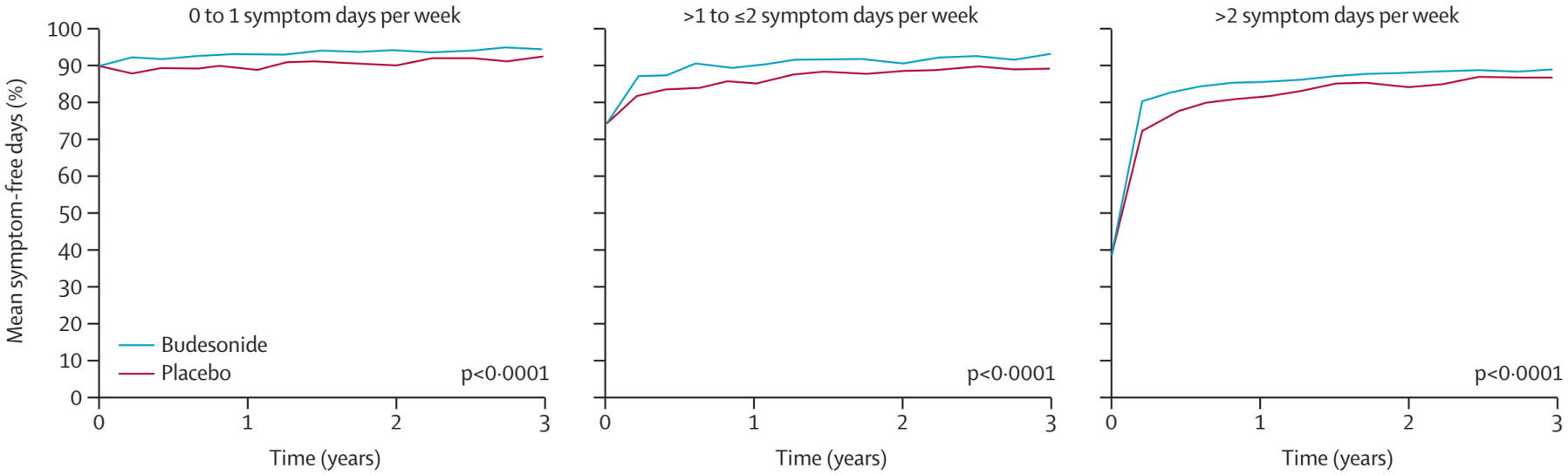


Postbronchodilator FEV1 (% predicted)

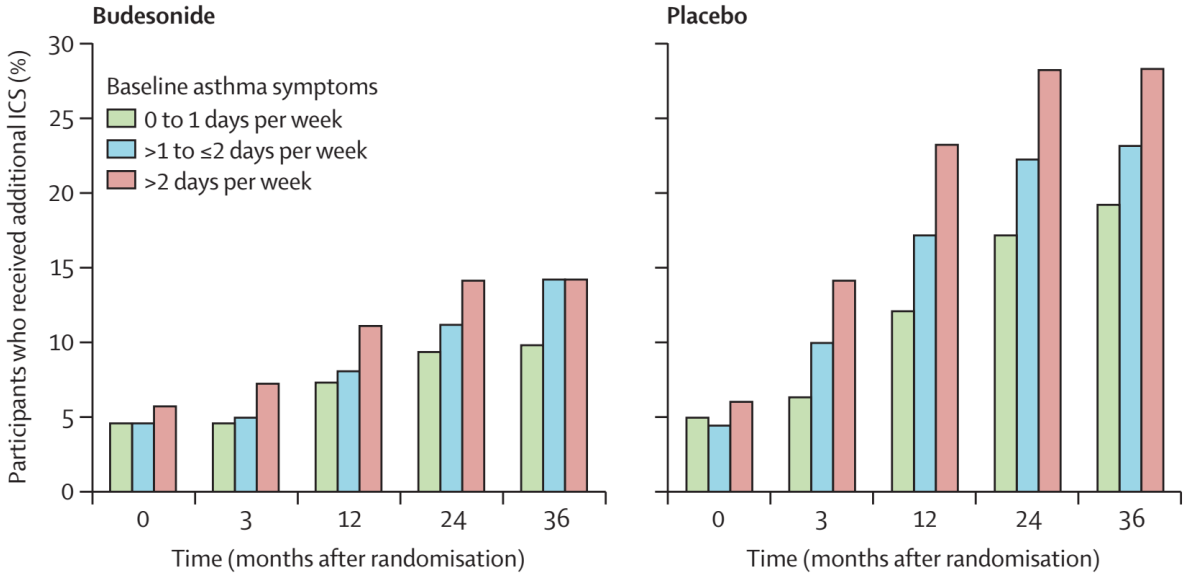


Reddel HK, Lancet 2017;389:157-66.

Symptom-free Days



Proportion of Participants Receiving Open-label ICS



Reddel HK, Lancet 2017;389:157-66.

- The findings challenge long-standing assumptions about the risks of so-called mild asthma, and suggest that decisions about **ICS treatment in such patients should be made on the basis of population risk reduction**, rather than only on symptom frequency.

- However, regular daily ICS treatment might not necessarily be appealing to clinicians and patients, because of **concerns about adherence and side-effects.**

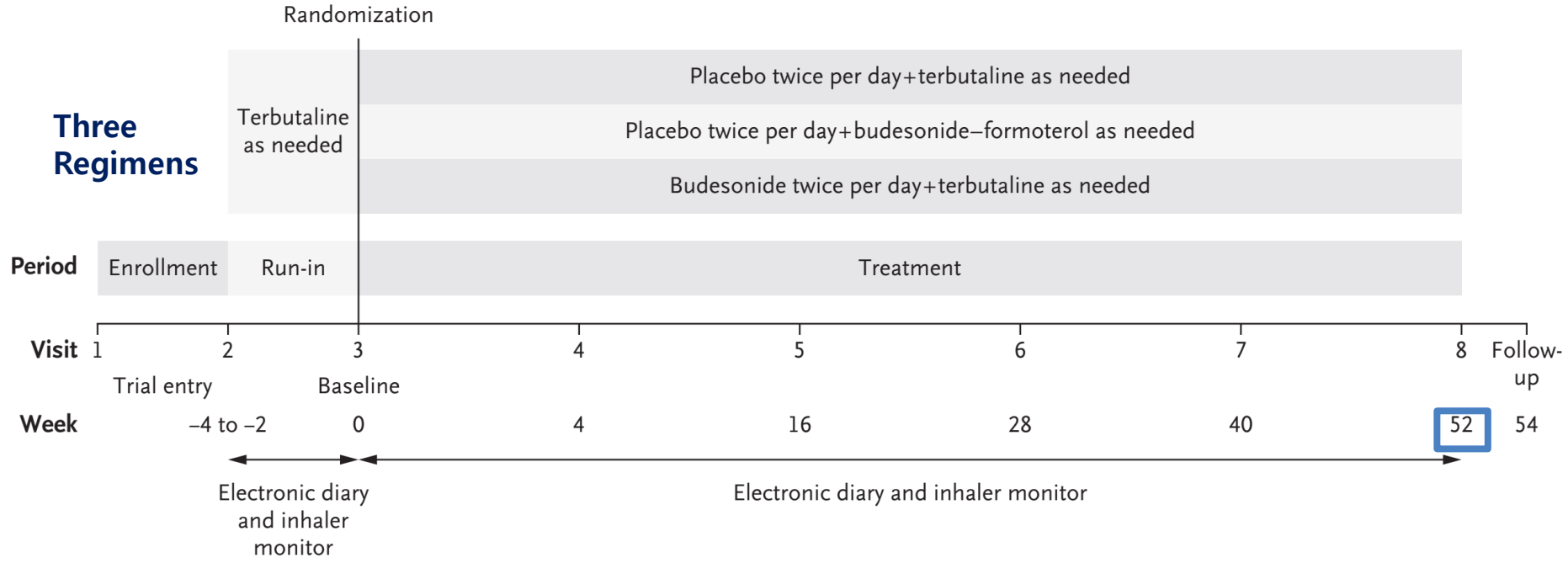
- **Alternative treatment options** with an **as-needed combination of ICS and β2 agonist** might be more acceptable to clinicians and patients, and are being investigated.

Reddel HK, Lancet 2017;389:157-66.

- SYGMA 1 -

Symbicort Given as Needed in Mild Asthma 1

- **12 years of age or older (n=3836), 52 weeks**
  - 200 μg of budesonide and 6 μg of formoterol (**Symbicort** Turbuhaler) as needed
  - 200 μg of budesonide (**Pulmicort** Turbuhaler) as twice-daily maintenance therapy plus terbutaline at a dose of 0.5 mg (Turbuhaler) used as needed
  - Terbutaline at a dose of 0.5 mg (Turbuhaler) used as needed.



O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

eWCAW
eDiary-Derived Well-Controlled Asthma Weeks

- The primary objective was to investigate the superiority of as-needed budesonide–form oterol to as-needed terbutaline with regard to electronically recorded weeks with well-c ontrolled asthma

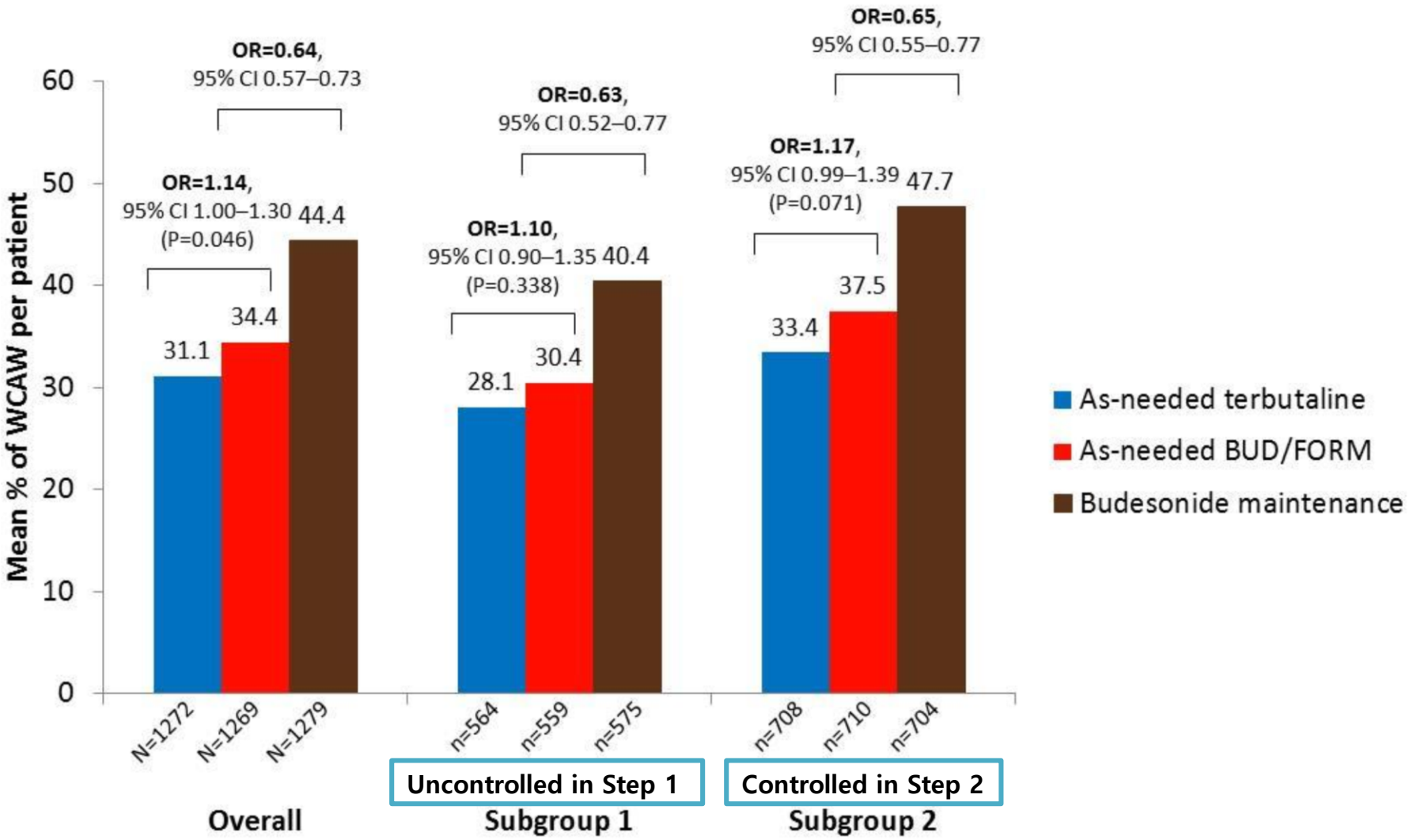
- Morning and evening PEF (transferred from PEF meter)
- Asthma symptoms (entered by patient)
- Nights with awakenings due to asthma symptoms (entered by patient)
- Use of ‘as needed’ and randomised maintenance treatment (transferred f rom Turbuhaler Usage Monitor, TUM)

Baseline Characteristics

Characteristic	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)	Total (N=3836)
Age — yr	40.0±16.3	39.8±16.9	39.0±16.7	39.6±16.6
Female sex — no. (%)	771 (60.4)	777 (60.8)	797 (62.2)	2345 (61.1)
Time since asthma diagnosis — yr				
Median	6.3	6.5	6.3	6.4
Range	0.5–62.4	0.4–65.7	0.5–57.1	0.4–65.7
ACQ-5 score†				
Mean score				
At trial entry	1.52±0.96	1.57±0.97	1.53±0.97	1.54±0.97
At baseline	1.54±0.95	1.61±0.97	1.55±0.96	1.57±0.96
Score ≥1.5 — no./total no. (%)				
At trial entry‡	549/1160 (47.3)	601/1174 (51.2)	568/1177 (48.3)	1718/3511 (48.9)
At baseline	602/1256 (47.9)	649/1257 (51.6)	596/1257 (47.4)	1847/3770 (49.0)
AQLQ score§	5.25±0.99	5.20±1.01	5.27±1.01	5.24±1.00
FEV_1 — % of predicted value				
Before bronchodilator use	84.13±14.08	84.18±14.24	84.23±13.91	84.18±14.07
After bronchodilator use	95.27±13.53	95.86±14.02	95.67±13.43	95.60±13.66
Peak expiratory flow ≥80% of the predicted value every morning — no./total no. (%)¶	362/1276 (28.4)	340/1277 (26.6)	376/1282 (29.3)	1078/3835 (28.1)
Bronchodilator reversibility — %	14.4±11.5	14.9±11.3	14.6±11.6	14.6±11.5
Asthma control according to pretrial treatment — no. (%)‖				
Uncontrolled with short-acting bronchodilator alone	565 (44.2)	565 (44.2)	576 (44.9)	1706 (44.5)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	712 (55.8)	712 (55.8)	706 (55.1)	2130 (55.5)
Severe exacerbation in previous 12 mo — no. (%)	256 (20.0)	257 (20.1)	241 (18.8)	754 (19.7)

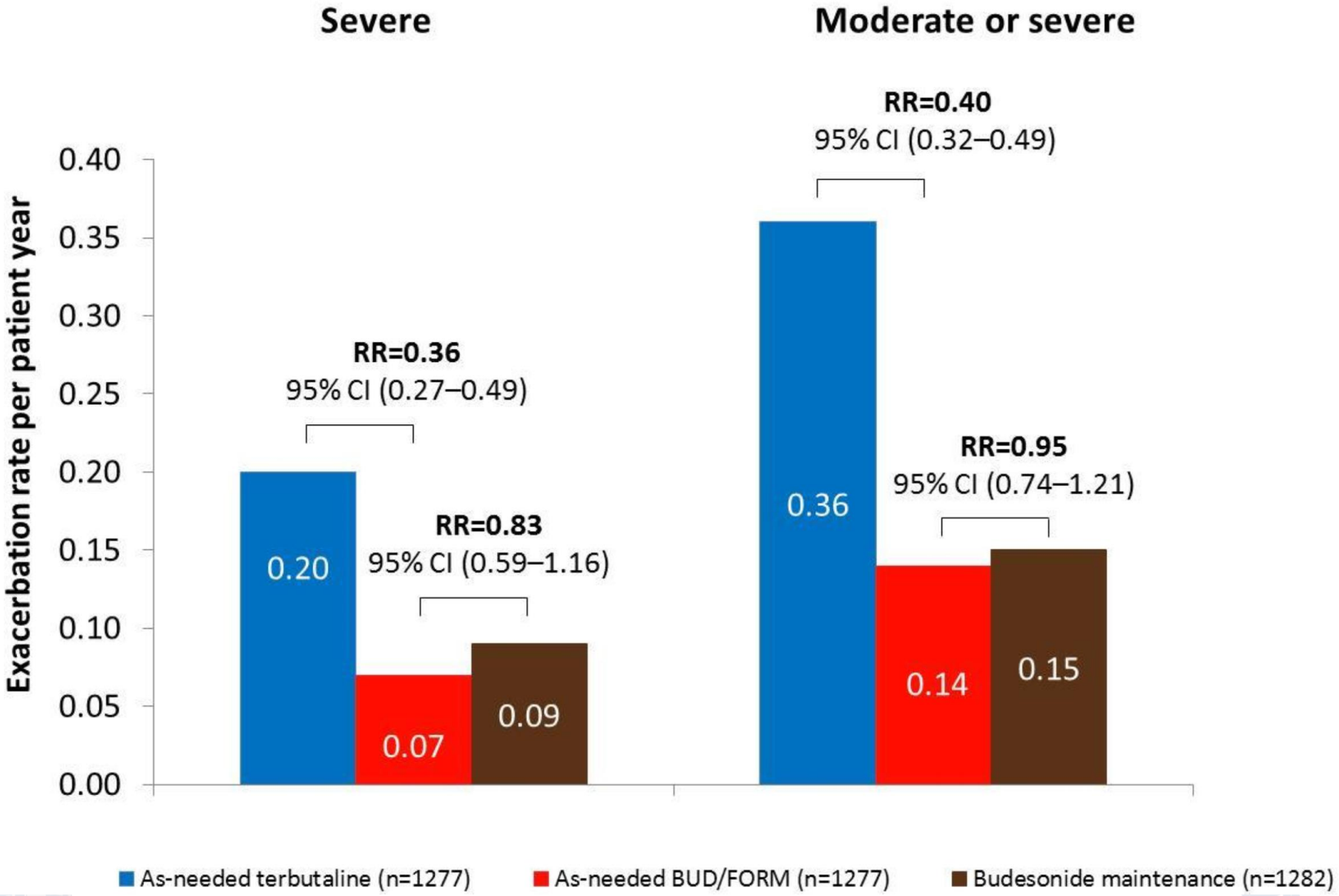
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Primary Outcome: eWCAW
eDiary-Derived Well-Controlled Asthma Weeks



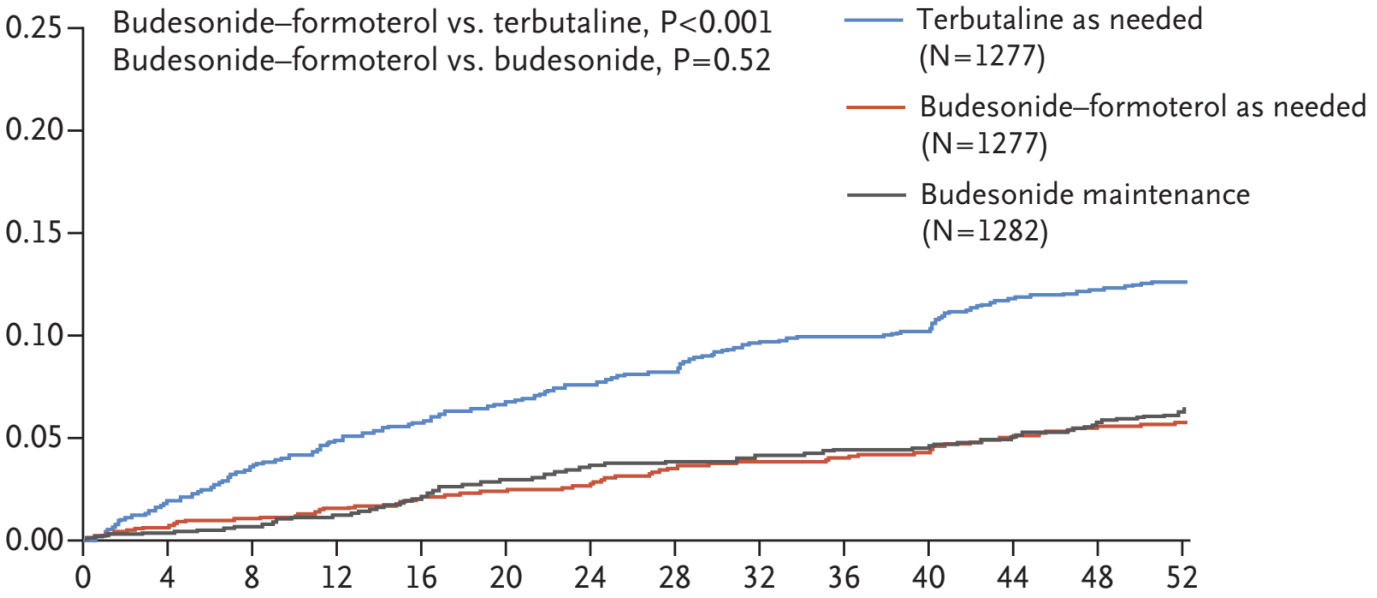
O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Annualized Exacerbation Rate

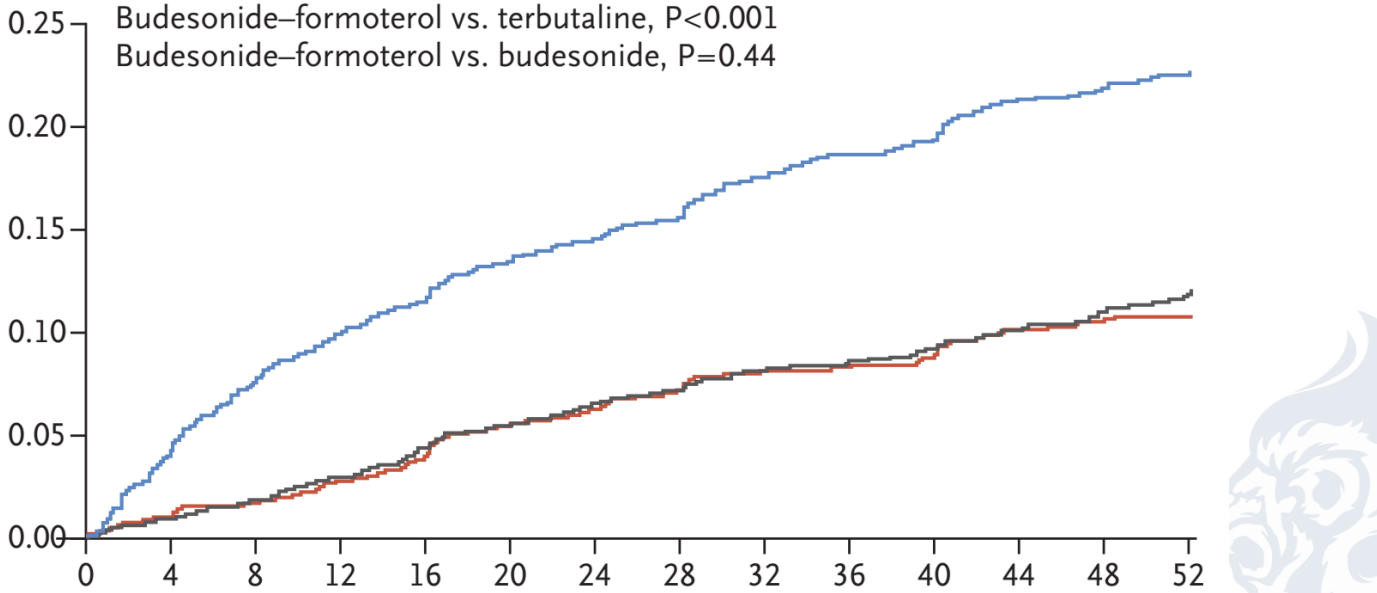


O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

Severe AE



Moderate or Severe AE

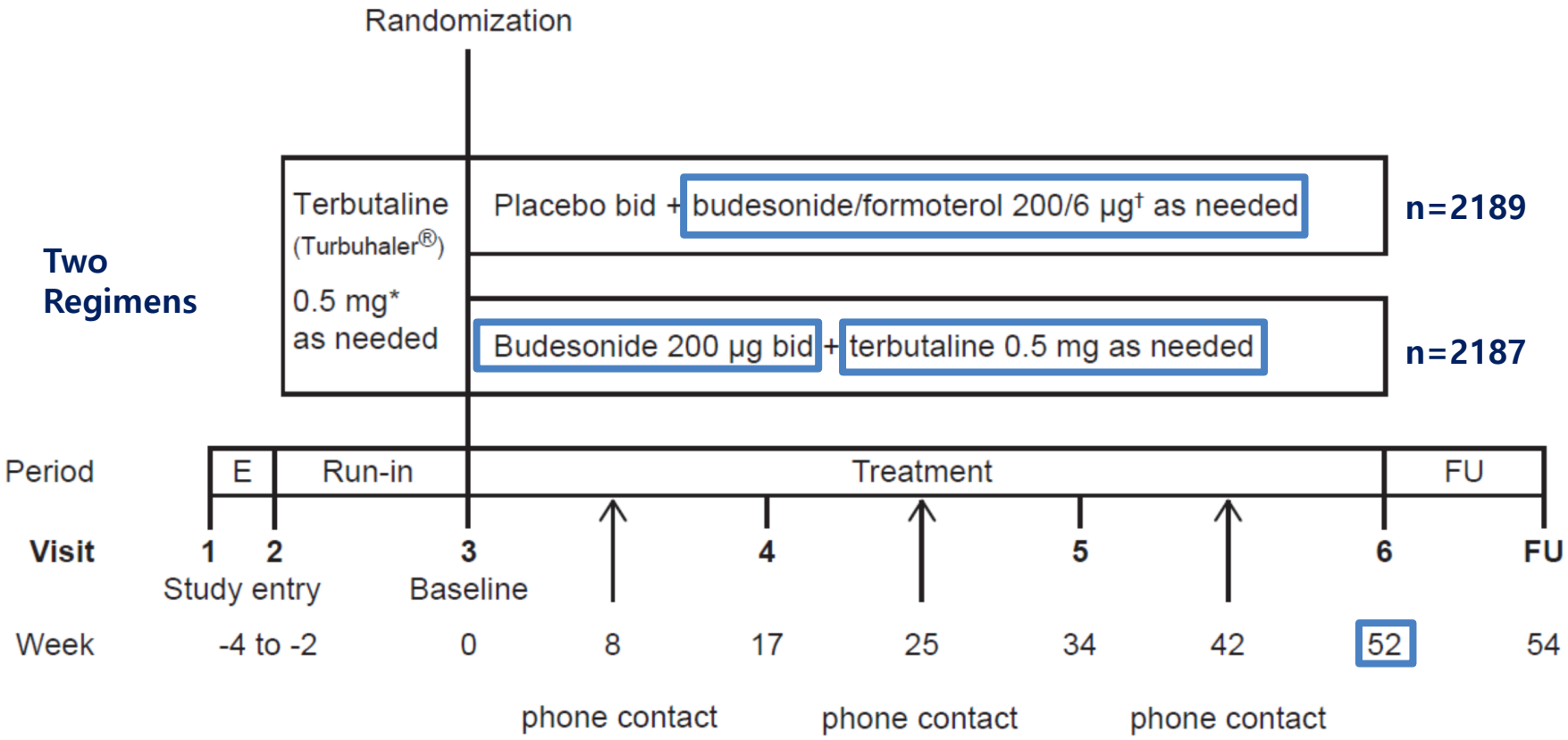


O'Byrne PM, et al. N Engl J Med 2018;378:1865-76.

- SYGMA 2 -

Symbicort Given as Needed in Mild Asthma 2

- A more **pragmatic study** design **without** daily **reminders** to use maintenance med.
- **Noninferiority** in preventing severe **exacerbation** in patients with mild asthma



Bateman ED, et al. N Engl J Med 2018;378:1877-87.

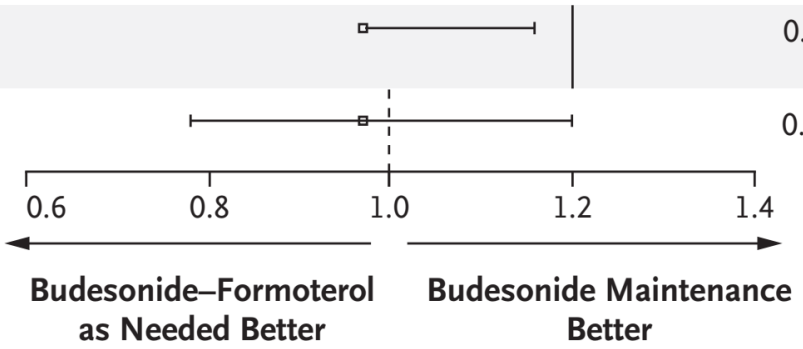
Baseline Characteristics

Characteristic	Budesonide–Formoterol as Needed (N=2089)	Budesonide Maintenance Therapy (N=2087)	Total (N=4176)
Age — yr			
Mean	41.3±16.8	40.7±17.1	41.0±17.0
Range	12–82	12–83	12–83
Female sex — no. (%)	1308 (62.6)	1289 (61.8)	2597 (62.2)
Current smoking — no. (%)	53 (2.5)	54 (2.6)	107 (2.6)
Time since asthma diagnosis — yr			
Median	7.9	7.3	7.6
Range	0.5–62.4	0.4–71.2	0.4–71.2
ACQ-5 score†			
Mean	1.49±0.89	1.53±0.90	1.51±0.90
Score ≥1.5 — no./total no. (%)	943/2043 (46.2)	1000/2037 (49.1)	1943/4080 (47.6)
FEV_1 — % of predicted value			
Before bronchodilator use	84.4±13.9	84.1±13.9	84.3±13.9
After bronchodilator use	96.3±13.8	96.0±13.5	96.1±13.6
Bronchodilator reversibility — %‡	15.1±12.4	15.2±13.0	15.2±12.7
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)

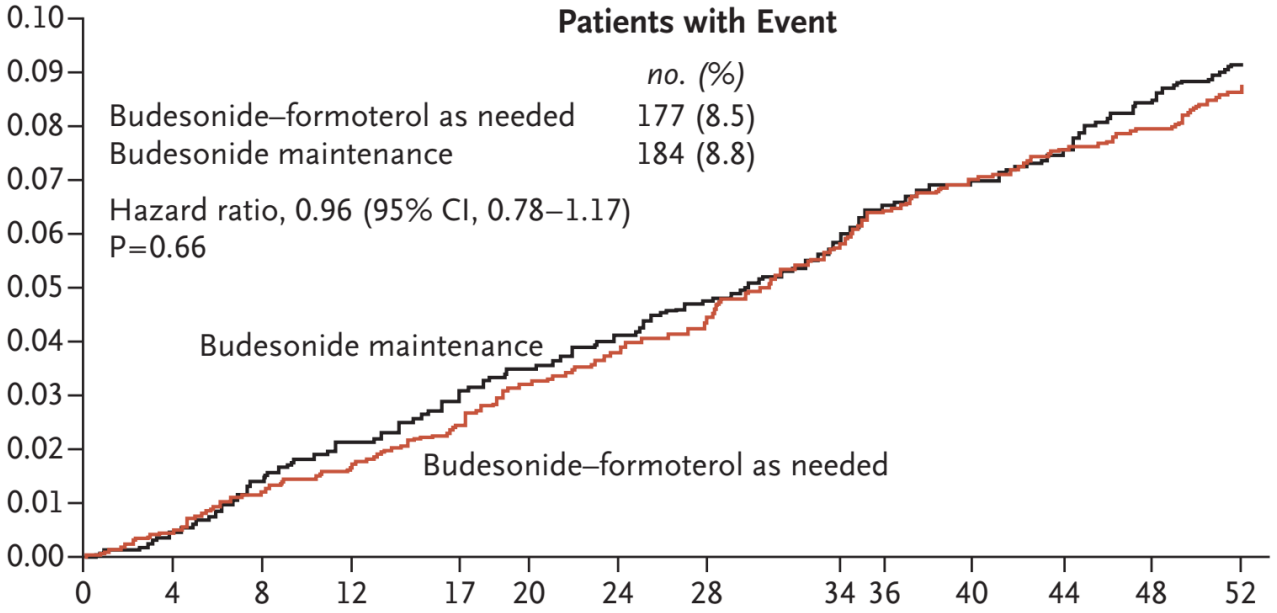
Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Annualized Rate of Severe Exacerbations

Test	Budesonide–Formoterol as Needed	Budesonide Maintenance	Rate Ratio (95% CI)	P Value
Noninferiority test	2084	2083	0.97 (NA–1.16)	—
Superiority test	2089	2087	0.97 (0.78–1.20)	0.75

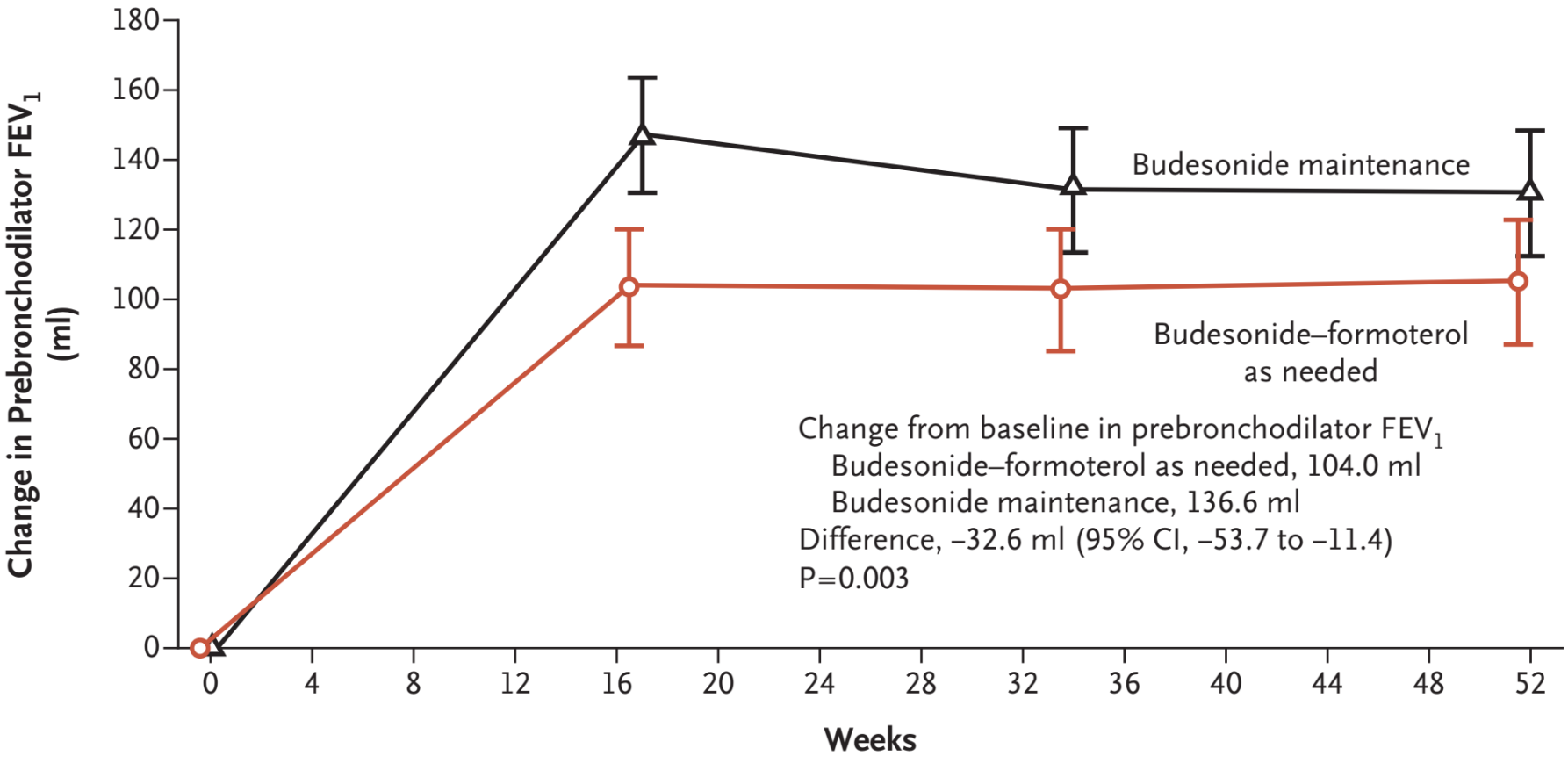


Time to First Severe Exacerbation



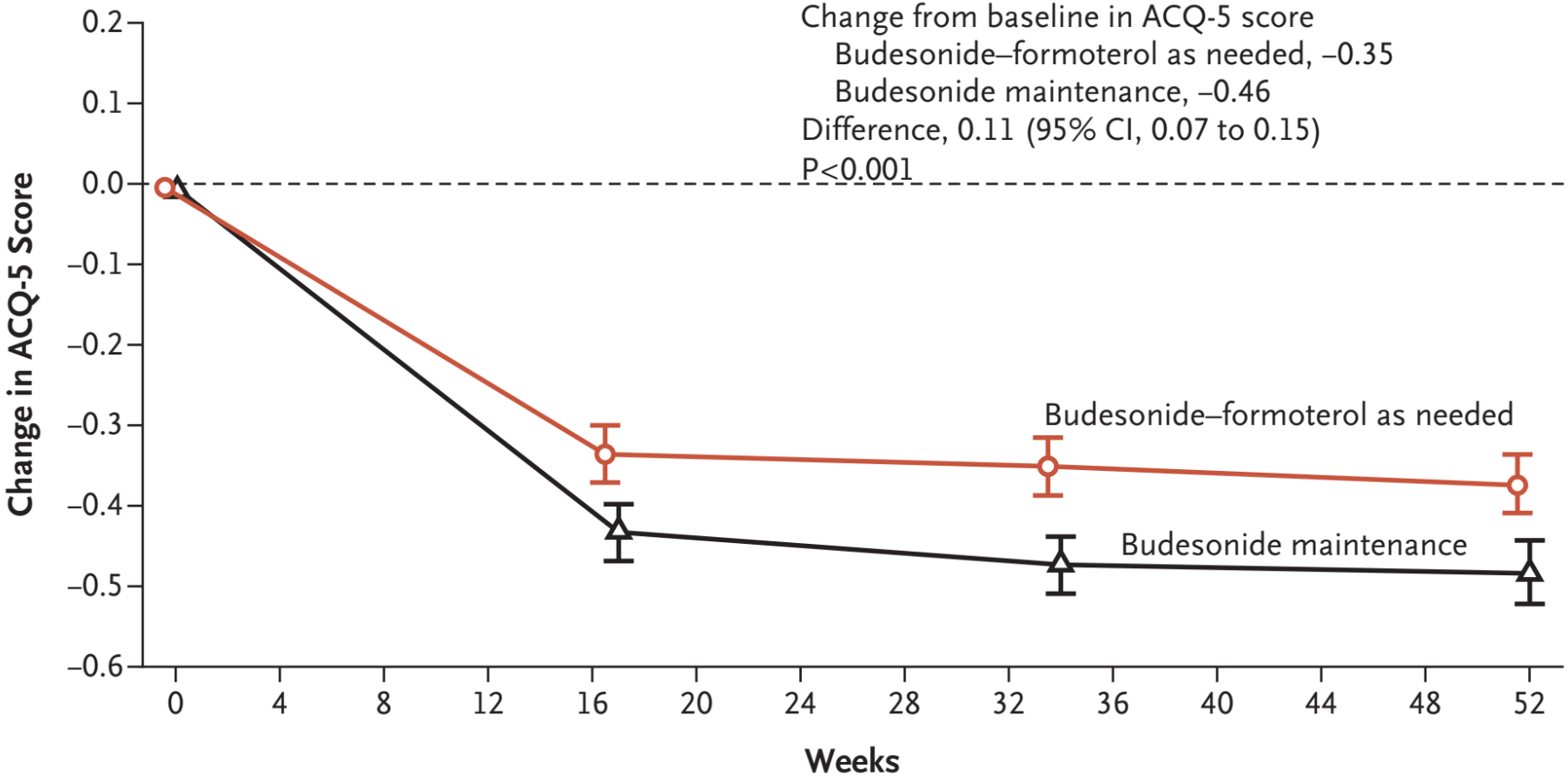
Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Change in Prebronchodilator FEV1 from Baseline



Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Change in ACQ-5 Score from Baseline

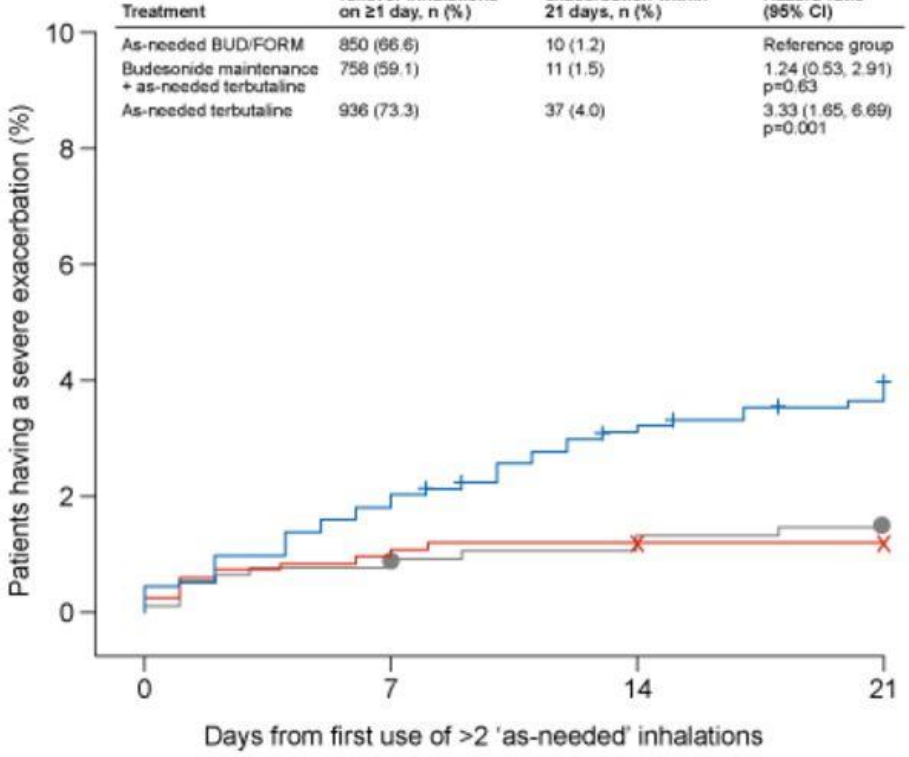


Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Risk of a Severe Exacerbation Following Higher Reliever Use: Post-hoc Analysis of SYGMA 1 in Mild Asthma

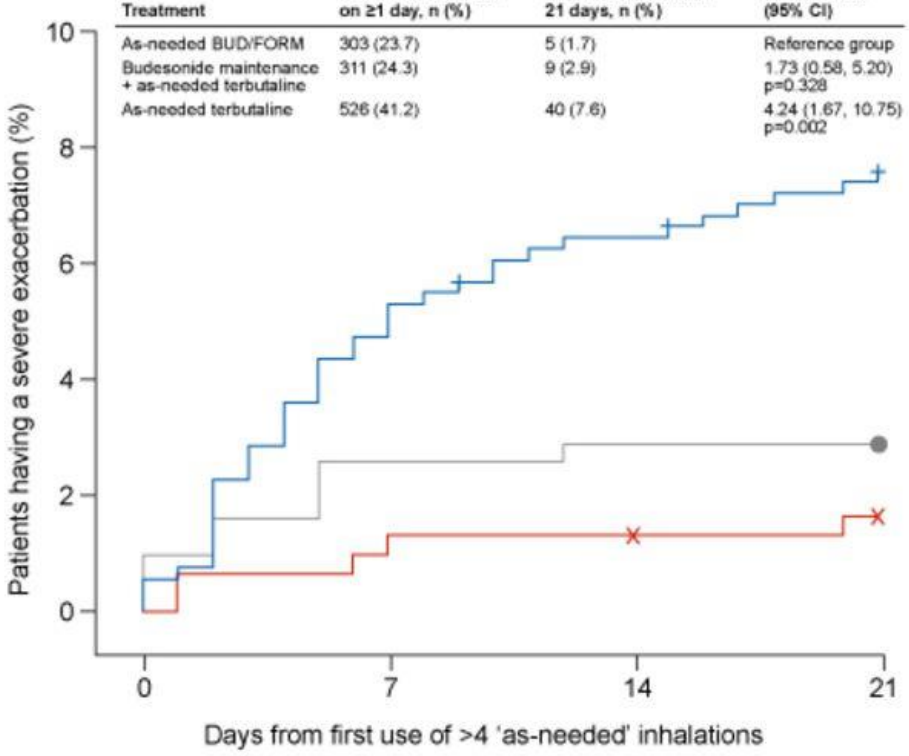
Number of 'as-needed' inhalations >2

Treatment	Patients with >2 reliever inhalations on ≥1 day, n (%)	Patients with severe exacerbation within 21 days, n (%)	Hazard ratio (95% CI)
As-needed BUD/FORM	850 (66.6)	10 (1.2)	Reference group
Budesonide maintenance + as-needed terbutaline	758 (59.1)	11 (1.5)	1.24 (0.53, 2.91) p=0.63
As-needed terbutaline	936 (73.3)	37 (4.0)	3.33 (1.65, 6.69) p=0.001



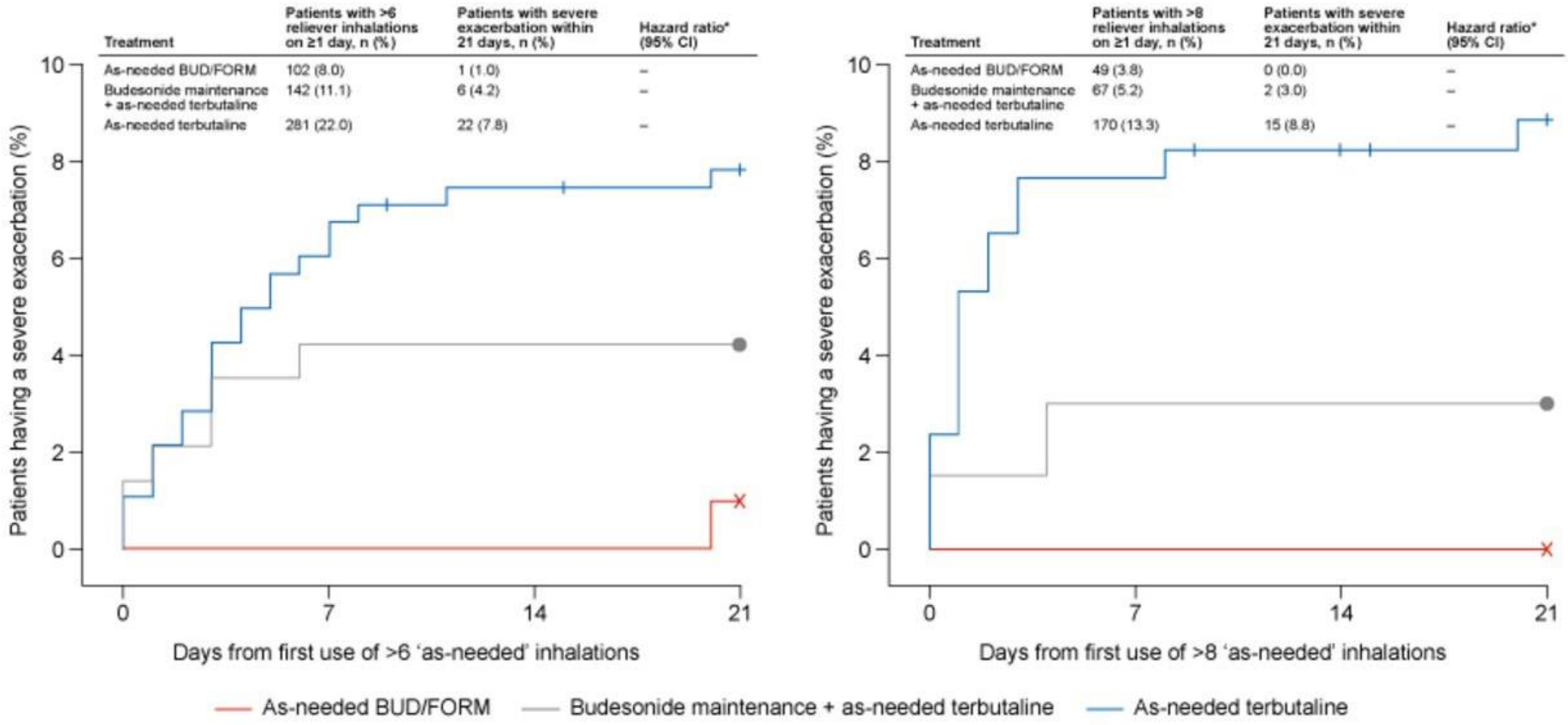
Number of 'as-needed' inhalations >4

Treatment	Patients with >4 reliever inhalations on ≥1 day, n (%)	Patients with severe exacerbation within 21 days, n (%)	Hazard ratio (95% CI)
As-needed BUD/FORM	303 (23.7)	5 (1.7)	Reference group
Budesonide maintenance + as-needed terbutaline	311 (24.3)	9 (2.9)	1.73 (0.58, 5.20) p=0.328
As-needed terbutaline	526 (41.2)	40 (7.6)	4.24 (1.67, 10.75) p=0.002



As-needed BUD/FORM — Budesonide maintenance + as-needed terbutaline — As-needed terbutaline

European Respiratory Journal 2018 52: Suppl. 62, OA1680.



*Hazard ratios were not calculated for the >6 and >8 as-needed inhalations subgroups, in view of the low event rate in the reference group (as-needed BUD/FORM; n=1 and n=0 exacerbations, respectively)

Fig. Kaplan-Meier plots showing time to first severe exacerbation in the 21 days following first day with >2, >4, >6 and >8 reliever inhalations

- The **proportion** of patients with >4, >6 or >8 as-needed inhalation use days was **lower** with **BUD/FORM as-needed** vs terbutaline as-needed ± maintenance budesonide, with **reduced risk of severe exacerbation** during the next 21 days vs terbutaline as-needed

European Respiratory Journal 2018 52: Suppl. 62, OA1680.

- **Will this strategy be effective** in patients with mild intermittent asthma?

- Will patients with asthma **who do not have eosinophilic airway inflammation** have a similar **response to inhaled glucocorticoid therapy**?

Wong GWK. N Engl J Med 2019;380:2064-6.

Novel START

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*

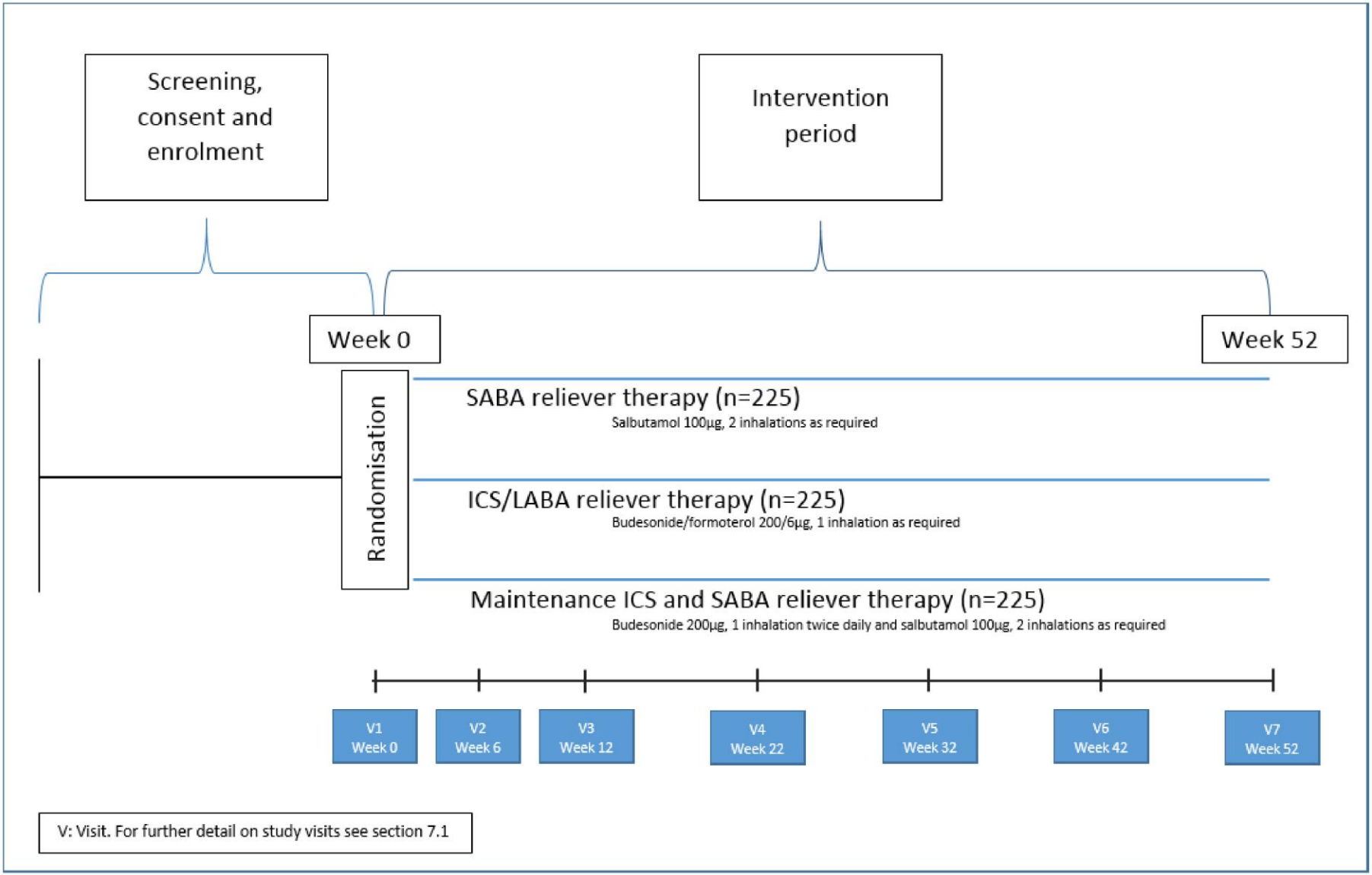
Beasley R, N Engl J Med 2019;380:2020-30.

- patients with **mild intermittent** asthma as well as patients with **mild persistent** asthma.
- In the 52-week multicenter study, adults were randomly assigned to one of three treat ments.
  - **albuterol** as needed for relief of asthma symptoms
  - **budesonide**, 200 μg twice daily, as maintenance therapy plus as needed albuterol
  - **budesonide–formoterol** as needed for relief of symptoms

- Primary outcome : **Annualized rate of asthma exacerbations**
- Secondary outcome : Score on the Asthma Control Questionnaire–5, the on treatment F EV1, the fraction of exhaled nitric oxide, the number of severe exacerbations
- **Exacerbation** defined as worsening asthma that resulted in an episode of **high β2-ago nist inhaler use**, in an **urgent medical care** consultation, or in a course of **systemic glu cocorticoids**

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

Study Design

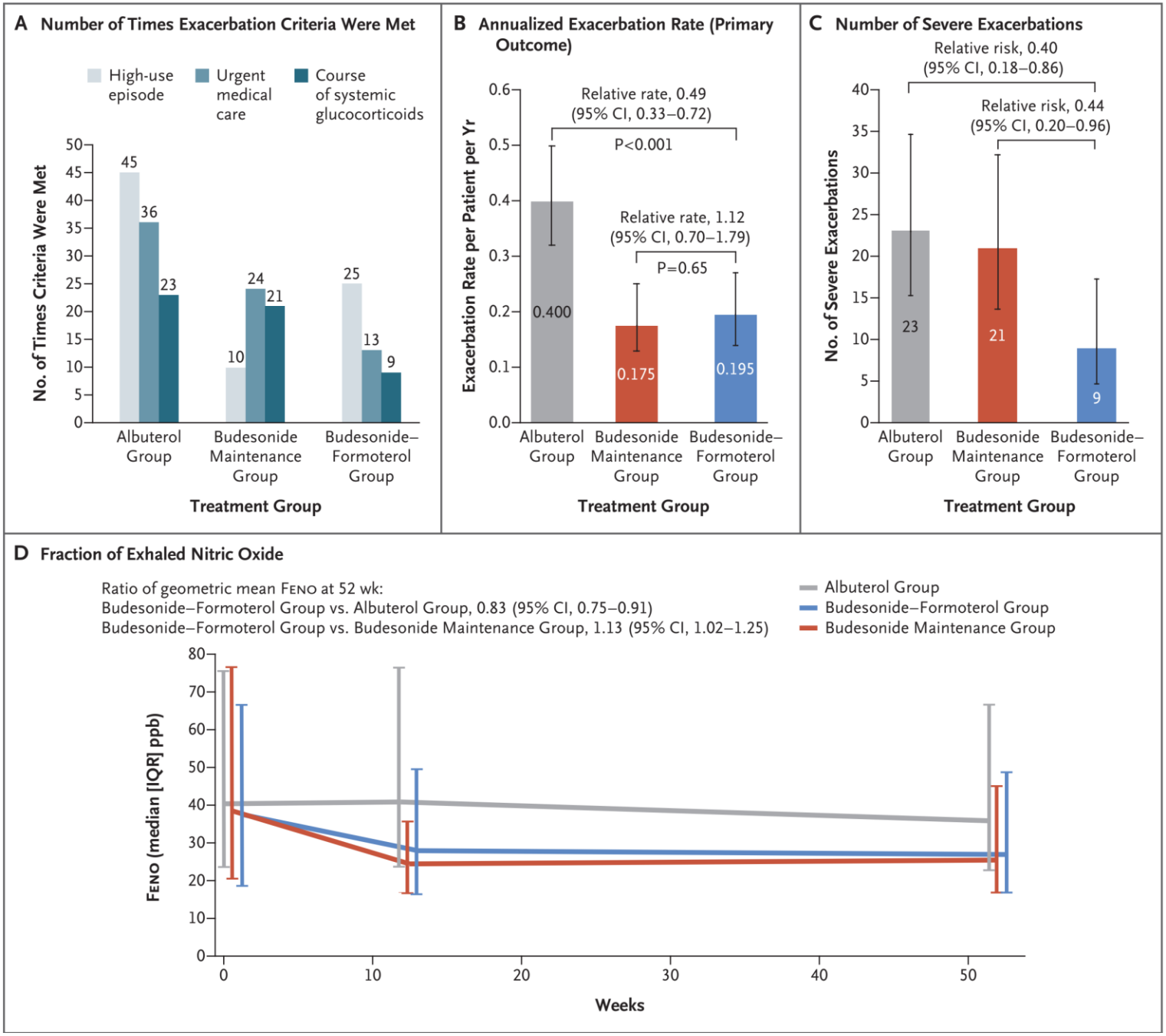


Beasley R, N Engl J Med 2019;380:2020-30.

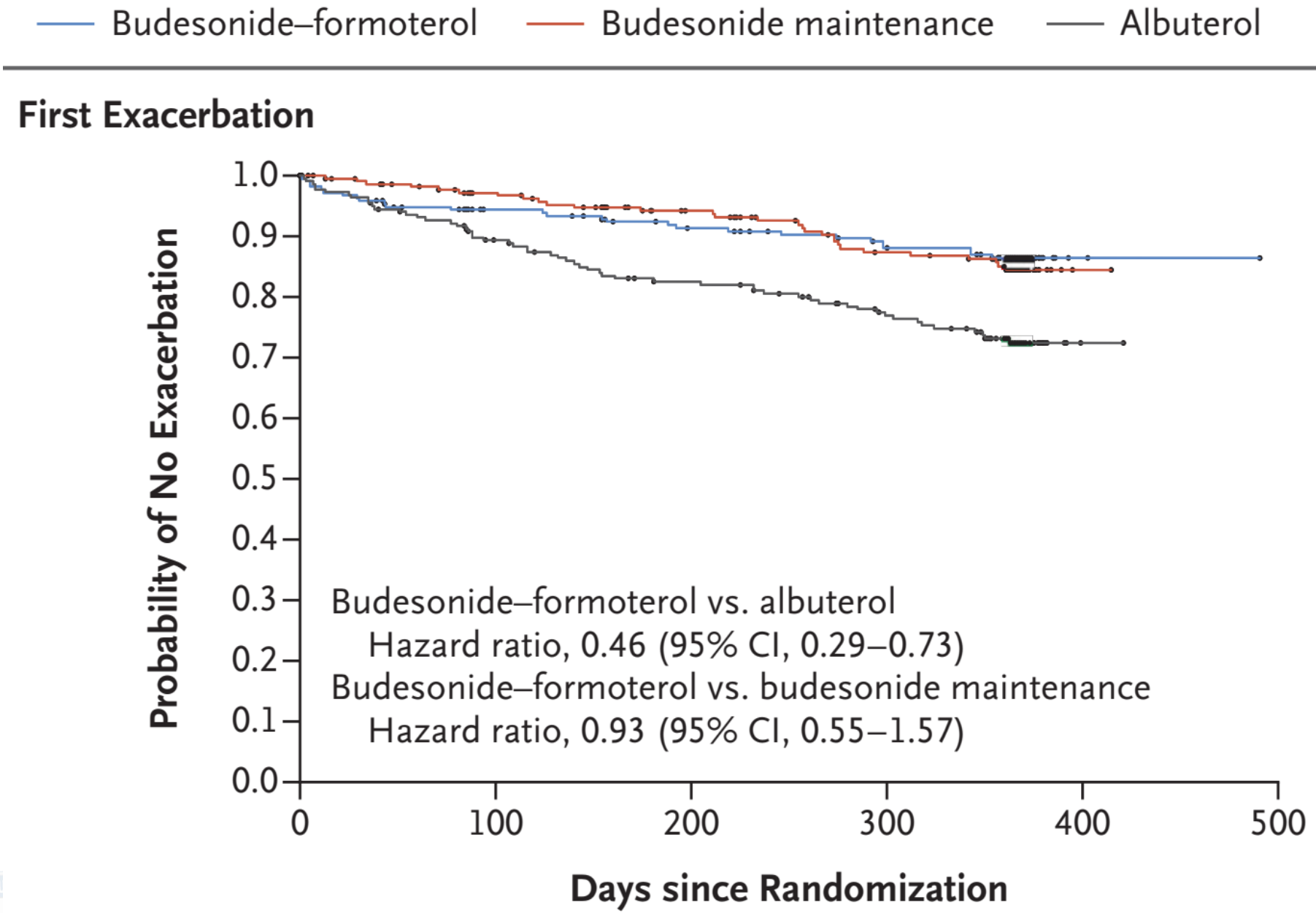
Baseline Characteristics

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

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

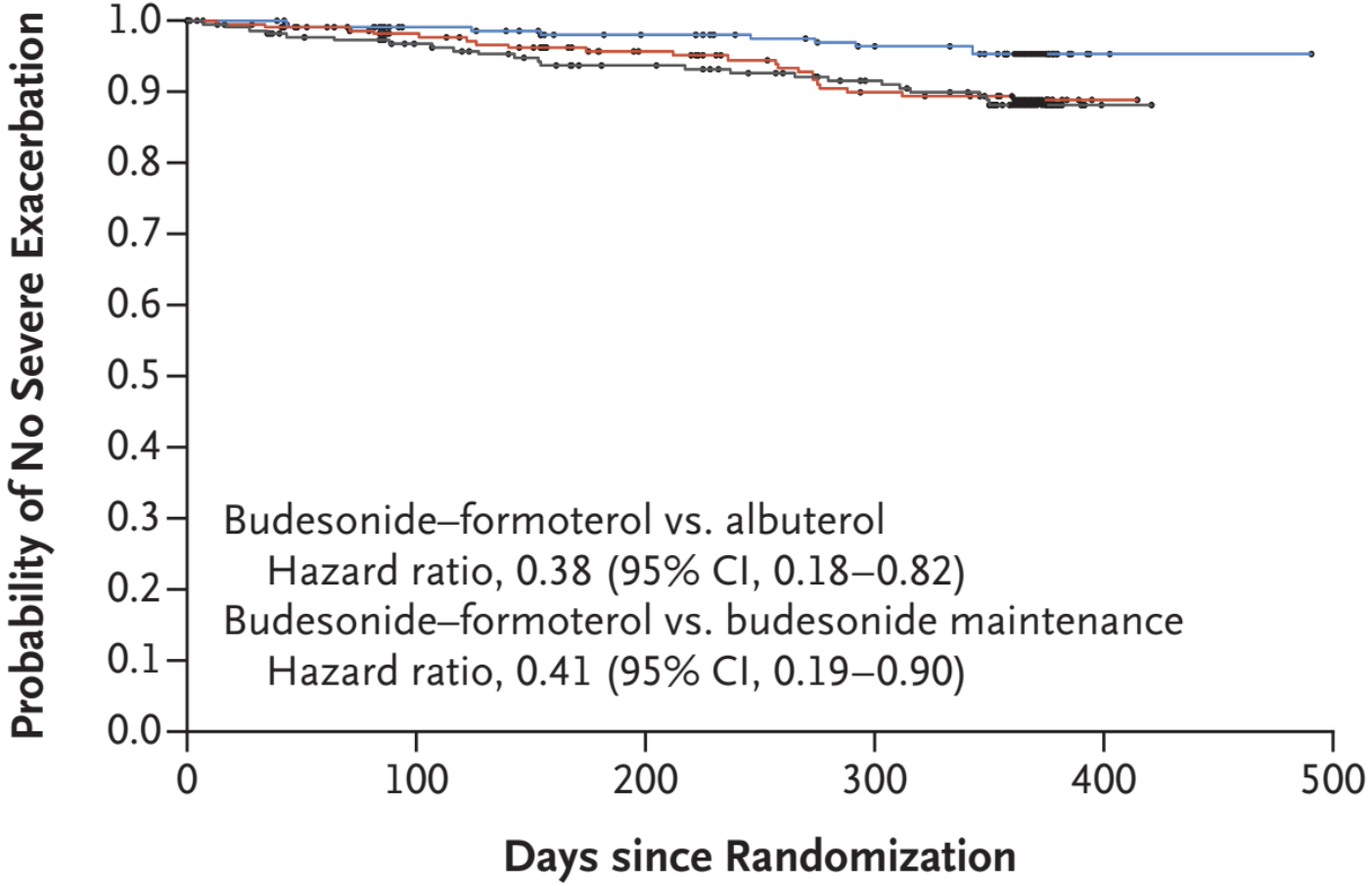


Beasley R, N Engl J Med 2019;380:2020-30.



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

First Severe Exacerbation



No. at Risk

Budesonide–formoterol	220	197	184	172	2
Budesonide maintenance	225	199	176	157	1
Albuterol	223	197	180	164	1

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

SIENA

ORIGINAL ARTICLE

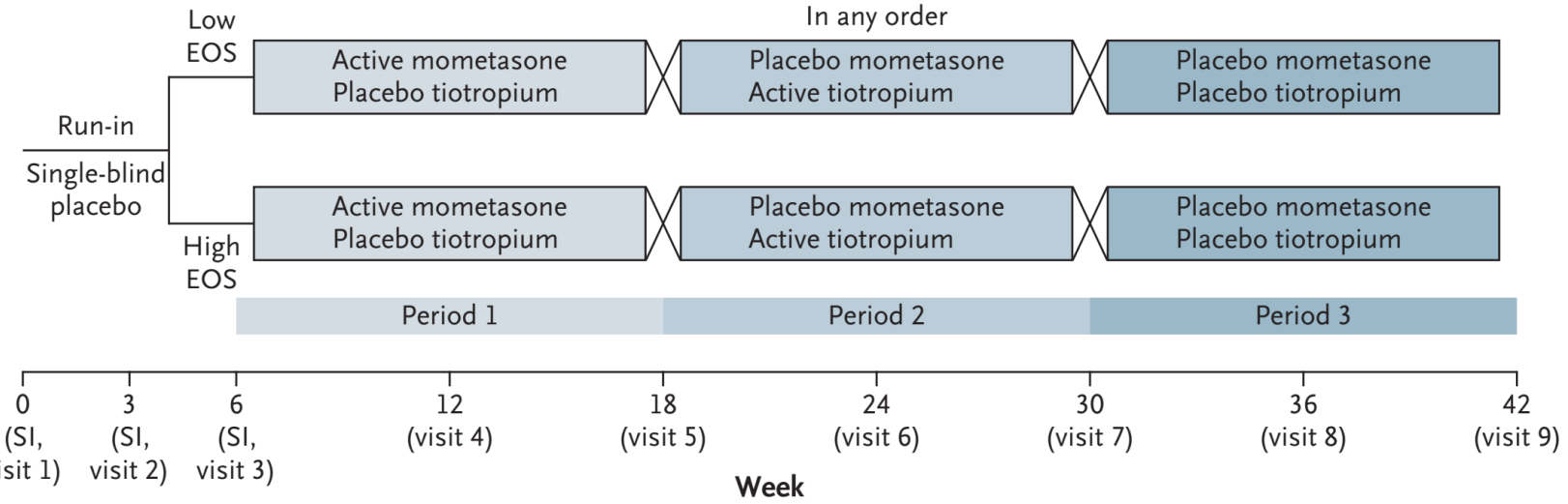
Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

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*

Lazarus SC, N Engl J Med 2019;380:2009-19.

Study Design

- A three-period, randomized, double-blind, placebo-controlled crossover trial.
  - Patients who were at least 12 years of age and had **mild, persistent asthma**.
  - Classified according to the **sputum eosinophil** level. (**<2%** or ≥2%).
- During each of the three 12-week periods
  - Twice-daily mometasone (an inhaled glucocorticoid) at a dose of 220 μg
  - Once-daily tiotropium (a long-acting muscarinic antagonist) at a dose of 5 μg
  - Twice-daily placebo
- Composite outcome: incorporated treatment failure, asthma control days, and FEV1



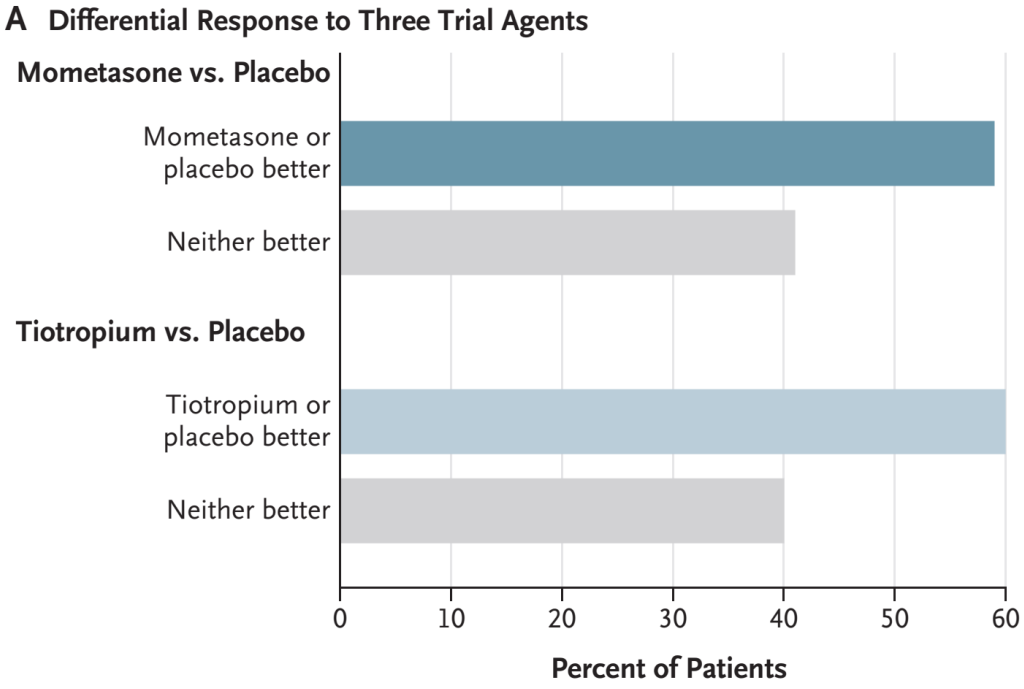
- Primary outcome : **response to mometasone** as compared with placebo and to tiotropium as compared with placebo among patients with **a low eosinophil level**

Lazarus SC, N Engl J Med 2019;380:2009-19.

Table 1. Characteristics of the Patients at Baseline.*

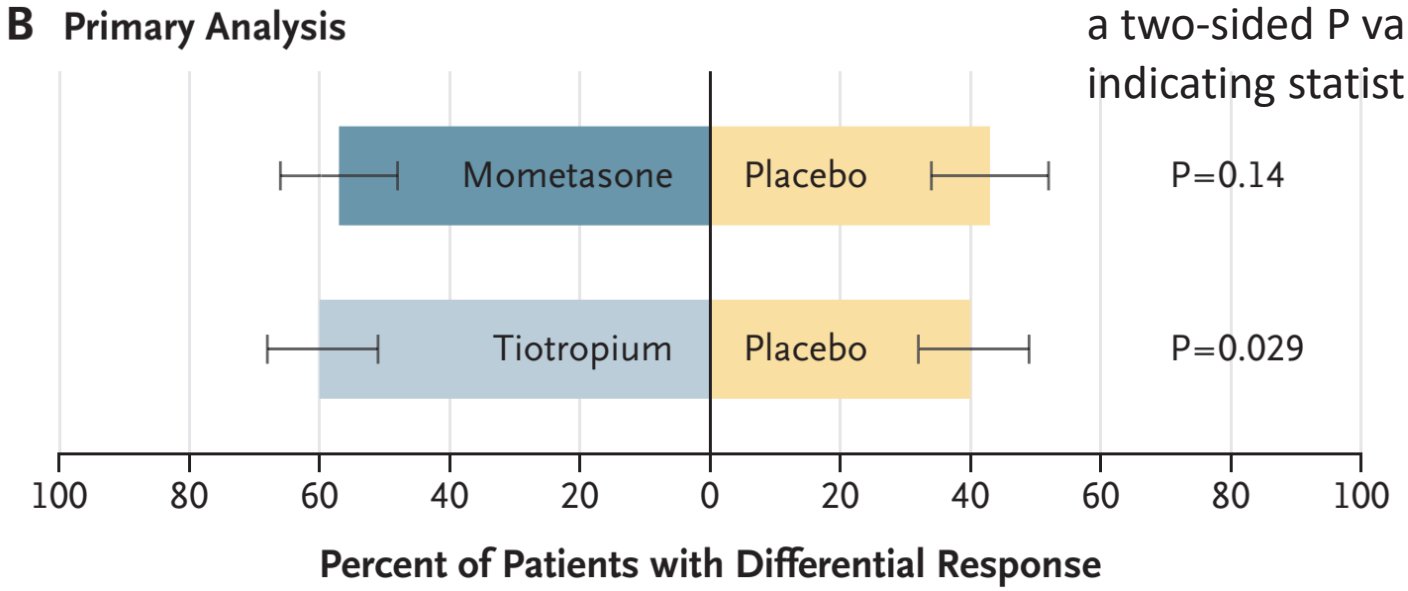
Characteristic	Low Eosinophil Level (N=221)	High Eosinophil Level (N=74)
Demographic features		
Age — yr	31.2±13.8	31.1±14.2
Male sex — no. (%)	76 (34)	35 (47)
Asthma history		
Median age at diagnosis (IQR) — yr	8.0 (3.0–15.0)	7.0 (3.0–14.0)
Duration of asthma — yr	19.2±10.9	20.0±12.2
One or more asthma episodes requiring emergency care or unscheduled office visit in previous yr — no. (%)	52 (24)	17 (23)
One or more courses of systemic glucocorticoids in previous yr — no. (%)	41 (19)	14 (19)
Clinical and spirometric features		
Body-mass index†	29.1±7.8	26.5±5.7
Predicted FEV_1 — %	92.7±12.4	89.5±10.8
Ratio of FEV_1 to FVC	0.77±0.08	0.75±0.08
Geometric mean PC_{20} (±CV) — mg/ml‡	2.42±1.28	1.24±1.27
Bronchodilator response (4 puffs) — % change	9.6±7.1	12.7±8.5
Median fraction of exhaled nitric oxide (IQR) — ppb	21.5 (14.0–35.5)	55.5 (35.0–81.0)
Median blood eosinophil level (IQR) — %	2.6 (1.1–4.0)	4.8 (3.9–7.0)
Median periostin level (IQR) — ng/ml	51.7 (43.3–63.6)	56.3 (49.3–75.2)
Median score on Asthma Control Test (IQR)§	21.0 (20.0–23.0)	21.0 (19.0–23.0)
Patients with eczema or atopic dermatitis — no. (%)	67 (30)	27 (36)
Patients with ≥1 positive allergen test — no./total no. (%)	172/216 (80)	70/72 (97)

Lazarus SC, N Engl J Med 2019;380:2009-19.



34% of the patients had better asthma control while receiving **mometasone**, **25%** had better control while receiving **placebo**

36% had better control while receiving tiotropium,
24% had better control while receiving placebo



a two-sided P value of less than 0.025 indicating statistical significance

Lazarus SC, N Engl J Med 2019;380:2009-19.

- PRACTICAL -

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†*

- **a 52-week, open-label**, parallel-group, multicentre, superiority, randomised controlled trial
- adults aged 18–75 years with a self-reported doctor's diagnosis of asthma who were **using SABA for symptom relief** with or without maintenance **low to moderate doses of inhaled corticosteroid s** in the previous 12 weeks (=**asthma patients in Step 1 to 3, without controllers other than ICS**)
- (1:1) to either **reliever therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler** (one inhalati on as needed for relief of symptoms) or **maintenance budesonide 200 µg Turbuhaler** (one inhalati on twice daily) plus **terbutaline 250 µg Turbuhaler** (two inhalations as needed)

- Primary outcome : **the number of severe exacerbations per patient per year**

Hardy J. Lancet 2019. (ePub)

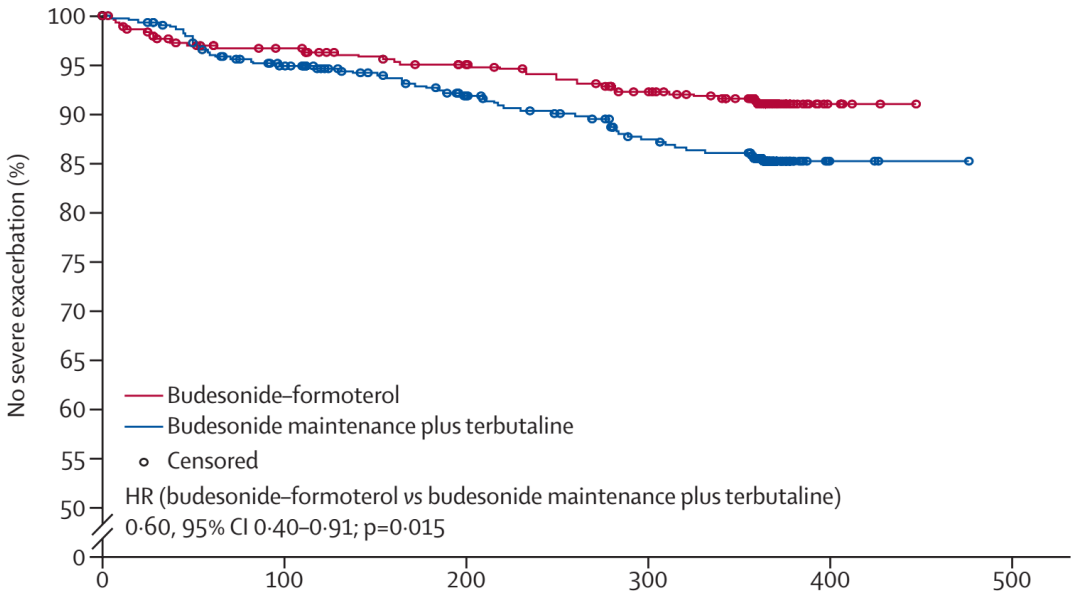
Baseline Characteristics

	Budesonide–formoterol as needed (n=437)	Budesonide maintenance plus terbutaline as needed (n=448)
Age (years)	43·3 (15·2)	42·8 (16·7)
BMI (kg/m²)	29·4 (7·1)	28·0 (5·8)
Sex		
Female	244 (56%)	241 (54%)
Male	193 (44%)	207 (46%)
Ethnic origin		
Asian	29 (7%)	34 (8%)
European	342 (78%)	357 (80%)
Māori	41 (10%)	31 (7%)
Pacific	20 (5%)	16 (4%)
Other	5 (1%)	10 (2%)
Smoking status		
Current	39 (9%)	24 (5%)
Ex-smoker	123 (28%)	112 (25%)
Never	275 (63%)	312 (70%)
Pack-years (among ever smokers)	4·5 (4·7)	4·6 (4·7)
Age at diagnosis (years)	19·5 (17·7)	18·8 (18·1)
Patient-reported use of inhaled corticosteroids in the 12 weeks before enrolment	305 (70%)	316 (71%)
Patient-reported adherence to inhaled corticosteroids in the 4 weeks before enrolment (percentage of prescribed dose)	54·8% (37·0; n=304)	58·6% (47·3; n=315)
Patient-reported use of inhaled corticosteroids ever	390 (89%)	381 (85%)
Patient-reported SABA use in 4 weeks before enrolment (occasions per week)		
Mean (SD)	4·3 (6·0)	4·9 (7·5)
Median (IQR)	2·0 (1·0–5·5)	2·3 (1·0–6·0)
Range	0–70	0–84
Hospital admissions for asthma during lifetime (number per patient)	0·7 (5·1)	0·5 (2·1)
Severe exacerbation in the previous 12 months		
0	384 (88%)	396 (88%)
1	45 (10%)	41 (9%)
2	5 (1%)	7 (2%)
3	3 (<1%)	3 (<1%)
4	0	1 (<1%)
Any	53 (12%)	52 (12%)
ACQ-5 score*	1·1 (0·8)	1·2 (0·8)
GINA symptom control		
Well controlled	101 (23%)	103 (23%)
Partly controlled	209 (48%)	226 (51%)
Uncontrolled	127 (29%)	119 (27%)
On-treatment FEV_1 (percentage of predicted value†)	87·8% (16·4)	87·4% (16·3)
FENO (parts per billion)	26·0 (15·0–51·0)	30·0 (18·0–62·5)
Blood eosinophil count (×10⁹ per L)	0·3 (0·2)	0·3 (0·2)

Hardy J. Lancet 2019. (ePub)

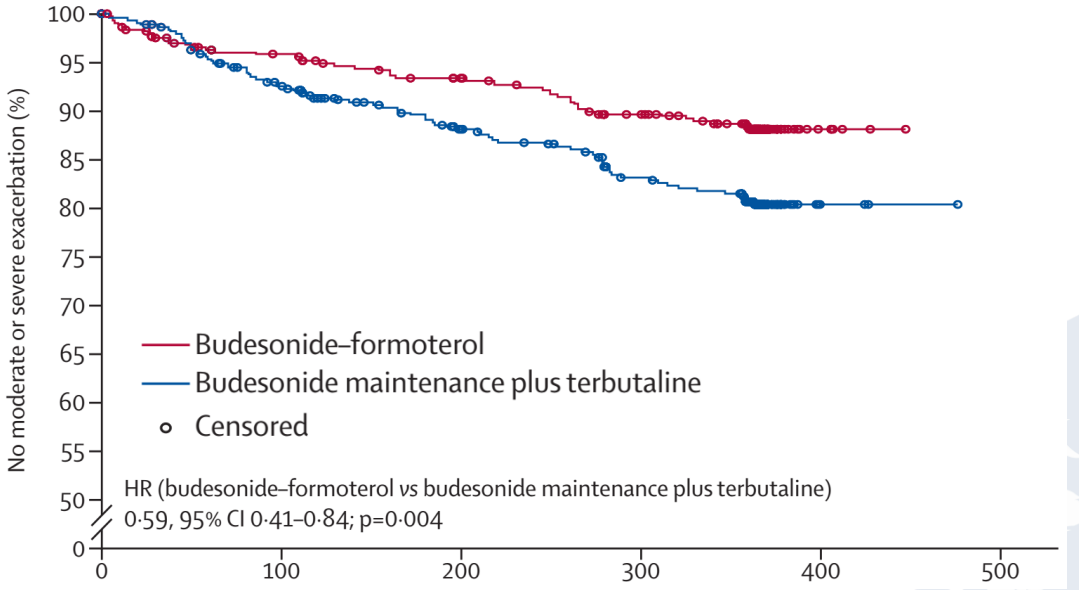
Time to First Severe AE

HR (budesonide–formoterol vs budesonide maintenance plus terbutaline)
0·60, 95% CI 0·40–0·91; p=0·015



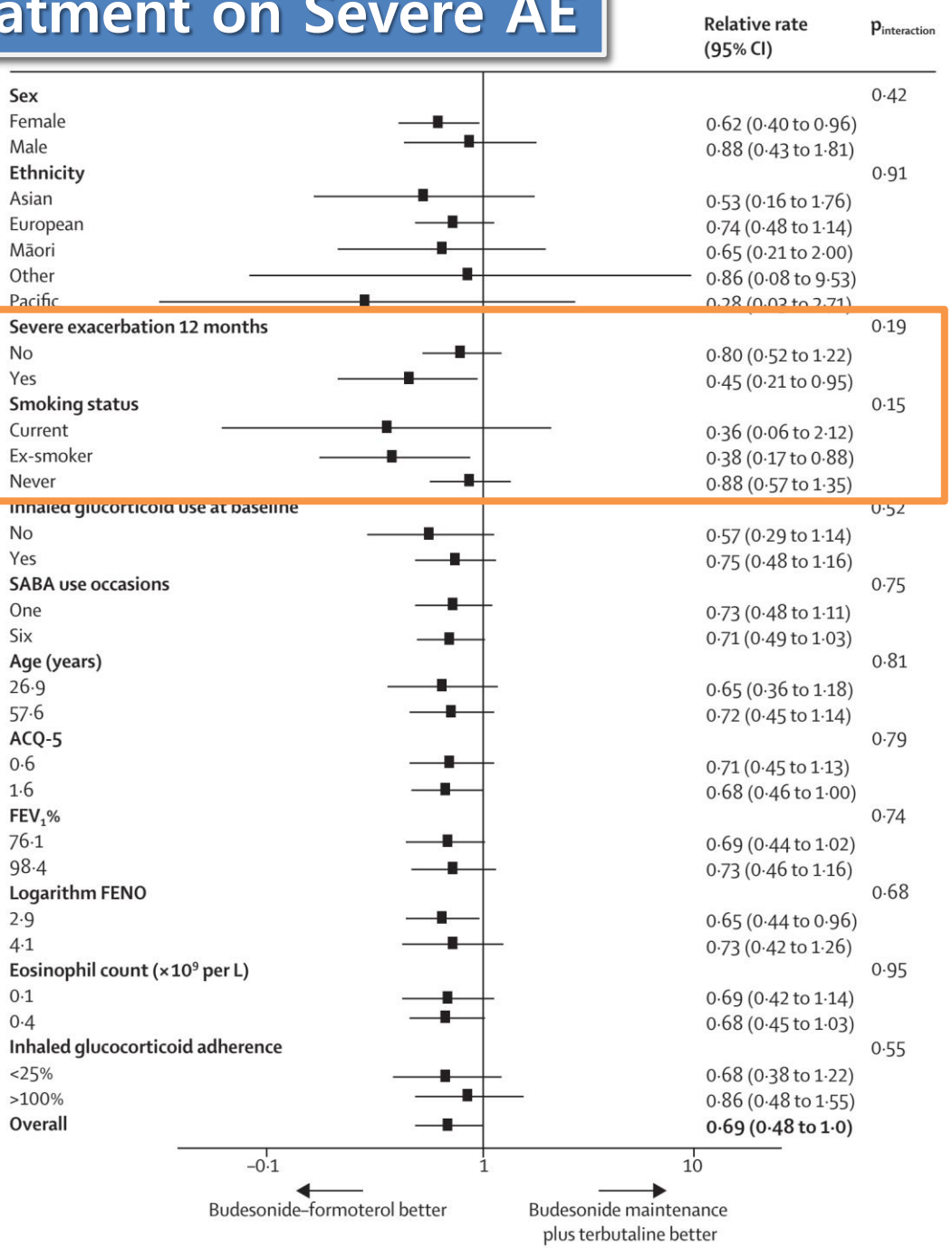
Time to First Moderate or Severe AE

HR (budesonide–formoterol vs budesonide maintenance plus terbutaline)
0·59, 95% CI 0·41–0·84; p=0·004



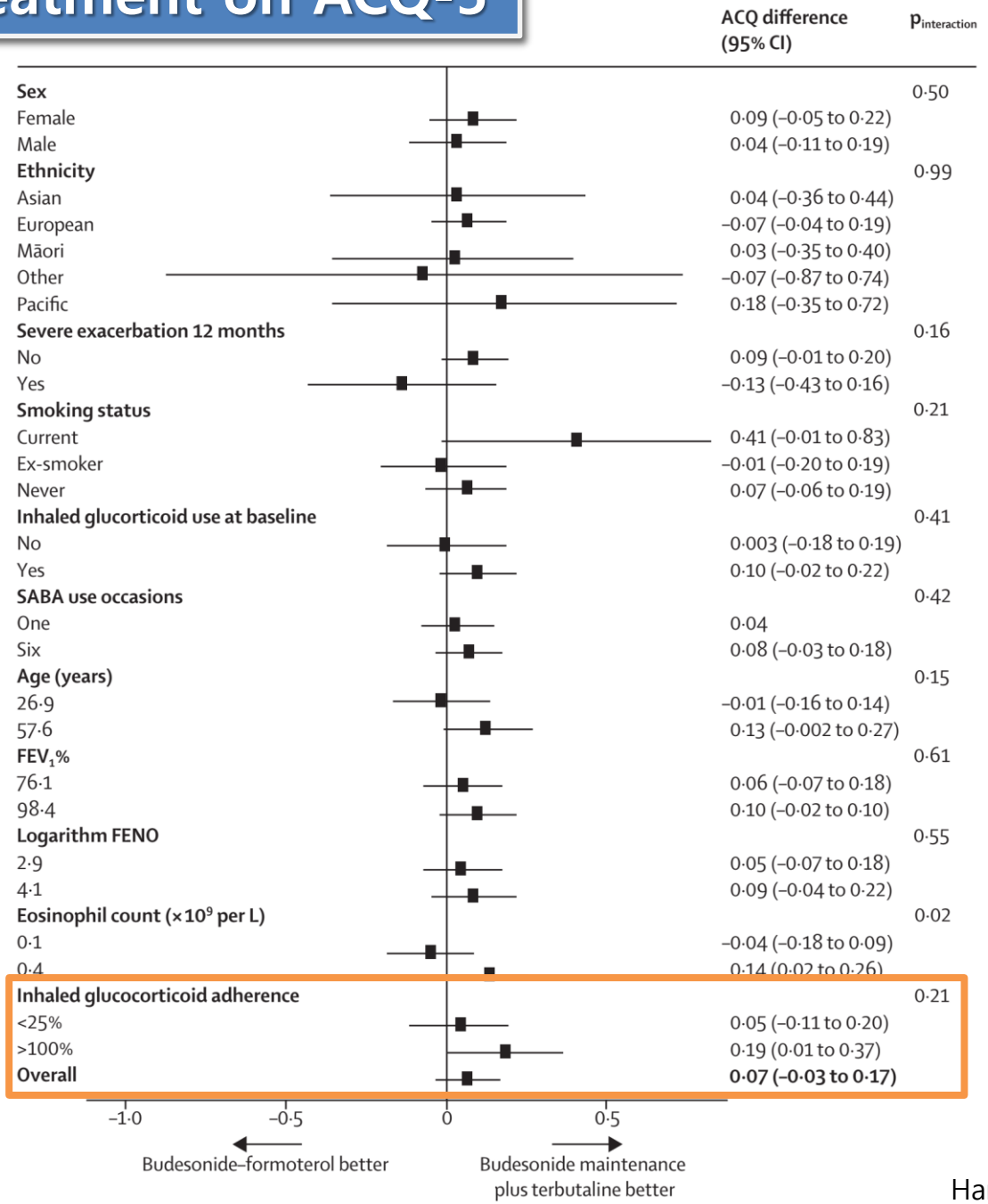
Hardy J. Lancet 2019. (ePub)

Effect of Treatment on Severe AE



Hardy J. Lancet 2019. (ePub)

Effect of Treatment on ACQ-5



Hardy J. Lancet 2019. (ePub)

Medication Outcomes in Electronic Monitoring Subgroups

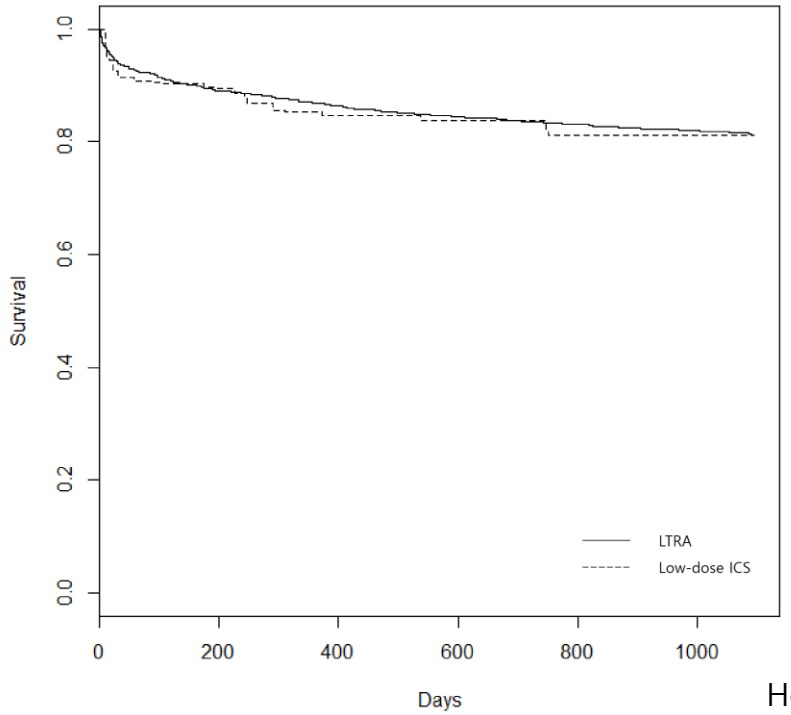
	Budesonide–formoterol as needed (n=55)	Budesonide maintenance plus terbutaline as needed (n=55)
Inhaled corticosteroid use		
Number of budesonide-containing actuations per day		
Mean (SD)	0·9 (0·7)	1·5 (0·4)
Median (IQR)	0·8 (0·4–1·3)	1·6 (1·2–1·8)
Range†	0·0–3·4	0·1–2·3
Daily budesonide dose (µg)		
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

Hardy J. Lancet 2019. (ePub)

A Comparison Of Leukotriene Receptor Antagonists To Low-dose Inhaled Corticosteroids In Elderly Mild Asthmatics

- the National Health Insurance Service-National Sample Cohort
- from January 2003 to December 2010
- over 65 years of age at the date when LTRAs or low-dose ICSs were newly prescribed
- The risks of asthma exacerbation / Cox proportional-hazard regression
- LTRA (n=1,571) vs ICSs (n=121)

Exacerbation-free Survival



Hong SH, J Allergy Clin Immunol Pract 2019.

GINA 2019 – landmark changes

- For safety, GINA **no** longer recommends **SABA-only** treatment for **Step 1**
  - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any **ICS significantly reduces the risk**
- GINA now recommends that all adults and adolescents with asthma should receive **symptom-driven** or **regular low dose ICS-containing controller treatment**, to reduce the risk of serious exacerbations
  - This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives

GINA 2019

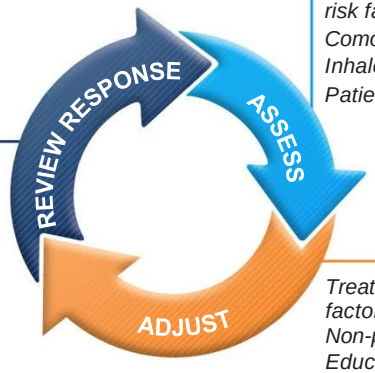
Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

'Controller' treatment means the treatment taken to prevent exacerbations

Asthma medication options:
Adjust treatment up and down for individual patient needs



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

Symptoms Exacerbations Side-effects Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training Asthma medications

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV_1 >70% predicted

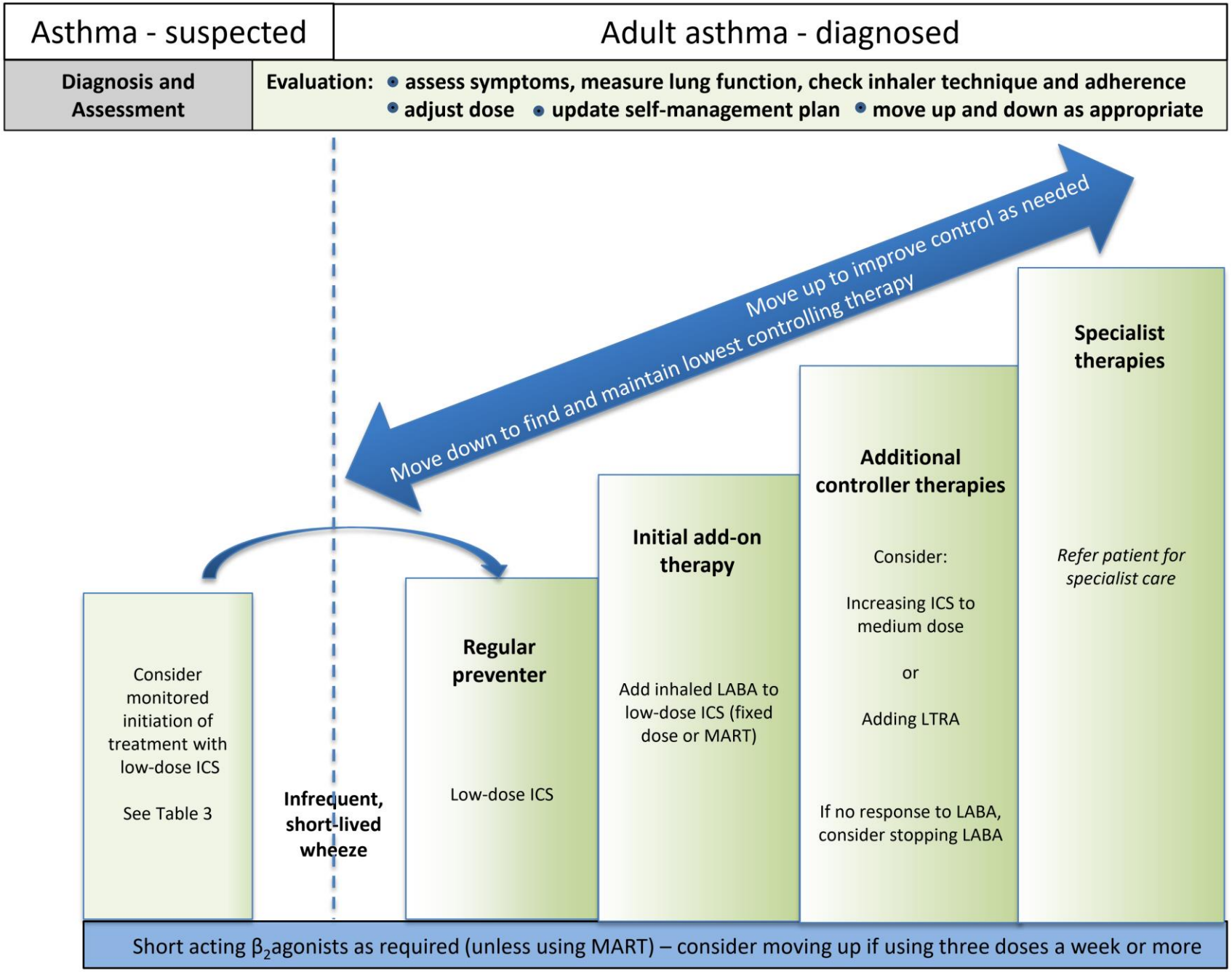
Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

SIGN 158

British guideline on the management of asthma

A national clinical guideline

First published 2003
Revised edition published July 2019



British guideline on the management of asthma 2019

Treatment Options for Mild Asthma

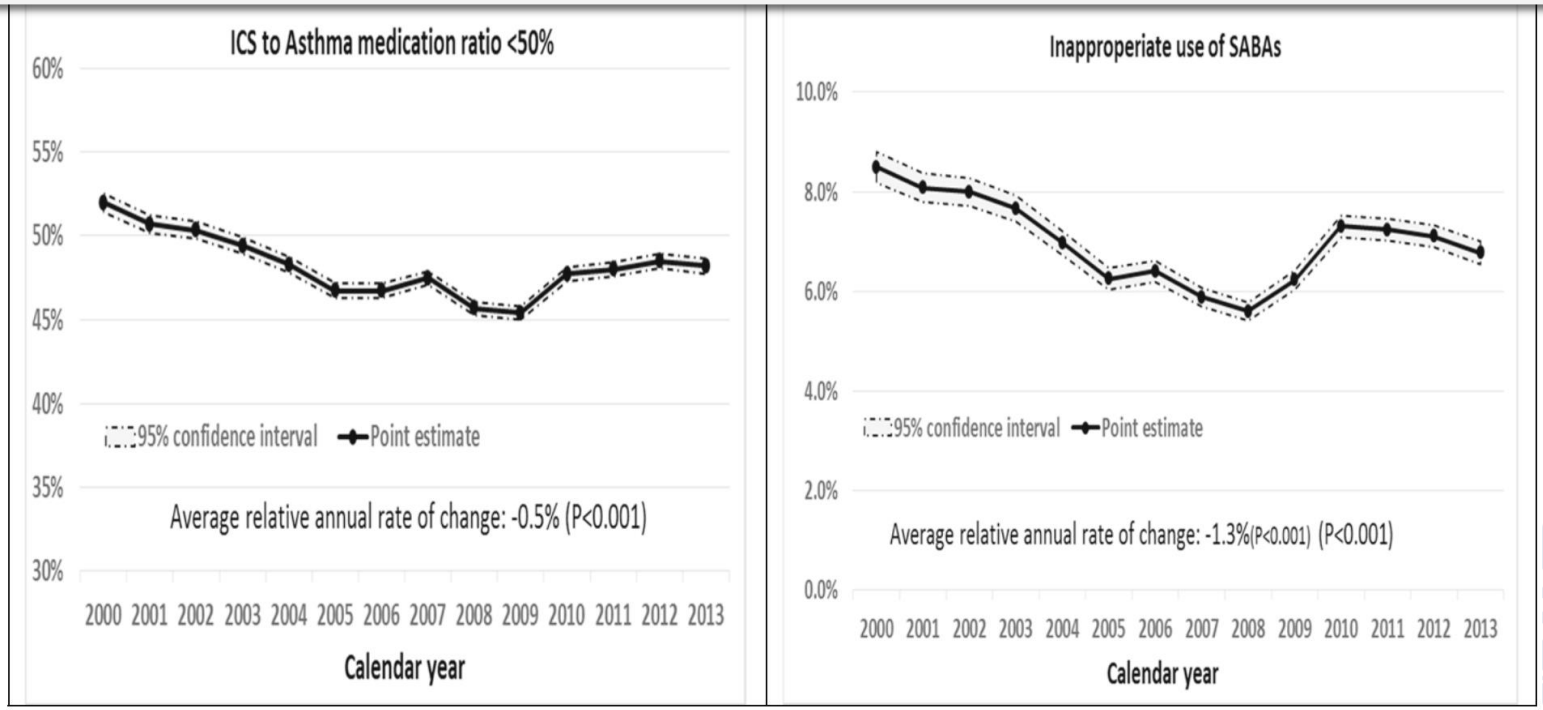
Treatment option	Comments
Low-dose ICS	Current first-line treatment; robust evidence of effectiveness. May be preferred in patients willing to have optimal asthma control and prevent any asthma-related lung function decline. Side effects are mild and local (hoarseness, oral candidiasis).
Low-dose ICS + formoterol as needed	Alternative treatment; good quality evidence for effectiveness. Compared with regular ICS: similar reduction in exacerbation risk, worse symptom control and lung function. May be preferred in patients with low adherence to treatment or afraid of side effects. Lower cumulative ICS dose.
LTRA	Alternative treatment; less effective than ICSs. May be preferred in patients with concomitant allergic rhinitis or those afraid of side effects (or experiencing such effects).
Theophylline	Alternative treatment mentioned in the GINA guidelines; less effective than ICS. Should not be used in settings when inhaled drugs are available due to the risk of serious side effects

O'Byrne PM, Pol Arch Intern Med 2018;128:545-9.

Extent, trends, and determinants of controller/reliever balance in mild asthma: a 14-year population-based study

a population-based cohort of adolescents/adults with mild asthma using validated case definition algorithms from administrative health databases in BC, Canada (2000 to 2013)

Trend of controller prescription to total medications (left panel) and inappropriate use of SABAs (right panel) over calendar year



Khakban A, Respir Res 2019;20:44.

Factors Associated With Suboptimal Controller Use And Inappropriate Use Of Relievers

Group	Variable	Controller to total medications < 50%			Inappropriate SABA use		
		Odds Ratio	95% CI (Lower, Upper)	*P* value	Odds Ratio	95% CI (Lower, Upper)	*P* value
Socio-demographic	Sex (female = 1)	0.97	0.95–0.99	<.0003	0.78	0.76–0.81	<.0003
	Higher SES	0.97	0.97–0.98	<.0001	0.98	0.97–0.98	<.0001
	Year	0.99	0.98–1.00	<.0001	0.96	0.96–0.97	<.0001
	Age	0.81	0.81–0.82	<.0001	0.9	0.89–0.91	<.0001
Asthma treatment variables	Asthma-related hospitalization	1.63	1.51–1.76	<.0001	0.99	0.83–01.18	0.9222
	Asthma-related outpatient visit	0.95	0.94–0.96	<.0001	0.89	0.88–0.91	<.0001
	Oral corticosteroid	1.28	1.25–1.30	<.0001	0.4	0.38–0.41	<.0001
	Severity of Asthma	1.18	1.16–1.20	<.0001	3.6	3.52–3.69	<.0001
Comorbidity-related variables	Modified Charlson score	1.11	1.09–1.12	<.0001	0.98	0.96–1.00	0.1033
	None asthma related hospitalization	1.01	1.00–1.02	0.0009	1.01	1.00–1.03	0.0789
	None asthma related outpatient visit	1.00	1.00–1.00	<.0001	1.00	1.00–1.00	0.0137
Type & quality of care	Having received pulmonary function test	0.95	0.92–0.97	<.0003	0.87	0.82–0.92	<.0001
	Respirologist consultation	0.57	0.54–0.59	<.0001	0.54	049–0.60	<.0001
	Internal medicine consultation	0.98	0.93–1.03	0.5501	0.74	0.67–0.81	0.0014
	General Practitioner Asthma visit	0.67	0.66–0.68	<.0001	1.16	1.12–1.19	<.0001
	Continuity of care (COC)						
	COC = 0	–	–	–		–	–
	COC > 0 and COC < 50%	0.84	0.82–0.86	<.0001	0.76	0.74–0.79	<.0001
	COC > =50% and OC < 100%	0.86	0.84–0.88	<.0001	0.84	0.80–0.88	0.0014
	COC = 100%	0.86	0.83–0.83	<.0001	0.85	0.80–0.90	<.0001

SABA short-acting beta agonist, *SES* socio-economic status, *CI* confidence interval

Khakban A, Respir Res 2019;20:44.