2018 Airway Symposium

Diagnosis and Treatment of

Mild Asthma

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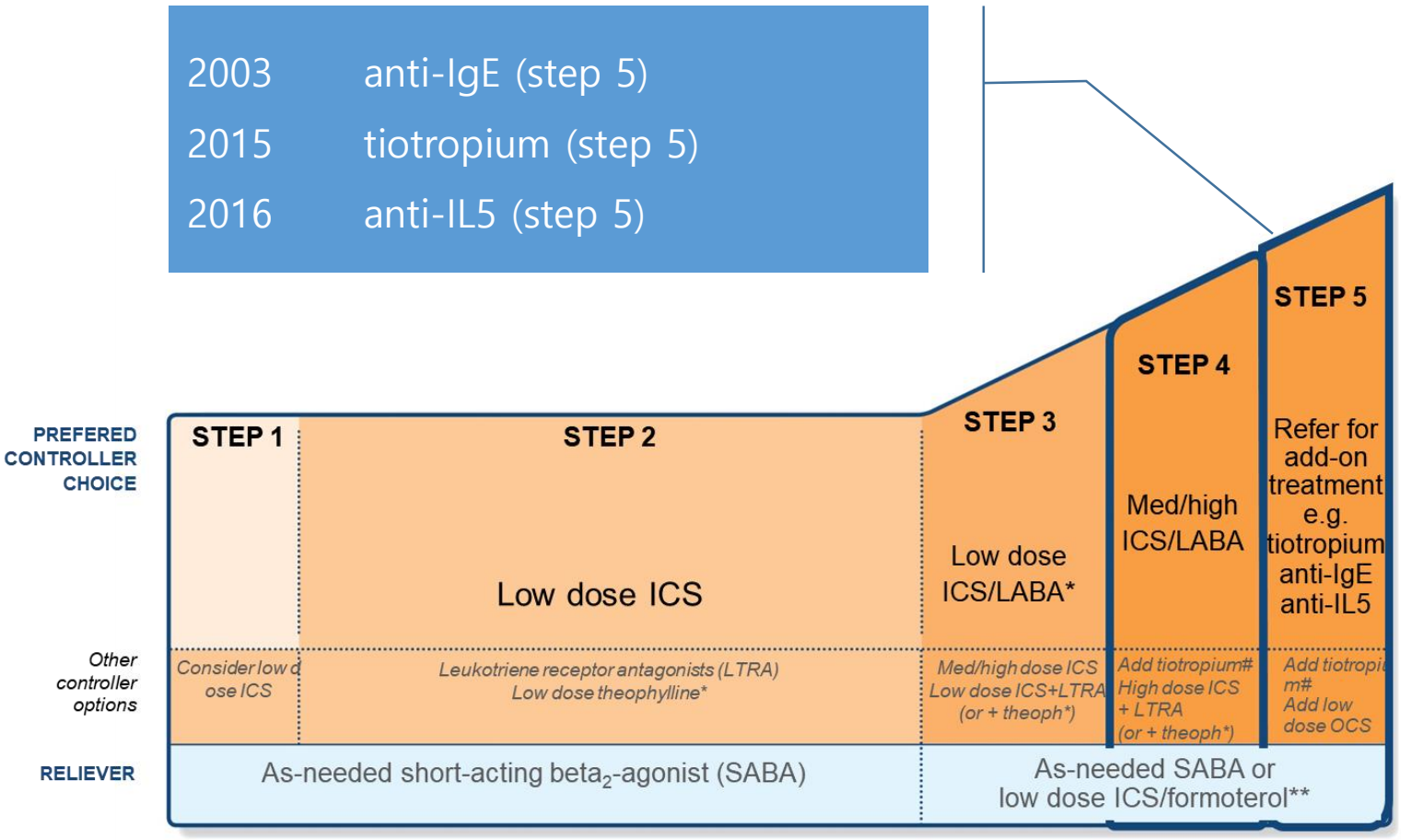
NEW Asthma Pharmacotherapy

2003	anti-IgE (step 5)
2015	tiotropium (step 5)
2016	anti-IL5 (step 5)



The Global Initiative for Asthma 2018, www.ginasthma.org

Severe Asthma Working Group, KAAACI

The Korean Academy of Asthma, Allergy and Clinical Immunology

The Korean Academy of Asthma, Allergy and Clinical Immunology

Severe Asthma Workgroup

- Researching New Targets for Severe Asthma Therapy -

한국어(KOREAN) · ENGLISH · REDCAP (REGISTRY)

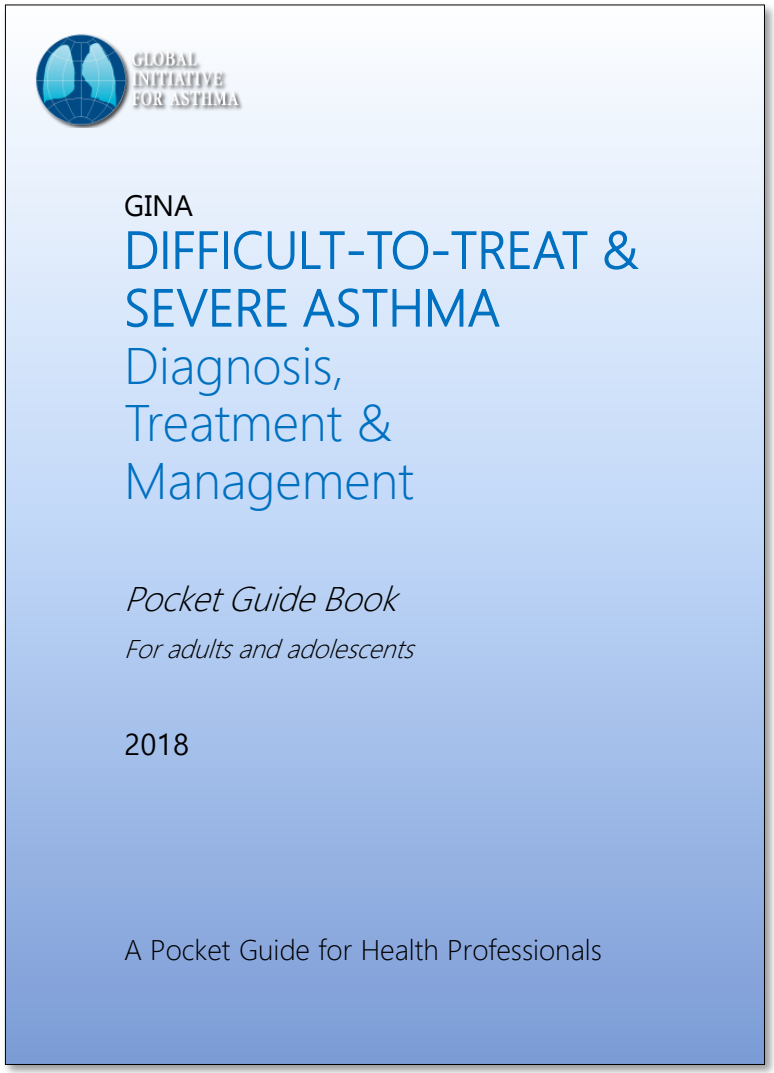
Severe Asthma Registry

What is severe asthma?

- Severe asthma is often defined as asthma requiring a high level of treatment to prevent it from becoming or remaining uncontrolled.
- Poor control of severe asthma is associated with frequent exacerbation, high medical costs, and mortality
- Even with vigorous research to understand severe asthma, neither an effective nor a comprehensive strategy has been determined to diagnose and treat severe asthma in clinical practice.

https://severeasthmawg.com/

Guideline of Severe Asthma by GINA (not published yet)



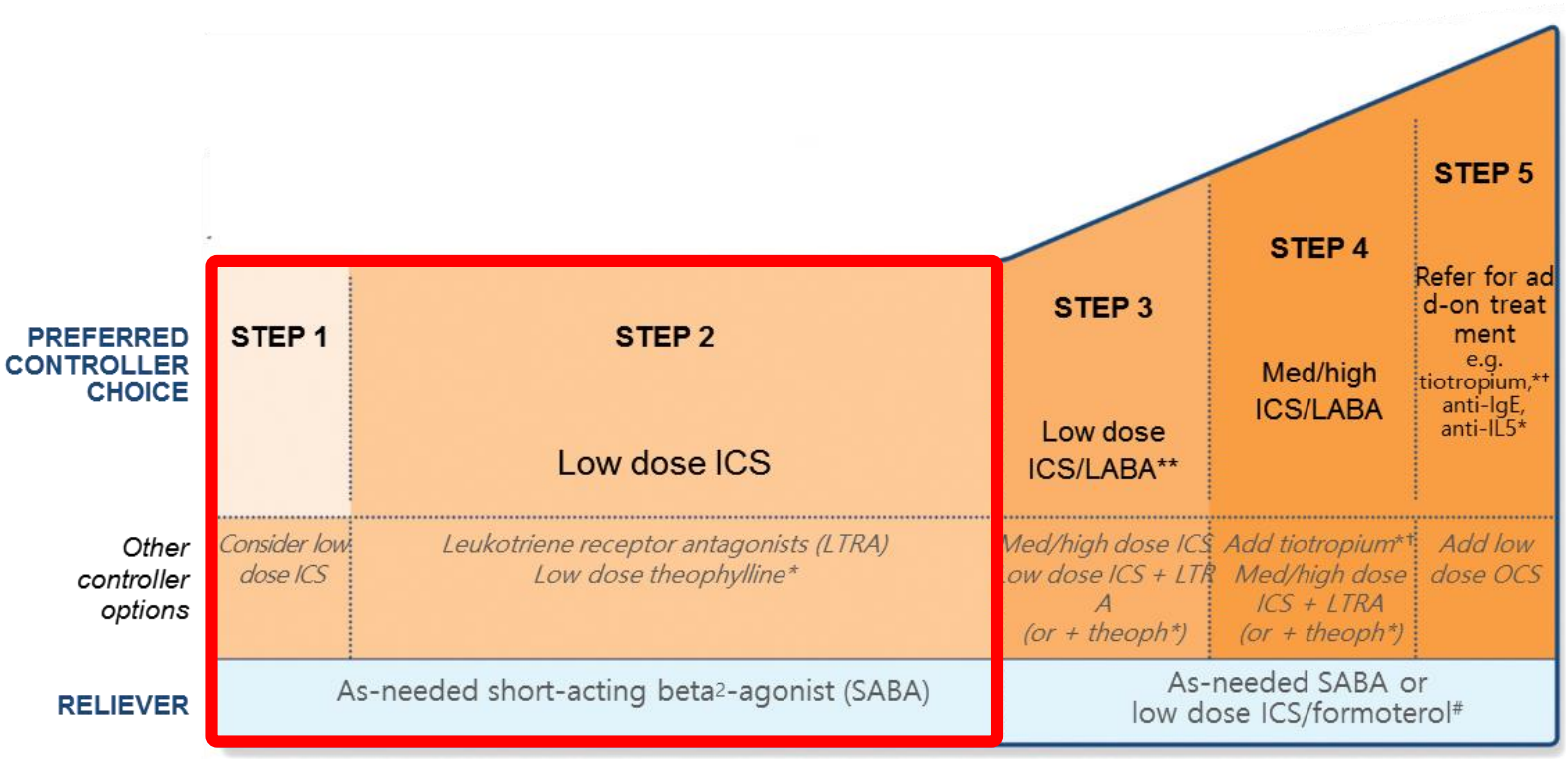
Mild Asthma: Overview

1. Definition and Prevalence
2. Stability and Transition of Severity
3. New Approach in Pharmacological Management

Mild Asthma: Definition by GINA

Mild asthma is ….

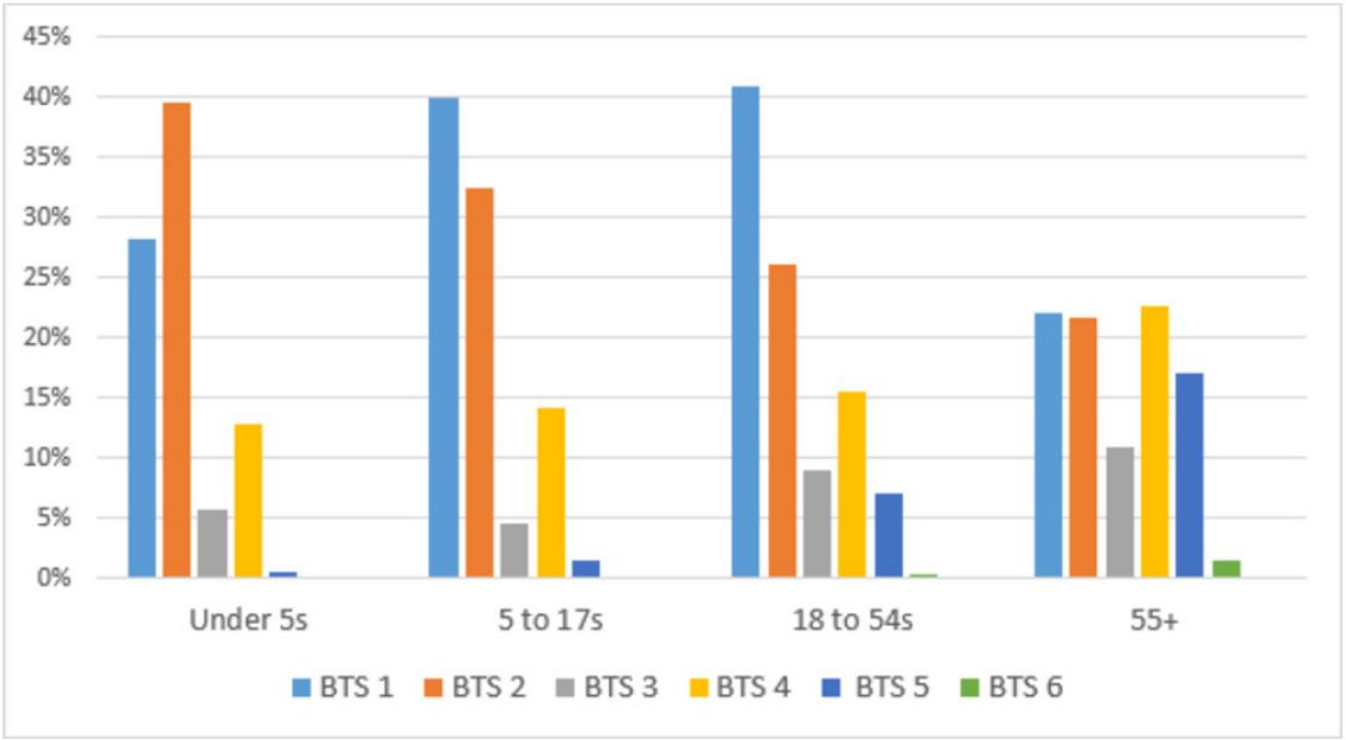
asthma **well controlled** with **Step 1 or Step 2** treatment.



The Global Initiative for Asthma 2018, www.ginasthma.org

Mild Asthma: Prevalence in UK

- Population-based cohort study in UK, 2007-2015 using primary and secondary care electronic healthcare records
- mild asthma (BTS steps 1/2) >60% of the total study population



Bloom CI et al. Thorax 2018; 73:313-20

Mild Asthma: Prevalence in China

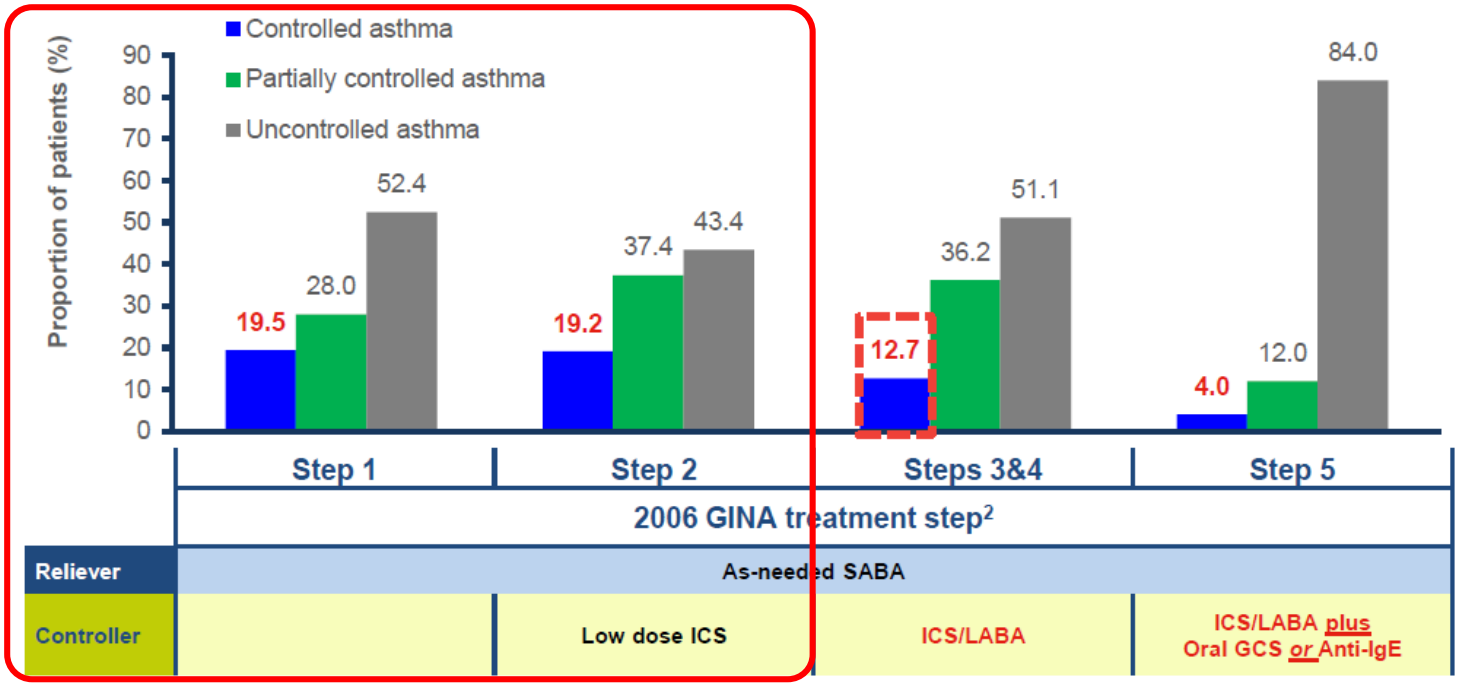
- China National Health and Wellness Surveys (NHWS) conducted between 2010 and 2013 (*N*=59,935), Internet-based surveys of adults in urban China
- mild asthma (GINA steps 1/2) ~77% of the patients with asthma

	Mild asthma (GINA2014 guidelines) among asthma patients* (*N* = 4,371,115)			
	N	%	95% LCL	95% UCL
Total	3375196	77.22	73.72	80.71
Age group				
18-29 years	503507	72.70	64.14	81.27
30-39 years	729033	78.59	71.68	85.5
40-49 years	875600	78.08	71.11	85.05
50-59 years	793616	77.38	69.79	84.96
60-69 years	368503	76.48	65.23	87.73
70 years and over	104937	85.97	67.83	100
Sex				
Male	1737458	75.00	70.24	79.77
Female	1637738	79.71	74.6	84.83

Ding B et al. J Asthma 2017; 54:632-43

Mild Asthma: Level of Control

- 1,363 asthma patients from primary and referral clinics (allergy or pulmonary) in Spain
- 80% of the patients on step 1-2 were not well controlled based on GINA definition.



※ GCS, glucocorticoids; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Olaguibel JM et al. Respir Res 2012; 13:50

Mild Asthma: Frequency of Exacerbation

- Cross-Sectional Real-World Survey in 8 countries including China, France, Germany, Italy, Japan, Spain, UK, or US
- 19% experience exacerbation (Physician-confirmed worsening of symptoms) in last 12 months

Consultations	Total	GINA Step, *n* (%)	
	n = 1115	1 *n* = 524 (47.0)	2 *n* = 591 (53.0)
Number of exacerbations[a] in last 12 months			
Mean (SD)	0.4 (1.3)	0.4 (1.4)	0.4 (1.3)
95% CI	0.3, 0.4	0.2, 0.5	0.3, 0.5
Missing	2	1	1
Number of exacerbations[a] in last 12 months, *n* (%)			
0	901 (81.0)	439 (83.9)	462 (78.3)
1	124 (11.1)	47 (9.0)	77 (13.1)
2	59 (5.3)	19 (3.6)	40 (6.8)
≥3	29 (2.6)	18 (3.4)	11 (1.9)
Missing	2	1	1

Ding B et al. Adv Ther 2017; 34:1109-27

Severe Exacerbations in mild asthma

- Adult asthma with emergency department visit in France

	Number of patients (n=4087)
Regular follow-up*	
None	1237 (30%)
General practitioner only	1555 (38%)
Pulmonologist only	962 (23%)
Pulmonologist and general practitioner	333 (8%)
Peak flow meter at home	652 (16%)
Regular treatment	3028 (74%)
Anti-inflammatory agents	
Inhaled corticosteroids	1924 (47%)
Oral corticosteroids	389 (9%)
Intramuscular corticosteroids	25 (0·6%)
Nedocromil	63 (1%)
Bronchodilators	
Long-acting inhaled β2 agonists	866 (21%)
Oral β2 agonists	198 (5%)
Oral theophylline	408 (10%)
Inhaled anticholinergics	179 (4%)
Frequency of asthma symptoms during preceding 3 months	
⩾1 per day	835 (20%)
⩾1 per week	903 (22%)
⩾1 per month	1211 (30%)
Not reported	1138 (28%)

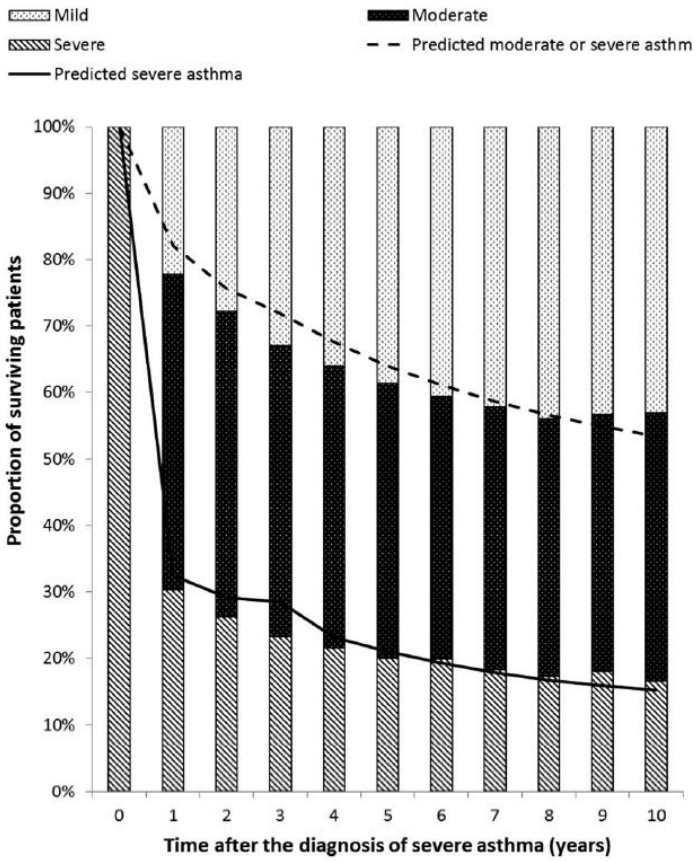
*At least two visits per year.

Table 2: **Regular follow-up, treatment, and symptoms during preceding 3 months**

Salmeron S et al. Lancet 2001; 358:629-35

Severe Asthma: Long-Term Prognosis

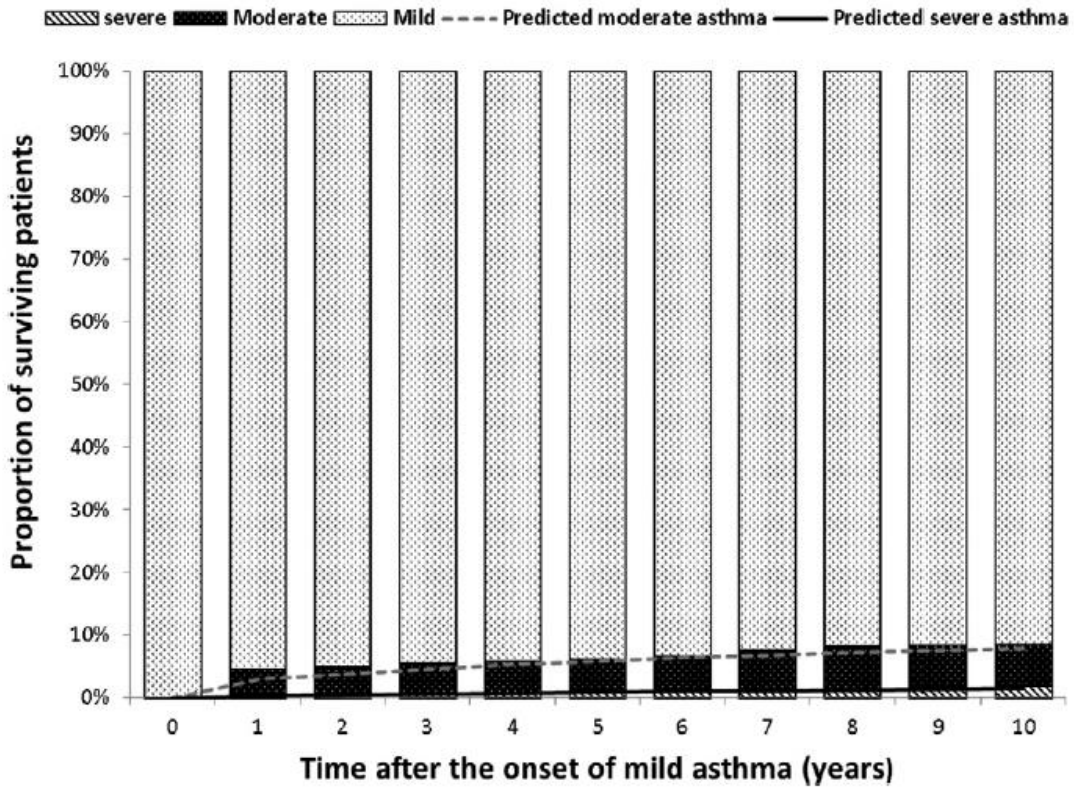
- retrospectively followed patients 14–55 years of age with newly diagnosed severe asthma, BC Canada



Chen W et al. Thorax 2016; 71:267-75

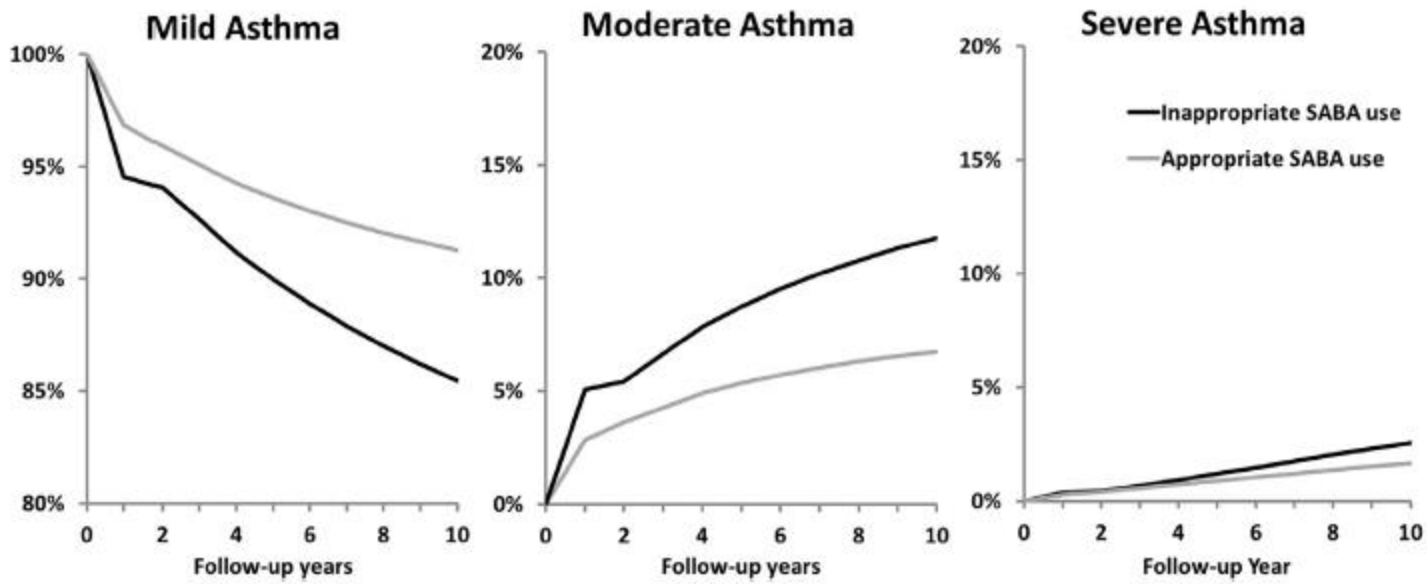
Mild Asthma: Long-Term Prognosis

- Long-Term Trajectories of newly diagnosed mild asthma (age 14-45)
- administrative health data of British Columbia, Canada (1997-2012)
- 1/10 patients with mild asthma transition to moderate or severe asthma over 10 years



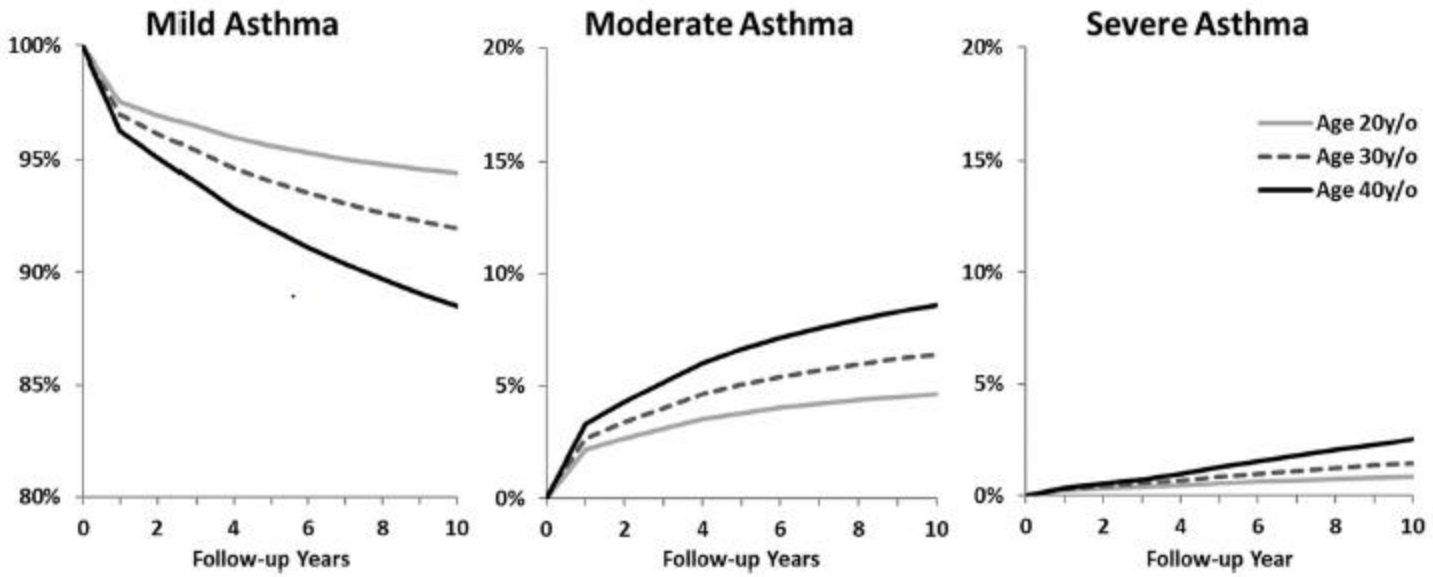
Chen W et al. J Allergy Clin Immunol Pract 2018

Predictors of Transition: Inappropriate SABA use



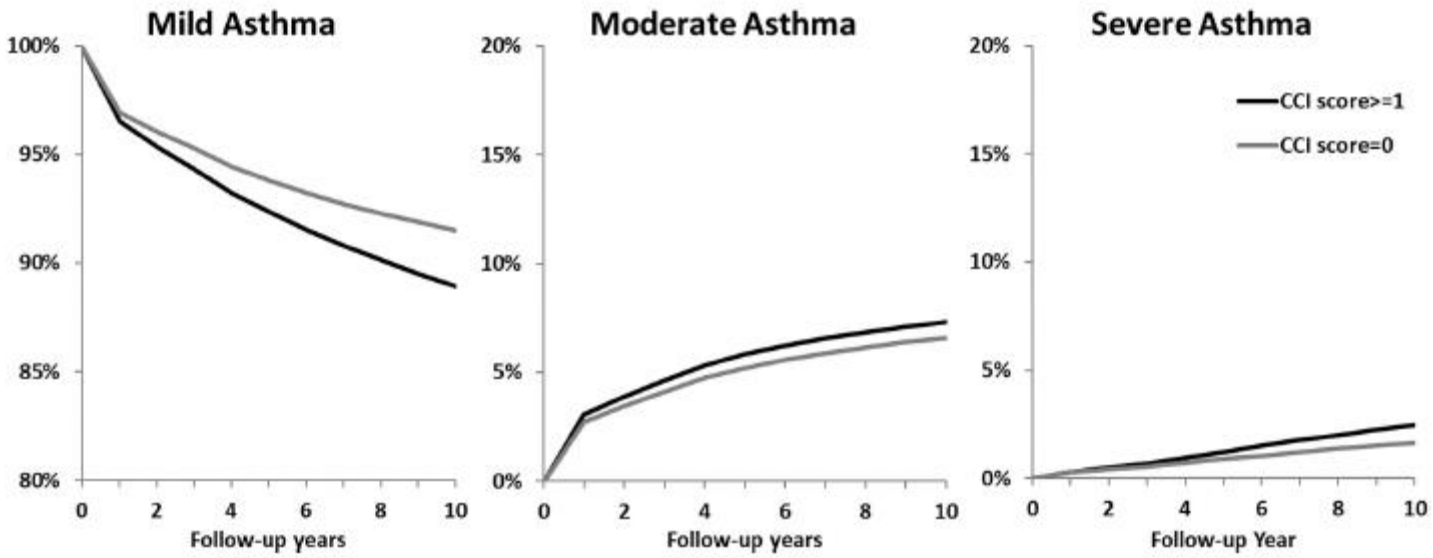
Chen W et al. J Allergy Clin Immunol Pract 2018

Predictors of Transition: Age of Diagnosis



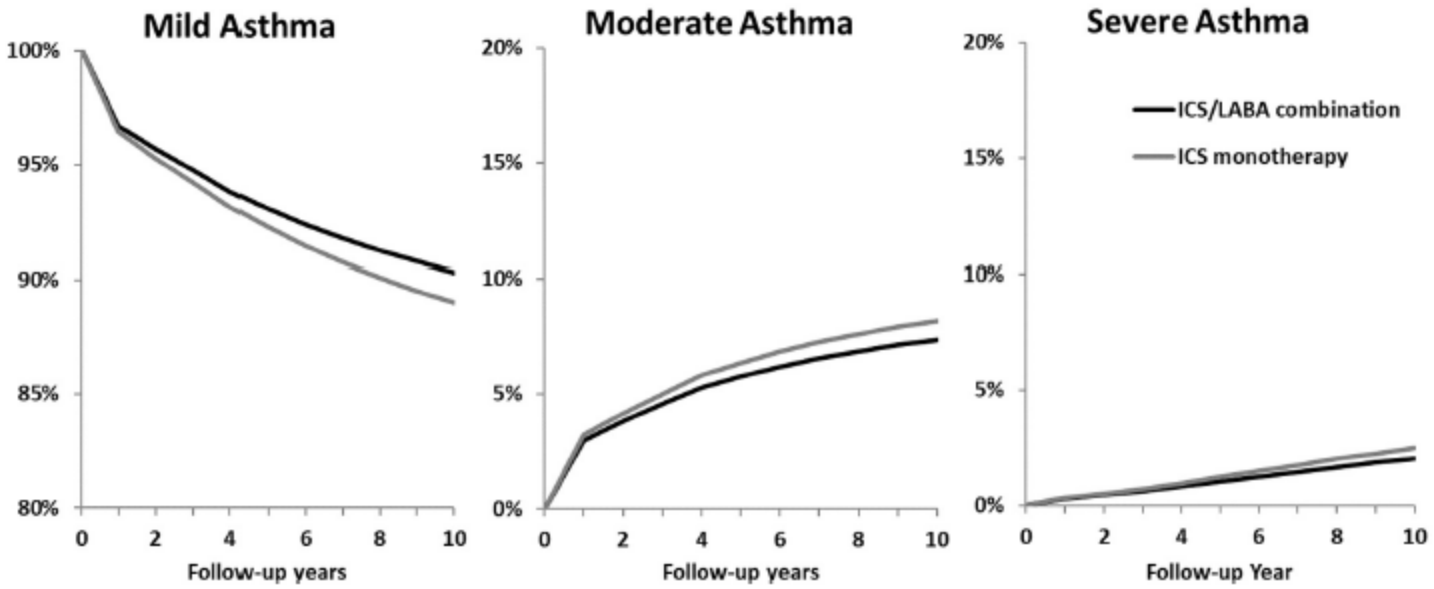
Chen W et al. J Allergy Clin Immunol Pract 2018

Predictors of Transition: Comorbidities



Chen W et al. J Allergy Clin Immunol Pract 2018

Predictors of Transition: ICS > ICS/LABA



Chen W et al. J Allergy Clin Immunol Pract 2018

Predictors of Transition

Pro-transition

- Inappropriate use of rescue medication
- More comorbidities
- Older age of diagnosis

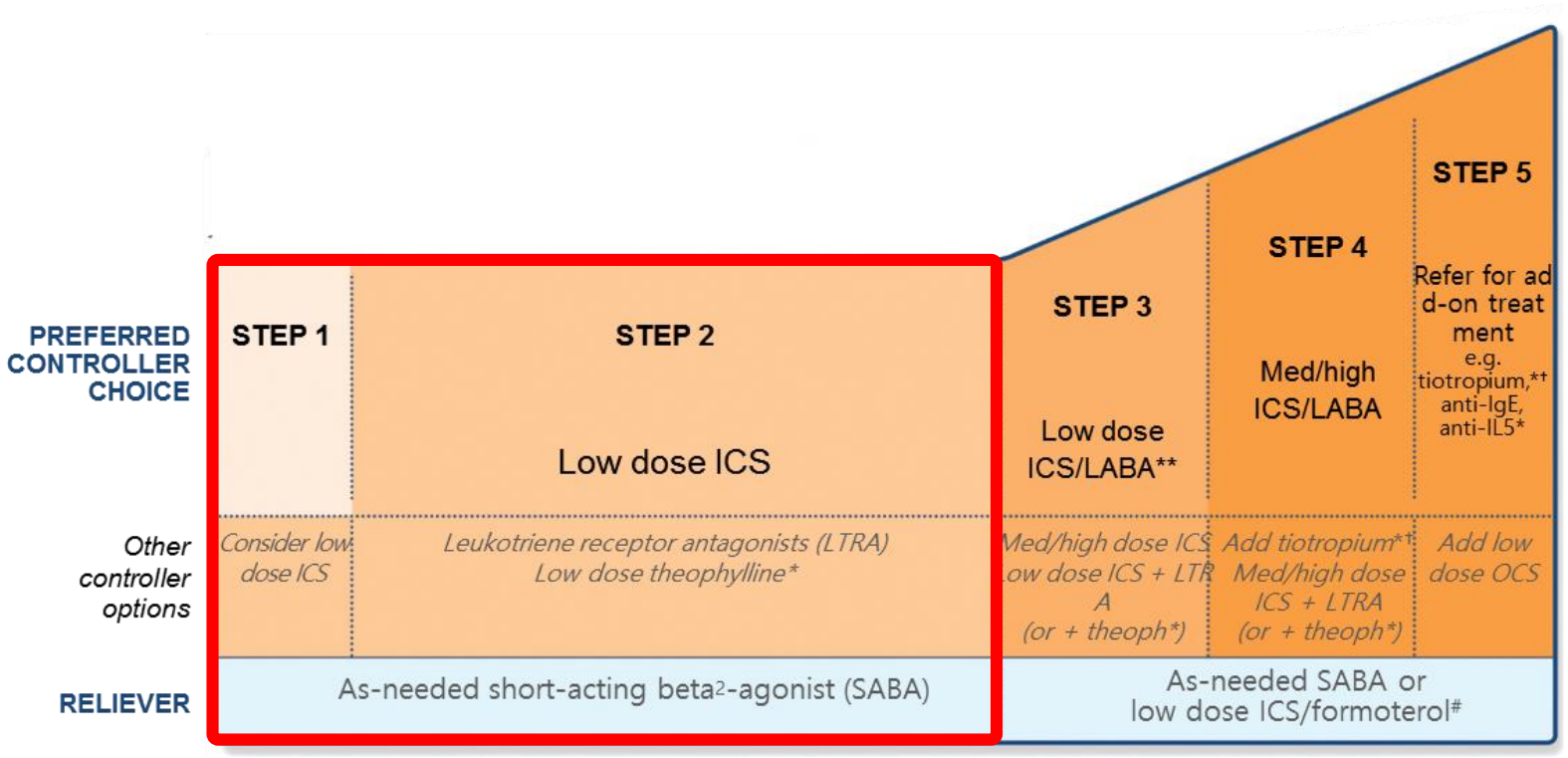
Protective

- Use of ICS/LABA compared to ICS

Chen W et al. J Allergy Clin Immunol Pract 2018

Mild Asthma: Step 1 or Step 2

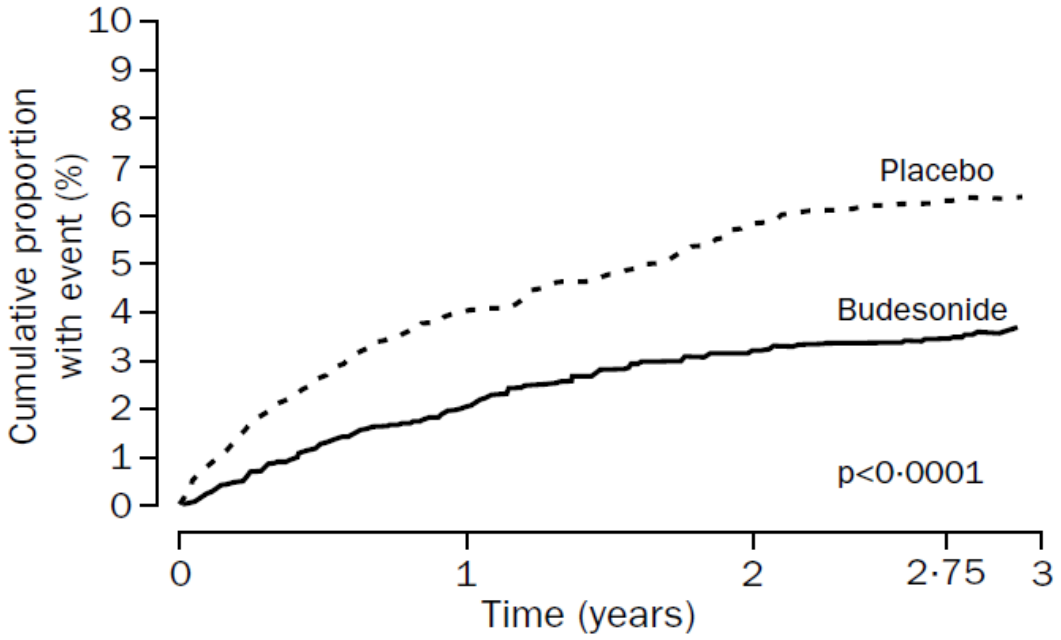
	Step 1	Step 2
Controller	X	ICS
Reliever	SABA	



The Global Initiative for Asthma 2018, www.ginasthma.org

START trial: Regular ICS for mild asthma

- Long-term, once-daily treatment with low-dose budesonide decreases the risk of severe exacerbations and improves asthma control in patients with mild persistent asthma of recent onset

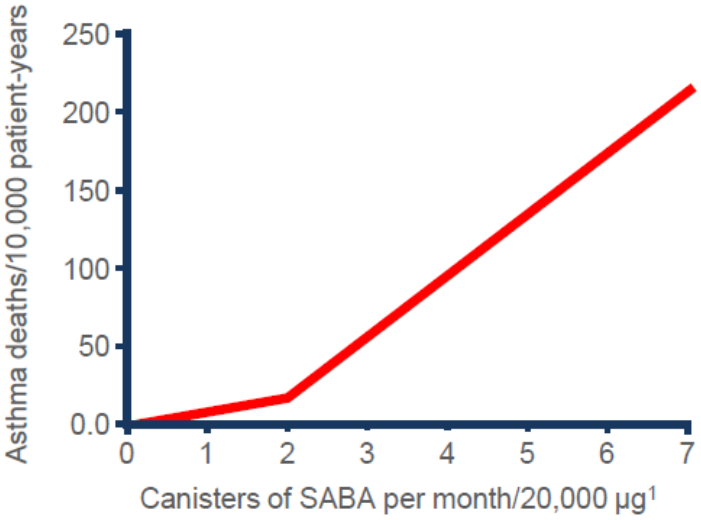


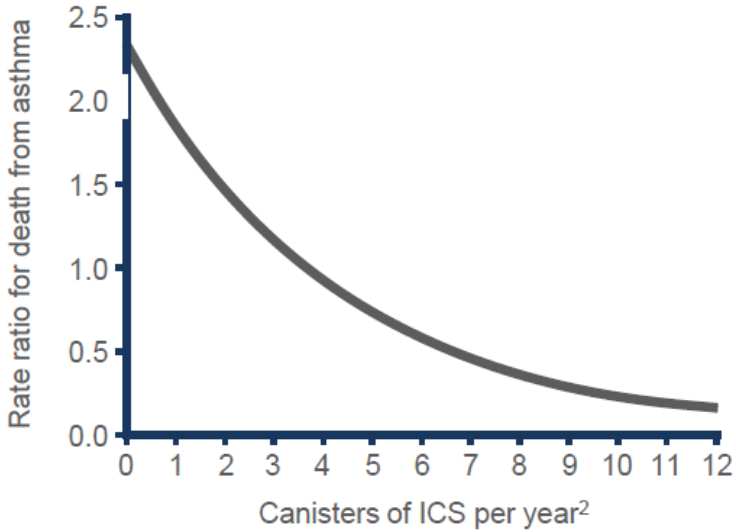
Number at risk

Placebo	3568	2865	2600	2438
Budesonide	3597	2998	2722	2570

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

Risk of SABA and Benefit of ICS on mortality

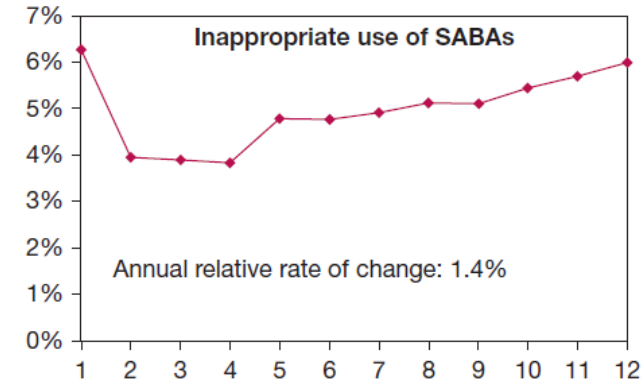




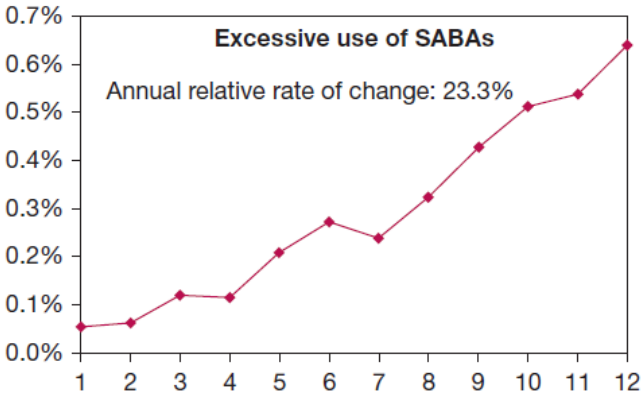
Suissa S et al., Am J Respir Crit Care Med 1994; 149:604-10
Suissa S et al., NEJM 2000; 343:332-6

SABA use in real world

- retrospective cohort study of individuals 15 to 67 years with validated case definition of asthma in the administrative DB of British Columbia, Canada between 2002 and 2013



(≥ 2 puffs/wk & no ICS)



(≥12 canisters/yr)

Sadatsafavi M et al., Chest 2017; 151:612-8

Disadvantages of regular ICS in mild asthma

- Poor adherence
- Overtreatment
- Increased cost
- Risk of local and systemic adverse reaction
- Hard to confirm asthma after initiation of medication

Paradoxes in Current Asthma Guideline

At Step 1, a SABA alone is recommended despite asthma being a disease of chronic inflammation with episodic worsening

At Step 1, use of as-needed SABA alone to control symptoms is accepted, but from Step 2 a fixed-dose approach is expected with the goal to minimize use of SABA

An ICS treats underlying inflammation, but patients still perceive their SABA as the medication benefitting them

Safety messages on SABA and LABA use within guidelines are conflicting

Disconnect exists between a patient's understanding of asthma control and their actual symptoms

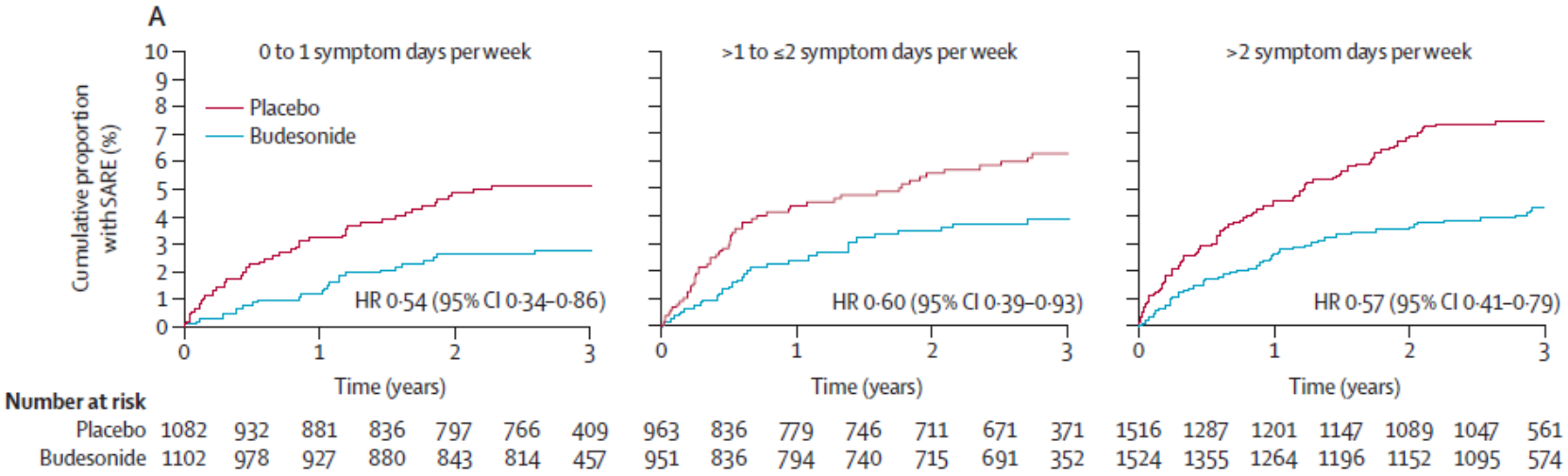
O'Byrne PM, Jenkins C, Bateman ED. Eur Respir J 2017; 50

Start from Step 1 or Step2 ???

	Intermittent	Persistent Mild	Persistent Moderate	Persistent Severe
Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Through out the day
Night time awakenings	≤2x/month	3–4x/month	>1x/week, but not nightly	Often 7x/week
short-acting $beta_2$-agoinst use for symptom control	≤2 days/week	>2 days/week but not daily and not more than 1x on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	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% FEV_1/FVC reduced >5%
Recommend step for Initiating treatment	Step 1	Step 2	Step 3	Step 4 or 5

Regular ICS for Mild Asthma

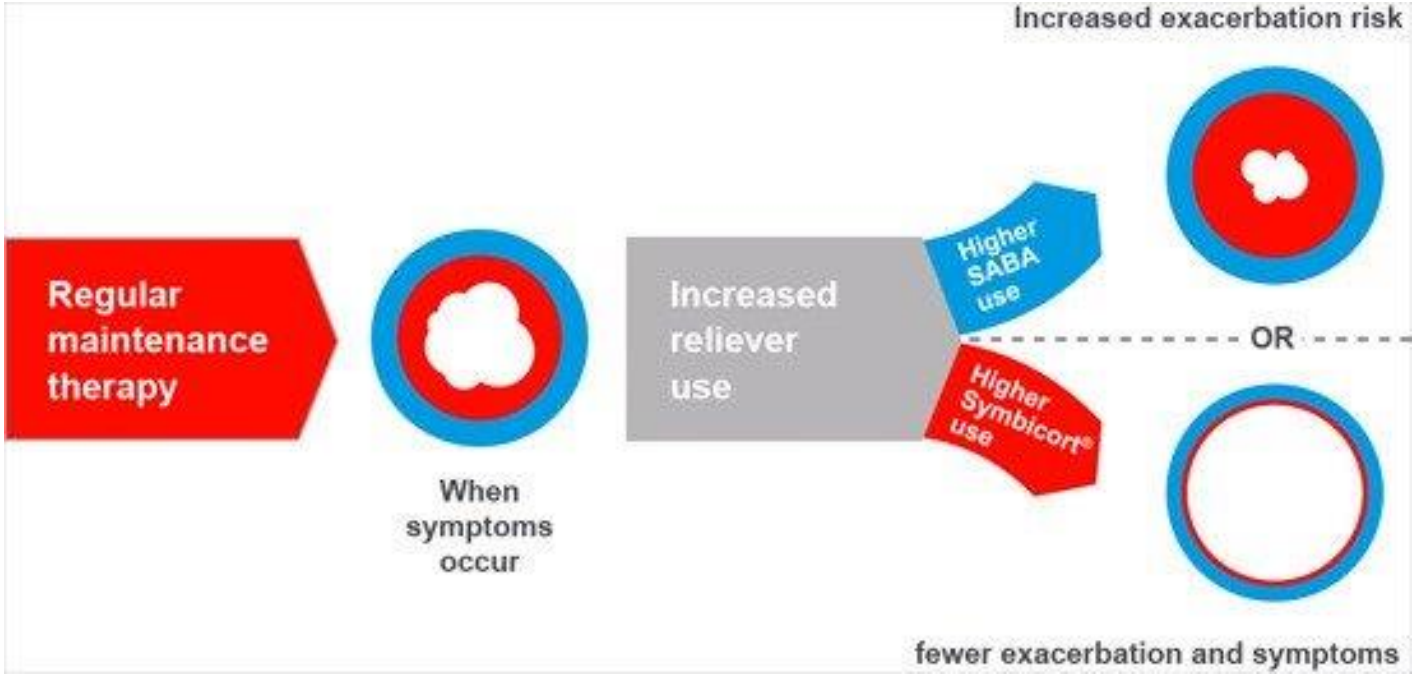
- post-hoc analysis of the 3 year START study in recent onset mild asthma



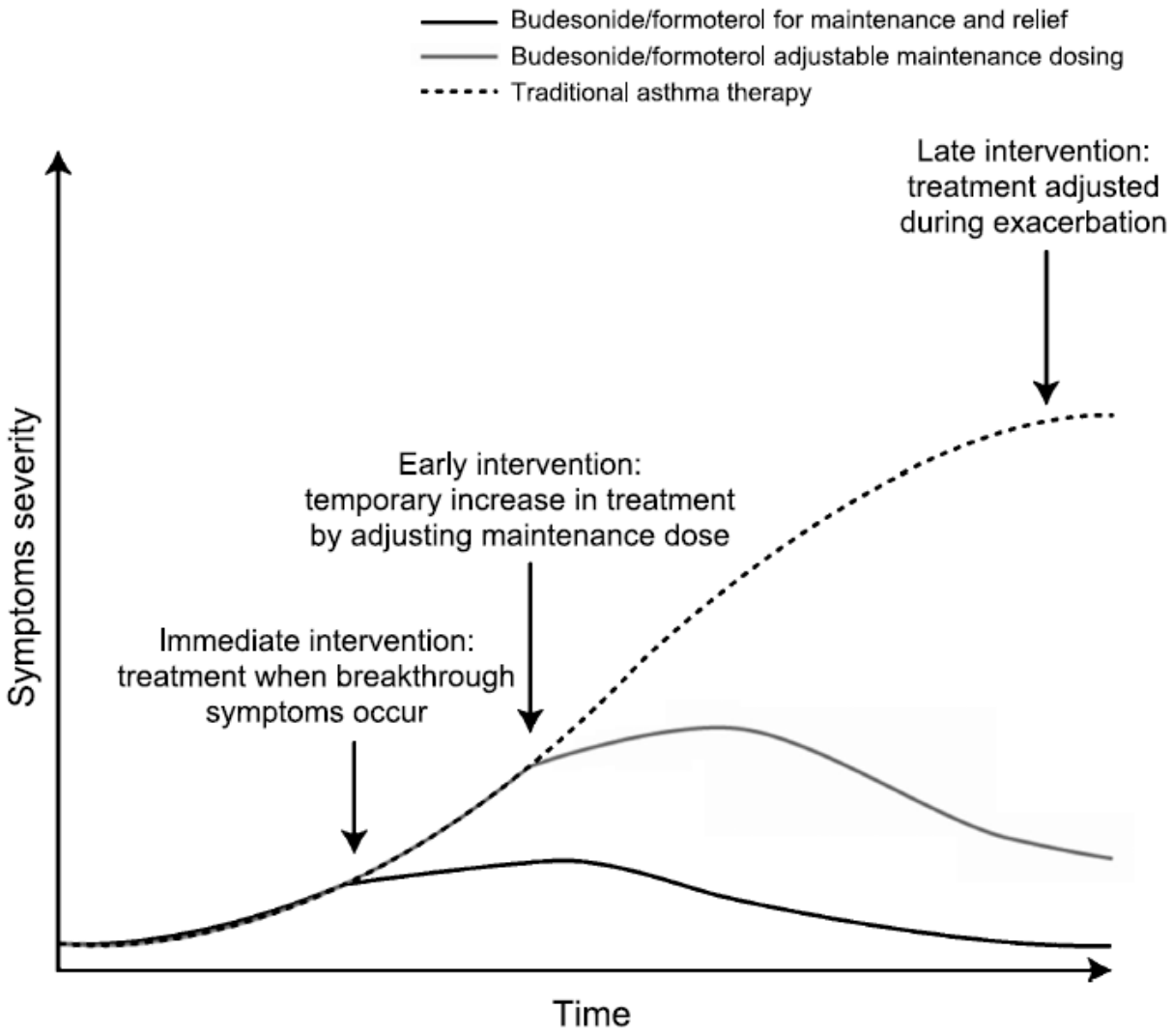
Reddel HK et al., Lancet 2017; 389:157-66

Single Inhaler Maintenance And Reliever Therapy

- treats inflammation and reduces symptoms
- reduces exacerbation

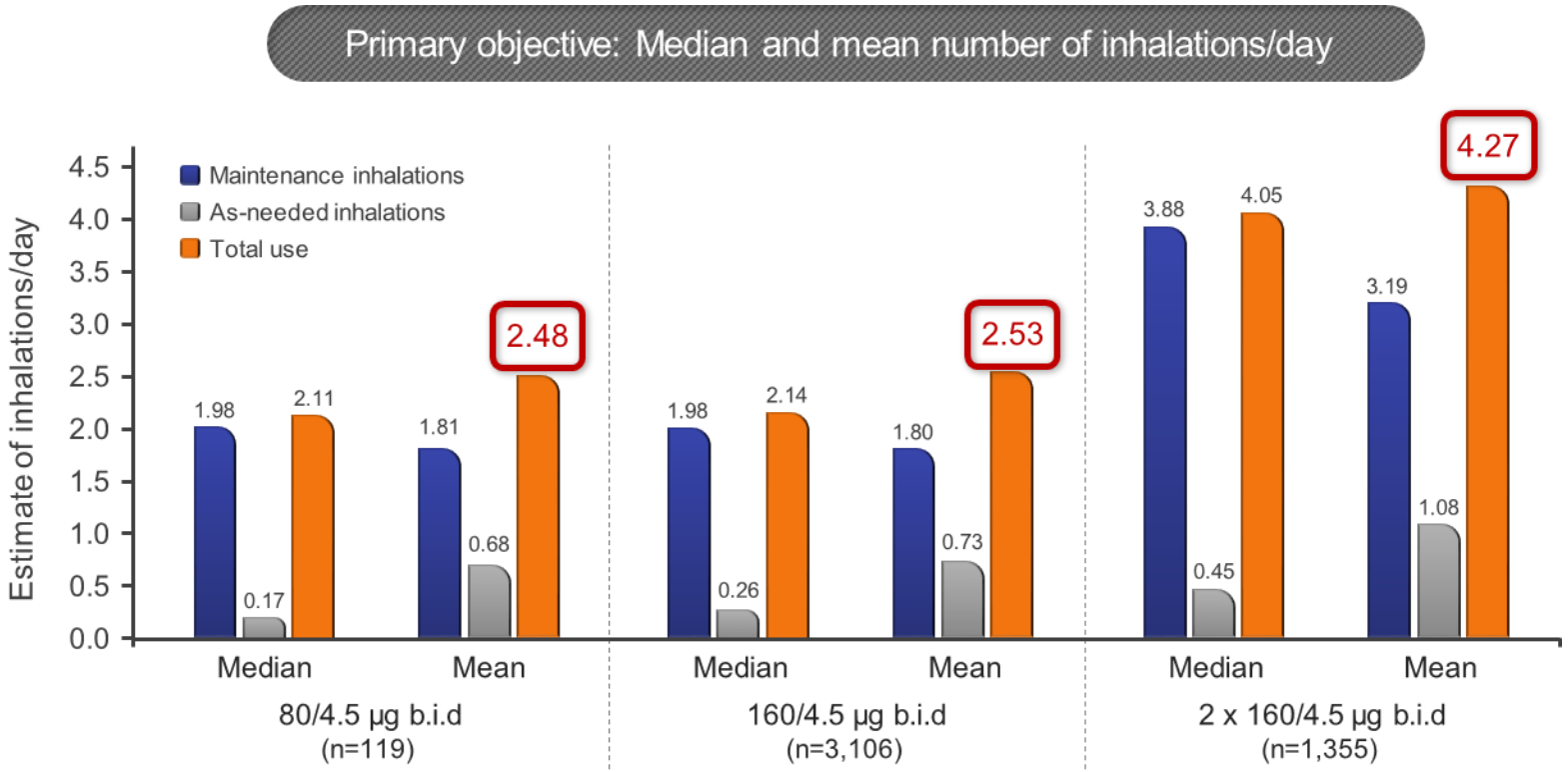


Bud/For in Worsening Asthma



Ankerst J et al., J Asthma 2005; 42:715-24

Real-life use of budesonide/formoterol in EU

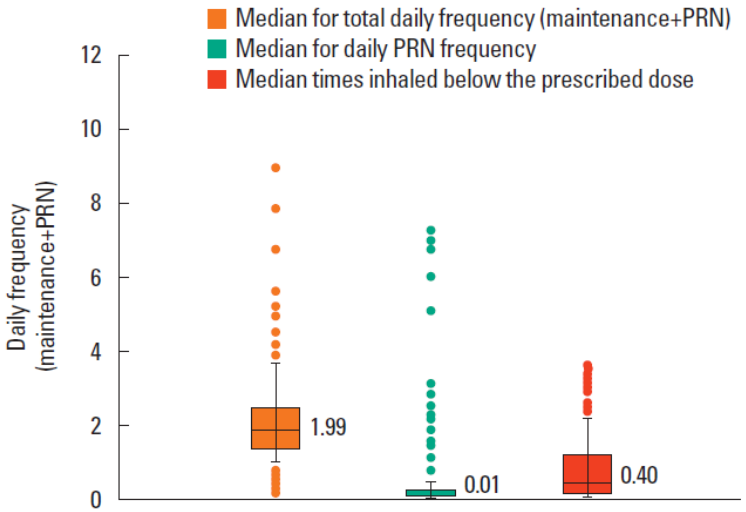


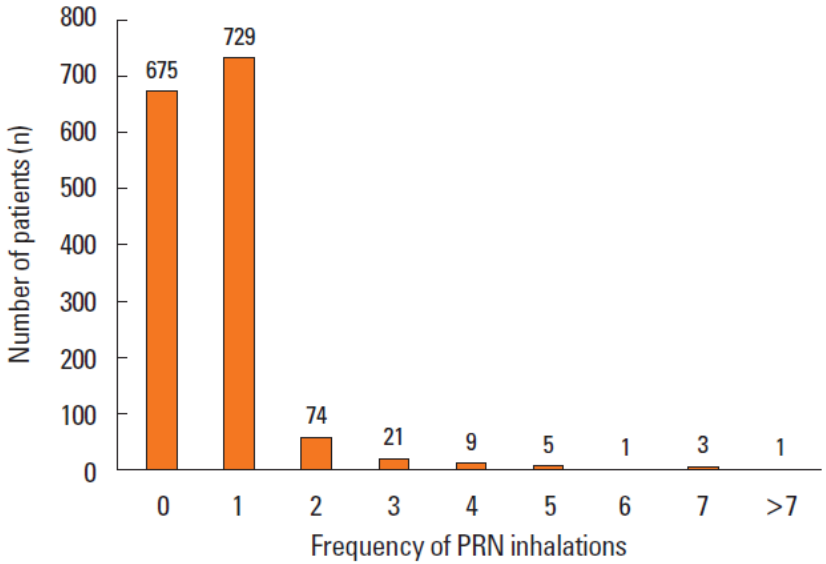
	numbers of as-needed inhalations/day mean (median)
80/4.5 µg b.i.d.	**0.68** (0.17)
160/4.5 µg b.i.d.	**0.73** (0.26)
2 × 160/4.5 µg b.i.d.	**1.08** (0.45)

Stallberg B et al., Int J Clin Pharmacol Ther 2015; 53:447-55

SMART in Korea

- Real-life Use of Symbicort® in 1,518 patients in Korea
- mean frequency of PRN use was 0.25±0.67 inhalations per day





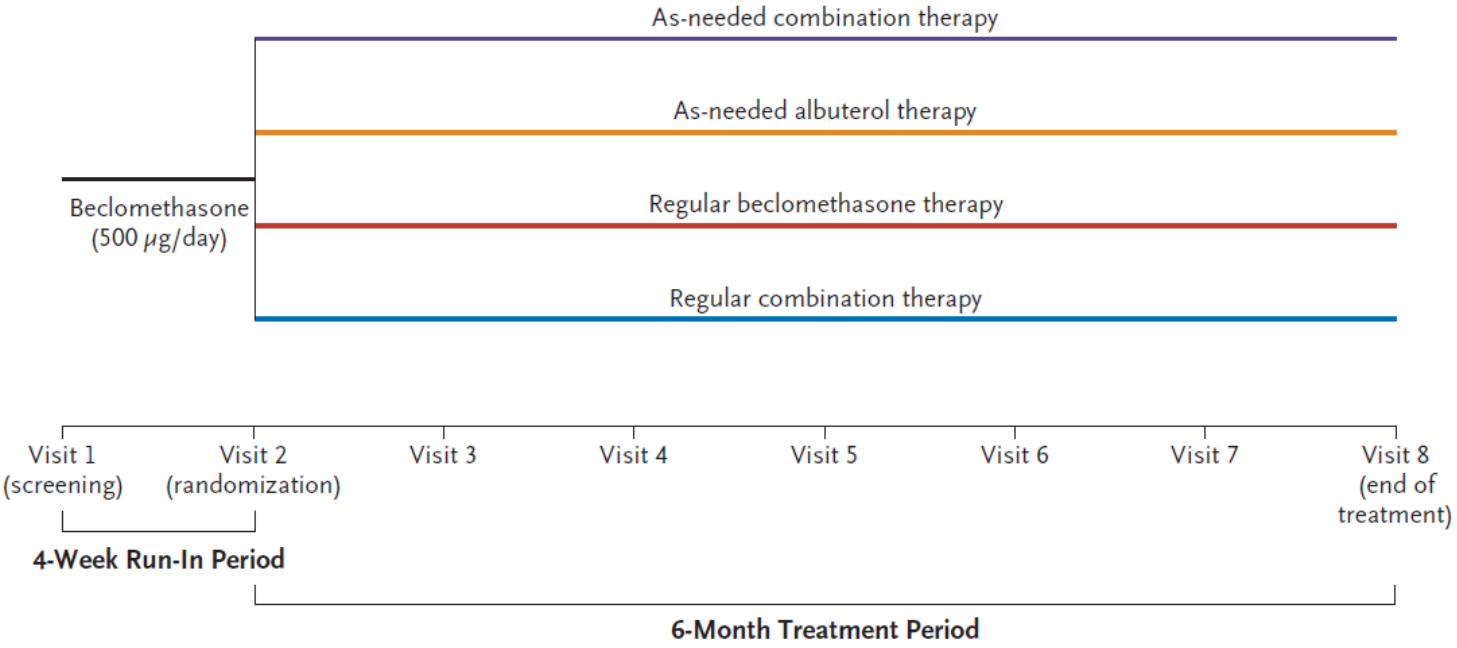
Kim SH et al., Allergy Asthma Immunol Res 2018; 10:88-94

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma

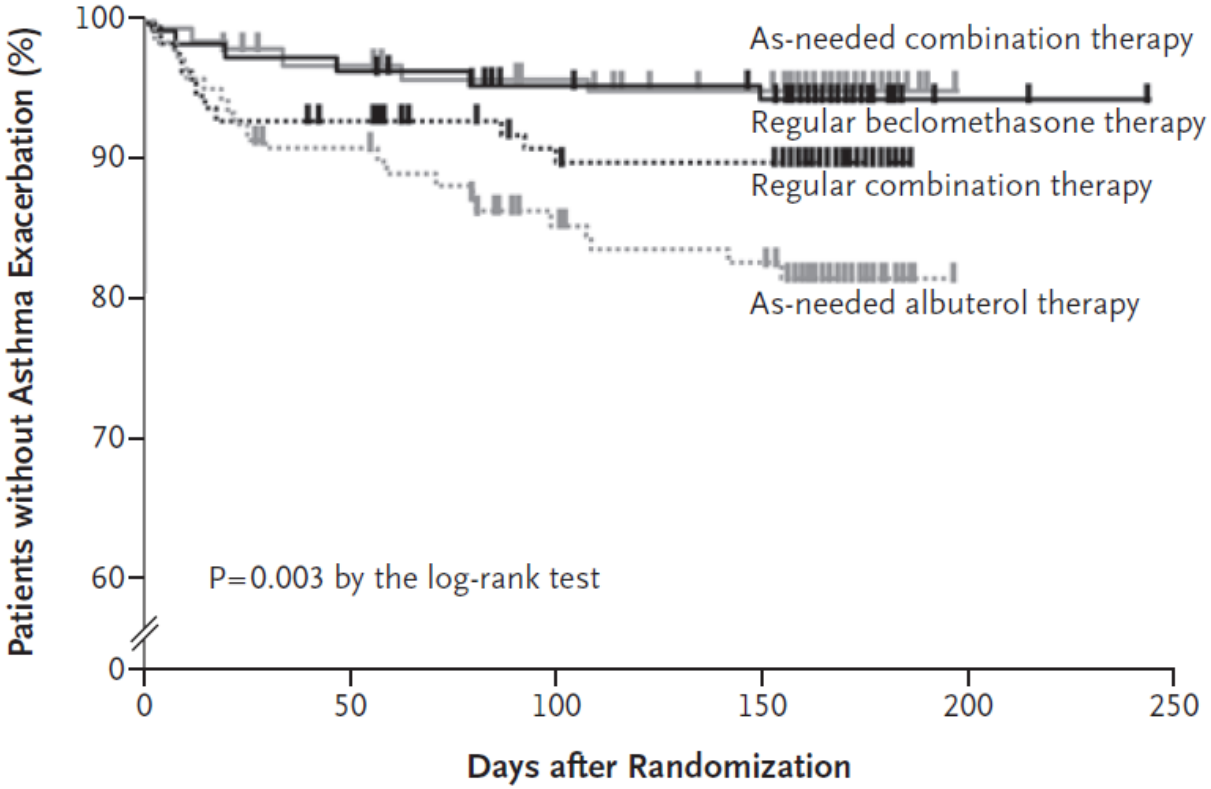
- BEST trial: As needed Single Inhaler ICS/SABA in Mild Asthma
- Symptom driven use of beclomethasone/salbutamol in single device



Papi A et al., N Engl J Med 2007; 356:2040-52

As needed Single Inhaler ICS/SABA in Mild Asthma

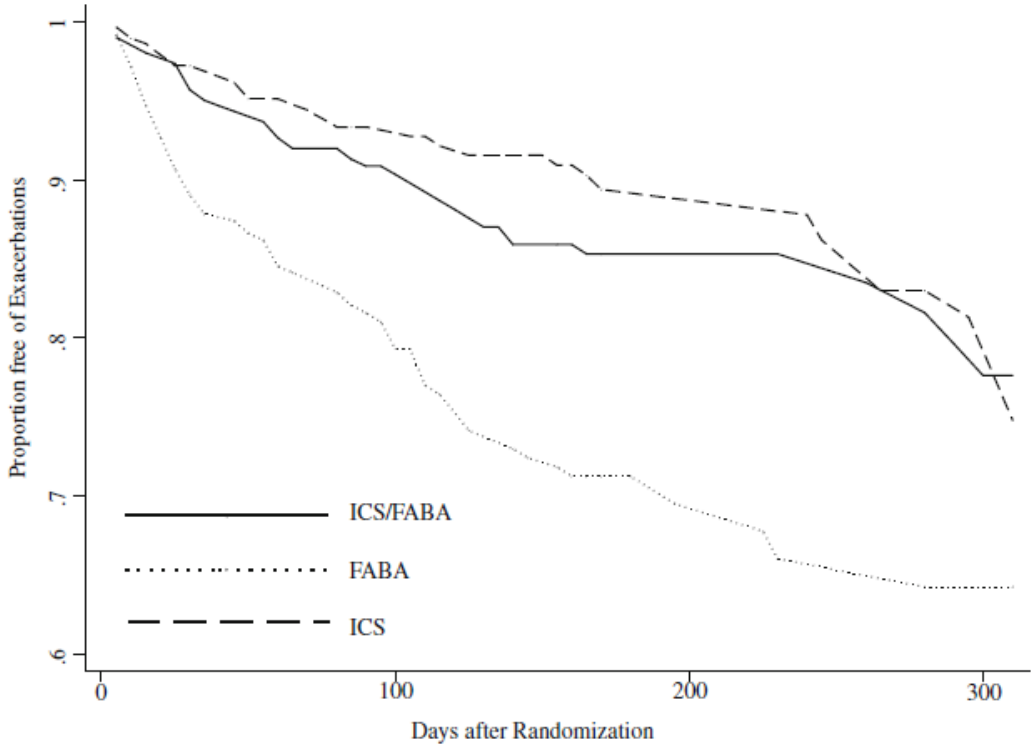
- 6 month RCT
- Symptom driven use of beclomethasone/salbutamol in single device



Papi A et al., N Engl J Med 2007; 356:2040-52

As needed Single Inhaler ICS/FABA in mild asthma : Meta-analysis

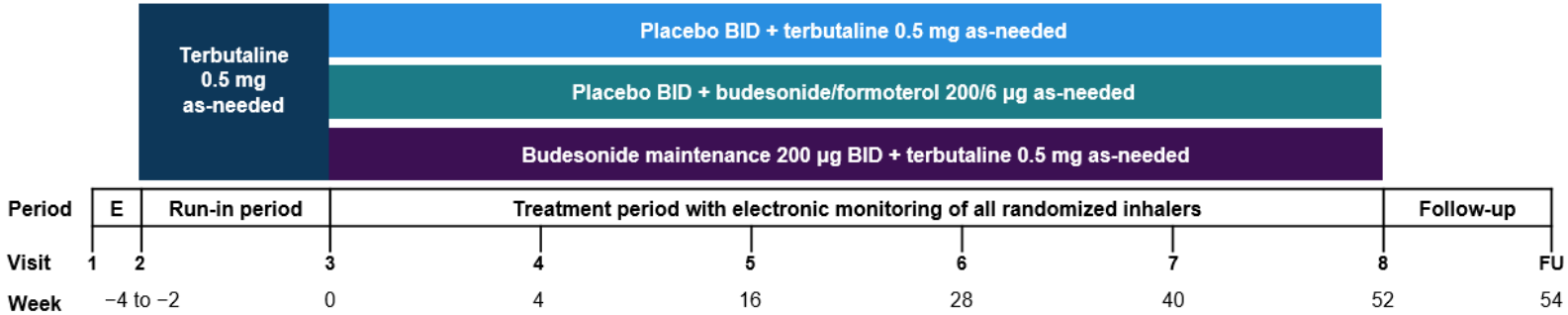
- Reliever use of ICS and fast-onset-acting beta2 agonist (SABA, formoterol) in single inhaler
- 6 RCT (n = 1300)



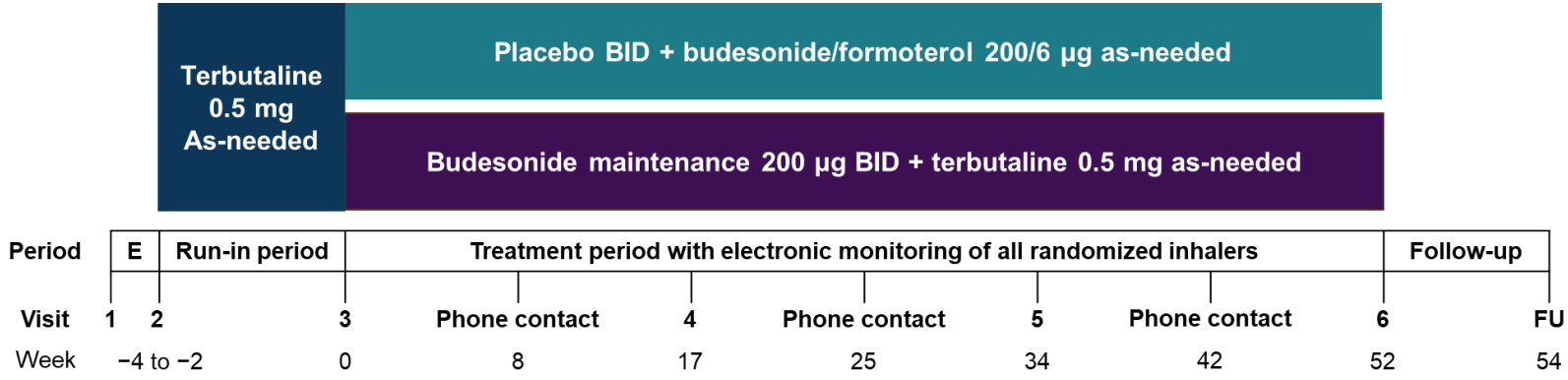
Wang G et al., Respir Res 2017; 18:203

SYGMA study in Mild Asthma
(Symbicort Given as Needed in Mild Asthma)

SYGMA 1



SYGMA 2



O'Byrne PM et al., N Engl J Med 2018; 378:1865-76
Bateman ED et al., N Engl J Med 2018; 378:1877-87

Inclusion Criteria

- Age ≥12 years
- Clinical diagnosis of asthma (GINA 2012 criteria) for ≥6 months
- Documented reversibility (FEV_1 ≥12% and 200 mL)
- Assessed by investigator as needing GINA Step 2 treatment (low-dose ICS or LTRA) for 30 days prior to Visit 2
  - ❖ Subgroup 1: Asthma uncontrolled on inhaled short-acting BD as needed
  - ❖ Subgroup 2: Asthma well-controlled on low-dose ICS or LTRA + short-acting BD as needed
- Lung function criteria
  - ❖ Subgroup 1: pre-BD FEV_1 ≥60% and post-BD FEV_1 ≥80% predicted
  - ❖ Subgroup 2: pre-BD FEV_1 ≥80%

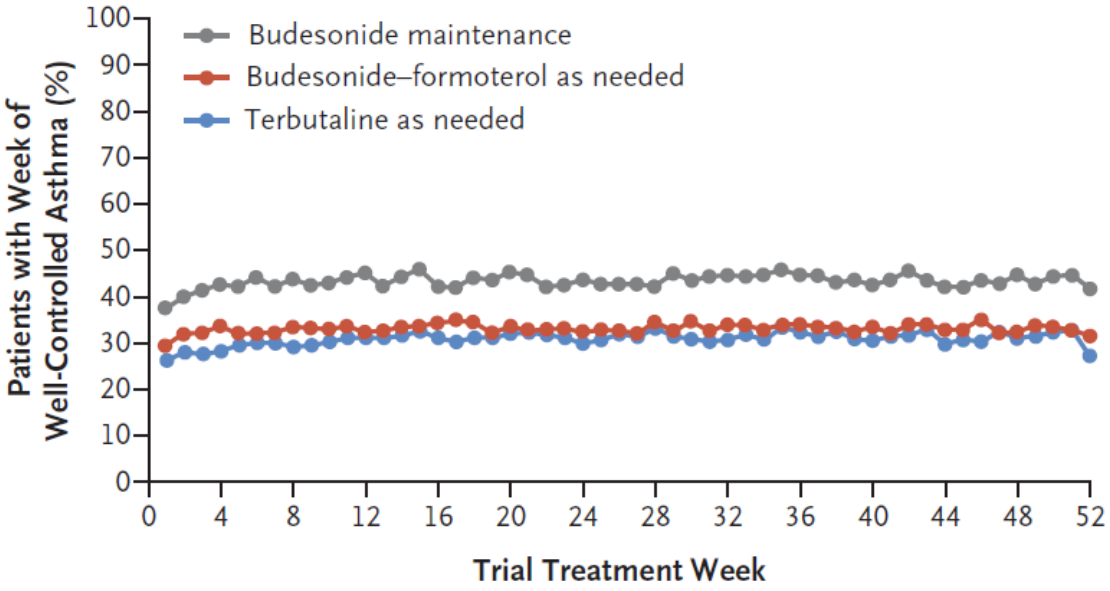
SYGMA 1: Well-Controlled Asthma Weeks

- budesonide–formoterol vs. terbutaline

  (34.4% vs. 31.1% of weeks; OR, 1.14; 95% CI, 1.00 to 1.30; P = 0.046)

- budesonide–formoterol vs. budesonide maintenance therapy

  (34.4% and 44.4%, OR, 0.64; 95% CI, 0.57 to 0.73)

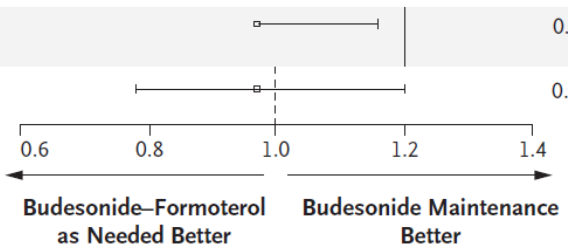


O'Byrne PM et al., N Engl J Med 2018; 378:1865-76

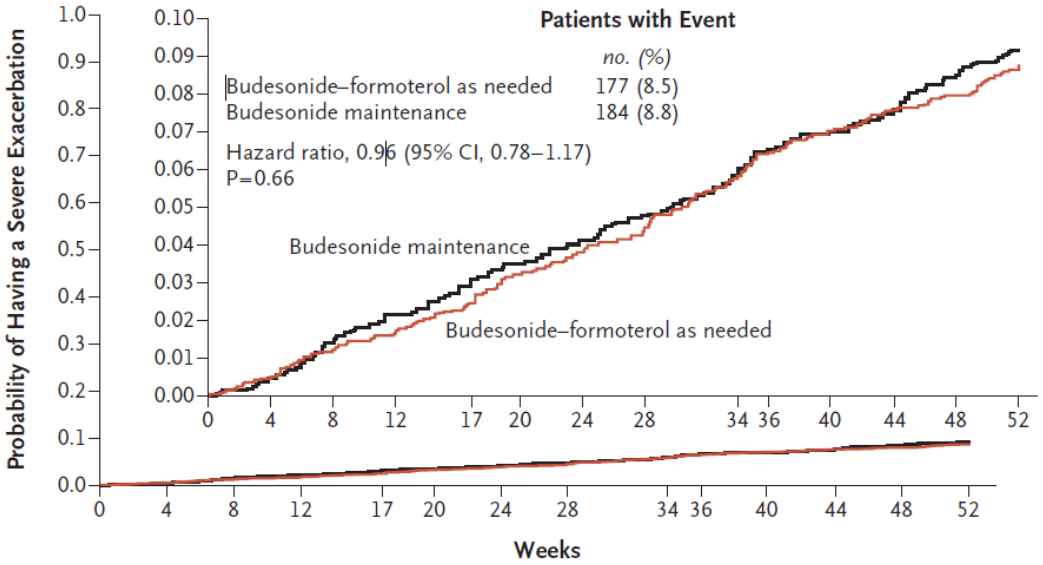
SYGMA 2: annualized rate of severe exacerbations

A Annualized Rate of Severe Asthma 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

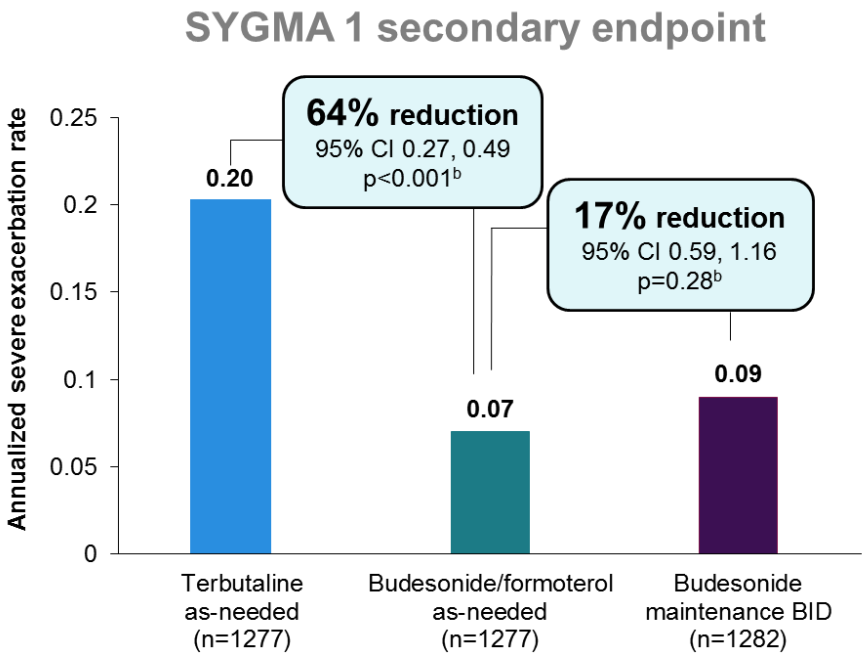


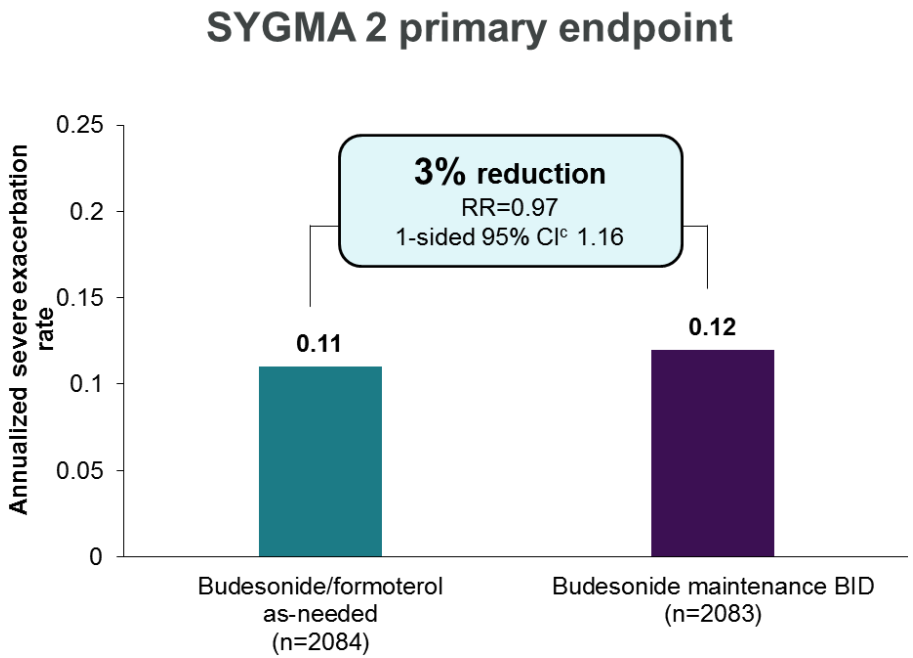
B Time to First Severe Exacerbation



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

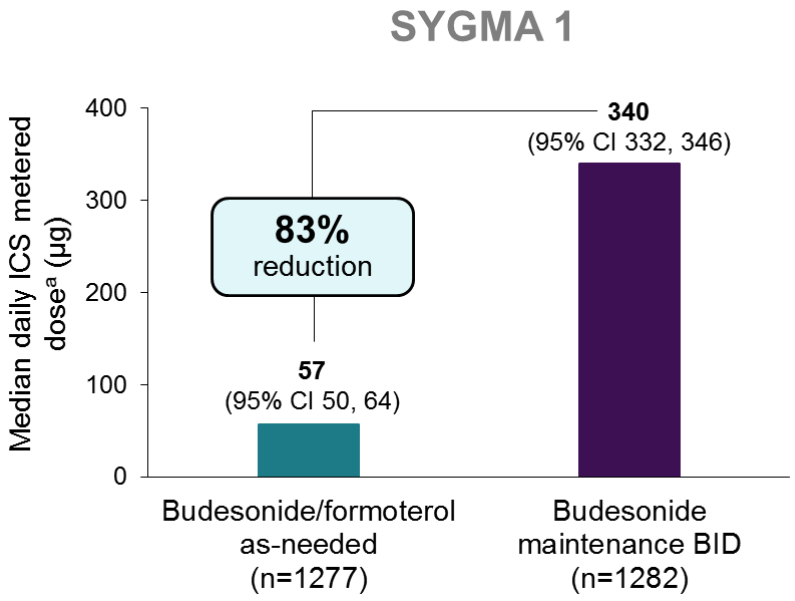
SYGMA 1 & 2: Severe Exacerbation

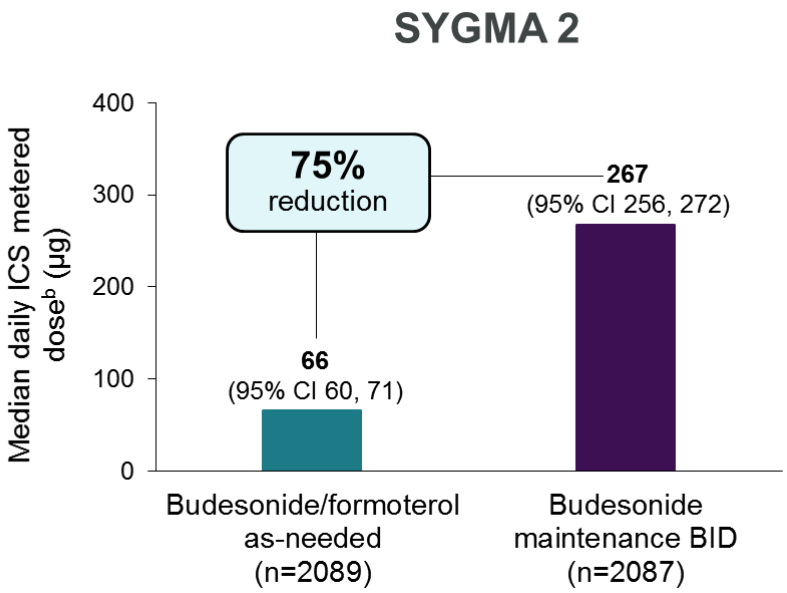




O'Byrne PM et al., N Engl J Med 2018; 378:1865-76
Bateman ED et al., N Engl J Med 2018; 378:1877-87

SYGMA 1 & 2: median daily ICS dose





O'Byrne PM et al., N Engl J Med 2018; 378:1865-76
Bateman ED et al., N Engl J Med 2018; 378:1877-87

Mild Asthma: Step 1 or Step 2

GINA now

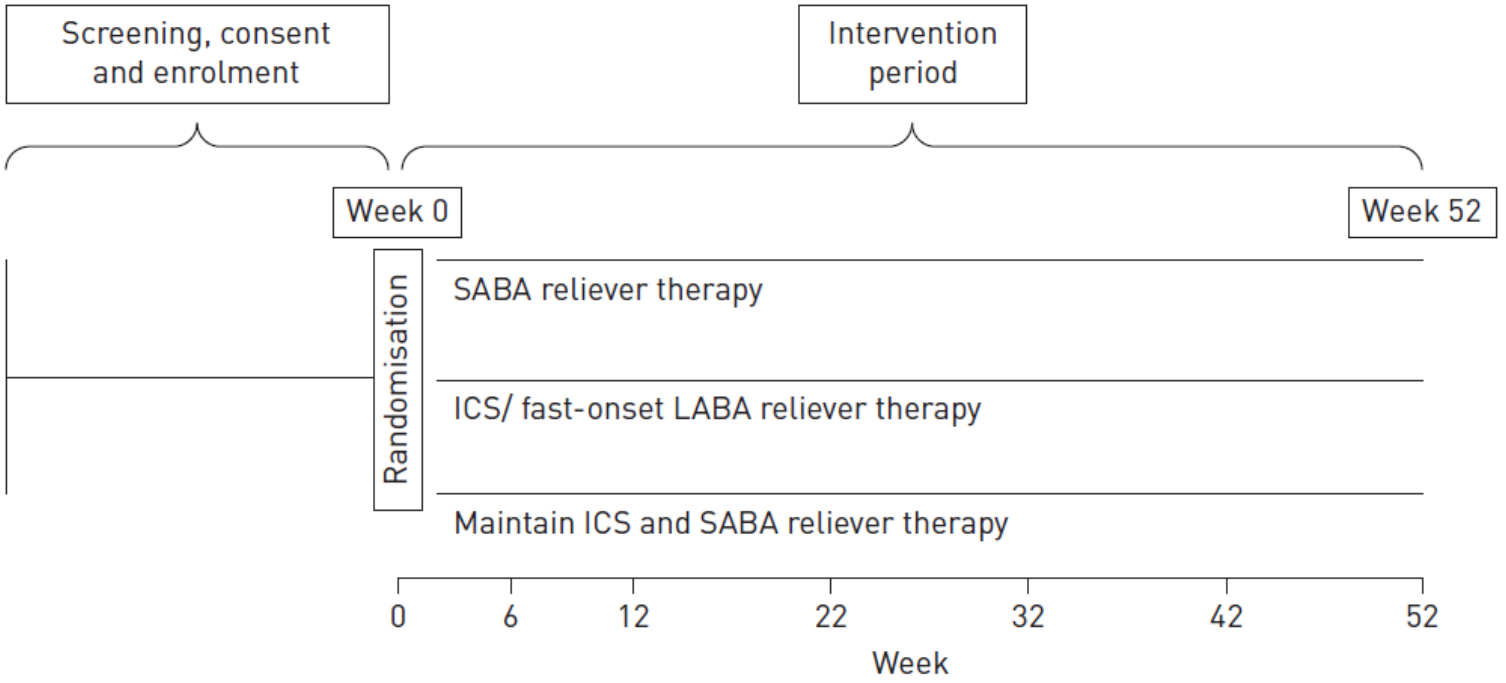
	Step 1	Step 2
Controller	X	ICS
Reliever	SABA	

Changes for mild asthma (future): **anti-inflammatory reliever (AIR)**

	Step 1	Step 2
Controller	X	ICS
Reliever	1) SABA or **2) single device low dose ICS/SABA or** **3) single device low dose ICS/formoterol**	

Novel START trial in mild asthma

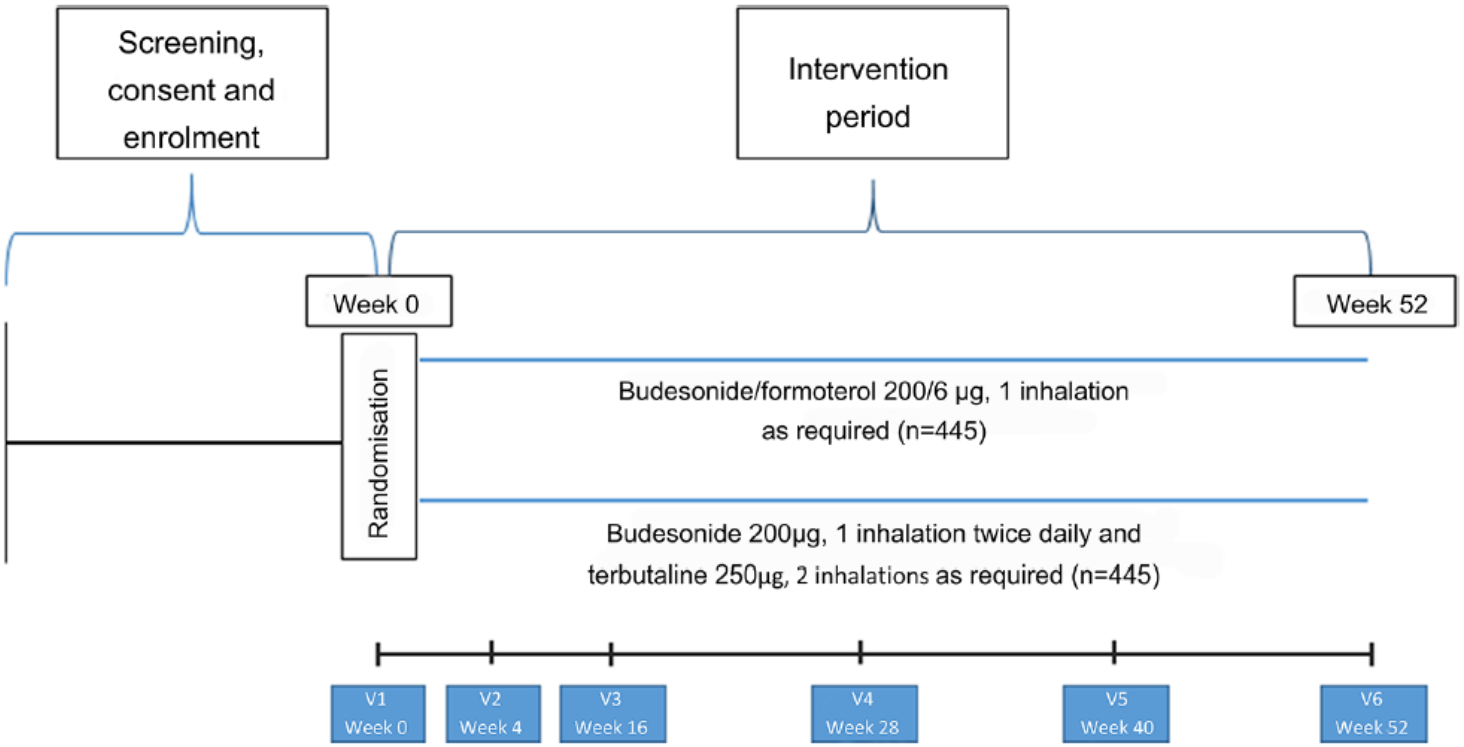
- Primary outcome: asthma exacerbation rate
- Open label RCT



Beasley R et al., Eur Respir J 2016; 47:981-4

PRACTICAL trial in mild asthma

- Primary outcome: severe asthma exacerbation rate
- Open label RCT



Fingleton J et al., BMJ Open Respir Res 2017; 4

Summary

- Mild asthma is defined as well controlled asthma with step 1 or step 2 treatment.

- Even mild asthma on step 1 or 2 treatment showed low level of control and risk of exacerbations.

- As a new approach, patient-adjusted symptom-driven use of single inhaler [low dose ICS + formoterol (or SABA)], so called anti-inflammatory reliever, is suggested in mild asthma.