2014 천식연구회 Workshop

GINA 2014
-revised-

서울의대
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Contents

- **Introduction to GINA 2014**

- **Updated points in each chapter**
  - Definition, description, and diagnosis of asthma
  - Assessment of asthma
  - Treating asthma to control symptoms and minimize risk
    - General principles of asthma management
    - Medications and strategies for symptom control and risk reduction
    - Guided asthma self-management education and skills training
    - Managing asthma with comorbidities and in special populations
  - Management of worsening asthma and exacerbations
  - Diagnosis of asthma, COPD, and ACOS

- **Summary**

"You Can Control Your Asthma."

Evidence Category in GINA guideline

Evidence Category	Sources of Evidence
A	Randomized clinical trials Rich body of data
B	Randomized clinical trials Limited body of data
C	Non-randomized trials Observational studies
D	Panel judgment consensus

In GINA 2014

- provision of a framework for asthma care was not adequate in itself

- **Clinically relevant and feasible recommendations for implementation** into busy clinical practice
  - recommendations for clinical practice in the core GINA Report, while appendices containing background supporting material
  - presented in a user friendly way with extensive use of summary tables and flow-charts
  - new two chapters
    - management of asthma in children aged 0-5years
    - diagnosis of asthma-COPD overlap syndrome

TABLE OF CONTENTS

BOXED TABLES AND FIGURES

2013updated

GINA report 2014 Online appendix

- Burden of asthma
- Factors affecting the development and expression of asthma
- Mechanism of asthma
- Tests for diagnosis and monitoring asthma
- Asthma pharmacotherapy
- Non-pharmacological therapies and strategies
- Implementing asthma management strategies in health systems

TABLE OF CONTENTS

What's new?

A 'new' definition of asthma, identifying its **heterogeneous nature**, and the core elements of **variable symptoms** and **variable expiratory airflow limitation**.

New definition of asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.

2012 GINA updated

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

2014 GINA

A ‘new’ definition of asthma, identifying its heterogeneous nature, and the core elements of variable symptoms and variable expiratory airflow limitation.

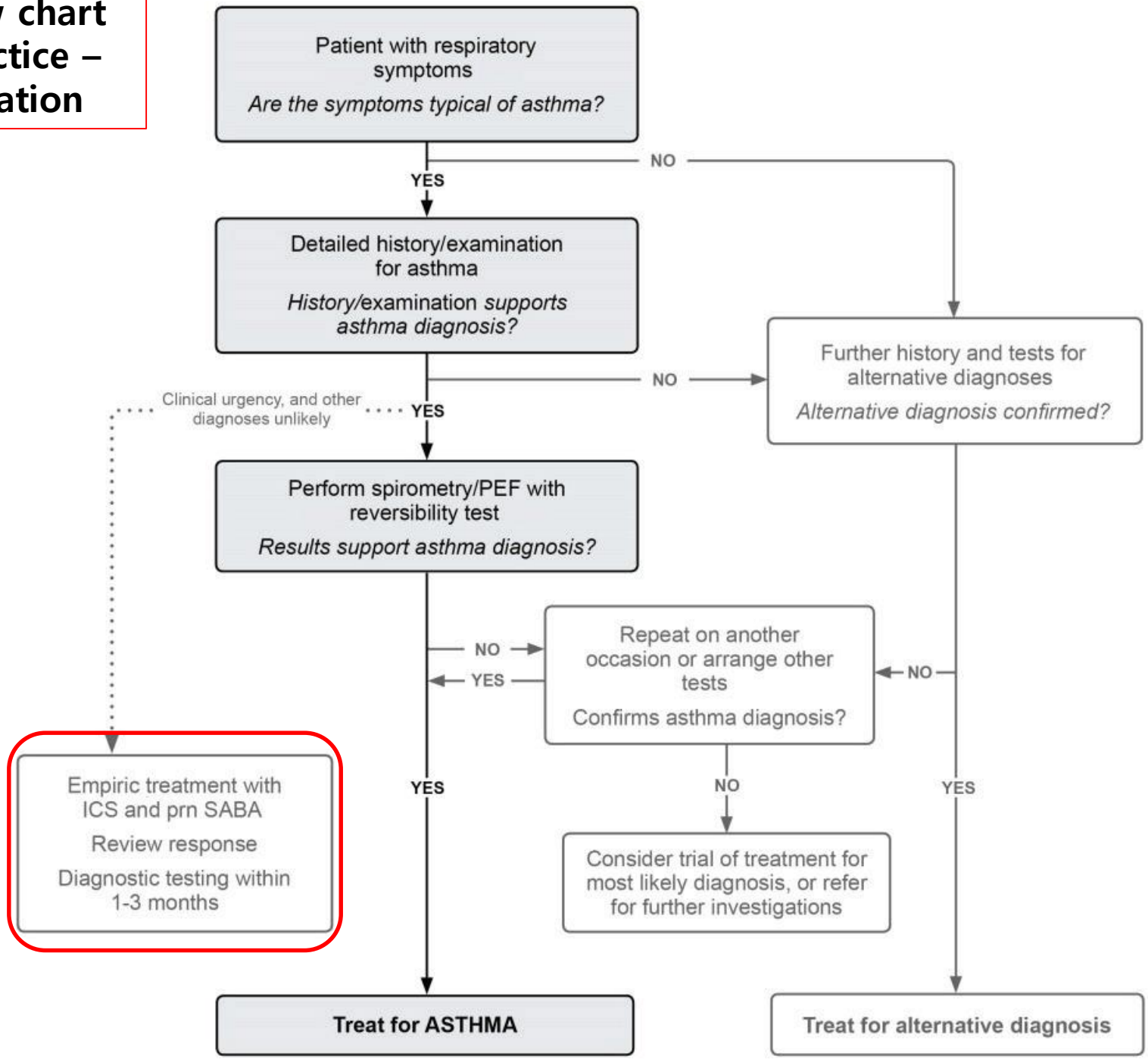
- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
- Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called ‘asthma phenotypes’; however, these do not correlate strongly with specific pathological processes or treatment responses.
- The diagnosis of asthma should be based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.
- If possible, the evidence for the diagnosis of asthma should be documented before starting controller treatment, as it is often more difficult to confirm the diagnosis afterwards.
- Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.

Symptoms and airflow limitation varying over time and in intensity

What's new?

An emphasis on confirming the diagnosis of asthma, to minimize both under- and over-treatment. Specific advice has been added about how to confirm the diagnosis in special populations including patients already on treatment.

Diagnostic flow chart for clinical practice – initial presentation



Box 1-2. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years

'Variability' - improvement and/or deterioration in symptoms and lung function.

Excessive variability may be identified over the course of one day (*diurnal variability), from day to day, from visit to visit,* or seasonally, or from a reversibility test.

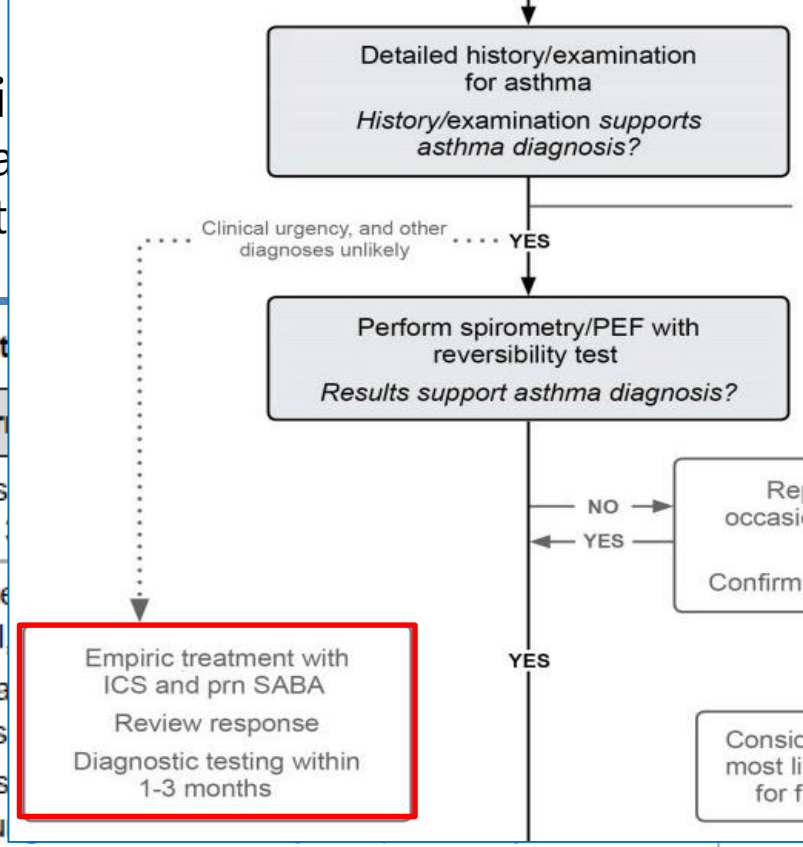
'Reversibility' - rapid improvements in FEV1 (or PEF),

measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol, or more sustained improvement over days or weeks after the introduction of effective controller treatment such as ICS.

function* (one or more of the tests below)	seen, the more confident the diagnosis
AND documented airflow limitation*	At least once during diagnostic process when FEV_1 is low, confirm that FEV_1/FVC is reduced (normally >0.75–0.80 in adults, >0.90 in children)
Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	*Adults*: increase in FEV_1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 of >12% predicted
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%** *Children*: average daily diurnal PEF variability >13%**
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults*: increase in FEV_1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	*Adults*: fall in FEV_1 of >10% and >200 mL from baseline *Children*: fall in FEV_1 of >12% predicted, or PEF >15%
Positive bronchial challenge test (usually only performed in adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	*Adults*: variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections *Children*: variation in FEV_1 of >12% in FEV_1 or >15% in PEF† between visits (may include respiratory infections)

When can variable airflow limitati

If possible, evidence of variable airflow limita
before treatment is st



Box 1-4. Confirming the diagnosis of asthma in a patient already t

Current status	Steps to confir
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. As and review controller treatment (Box
Variable respiratory symptoms but no variable airflow limitation	Repeat BD reversibility test again afte hours) or during symptoms. If normal, *If FEV_1 is >70% predicted*: consider a stepping down controller treatment (s *If FEV_1 is <70% predicted*: consider s 3-5), then reassess symptoms and lu treatment and refer patient for diagnosis and investigation
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12+ hours) or during symptoms. If normal, consider alternative diagnoses (Box 1-3). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to lowest previous effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and fixed airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5, p31), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap syndrome (Chapter 5, p73).

What's new?

Practical tools for assessment of both symptom control and risk factors for adverse outcomes

How to assess a patient with asthma

CONTROL TREATMENT COMORBIDITIES

Box 2-1. Assessment of asthma in adults, adolescents, and children 6–11 years

1. Assess asthma control = symptom control and future risk of adverse outcomes
• Assess symptom control over the last 4 weeks (Box 2-2A) • Identify any other risk factors for exacerbations, fixed airflow limitation or side-effects (Box 2-2B) • Measure lung function at diagnosis/start of treatment, 3–6 months after starting controller treatment, then periodically
2. Assess treatment issues
• Document the patient's current treatment step (Box 3-5, p31) • Watch inhaler technique, assess adherence and side-effects • Check that the patient has a written asthma action plan • Ask about the patient's attitudes and goals for their asthma and medications
3. Assess comorbidities
• Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control

Levels of Asthma Control

(Assess patient impairment)

Characteristic	Controlled (All of the following)	Partly controlled (Any present in any week)	Uncontrolled
Daytime symptoms	Twice or less per week	More than twice per week	3 or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms / awakening	None	Any	
Need for rescue / "reliever" treatment	Twice or less per week	More than twice per week	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known) on any day	

Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)

How to assess asthma control?

Box 2-2. GINA assessment of asthma control in adults, adolescents and children 6–11 years

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

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.

Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

Potentially modifiable independent risk factors for flare-ups (exacerbations)

- Uncontrolled asthma symptoms[68]
- Excessive SABA use (>1 x 200-dose canister/month)[69]
- Inadequate ICS: not prescribed ICS; poor adherence;[70] incorrect inhaler technique[71]
- Low FEV_1, especially if <60% predicted[72,73]
- Major psychological or socioeconomic problems[74]
- Exposures: smoking;[73] allergen exposure if sensitized[73]
- Comorbidities: obesity;[75] rhinosinusitis;[76] confirmed food allergy[77]
- Sputum or blood eosinophilia[78,79]
- Pregnancy[80]

Other major independent risk factors for flare-ups (exacerbations)

- Ever intubated or in intensive care unit for asthma[81]
- ≥1 severe exacerbation in last 12 months[82]

Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled.

Risk factors for developing fixed airflow limitation

- Lack of ICS treatment[83]
- Exposures: tobacco smoke;[84] noxious chemicals; occupational exposures[28]
- Low initial FEV_1;[85] chronic mucus hypersecretion;[84,85] sputum or blood eosinophilia[85]

Risk factors for medication side-effects

- *Systemic*: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors[86]
- *Local*: high-dose or potent ICS;[86,87] poor inhaler technique[88]

Treating asthma to control symptoms and minimize risk

What's New?

A comprehensive approach to asthma management that acknowledges the **foundational role of inhaled corticosteroid therapy**, but also provides **a framework for individualizing patient** care based on patient characteristics, modifiable risk factors, patient preference, and practical issues.

An emphasis on maximizing the benefit that can be obtained from available medications by addressing **common problems such as incorrect inhaler technique and poor adherence before considering a step-up in treatment**

Management of asthma -general principles-

- **Treating to control symptoms and minimize risk**
  - Medications; a reliever +/- controller
  - Treating modifiable risk factors
  - Non-pharmacological therapies and strategies

- **Training essential skills and guided asthma self-management**
  - Asthma information
  - Inhaler skills
  - Adherence
  - Written asthma action plan
  - Self-monitoring
  - Regular medical review

Initial controller treatment

- **Regular daily controller treatment** should be initiated as soon as possible after the diagnosis of asthma is made, because:
  - Early treatment with low dose ICS leads to better lung function than if symptoms have been present for more than 2–4 years
  - Patients not taking ICS who experience a severe exacerbation have lower long-term lung function than those who have started ICS
  - In occupational asthma, early removal from exposure and early treatment increase the probability of recovery

Initial controller selection

Presenting symptoms	Preferred controller (Evidence)
Asthma symptoms or need for **SABA < x2/month**, and No risk factor for exacerbation No exacerbation in the last year	No controller (D)
Infrequent asthma symptoms but, **with one or more risk factors** **(low PFT, AE requiring OCS in the last year, hx. of ICU care for asthma)**	**Low dose ICS (D)**
x2/month< asthma symptoms or need for SABA ≤ x2/week Patient wakes due to asthma≥ x1/month	**Low dose ICS (B)**
asthma symptoms or need for **SABA > x2/week**	**Low dose ICS (A)**, Less effective options – LTRA, theophylline
Asthma symptoms in most days **Waking with asthma ≥ x1/week, especially if any risk factor (+)**	**Medium/high dose ICS (A)** or **low dose ICS/LABA (A)**
Initial presentation with **severely uncontrolled asthma or acute exacerbation**	Short course of OCS + high dose ICS (A) or moderate dose ICS/LABA (D)

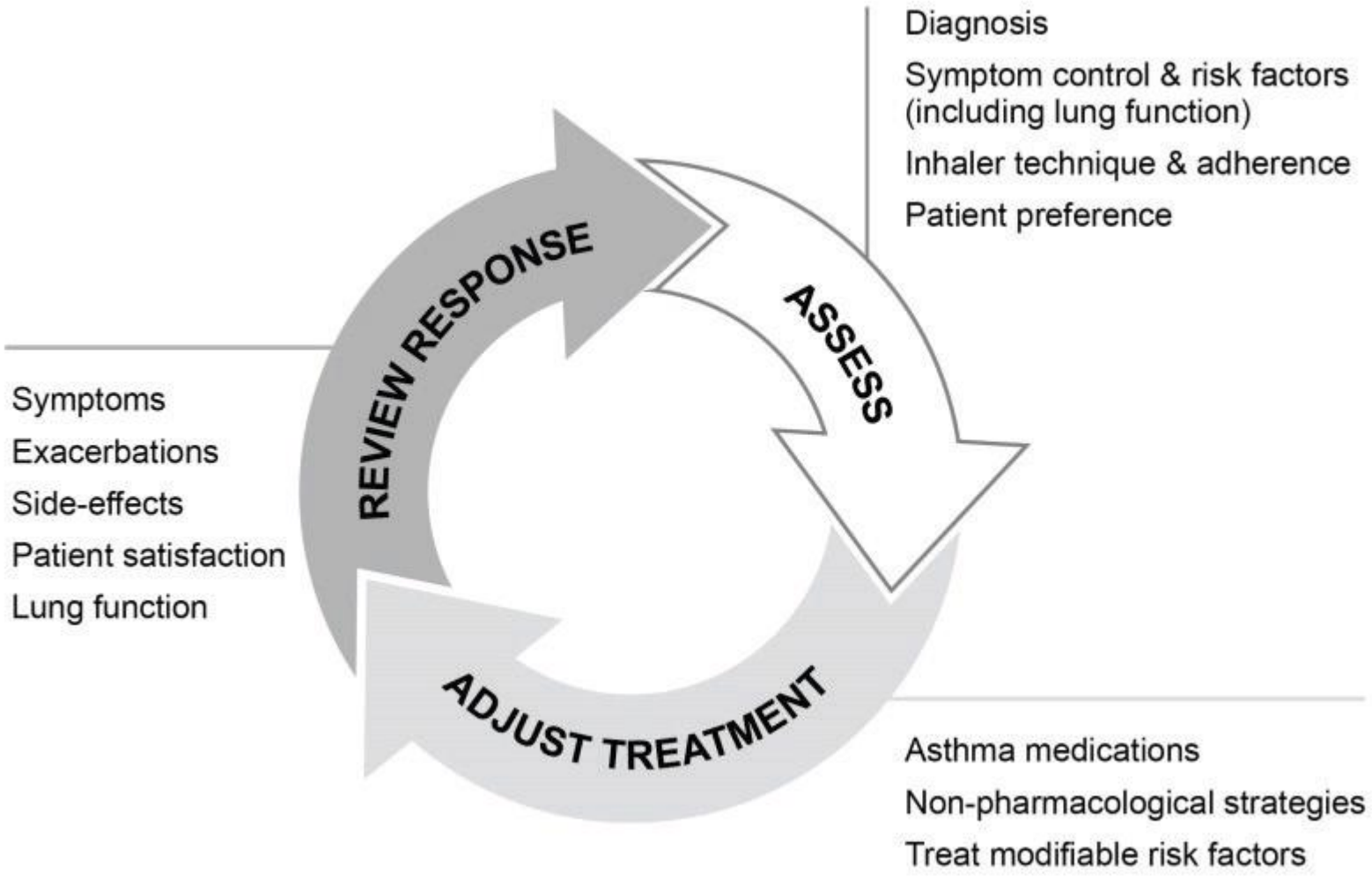
Regular low dose ICS is recommended for patients with any of the followings;

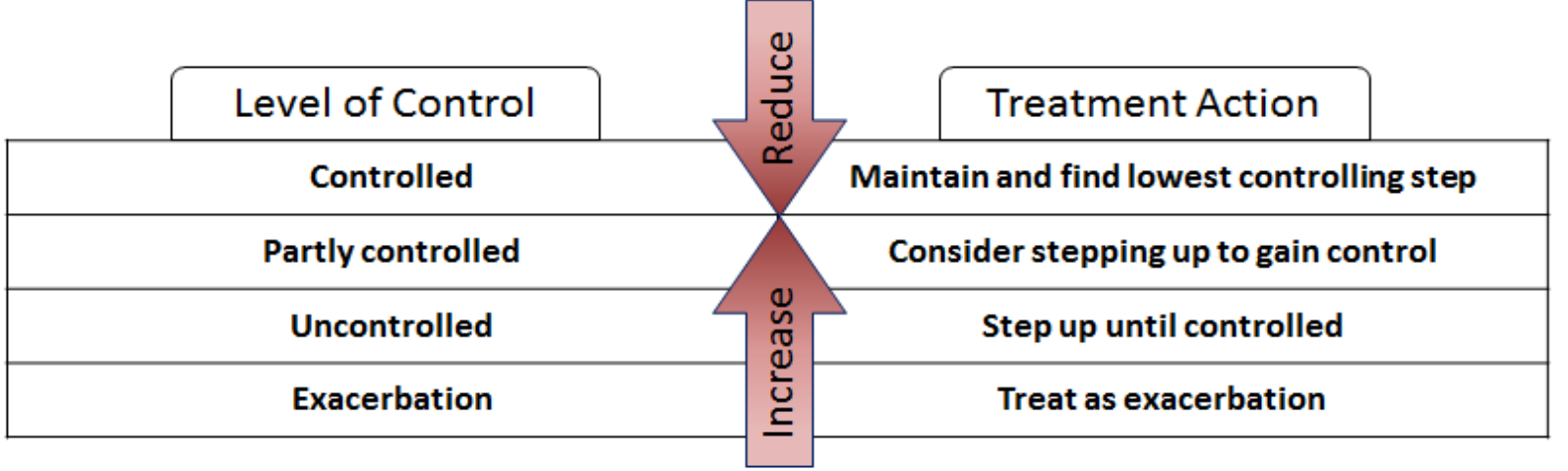
- Asthma symptoms more than twice a month
- Waking due to asthma more than once a month
- Any asthma symptoms plus any **risk factor(s) for exacerbations** (e.g. needing OCS for asthma within the last 12 months; low FEV1; ever in intensive care unit for asthma)
- Consider starting at a higher step (e.g. medium/high dose ICS, or ICS/LABA)
  - if the patient has troublesome asthma symptoms on most days; or is waking from asthma once or more a week, especially if there are any risk factors for exacerbations.

Risk factors for flare-up (exacerbation)

Potentially modifiable independent risk factors	Other major independent risk factors
Uncontrolled asthma symptoms	Ever **intubated or ICU** for asthma
Excessive SABA use (> 1x200-dose canister/month)	**≥1 severe exacerbation** in last 12 months
Inadequate ICS -Not prescribed ICS -Poor adherence -Incorrect inhaler technique	
Low FEV1, especially if <60% predicted	
Major psychological or socioeconomic problems	
Exposures: smoking, sensitized allergen	
Comorbidities: obesity, rhnosinusitis, confirmed food allergy	
Sputum or blood **eosinophilia**	
Pregnancy	

The control-based asthma management cycle





Asthma education – Environmental control				
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options**	Select one	Select one	To Step 3 treatment, select one or more	To Step 4 treatment, add either
	Low-dose ICS*	Low-dose ICS plus long-acting β_2-agonist	Medium- or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

* ICS = inhaled glucocorticosteroid

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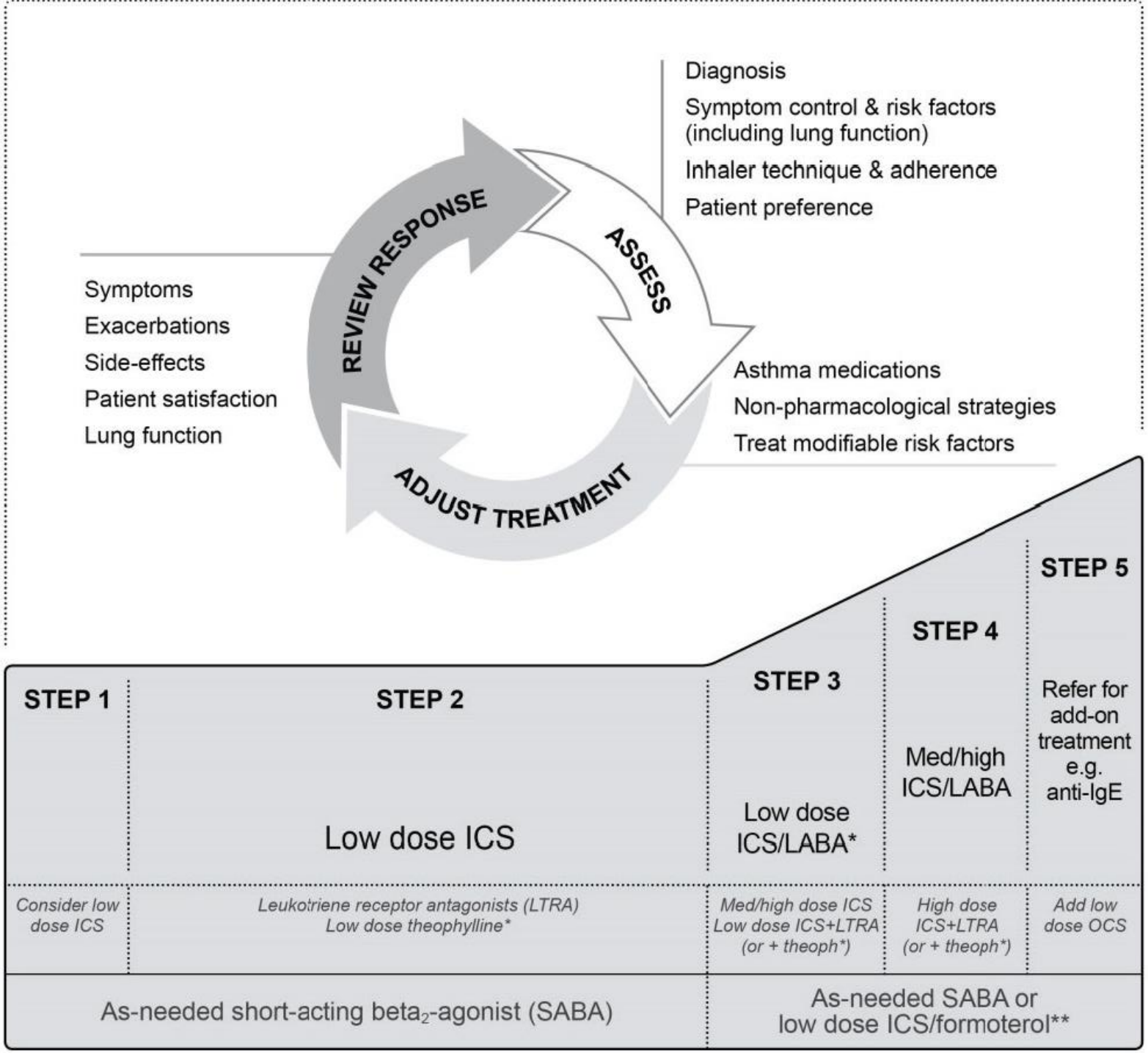

Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference
REVIEW RESPONSE
ASSESS
ADJUST TREATMENT
Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function
Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors
PREFERRED CONTROLLER CHOICE
STEP 1
STEP 2
STEP 3
STEP 4
STEP 5
Low dose ICS
Low dose ICS/LABA*
Med/high ICS/LABA
Refer for add-on treatment e.g. anti-IgE
Other controller options
Consider low dose ICS
Leukotriene receptor antagonists (LTRA)
Low dose theophylline*
Med/high dose ICS
Low dose ICS+LTRA
(or + theoph*)
High dose ICS+LTRA
(or + theoph*)
Add low dose OCS
RELIEVER
As-needed short-acting beta2-agonist (SABA)
As-needed SABA or
low dose ICS/formoterol**

Figure 3-1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteriods for Adults†			
Drug	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)‡**
Beclomethasone dipropionate - CFC	200-500	>500-1000	>1000-2000
Beclomethasone dipropionate - HFA	100 - 250	>250 - 500	>500 - 1000
Budesonide*	200-400	>400-800	>800-1600
Ciclesonide*	80-160	>160-320	>320-1280
Flunisolide	500-1000	>1000-2000	>2000
Fluticasone propionate	100-250	>250-500	>500-1000
Mometasone furoate*	200	≥400	≥800
Triamcinolone acetonide	400-1000	>1000-2000	>2000

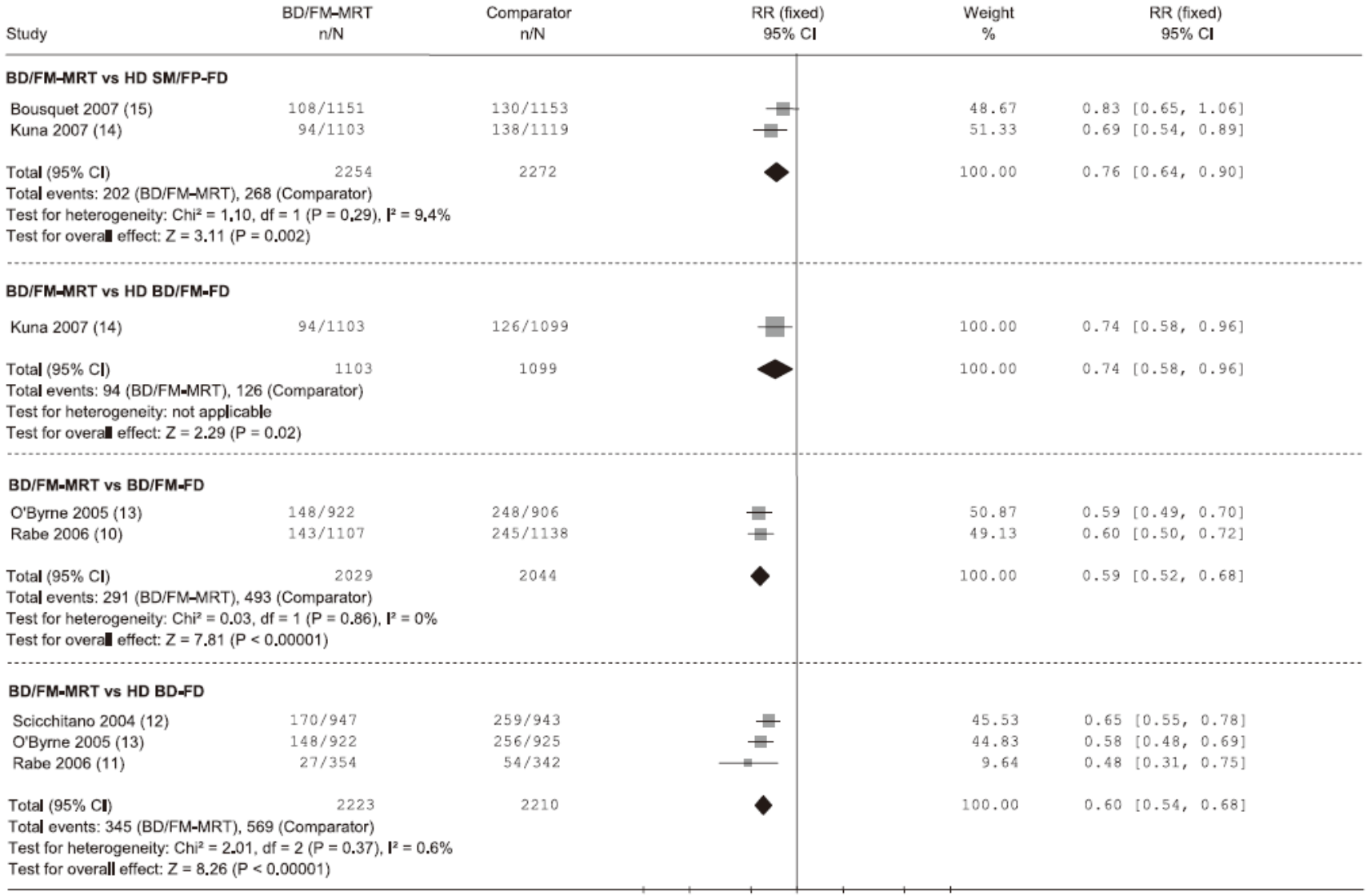
Box 8. Low, medium and high daily doses of inhaled corticosteroids (mcg)

Inhaled corticosteroid	Adults and adolescents			Children 6–11 years		
	Low	Medium	High	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	100–200	>200–400	>400	50-100	>100-200	>200
Budesonide (DPI)	200–400	>400–800	>800	100–200	>200–400	>400
Budesonide (nebules)				250–500	>500–1000	>1000
Ciclesonide (HFA)	80–160	>160–320	>320	80	>80-160	>160
Fluticasone propionate(DPI)	100–250	>250–500	>500	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–250	>250–500	>500	100–200	>200–500	>500
Mometasone furoate	110–220	>220–440	>440	110	≥220–<440	≥440
Triamcinolone acetonide	400–1000	>1000–2000	>2000	400–800	>800–1200	>1200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant.
*Included for comparison with older literature.

Single maintenance and reliever therapy (SMART) in BA

Meta-analysis (6 RCTs). Symbicort SMART vs Comparators, Primary outcome: severe exacerbation

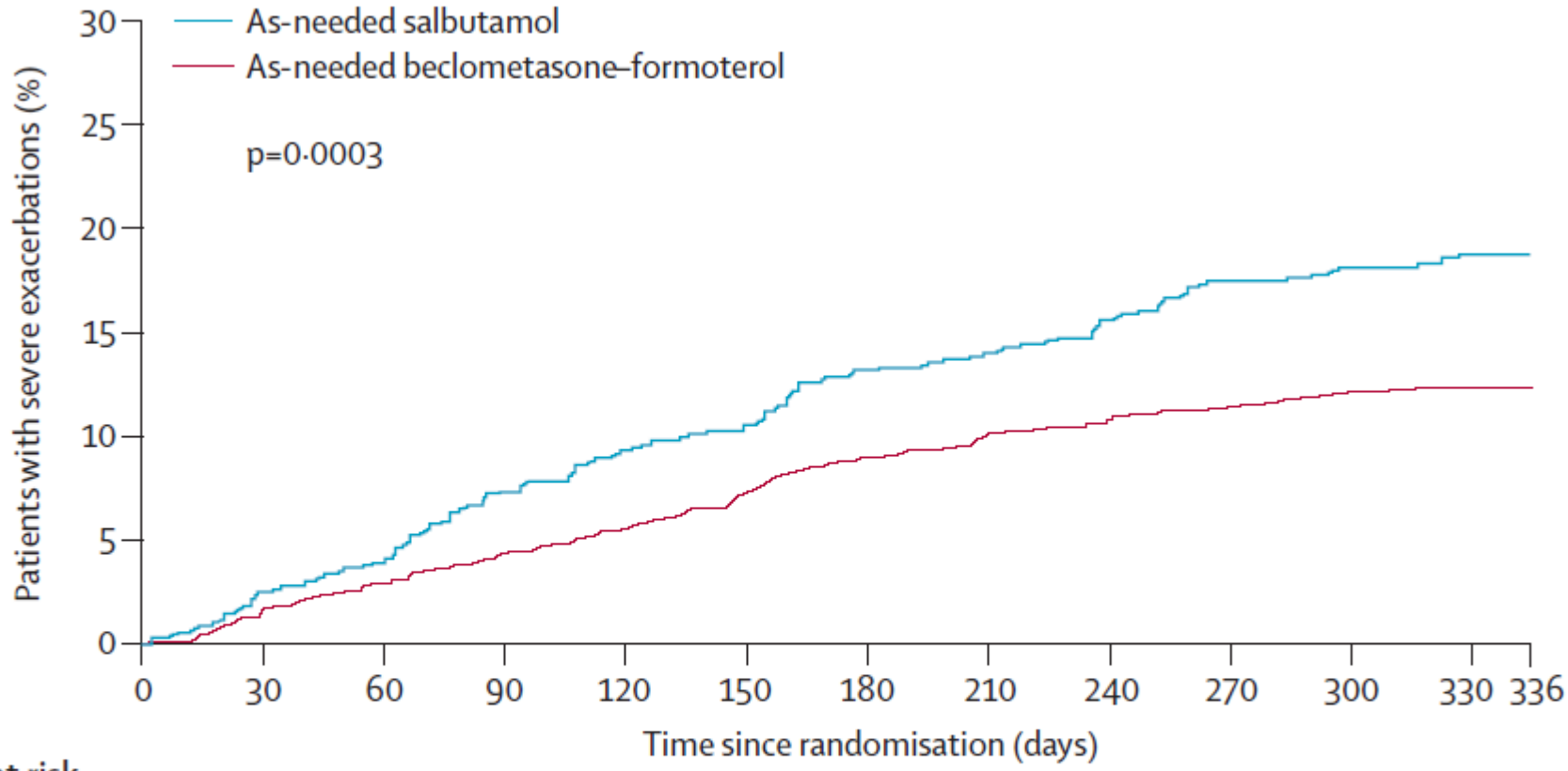


Edwards SJ. Int J Clin Pract 2010;64:619.

Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial

Lancet Respir Med 2013;1: 23–31

Alberto Papi, Massimo Corradi*, Catherine Pigeon-Francisco, Roberta Baronio, Zenon Siergiejko, Stefano Petruzzelli, Leonardo M Fabbri†, Klaus F Rabe‡*



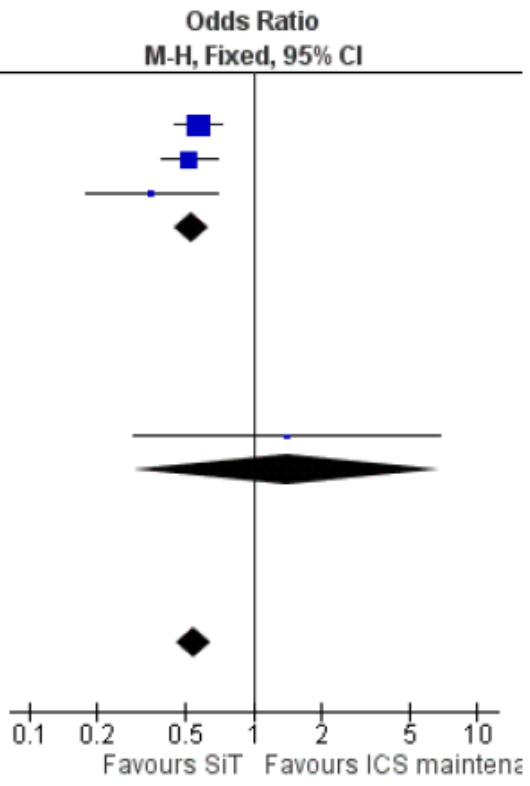
Number at risk												
Beclometasone–formoterol	852	822	800	779	761	743	719	704	696	681	673	658
Salbutamol	849	813	792	753	732	719	686	677	660	636	627	596

Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children (Review)

Cates CJ, Karner C

Figure 6. Forest plot of comparison: 2 adults and adolescents treated with Single Inhaler Therapy versus higher fixed dose ICS, outcome: 2.2 Patients with exacerbations treated with oral steroids.

	Single inhaler therapy		ICS maintenance			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.2.1 Single inhaler therapy versus higher dose ICS						
Scicchitano 2004	129	947	204	943	51.6%	0.57 [0.45, 0.73]
STAY - Adults	83	804	149	819	38.7%	0.52 [0.39, 0.69]
STEAM	12	354	31	342	8.9%	0.35 [0.18, 0.70]
Subtotal (95% CI)		**2105**		**2104**	**99.2%**	**0.53 [0.44, 0.63]**
Total events	224		384			
Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 6.96 (P < 0.00001)						
3.2.2 Single inhaler therapy versus same dose ICS						
Sovani 2008	4	35	3	36	0.8%	1.42 [0.29, 6.86]
Subtotal (95% CI)		**35**		**36**	**0.8%**	**1.42 [0.29, 6.86]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**2140**		**2140**	**100.0%**	**0.54 [0.45, 0.64]**
Total events	228		387			
Heterogeneity: Chi² = 3.24, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 6.87 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.48, df = 1 (P = 0.22), I² = 32.4%						



Cochrane Database Syst Rev. 2013 Apr 30;4:CD007313

Stepwise approach for adjusting treatment

	1st choice	Other options	Vs. 2013
Step 1	**As-needed SABA with no controller** (only if symptoms are rare, there is no night waking due to asthma, no exacerbations in the last year, and normal FEV1)	**Regular low dose ICS** for patients with exacerbation risks	As needed SABA only
Step 2	**Regular low dose ICS + as-needed SABA**	**LTRA** < ICS **ICS/LABA** (pts not previously using controllers) Not recommended for routine use: Theophylline, chromones	ICS/LABA (not appeared in step 2) > ICS in Sx. & FEV1, ICS/LABA=ICS in AE
Step 3	**Low dose ICS/LABA + as need SABA or ICS/formoterol (S)MART**	Medium dose ICS < ICS + LTRA, ICS + theophylline	
Step 4	**Low dose ICS/formoterol (S)MART or medium dose ICS/LABA + as-needed SABA**	high dose ICS/LABA extra controller, e.g. LTRA or slow-release theophylline A,	High dose ICS/LABA little additional benefit
Step 5	**Refer for expert investigation and add-on treatment**	Add-on treatments: anti-IgE (omalizumab), Sputum-guided treatment, Bronchial thermoplasty	Anti Ig-E in first Sputum-guided treatment, Bronchial

Step-up

- ***Sustained step-up (for at least 2–3 months):***

  if symptoms and/or exacerbations persist despite 2–3 months of controller treatment, assess the following common issues before considering a step-up

  - **Incorrect inhaler technique**
  - **Poor adherence**
  - **Modifiable risk factors, e.g. smoking**
  - **Are symptoms due to comorbid conditions, e.g. allergic rhinitis**
- ***Short-term step-up (for 1–2 weeks)*** by clinician or by patient with written asthma action plan, e.g. during viral infection or allergen exposure
- ***Day-to-day adjustment by*** patients prescribed low dose beclometasone/formoterol or budesonide/formoterol as maintenance and reliever therapy

Step-down

- Consider stepping down
  - Well controlled symptoms & stable lung function for 3 or more months
  - Step down through available formulations to reduce the ICS dose by 25–50% at 2–3 month intervals
- Do not step-down without close supervision
  - in patients with risk factors for exacerbation or fixed flow limitation
- Do not completely withdraw ICS (in adults or adolescents) unless it is needed temporarily to confirm the diagnosis of asthma

Current step Current medication/dose	Options of step down	Evidence
Step 5		
High dose ICS/LABA + OCS	**Continue high dose ICS/LABA and reduce OCS** Use sputum-guided approach to reducing OCS Alternate-day OCS treatment Replace OCS with high dose ICS	D B D D
High dose ICS/LABA + other add-on agents	Refer to expert advice	D
Step 4		
Moderate to high dose ICS/LABA maintenance treatment	**Continue combination ICS/LABA with 50% reduction in ICS component.** **Discontinuing LABA is more likely to lead to deterioration**	B A
Medium dose ICS/formoterol as (S)MART	**Reduce maintenance ICS/formoterol to low dose**, and continue as needed low dose ICS/formoterol reliever	D
High dose ICS + 2nd controller	Reduce ICS dose by 50% and continue 2nd controller	B
Step 3		
Low dose ICS/LABA maintenance	**Reduce ICS/LABA to once daily** Discontinuing LABA is more likely to lead to deterioration	D A
Low dose ICS/formoterol as (S)MART	**Reduce maintenance ICS/formoterol dose to once daily** and continue as needed low-dose ICS/formoterol reliever	C
Moderate- or high-dose ICS	**Reduce ICS dose by 50%**	B
Step 2		
Low dose ICS	**Once daily dosing**	A
Low dose ICS or LTRA	Consider stopping controller only if no symptoms for 6-	D

Treating modifiable risk factors to reduce exacerbations

Risk factor	Treatment strategy	Evidence
Any patient with ≥1 risk factor for exacerbations (including poor symptom control)	• Ensure patient is prescribed regular ICS-containing controller • Ensure patient has a written action plan appropriate for their health literacy • Review patient more frequently than low-risk patients • Check inhaler technique and adherence frequently • Identify any modifiable risk factors (Box 2-2, p17)	A A A A D
≥1 severe exacerbation in last year	• Consider alternative controller regimens to reduce exacerbation risk, e.g. ICS/formoterol maintenance and reliever regimen • Consider stepping up treatment if no modifiable risk factors • Identify any avoidable triggers for exacerbations	A A C
Exposure to tobacco smoke	• Encourage smoking cessation by patient/family; provide advice and resources • Consider higher dose of ICS if asthma poorly-controlled	A B
Low FEV_1, especially if <60% predicted	• Consider trial of 3 months' treatment with high-dose ICS and/or 2 weeks' OCS • Exclude other lung disease, e.g. COPD • Refer for expert advice if no improvement	B D D
Obesity	• Strategies for weight reduction • Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea	B D
Major psychological problems	• Arrange mental health assessment • Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks	D D
Major socioeconomic problems	• Identify most cost-effective ICS-based regimen	D
Confirmed food allergy	• Appropriate food avoidance; injectable epinephrine	A
Allergen exposure if sensitized	• Consider trial of simple avoidance strategies; consider cost • Consider step up of controller treatment • The efficacy of allergen immunotherapy in asthma is limited	C D A
Sputum eosinophilia (limited centers)	• Increase ICS dose independent of level of symptom control	A*

FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; OCS: oral corticosteroids.
* Based on evidence from relatively small studies in selected populations. Also see Box 3-9 and Appendix Chapter 6 for more information about non-pharmacological interventions.

Indications for referral for expert advice

Box 3-10. Indications for considering referral for expert advice, where available

Difficulty confirming the diagnosis of asthma
• Patient has symptoms of chronic infection, or features suggesting a cardiac or other non-pulmonary cause (Box 1-3, p8) (immediate referral recommended) • Diagnosis is unclear even after a trial of therapy with ICS or systemic corticosteroids • Patients with features of both asthma and COPD, if there is doubt about priorities for treatment
Suspected occupational asthma
• Refer for confirmatory testing and identification of sensitizing or irritant agent, specific advice about eliminating exposure and pharmacological treatment. See specific guidelines (e.g. [28]) for details.
Persistent uncontrolled asthma or frequent exacerbations
• Patient's symptoms remain uncontrolled, or patient has ongoing exacerbations or low lung function despite correct inhaler technique and good adherence with Step 4 treatment (moderate or high-dose ICS/LABA, Box 3-5, p31). Before referral, depending on the clinical context, identify and treat modifiable risk factors (Box 2-2, p17; Box 3-8, p38) and comorbidities (p47) • Patient has frequent asthma-related health care utilization (e.g. multiple ED visits or urgent primary care visits)
Any risk factors for asthma-related death (see Box 4-1, p59)
• Near-fatal asthma attack (ICU admission, or mechanical ventilation for asthma) at any time in the past • Anaphylaxis or confirmed food allergy in a patient with asthma
Evidence of, or risk of, significant treatment side-effects
• Patients with significant side-effects from treatment • Need for long-term oral corticosteroid use • Frequent courses of oral corticosteroids (e.g. two or more courses a year)
Symptoms suggesting complications or sub-types of asthma
• e.g. aspirin-exacerbated respiratory disease (p53); allergic bronchopulmonary aspergillosis
Additional reasons for referral in children 6–11 years
• Doubts about diagnosis of asthma e.g. respiratory symptoms are not responding well to treatment in a child who was born prematurely • Symptoms or exacerbations remain uncontrolled despite moderate dose ICS (Box 3-6B, p32) with correct inhaler technique and good adherence • Suspected side-effects of treatment (e.g. growth delay) • Asthma and confirmed food allergy

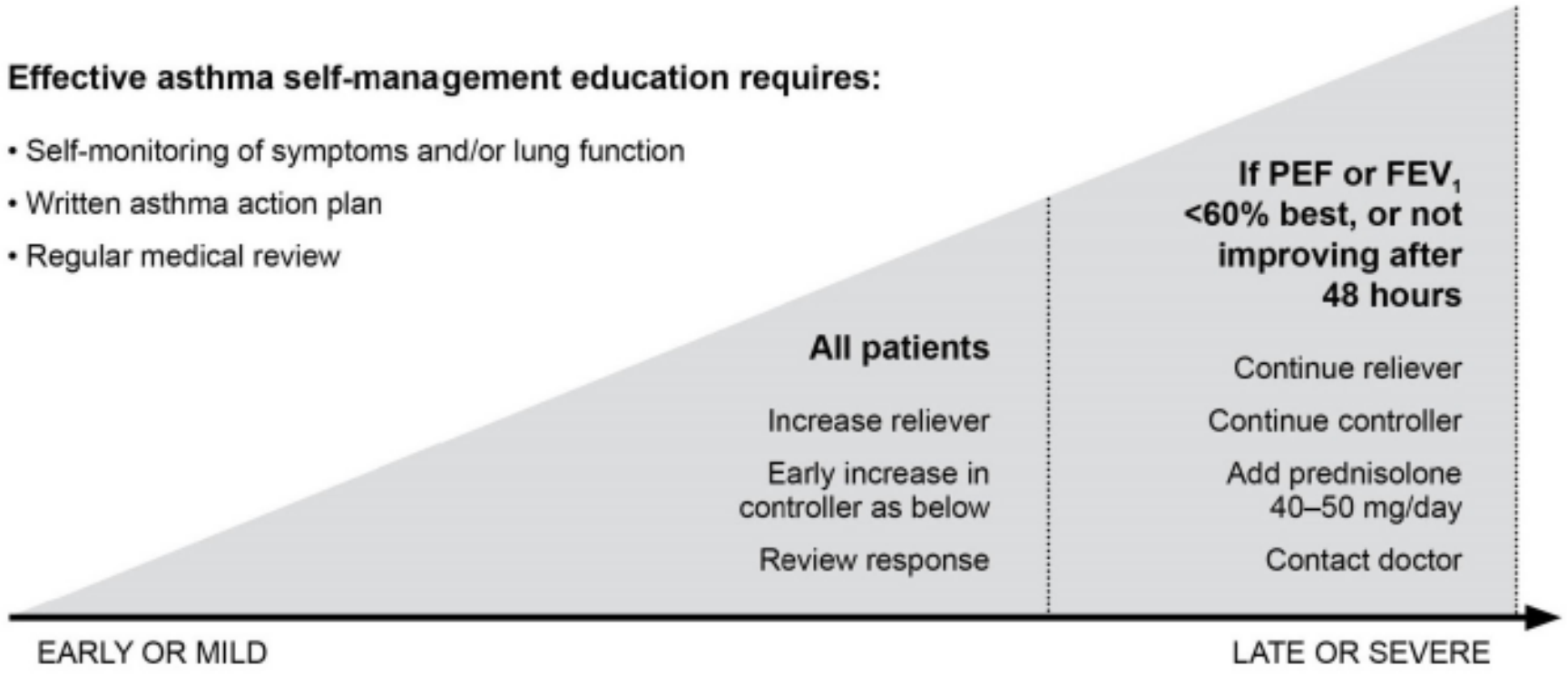
What's New?

A continuum of care for worsening asthma, starting with **early self-management with a written asthma action plan**, and progressing if necessary through to primary care management and acute care, to follow-up

Effective guided asthma self-management

- Self-monitoring of symptoms and/or peak flow
- A **written asthma action plan** to show how to recognize and respond to worsening asthma; and
- Regular review of asthma control, treatment and skills by a health care provider

Self-management of worsening asthma with a written action plan



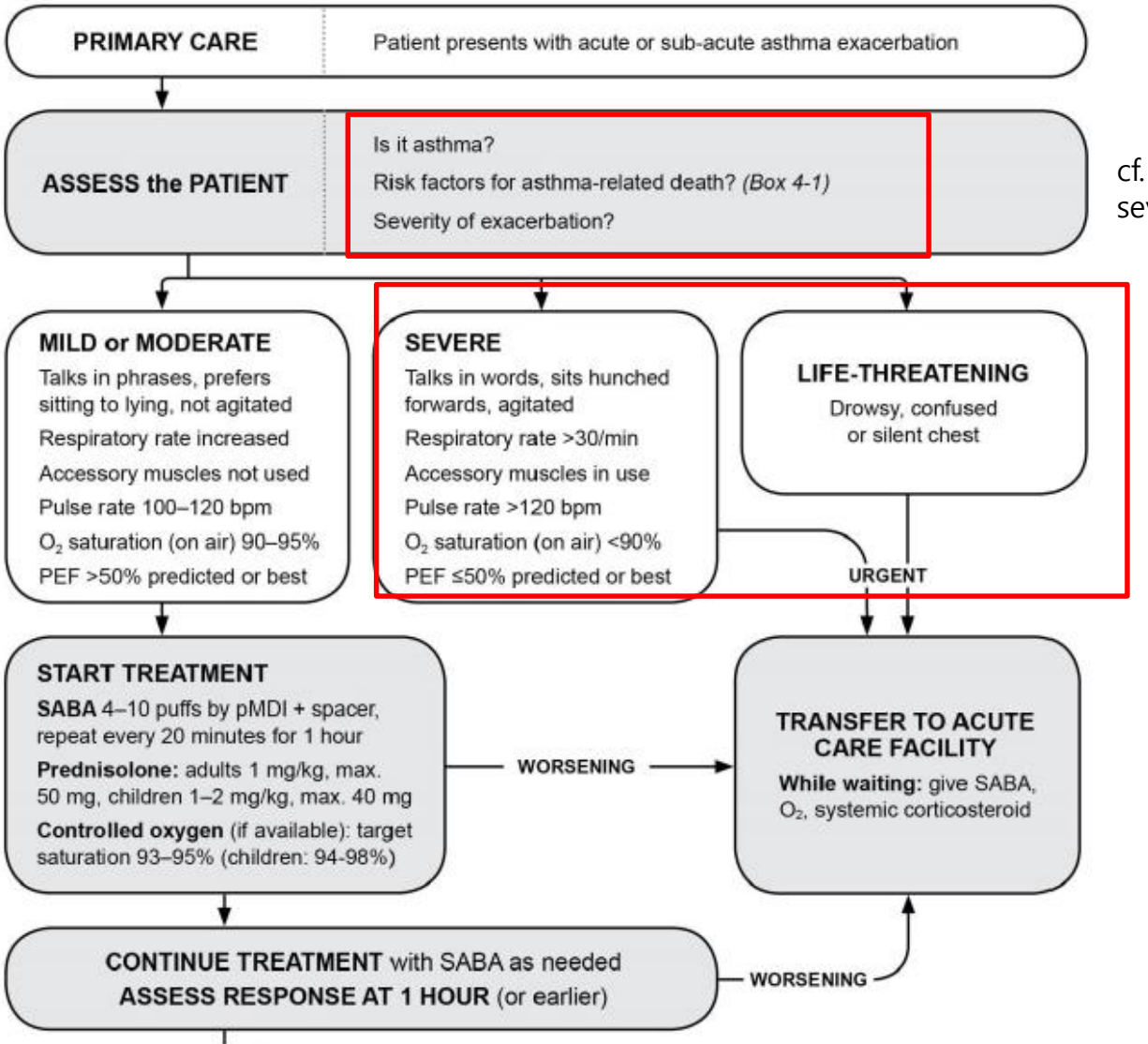
The written asthma action plan should include:

- The patient's usual asthma medications
- When and how to increase medications, and start OCS
- How to access medical care if symptoms fail to respond

Self-management of worsening asthma with a written action plan

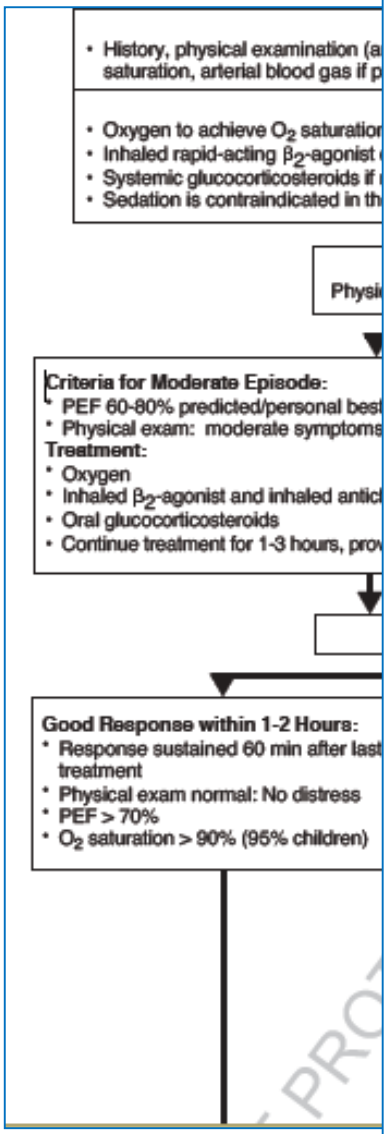
Medication	Short-term change (1-2 weeks) for worsening asthma	Evidence Level
Increase usual reliever:		
Short-acting beta$_2$-agonist (SABA)	Increase frequency of SABA use For pMDI, add spacer	A A
Low dose ICS/formoterol *	Increase frequency of reliever use (maximum formoterol total 72 mcg/day)	A
Increase usual controller:		
Maintenance and reliever ICS/formoterol *	Continue maintenance ICS/formoterol and increase reliever ICS/formoterol as needed* (maximum formoterol total 72 mcg/day)	A
Maintenance ICS with SABA as reliever	At least double ICS; consider increasing ICS to high dose (maximum 2000 mcg/day BDP equivalent)	B
Maintenance ICS/formoterol with SABA as reliever	Quadruple maintenance ICS/formoterol (maximum formoterol 72 mcg/day)	B
Maintenance ICS/salmeterol with SABA as reliever	Step up to higher dose formulation of ICS/salmeterol, or consider adding a separate ICS inhaler (to maximum total 2000 mcg/day BDP equivalent)	D
Add oral corticosteroids (OCS) and contact doctor		
OCS (prednisone or prednisolone)	Add OCS for severe exacerbations (e.g. PEF or FEV$_1$ <60% personal best or predicted), or patient not responding to treatment over 48 hours	A
	Adults: prednisolone 1 mg/kg/day (maximum 50 mg) usually for 5–7 days. *Children:* 1–2 mg/kg/day (maximum 40 mg) usually for 3–5 days.	D
	Tapering is not needed if OCS are prescribed for <2 weeks	B

Management of asthma exacerbations in primary care



cf. assessment of severity in 2013 version

Management of asthma exacerbations in acute care facility



INITIAL ASSESSMENT

A: airway **B:** breathing **C:** circulation

Are any of the following present?

Drowsiness, Confusion, Silent chest

NO

YES

Further TRIAGE BY CLINICAL STATUS
according to worst feature

Consult ICU, start SABA and O_2, and prepare patient for intubation

MILD or MODERATE

Talks in phrases
Prefers sitting to lying
Not agitated
Respiratory rate increased
Accessory muscles not used
Pulse rate 100–120 bpm
O_2 saturation (on air) 90–95%
PEF >50% predicted or best

Short-acting beta$_2$-agonists
Consider ipratropium bromide
Controlled O_2 to maintain saturation 93–95% (children 94-98%)
Oral corticosteroids

SEVERE

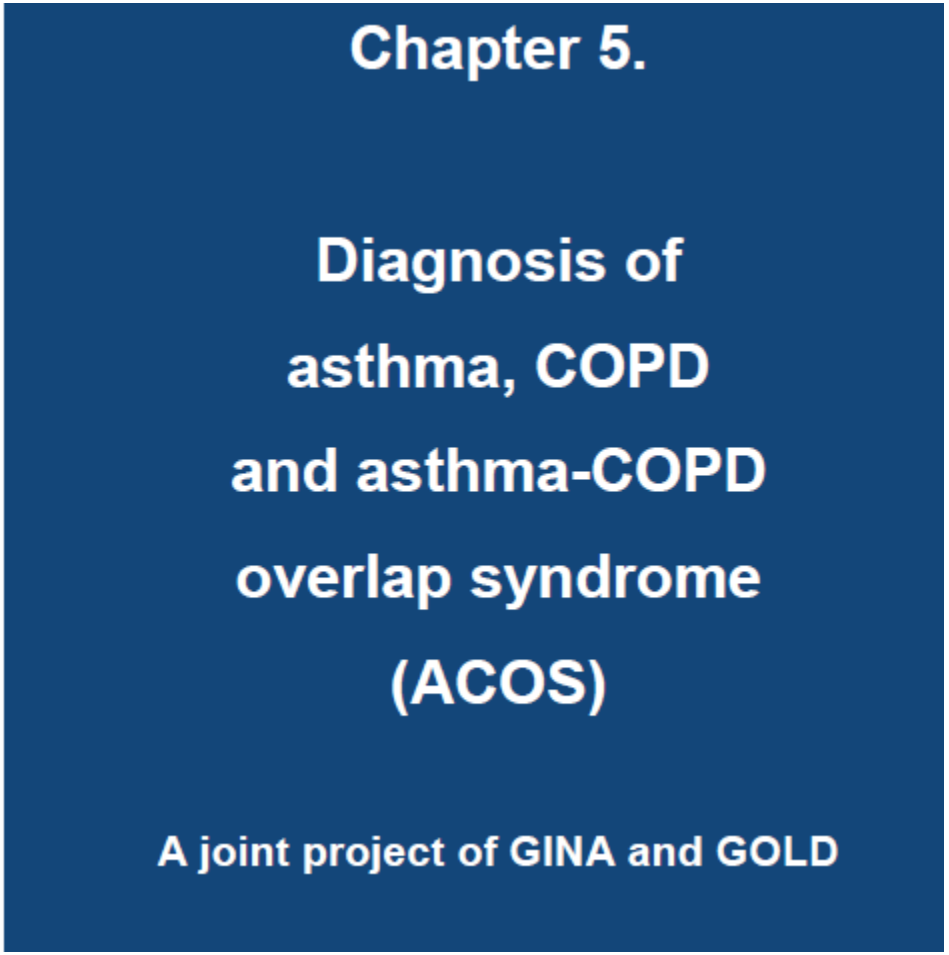
Talks in words
Sits hunched forwards
Agitated
Respiratory rate >30/min
Accessory muscles being used
Pulse rate >120 bpm
O_2 saturation (on air) < 90%
PEF ≤50% predicted or best

Short-acting beta$_2$-agonists
Ipratropium bromide
Controlled O_2 to maintain saturation 93–95% (children 94-98%)
Oral or IV corticosteroids
Consider IV magnesium
Consider high dose ICS

If continuing deterioration, treat as severe and re-assess for ICU

ASSESS CLINICAL PROGRESS FREQUENTLY

ACOS


Chapter 5.
Diagnosis of
asthma, COPD
and asthma-COPD
overlap syndrome
(ACOS)
A joint project of GINA and GOLD

Summary on ACOS in GINA 2014

This consensus-based document aims to assist clinicians to:

- *Identify* patients who have a disease of chronic airflow limitation
- *Distinguish* asthma from COPD and the Asthma-COPD Overlap Syndrome (ACOS)
- *Decide* on initial treatment and/or need for referral

- Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults.
- ACOS is identified by the features that it shares with both asthma and COPD.
- A stepwise approach to diagnosis is advised, comprising recognition of the presence of a chronic airways disease, syndromic categorization as asthma, COPD or the overlap between asthma and COPD (the Asthma COPD Overlap Syndrome (ACOS)), confirmation by spirometry and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACOS may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACOS are often worse than for asthma or COPD alone.
- Initial treatment should be selected to ensure that:
  - Patients with features of asthma receive adequate controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone (as monotherapy), and
  - Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (as monotherapy).
- The consensus-based description of the Asthma COPD Overlap Syndrome (ACOS) is intended to stimulate further study of the character and treatments for this common clinical problem.

Definition

Asthma
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2014]
COPD
COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. [GOLD 2014][36]
Asthma-COPD overlap syndrome (ACOS) – a description for clinical use
Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.

Box 5-2a. Usual features of asthma, COPD and ACOS

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV_1 may be improved by therapy, but post-BD $FEV_1/FVC < 0.7$ persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Typical airway inflammation	Eosinophils and/or neutrophils	Neutrophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

Box 5-2b. Features that favor asthma or COPD*

Favors asthma	Favors COPD
☐ Onset before age 20 years	☐ Onset after age 40 years
☐ Variation in symptoms over minutes, hours or days	☐ Persistence of symptoms despite treatment
☐ Symptoms worse during the night or early morning	☐ Good and bad days but always daily symptoms and exertional dyspnea
☐ Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
☐ Record of variable airflow limitation (spirometry, peak flow)	☐ Record of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$)
☐ Lung function normal between symptoms	☐ Lung function abnormal between symptoms
☐ Previous doctor diagnosis of asthma	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema
☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Heavy exposure to a risk factor: tobacco smoke, biomass fuels
☐ No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year	☐ Symptoms slowly worsening over time (progressive course over years)
☐ May improve spontaneously or have an immediate response to BD or to ICS over weeks	☐ Rapid-acting bronchodilator treatment provides only limited relief.
☐ Normal	☐ Severe hyperinflation

Syndromic diagnosis of airways disease: how to use Box 5-2b

Shaded columns list features that, when present, best distinguish between asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, that diagnosis is suggested. If there are similar numbers of checked boxes in each column, the diagnosis of ACOS should be considered. See Step 2 for more details.

Spirometric measures

Box 5-3. Spirometric measures in asthma, COPD and ACOS

Spirometric variable	Asthma	COPD	ACOS
Normal FEV_1/FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis (GOLD)	Usually present
FEV_1 ≥80% predicted	Compatible with diagnosis (good asthma control or interval between symptoms)	Compatible with GOLD classification of mild airflow limitation (categories A or B) if post-BD FEV_1/FVC <0.7	Compatible with diagnosis of mild ACOS
FEV_1 <80% predicted	Compatible with diagnosis. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and exacerbations)
Post-BD increase in FEV_1 ≥12% and 200 ml from baseline (reversible airflow limitation).	Usual at some time in course of asthma, but may not be present when well-controlled or on controllers	Common and more likely when FEV_1 is low, but ACOS should also be considered	Common and more likely when FEV_1 is low, but ACOS should also be considered
Post-BD increase in FEV_1 >12% and 400ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

ACOS: asthma-COPD overlap syndrome; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE

Do symptoms suggest chronic airways disease?

Yes → STEP 2

No → Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS

(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Feature: if present suggests -	**ASTHMA**	**COPD**
Age of onset	☐ Before age 20 years	☐ After age 40 years
Pattern of symptoms	☐ Variation over minutes, hours or days	☐ Persistent despite treatment
	☐ Worse during the night or early morning	☐ Good and bad days but always daily symptoms and exertional dyspnea
	☐ Triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	☐ Record of variable airflow limitation (spirometry or peak flow)	☐ Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
Lung function between symptoms	☐ Normal	☐ Abnormal
Past history or family history	☐ Previous doctor diagnosis of asthma	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema
	☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	☐ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year	☐ Symptoms slowly worsening over time (progressive course over years)
	☐ May improve spontaneously or have an	☐ Rapid-acting bronchodilator treatment

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Possible asthma	Could be ACOS	Possibly COPD	COPD

STEP 3
PERFORM SPIROMETRY

Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation

$FEV_1/FVC < 0.7$ post-BD

STEP 4
INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS and consider LABA +/or LAMA	COPD drugs	COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5
SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

What's New in GINA 2014

- New two chapters
  - Management of BA in children <5yrs old
  - Diagnosis of BA, COPD, and ACOS
- New d
  - He
    exp
- Empha
- Practic
  factors
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- Empha
  techni
- Contin
  - Ear
  - Primary care ⇒ acute care
- Updating strategies for effective adaptation and implementation of GINA recommendations for various health systems

GINA 2014

More user friendly version – enhance clinical utility
- more precise figure and tables
- flare up (exacerbation)
- emphasis on practical points rather than detailed descriptions
  eg. Initial inhalers selection, step-down strategy

Emphasis on treatment based on ICS and ICS/formoterol

Consideration of future risk in medical treatment
- risk factors for exacerbations

Initiation of syndromic approch to ACOS in primary care

Q & A

THANKS FOR YOUR ATTENTION

천식행동지침

양호	행동지침
• 기침, 쌕쌕거림, 가슴답답함, 주야간 호흡곤란이 없다. • 일상활동에 지장이 없다. • 잠을 잘 잔다. • 증상완화흡입제를 일주일에 2번 이하 사용한다. • 최대호기유량이 개인최고치의 80%이상이다.	• 기존에 처방 받은 치료제를 유지하세요. (흡입제) _____( )번/회, 아침/저녁 _____( )번/회, 아침/저녁 _____( )번/회, 아침/저녁 (경구약) _____( ) 회/일, _____( ) 회/일 _____( ) 회/일, _____( ) 회/일 • 흡연과 원인 알레르겐 등 악화인자를 피하세요. • 정기적인 의사의 진료를 받으세요 • 운동 후 악화소견이 있다면 운동 15분 전에 증상완화제_____를 ( )회 흡입하세요.

주의	행동지침
• 기침, 쌕쌕거림, 가슴답답함, 호흡곤란이 있다. • 밤에 천식증상으로 잠에서 깬다. • 일상활동에 지장이 있다. • 증상완화흡입제를 일주일에 3번 이상 사용한다. • 최대호기유량이 개인최고치의 60%~80% 사이이다.	• 기존에 처방 받은 치료제를 지속하면서 증상이 호전될 때 까지 증상완화제를 추가로 사용하세요 • 증상완화제_____를 ( )번/회를 2~4회 흡입하세요. • 호전되면 ( )동안 매( )시간 마다 사용하세요 • 증상이 호전되지 않거나 양호로 돌아가지 않는다면 경구 스테로이드 ( )를 시작하세요. -용량 ( )알/회, 하루 ( ) -기간 ( )일 • **호전이 없거나 악화된다면 위험행동을 따라 하세요.**

위험	행동지침
• 치료제가 도움이 되지 않는다. • 숨쉬기가 너무 힘들다. • 숨이 많이 차서 일상 활동을 할 수 없다. • 숨이 많이 차서 잠을 잘 수 없다. • 숨이 많이 차서 움직일 수 없다. • 숨이 많이 차서 말을 할 수 없다 • 손톱과 입술이 파랗다. • 최대호기유량이 개인최고치의 60% 이하이다.	• 경구 스테로이드 ( )를 시작하세요. 용량 ( )알/회 • 119 혹은 타인에게 도움을 요청하여 **즉시 응급실에 방문하세요.** • 동시에 병원에 도착할 때까지 증상완화제 _____를 20분마다 흡입하세요.

주의 및 위험시 각 행동지침에 의한 자가 치료 후에는 1-2주 안에 의사를 방문한다.

Process

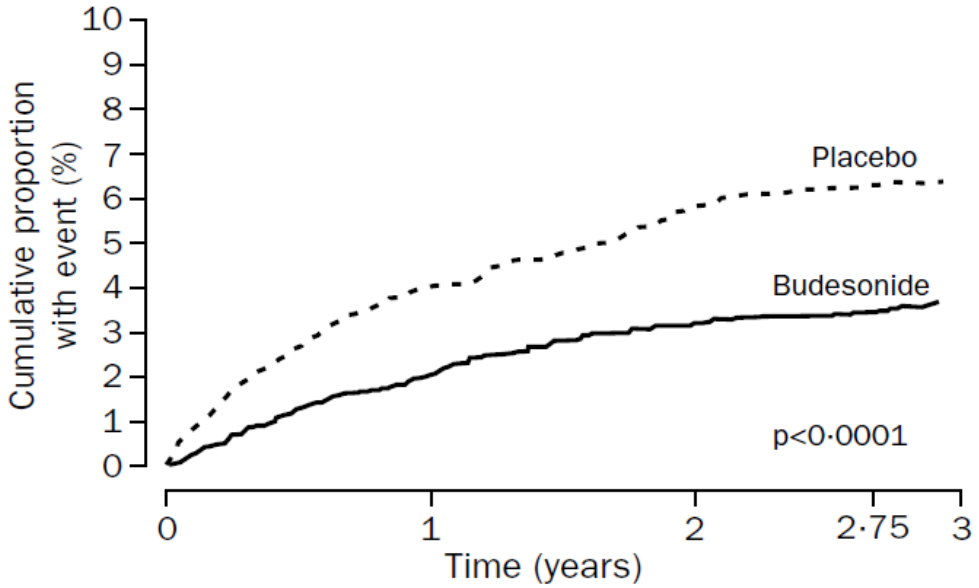
- Pubmed search
  - GINA scientific committee
  - [Search fields]
    - 1) asthma, all fields, all ages, only items with abstracts, clinical trial, human; and 2) asthma and metaanalysis,
    - all fields, all ages, only items with abstracts, human. Publications from July 1 to December 30 are reviewed during the following ATS meeting, and those from January 1 to June 30 during the following ERS meeting.
- Decided not to adopt GRADE system
  - ongoing twice-yearly update of the evidence base for its recommendations
  - levels of evidence are assigned as with all previous GINA reports

Key New Features in GINA 2014 REVISION

- A 'new' definition of asthma, identifying its heterogeneous nature, and the core elements of variable symptoms and variable expiratory airflow limitation.
- An emphasis on confirming the diagnosis of asthma, to minimize both under- and over-treatment. Specific advice has been added about how to confirm the diagnosis in special populations including patients already on treatment.
- Practical tools for assessment of both symptom control and risk factors for adverse outcomes (a concept endorsed by GINA in 2009).
- A comprehensive approach to asthma management that acknowledges the foundational role of inhaled corticosteroid therapy, but also provides a framework for individualizing patient care based on patient characteristics, modifiable risk factors, patient preference, and practical issues.
- An emphasis on maximizing the benefit that can be obtained from available medications by addressing common problems such as incorrect inhaler technique and poor adherence before considering a step-up in treatment
- A continuum of care for worsening asthma, starting with early self-management with a written asthma action plan, and progressing if necessary through to primary care management and acute care, to follow-up
- Updated strategies for effective adaptation and implementation of GINA recommendations for different health systems, available therapies, socioeconomic status, health literacy and ethnicity.

Regular ICS for mild-persistent asthma

Double-blind multicenter RCT (START trial). **Mild-persistent** (≥2yr) BA (BDR+, FEV1 15% fall by ExPT or PEF variability >15% dur 14d) pts aged 5-66 without regular ICS tx (N=7,241) → **Budesonide** 400μg (<11YO, 200μg) qd vs Placebo for 3yr. Primary outcome: time to 1st severe asthma-related event.



HR, 0.56; 95% CI, 0.45-0.71; p<0.001

Number at risk

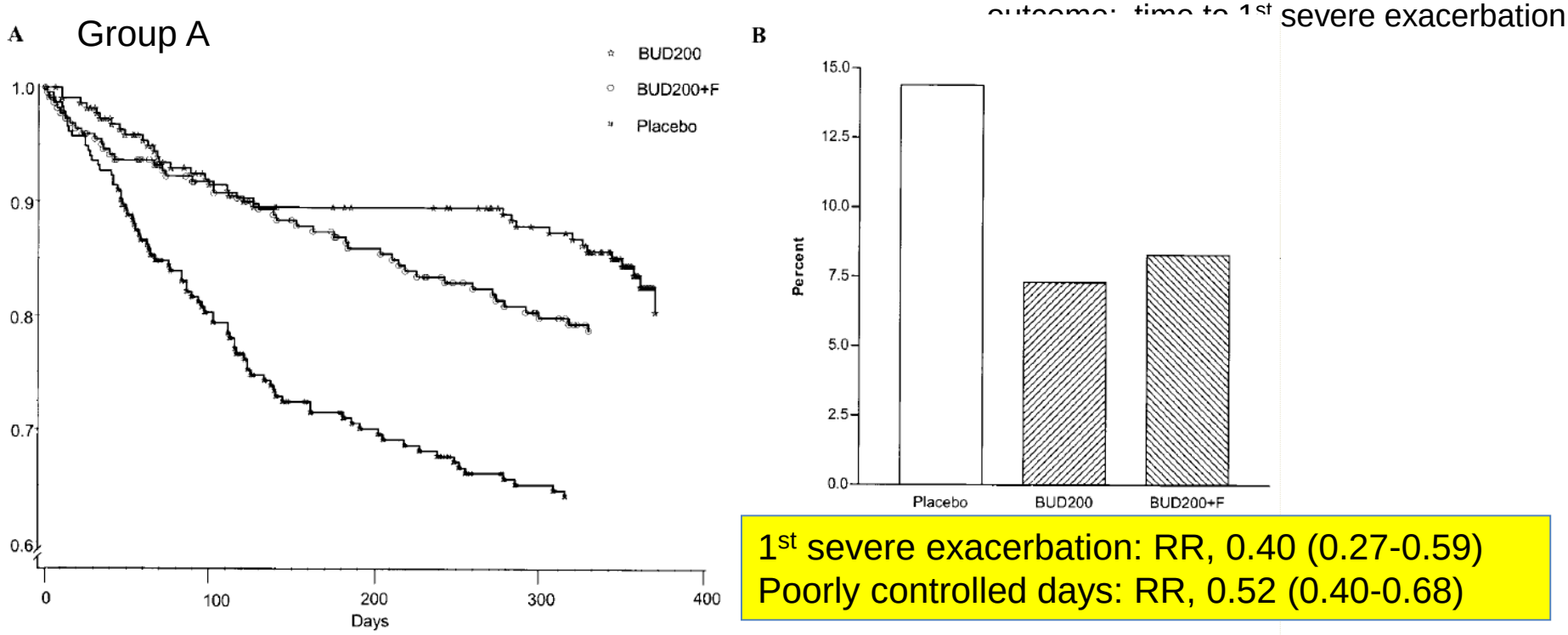
Placebo	3568	2865	2600	2438
Budesonide	3597	2998	2722	2570

Figure 2: **Kaplan-Meier curve of time to first severe asthma related event**

Pauwels RA. Lancet 2003;361:1071.

ICS only ≈ ICS+LABA in ICS-naïve mild BA pts

Double-blinded multicenter RCT (OPTIMA trial). Pts aged ≥ 12 with **mild asthma**. (1) Group A (corticosteroid-free for at least 3mo) → run-in with placebo (pts need rescue medication ≥ 2/week) → **Budesonide 100μg bid vs Budesonide 100μg + Formoeterol 4.5μg bid vs Placebo bid** (2) Group B (ICS 400≤μg/d budesonide) → run-in with Budesonide 100μg bid (pts need rescue medication ≥ 2/week) → Budesonide 100μg bid vs Budesonide 100μg + Formoeterol 4.5μg bid vs Budesonide 200μg bid vs Budesonide 200μg + Formoeterol 4.5μg bid. Primary outcome: time to 1st severe exacerbation



1st severe exacerbation: RR, 0.40 (0.27-0.59)
Poorly controlled days: RR, 0.52 (0.40-0.68)

Figure 1. (*A*) Kaplan-Meier survival curve for the time to the first severe asthma exacerbation. (*B*) Proportion (%) of poorly controlled asthma days in Group A (corticosteroid-free patients). BUD 200 = budesonide 100 μg twice daily; F = formoterol 4.5 μg twice daily.

O'Byrne PM. AJRCCM 2001;164:1392.

SMART
(single maintenance and reliever therapy)

- For both maintenance and symptom relief
  - Regular maintenance dose
    - to achieve day-to-day asthma control
  - Additional inhalations
    - for symptom relief

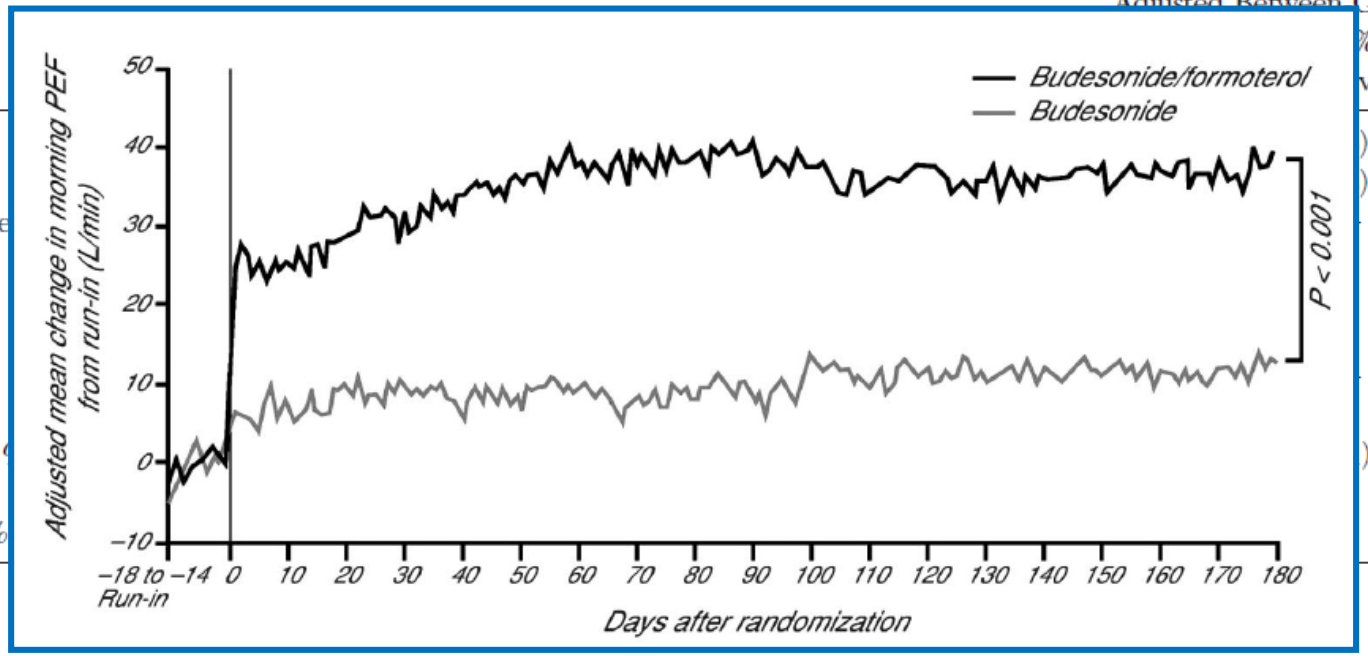
- Concept
  - One inhaler therapy automatically adapts to patients' changing needs, providing appropriate adjustments in both ICS and LABA therapy in a way that is not possible with separate maintenance and reliever inhalers

Humbert M. Allergy 2008;63:1567.

SMART in mild-to-moderate BA

Double-blind RCT. Pts aged 12-80 with **mild-to-moderate asthma** (at least 6mo) + at least 3mo ICS 200-500µg/d (N=697, mean age 38, FEV1 75%, ICS 348µg/d). Budesonide 100µg bid + terbutaline as needed (run-in) → **Budesonide/formoterol 80/4.5µg 2 doses qd + as needed** vs **Budesonide 160µg 2 doses qd + Terbutaline 0.4mg as needed for 6mo**. Primary efficacy variable: morning PEF

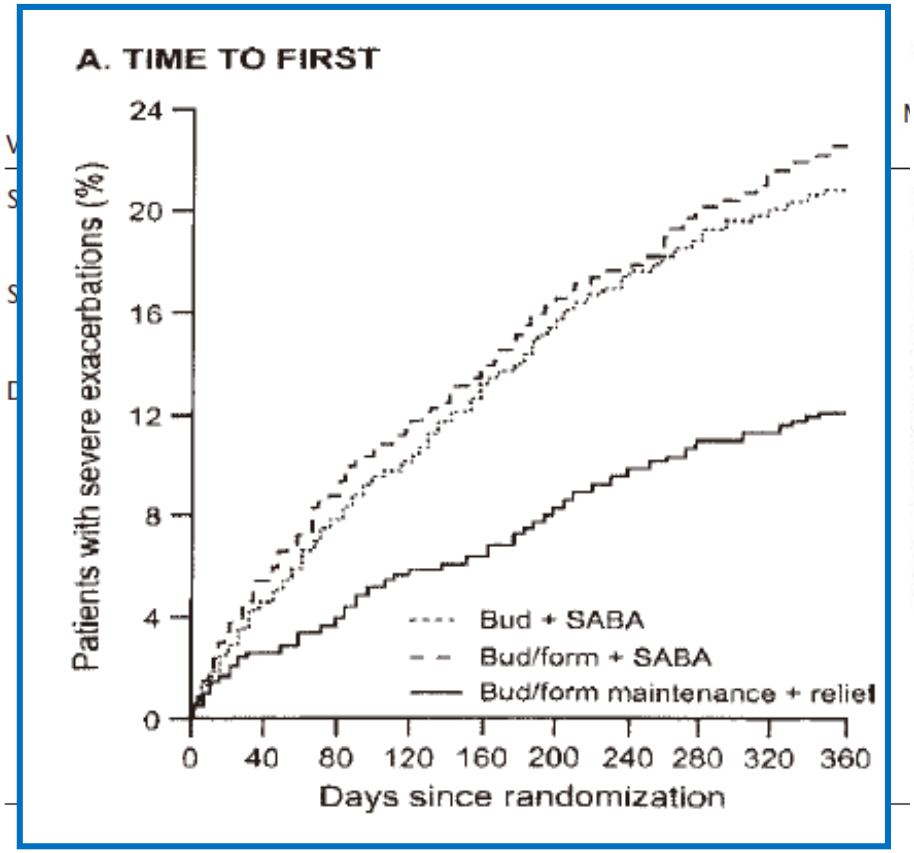
Efficacy Variables	Budesonide/Formoterol, 80 µg/4.5 µg, Two Inhalations qd	Budesonide, 160 µg, Two Inhalations qd	Adjusted Between Group % (95% CI)	p Value
Morning PEF, L/min				< 0.001
Evening PEF, L/min				< 0.001
As needed inhalations per day			0.17)	< 0.001
As needed medication-free days,‡ %				< 0.001
Total asthma symptom score (0 to 6)§			0.07)	< 0.001
Nighttime awakenings,‖				0.065
Symptom-free days,¶ %				0.0043
Asthma-control days,# %				0.0012

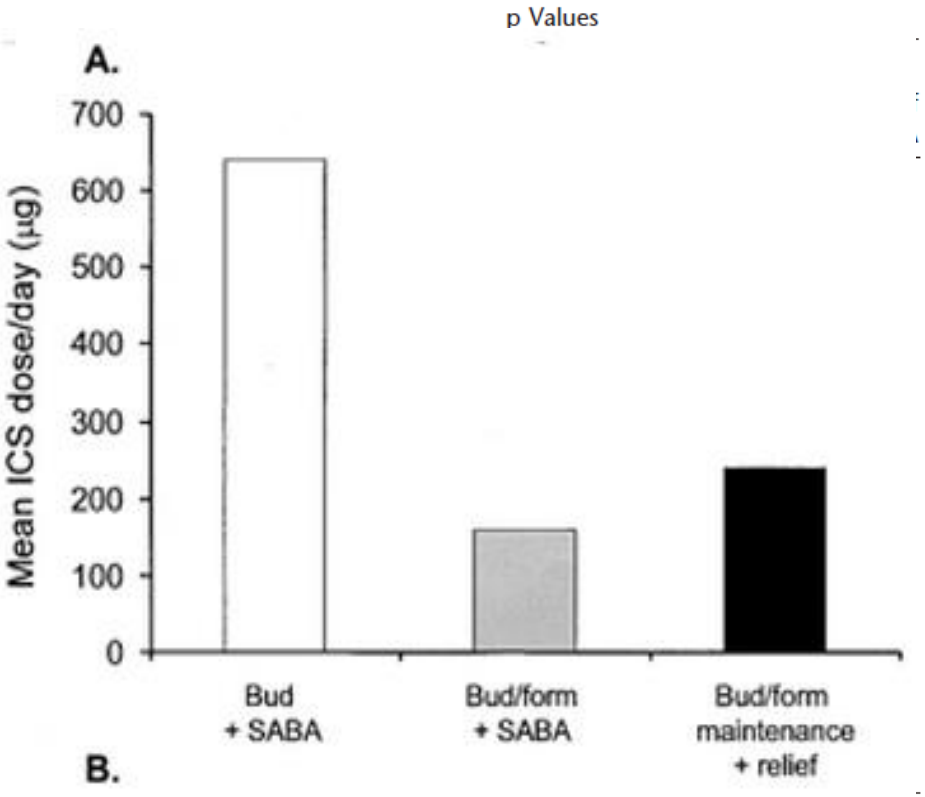


Rabe KF. Chest 2006;129:246.

SMART in moderate-to-severe BA

Double-blind multicenter (246 centers in 22 countries) RCT. Pts aged 4-80 (adult: child=8:1) with **asthma treated with ICS 400-1,000µg/d** (4-11YO: 200-500µg/d) **+ at least 1 exacerbation in the last year** (N=2,760). Run-in (pts should have used at least 12 dose during the last 10days) → **Budesonide/Formoterol 80/4.5µg bid+ as needed vs Budesonide/Formoterol 80/4.5µg bid+ Terbutaline 0.4mg as needed** vs **Budesonide 320µg bid + Terbutaline 0.4mg as needed** (Children: half maintenance dose qd hs). Primary efficacy outcome: time to 1st exacerbation

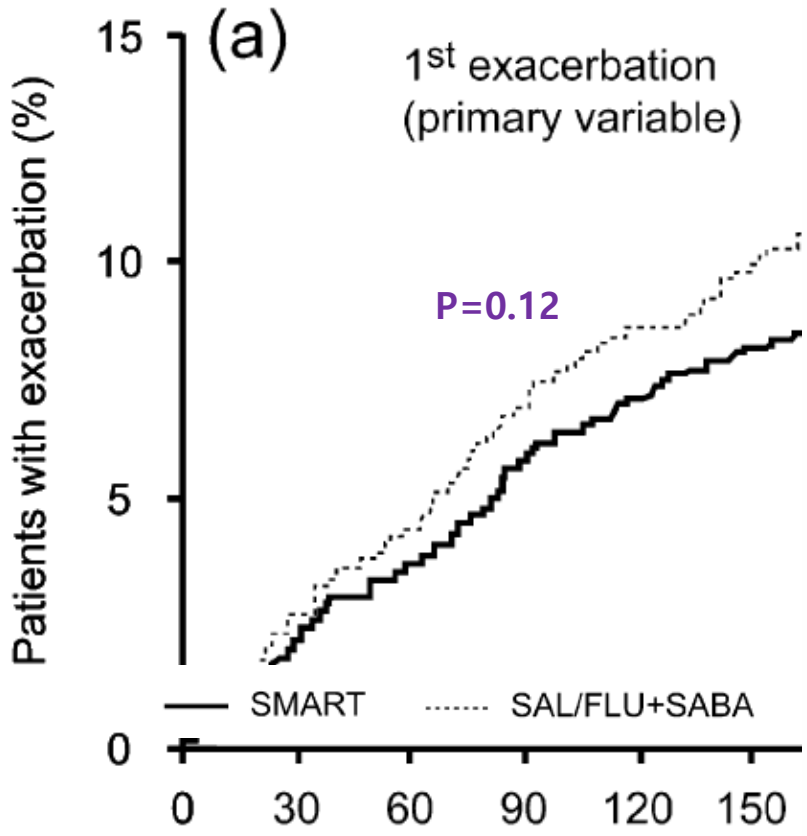




O'Byrne PM. AJRCCM 2005;171:129.

SMART vs Seretide in BA

Double-blind RCT. Pts aged ≥ 12 with persistent asthma treated with ICS 800-1,600μg/d alone or ICS 400-1,000μg/d +LABA for at least 3mo (N=2,309). Run-in 2weeks (pts should have used reliever on at least 5 days of previous 7days) → **Bud/Form 160/4.5μg 2 doses bid + as needed vs Flut/Salm 500/50μg bid + Terbutaline 0.4mg as needed for 6mo**. Primary end point: time to 1st severe exacerbation

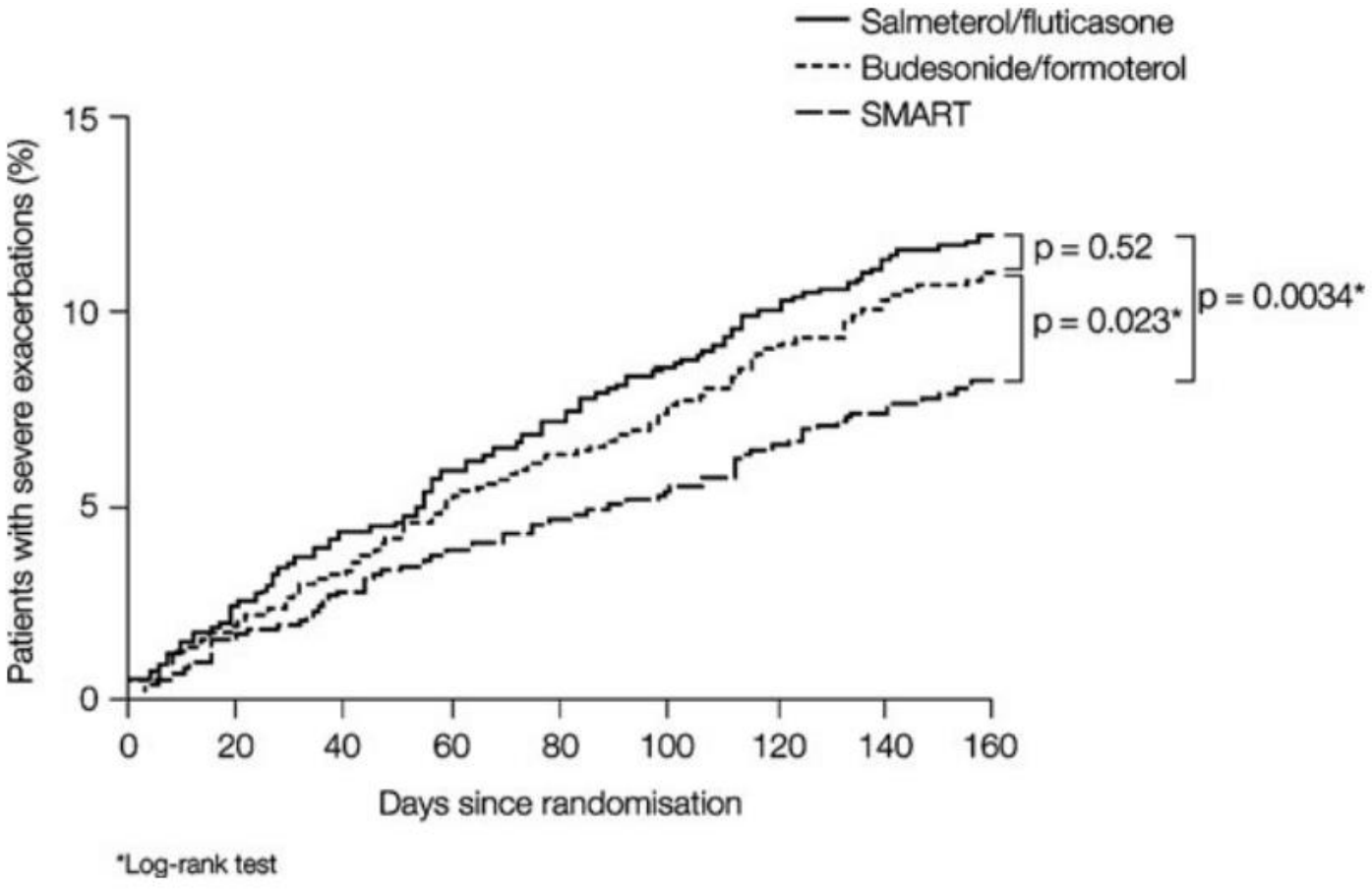


Bousquet J. Respir Med 2007;10:2437.

	Treatment group		Treatment comparison (95% CI); *P*-value[a]
	Budesonide/formoterol maintenance and reliever therapy (*N* = 1144)	High-dose salmeterol/ fluticasone + SABA (*N* = 1145)	
Use of as-needed medication			
Total inhalations daily			
Run-in	2.23	2.29	−0.04 (−0.12, 0.04);
On-treatment	0.95	1.01	*P* = 0.36
As-needed free days, %			
Run-in	10.3	9.3	−0.80 (−3.6, 1.9);
On-treatment	58.2	58.4	*P* = 0.56
Asthma symptoms			
Total symptom score, 0–6 scale			
Run-in	1.87	1.89	0.00 (−0.06, 0.07);
On-treatment	0.98	0.98	*P* = 0.92
Symptom-free days, %			
Run-in	10.7	11.2	−0.50 (−3.3, 2.3);
On-treatment	47.2	48.1	*P* = 0.73
Awakenings, %			
Run-in	32.1	32.2	−1.30 (−2.8, 0.3);
On-treatment	12.0	13.3	*P* = 0.11
Asthma control days, %			
Run-in	6.3	5.8	−1.30 (−4.1, 1.5);
On-treatment	44.0	44.9	*P* = 0.37
ACQ-5 (0–6 scale)			
Run-in	1.84	1.89	−0.02 (−0.07, 0.04);
On-treatment	1.08	1.12	*P* = 0.59
PEF (l/min)			
Morning			
Run-in	330.1	329.0	−0.8 (−4.4, 2.8);
On-treatment	359.5	359.4	*P* = 0.67
Evening			
Run-in	336.7	337.7	1.4 (−2.1, 4.9);
On-treatment	362.3	361.7	*P* = 0.42

SMART vs Seretide in BA

Double-blind, double-dummy RCT. Pts aged ≥ 12 with persistent BA treated with ICS (≥500µg/d of Bud, Flut, ≥1,000µg/d of another ICS). Run-in 2weeks (pts should have used reliver on ≥ 5d/previous 7d) (N=3,335) → **Bud/Form 160/4.5µg bid+ as needed vs Bud/Form 320/9 µg bid vs Flut/Salm 125/25µg 2 doses bid + Terbutaline 0.4mg as needed for 6mo**. Primary end point: time to 1st severe exacerbation



Kuna P. Int J Clin Pract 2007;61:725.