المؤتمر السنوي
الرابطة السورية لطب و جراحة الصدر

د لبنى حويجة

٦- ٧- ٨ / ١٠ / ٢٠٢٢

طرطوس

Asthma control

&

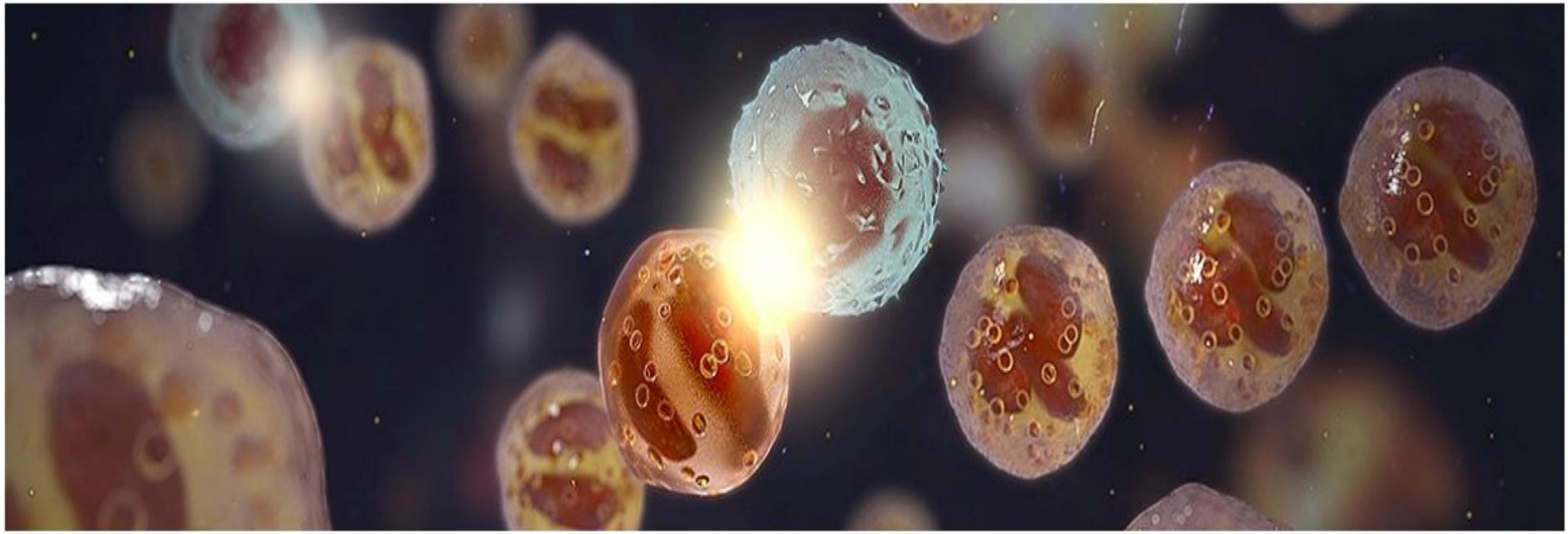
Efficacy when it matters

AstraZeneca

Symbicort®
budesonide/formoterol

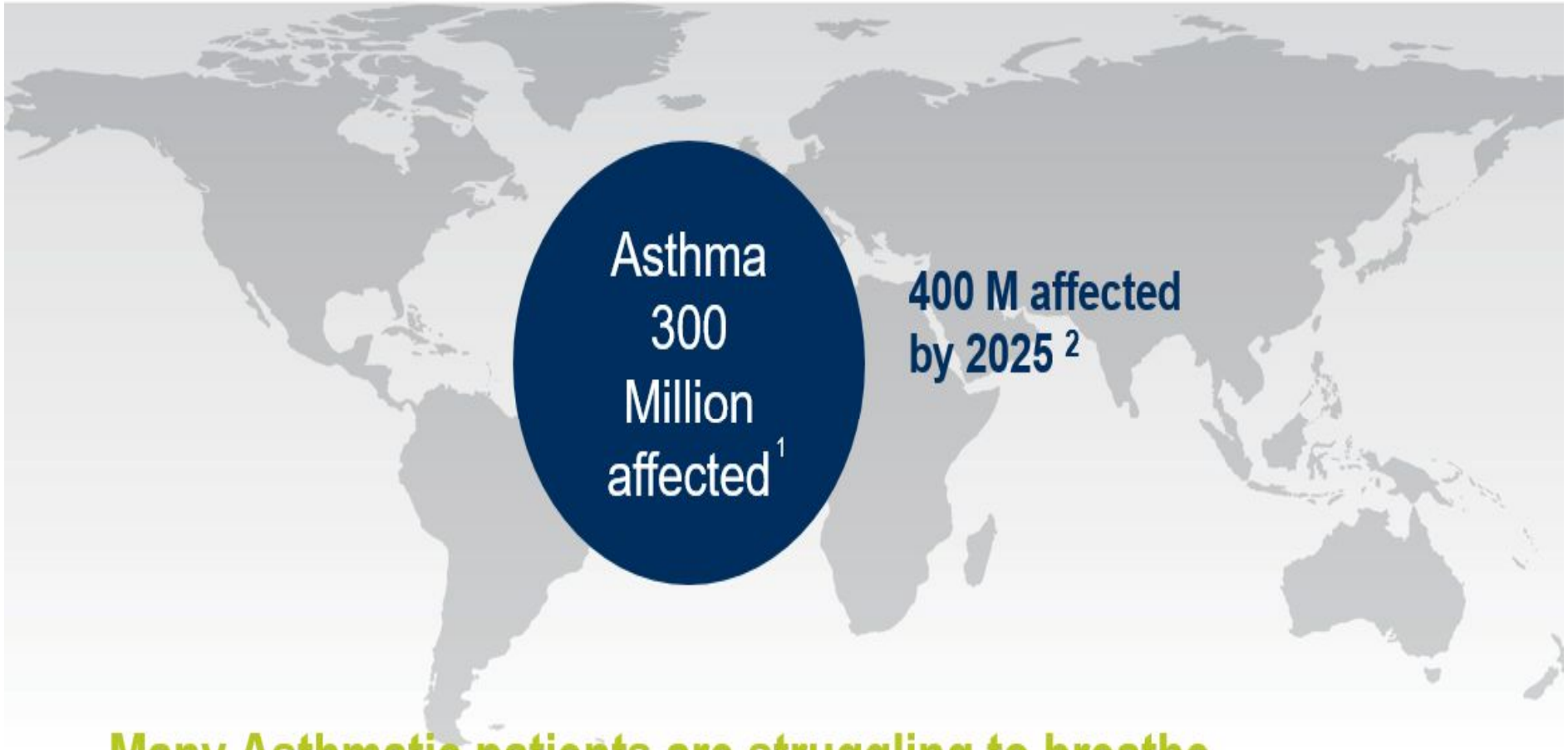
Efficacy When It Matters
Asthma

SYM-67-SK-0222-0224-NE



Asthma and its global burden

Global Asthma Burden



Many Asthmatic patients are struggling to breathe…

1. Global Initiative for Asthma. Available at: http://ginasthma.org/2019-pocket-guide-for-asthma-management-and-prevention Last accessed December 2019 2. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy2004;59:469-78

Asthma is a global health concern

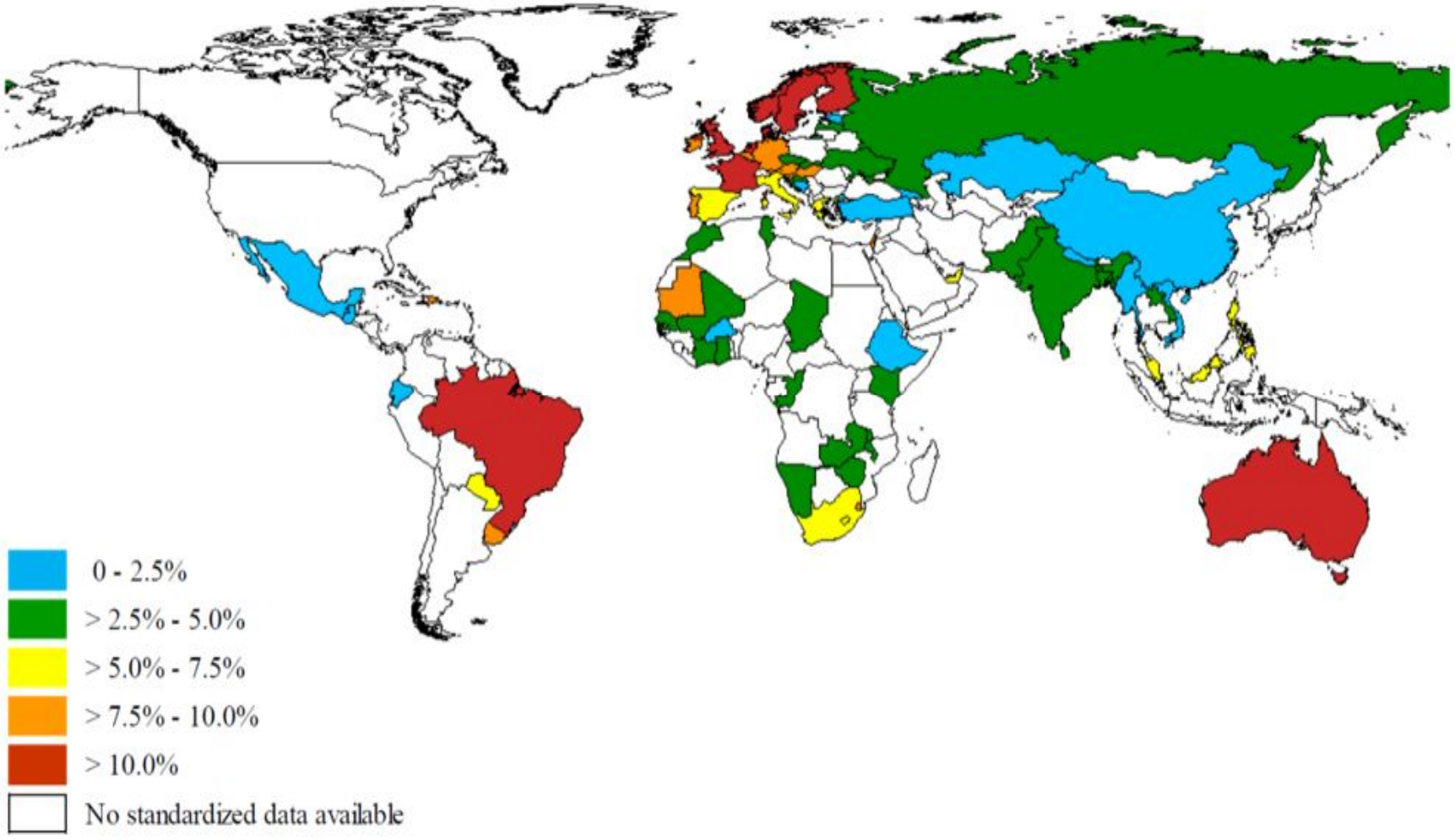
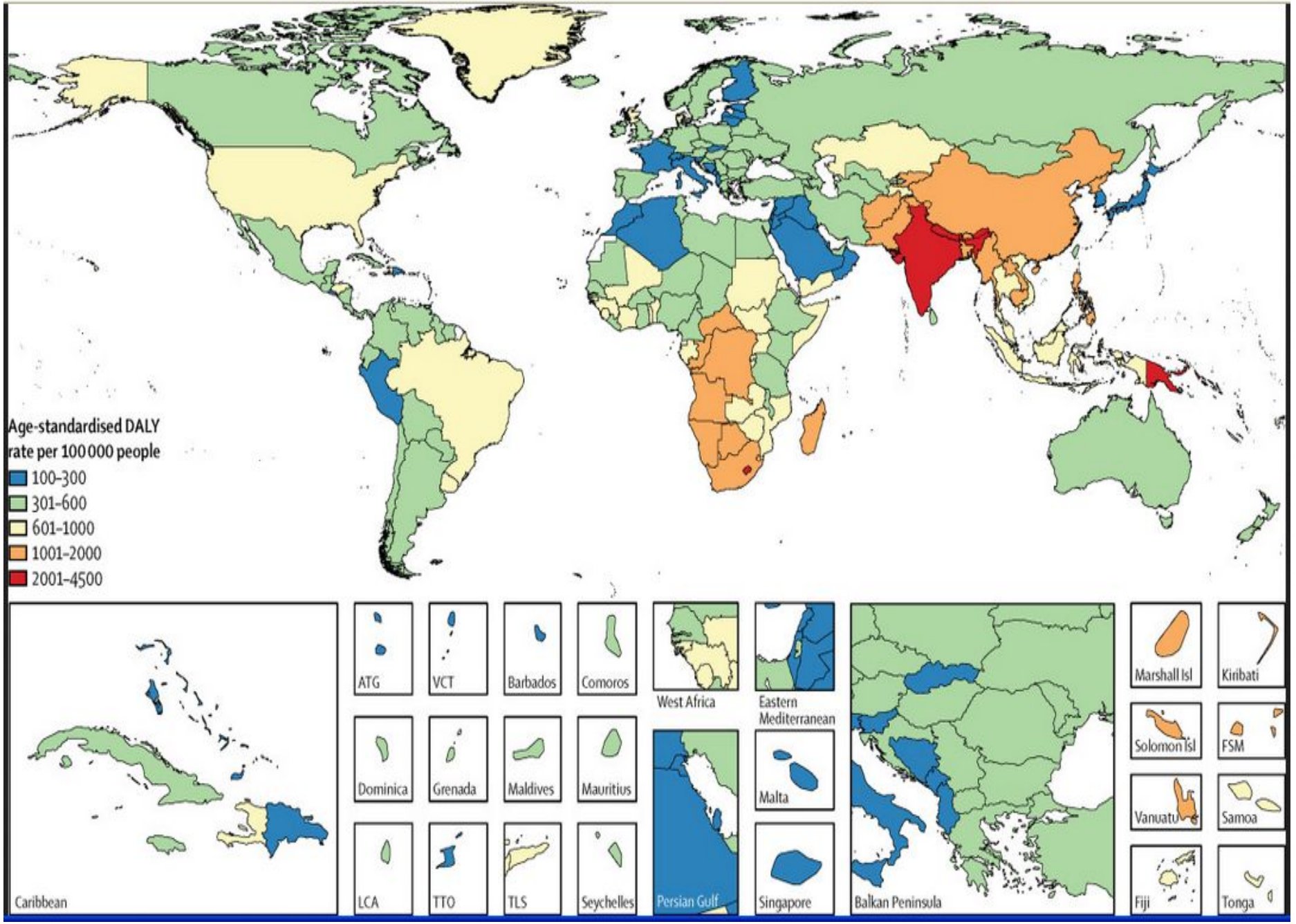


Figure source: To T et al. 2012

To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC public health. 2012 Dec;12(1):204.


Age-standardised DALY
rate per 100 000 people
100–300
301–600
601–1000
1001–2000
2001–4500
Caribbean
ATG
VCT
Barbados
Comoros
West Africa
Eastern Mediterranean
Dominica
Grenada
Maldives
Mauritius
Malta
LCA
TTO
TLS
Seychelles
Persian Gulf
Singapore
Balkan Peninsula
Marshall Isl
Kiribati
Solomon Isl
FSM
Vanuatu
Samoa
Fiji
Tonga

THE LANCET
Respiratory Medicine

Global, regional, and national deaths, prevalence, disability-ad...

Disability-adjusted life years (DALYs)

The overall burden of disease is assessed using the disability-adjusted life year (DALY), a time-based measure that combines

- **years of life lost due to premature mortality (YLLs) and**
- **years of life lost due to time lived in states of less than full health,**
- **or years of healthy life lost due to disability (YLDs).**

Global Strategy for Asthma Management and Prevention (2022 update)

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Asthma Definition

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation
- It is defined by history of respiratory symptoms such as:
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough

  that vary over time and in intensity, together with variable expiratory airflow limitation

- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, these are not necessary or sufficient to make the diagnosis.

- People with asthma often have periods of worsening symptoms and worsening airway obstruction, called exacerbations (also called attacks or flare-ups), that can be fatal.

- Most of the morbidity and mortality associated with asthma is preventable, particularly with use of inhaled corticosteroids.

Global Initiative for Asthma. Available at: http://ginasthma.org/2019-pocket-guide-for-asthma-management-and-prevention Last accessed December 2019

DEFINITION OF 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.

- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, these are not necessary or sufficient to make the diagnosis.

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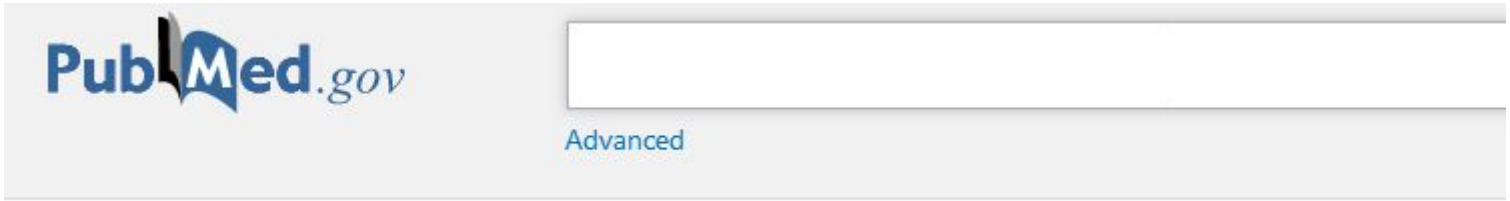
- Most of the morbidity and mortality associated with asthma is preventable, particularly with use of inhaled corticosteroids.



> Chest. 2003 Jan;123(1):119-27. doi: 10.1378/chest.123.1.119.

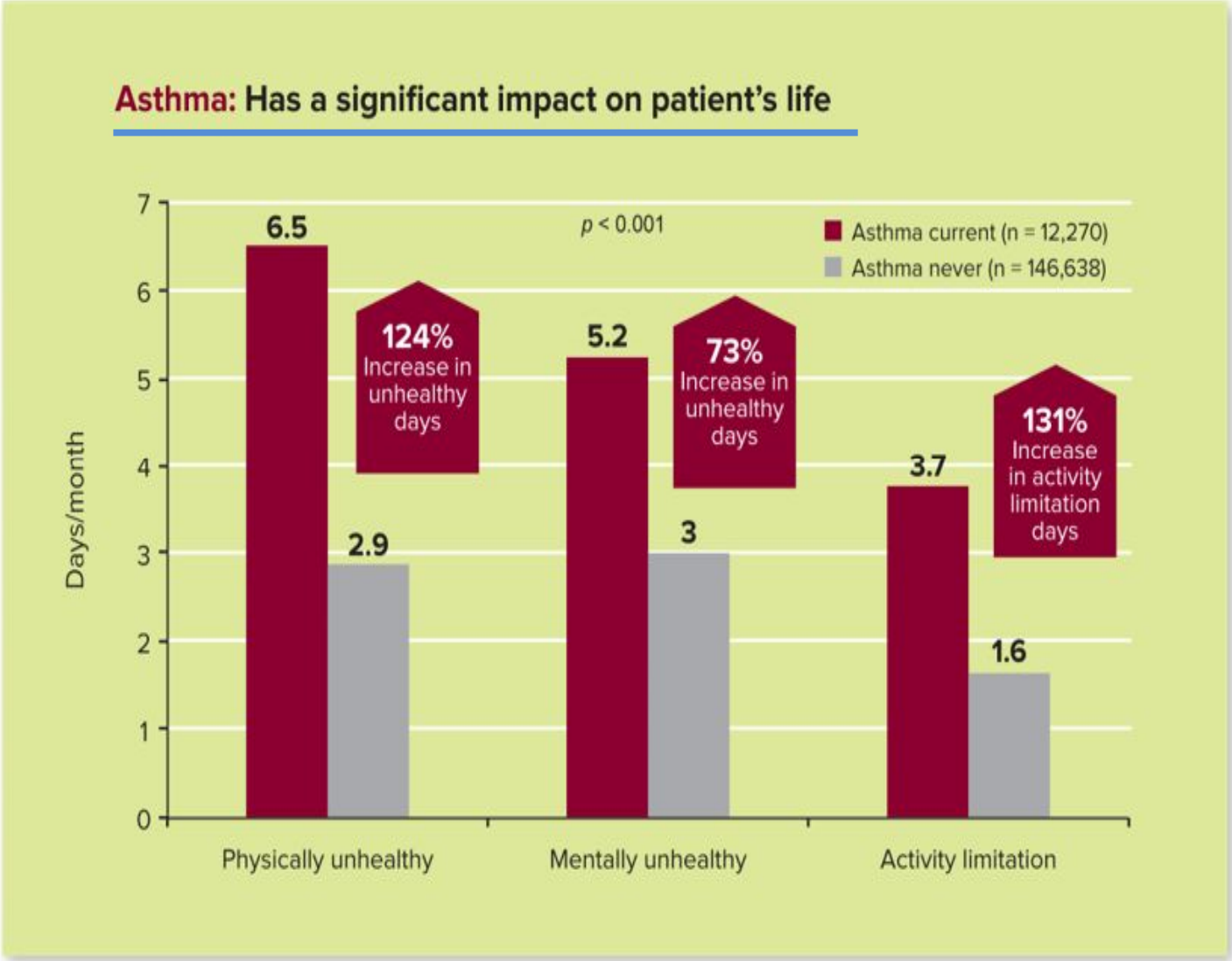
Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system

Earl S Ford [1], David M Mannino, David M Homa, Charon Gwynn, Stephen C Redd, David G Moriarty, Ali H Mokdad

Affiliations + expand

PMID: 12527612 DOI: 10.1378/chest.123.1.119

Asthma is a real restriction to life



Adapted from Ford ES, Mannino DM, Homa DM, Gwynn C, Redd SC, Moriarty DG, Mokdad AH. Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. Chest. 2003 Jan 1;123(1):119-27.

Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

Contents lists available at ScienceDirect

Respiratory Medicine

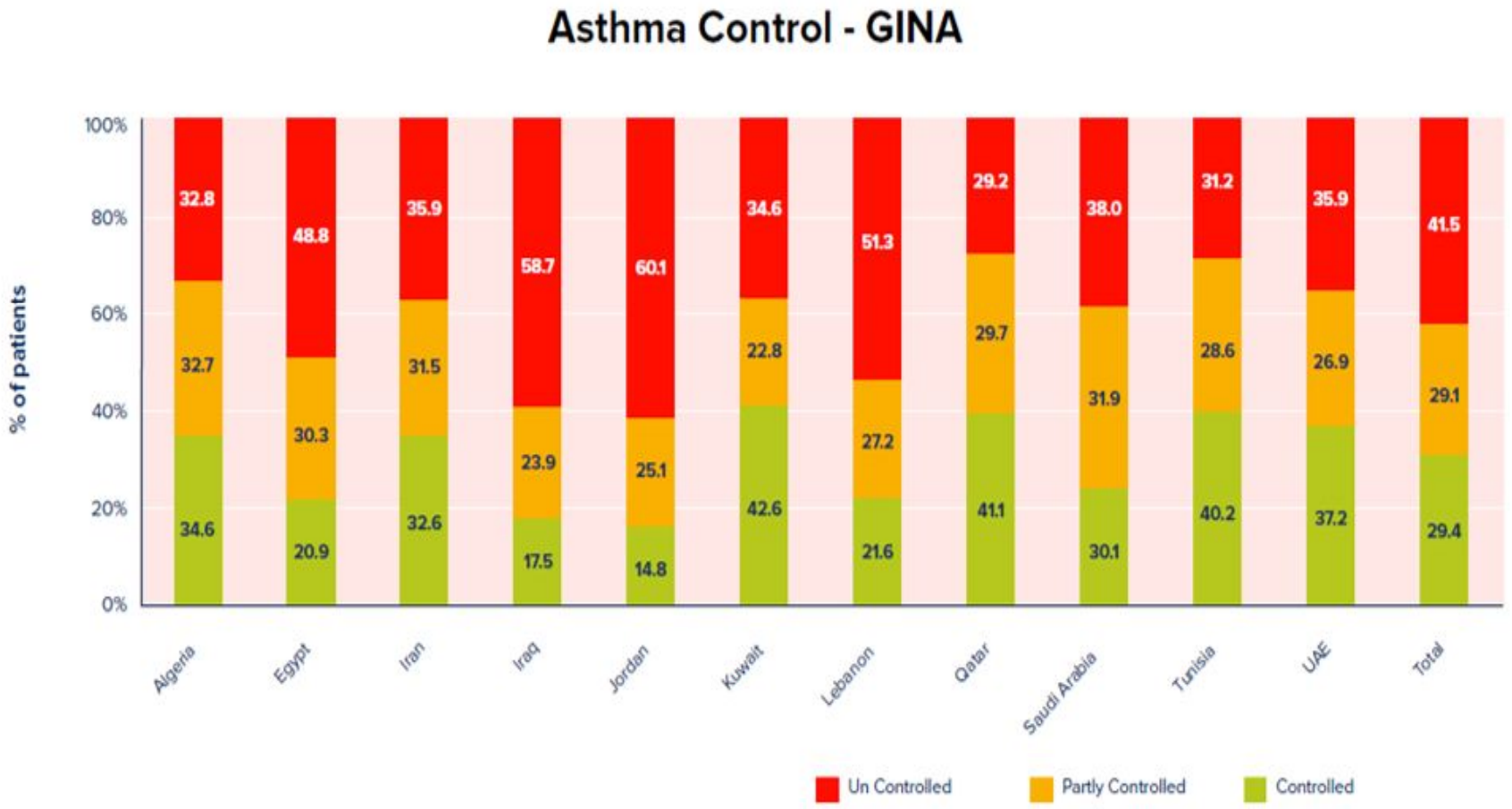
journal homepage: www.elsevier.com/locate/rmed

Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

Hesham Tarraf[a,*], Hamdan Al-Jahdali[b], Abdul Hameed Al Qaseer[c], Anamarija Gjurovic[d], Houria Haouichat[e], Basheer Khassawneh[f], Bassam Mahboub[g], Roozbeh Naghshin[h], François Montestruc[i], Naser Behbehani[j]

Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study

- Overall **7236** eligible patients were included in **577** sites between June 2014 and December 2015 (median 10 patients/site).



Tarraf H, Al-Jahdali H, Al Qaseer AH, Gjurovic A, Haouichat H, Khassawneh B, Mahboub B, Naghshin R, Montestruc F, Behbehani N. Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study. Respiratory medicine. 2018 May 1;138:64-73.

What is meant by 'asthma control'?

The level of asthma control is the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment.[24,65] It is determined by the interaction between the patient's genetic background, underlying disease processes, the treatment that they are taking, environment, and psychosocial factors.[65]

Asthma control has two domains: symptom control and future risk of adverse outcomes (Box 2-2, p.36). Both should always be assessed. Lung function is an important part of the assessment of future risk; it should be measured at the start of treatment, after 3–6 months of treatment (to identify the patient's personal best), and periodically thereafter for ongoing risk assessment.

How to describe a patient's asthma control

Asthma control should be described in terms of both symptom control and future risk domains. For example:

Ms X has good asthma symptom control, but she is at increased risk of future exacerbations because she has had a severe exacerbation within the last year. Mr Y has poor asthma symptom control. He also has several additional risk factors for future exacerbations including low lung function, current smoking, and poor medication adherence.

What does the term 'asthma control' mean to patients?

Many studies describe discordance between the patient's and health provider's assessment of the patient's level of asthma control. This does not necessarily mean that patients 'over-estimate' their level of control or 'under-estimate' its severity, but that patients understand and use the word 'control' differently from health professionals, e.g. based on how quickly their symptoms resolve when they take reliever medication.[65,66] If the term 'asthma control' is used with patients, the meaning should always be explained.

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study

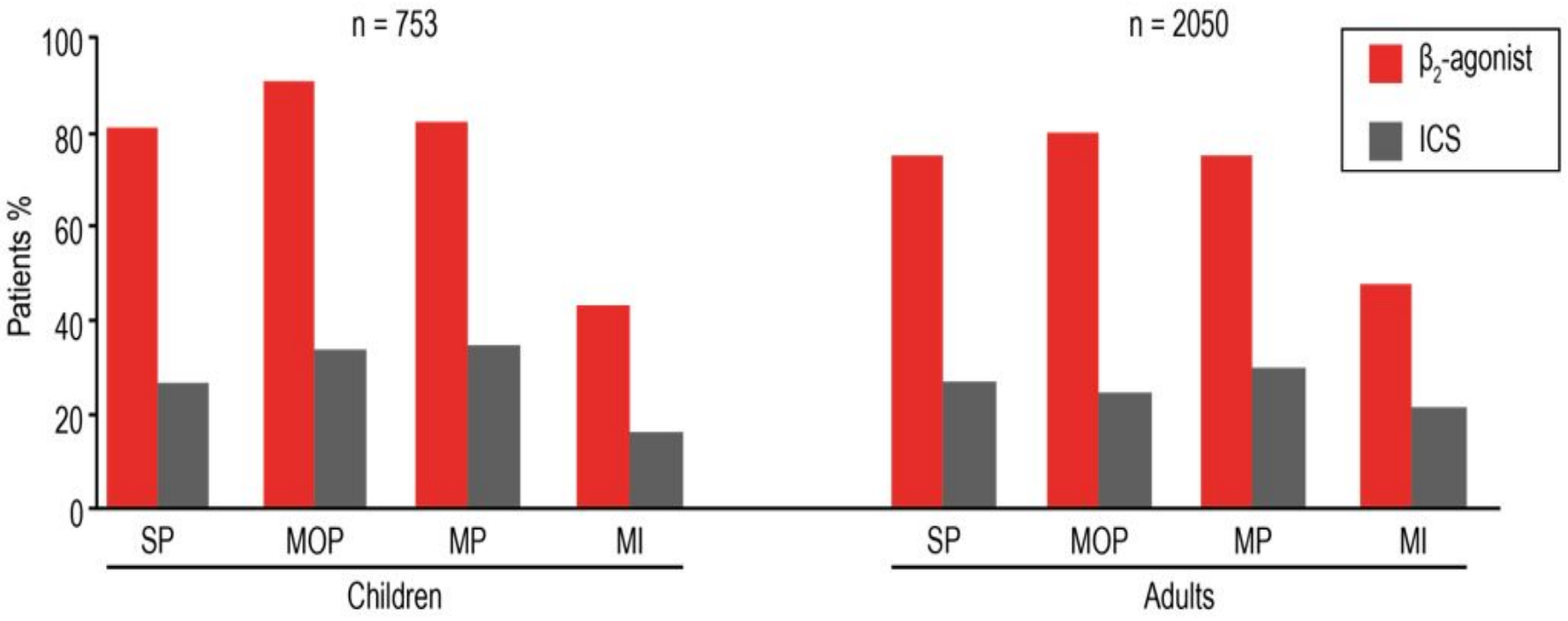
KF Rabe, PA Vermeire, JB Soriano, WC Maier

European Respiratory Journal 2000 16: 802-807; **DOI:**

Over-reliance on SABA occurs in children and adults and is irrespective of asthma severity

- In the AIRE survey, ~3 times as many patients were using rescue medication (SABA) than their maintenance inhaler (ICS) over a 4-week period

Medicines used to treat asthma by Symptoms Severity Index: Anti-inflammatories versus quick-relief medications



ICS, inhaled corticosteroid; MI, mild intermittent; MP, mild persistent; MOP, moderate persistent; SABA, short-acting β_2-agonist; SP, severe persistent.

Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. European Respiratory Journal. 2000 Nov 1;16(5):802-7.

Attitudes and actions of asthma patients on regular maintenance therapy:

the INSPIRE study

Published: 13 June 2006

- **Background**

This study examined the attitudes and actions of **3415** physician-recruited **adults aged ≥ 16 years** with **asthma** in **eleven countries** who were

prescribed

-regular **maintenance** therapy with **ICS**

-or **ICS plus LABA**

This study shows that patients with asthma receiving regular maintenance therapy

still have high levels of inadequately controlled asthma.

- The study also **shows** that patients recognize deteriorating asthma control

due to

- Patients adjust their medication during episodes of worsening.

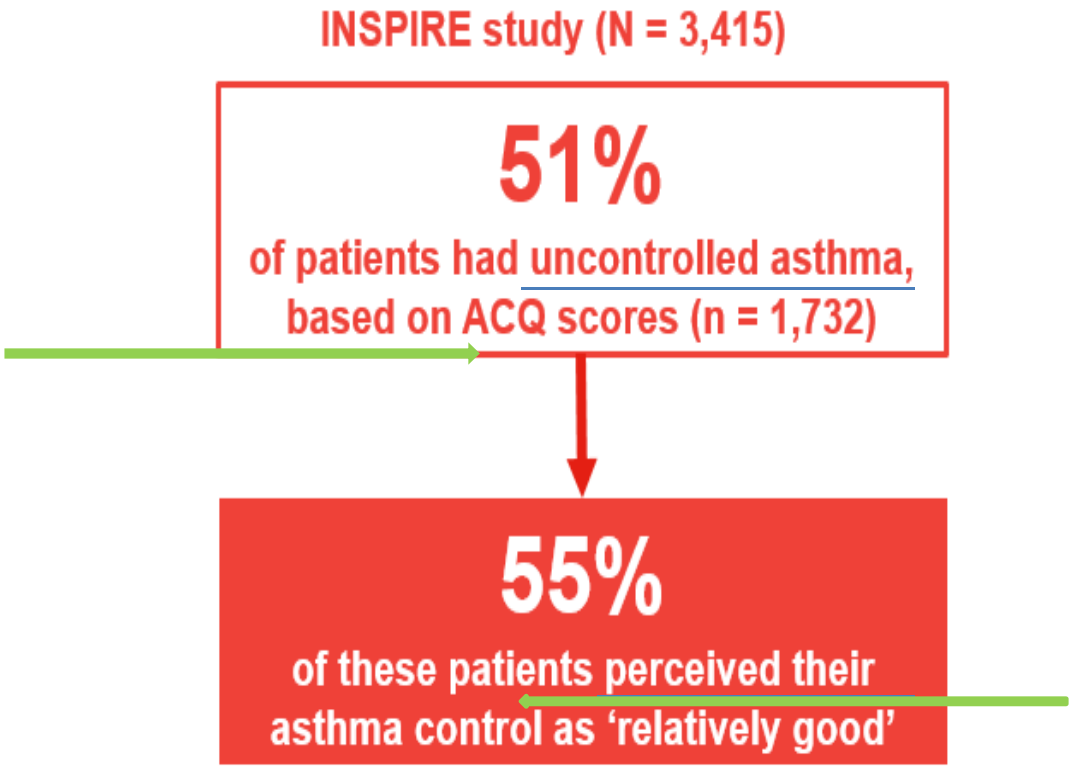
- However, they often adjust treatment in an inappropriate manner,

  which represents a **window of missed opportunity**.

Patient attitudes to asthma management

A total of 2992 patients (88%) stated that they were very or quite confident that they could self-manage their asthma worsenings without physician visits. Many patients (n = 1858 [54%]) were concerned about taking too much medication when they felt well or during periods with no symptoms (Table 2). The majority of patients reported that they used their medication as and when necessary and were much more likely to try to manage their asthma themselves, rather than consulting their physician, when symptoms become bothersome (Table 2). Nearly 70% of patients also agreed that they preferred to adjust their maintenance ICS/combination medication to the changes in their asthma, i.e. taking less medication when well and more when their asthma worsens (Table 2). Ninety per cent of patients (n = 3075) stated that they wanted immediate relief from symptoms and 85% (n = 2898) felt confident that they knew their asthma well enough to intervene early to try to prevent a worsening of symptoms.

Patients' perception of asthma control does not match the reality

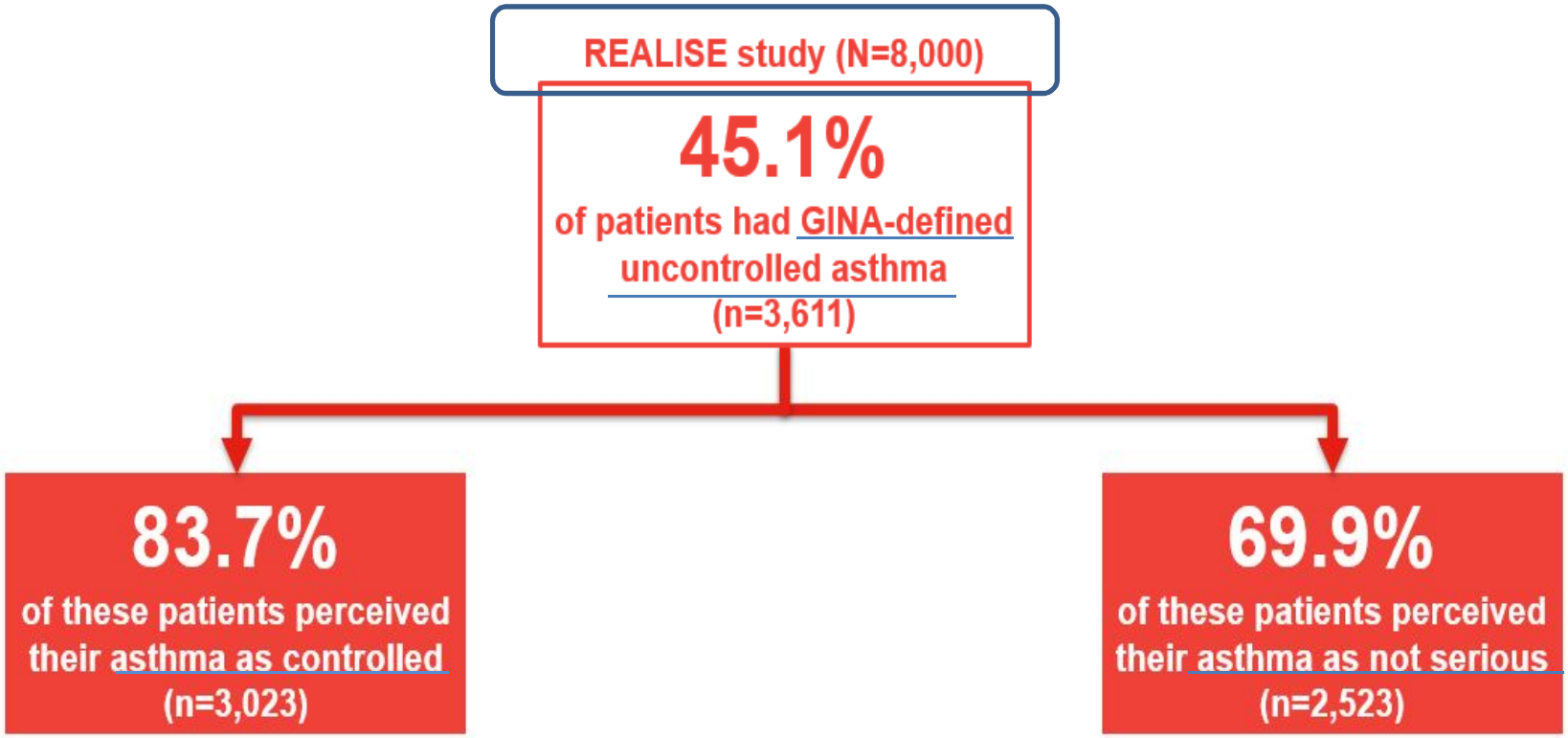


- Levels of asthma control were poor in the INSPIRE study
- However, most patients with poorly controlled asthma were unaware of their asthma control status
- In addition, 74% of patients used ≥1 SABA inhalation every day in the previous 7 days

ACQ, Asthma Control Questionnaire

Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC pulmonary medicine. 2006 Dec;6(1):13.

There is an unmet need for improved understanding and attainment of asthma control



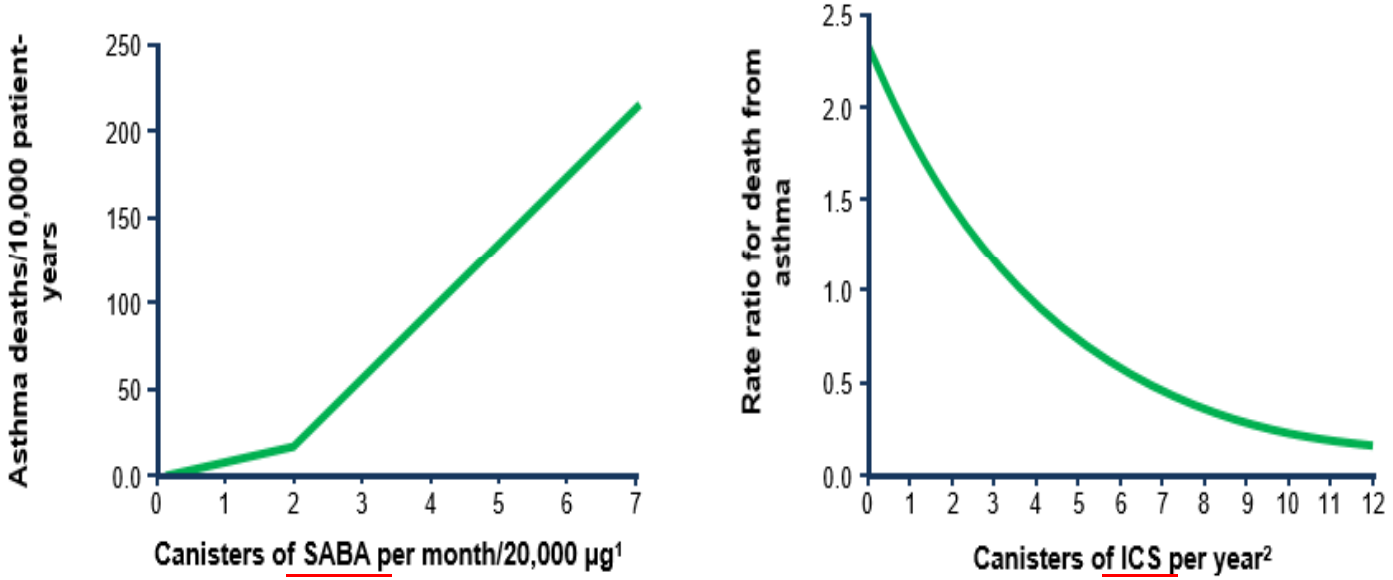
- The REALISE study demonstrated a large gap between patients' perception of asthma control, and the clinical reality of asthma control

The REALISE survey was conducted in patients aged 18–50 years who were active on social media.

Price D, Fletcher M, Van Der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ primary care respiratory medicine. 2014 Jun 12;24:14009.

Over-reliance on SABA and under-use of ICS are both associated with an increase in mortality

- Over-reliance on SABA at the expense of ICS controller therapy is associated with an increased risk of asthma-related death, as a result of under-treatment of inflammation[1-2]



- Episodes of high reliever use (>6 inhalations/day on at least one day) are also predictive of an increased risk of exacerbations[3]

1. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick BR, Cockroft D, Blais L, McNutt M, Buist AS, Spitzer WO. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. American journal of respiratory and critical care medicine. 1994 Mar;149(3):604-10. 2. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. New England Journal of Medicine. 2000 Aug 3;343(5):332-6. 3. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, Rabe KF. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respiratory research. 2012 Dec;13(1):59.

NRAD report reveals excessive prescribing of SABAs and under-prescribing of preventer medication

- The NRAD report was an investigation of recent asthma deaths in the UK by the Royal College of Physicians

Evidence of excessive prescribing of reliever medication

39% of patients who were on short-acting relievers at the time of death had been prescribed more than

12 short-acting reliever inhalers in the year before they died

4% had been prescribed more than

50 reliever inhalers

Evidence of under-prescribing of preventer medication

To comply with recommendations, most patients would usually need at least

12 preventer prescriptions per year

38% of patients on preventer inhalers* received fewer than

4 inhalers in the year leading up to their death.

and **80%** received fewer than 12 preventer inhalers

*Of those patients for which the number of prescriptions was known. Among 189 patients who were on short-acting relievers at the time of death, the number of prescriptions was known for 165. Among 168 patients on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128.

NRAD, National Review of Asthma Deaths; SABA, short-acting β_2-agonist

Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Last accessed: December, 2019].

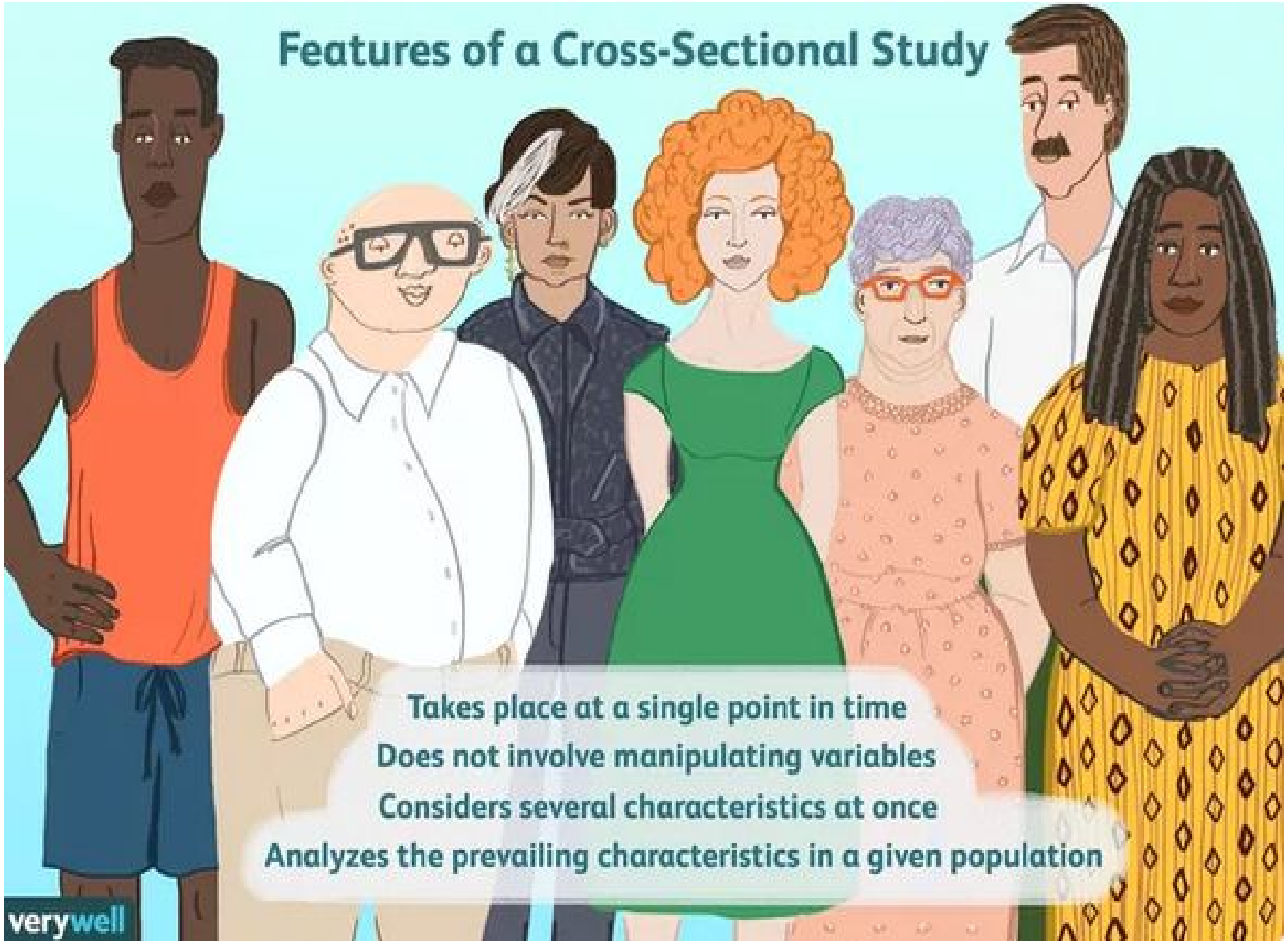
EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Check for updates

Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study

Eric D. Bateman, David B. Price, Hao-Chien Wang, Adel Khattab, Patricia Schonffeldt, Angelina Catanzariti, Ralf J.P. van der Valk, Maarten J.H.I. Beekman

European Respiratory Journal 2022 59: 2101402; **DOI:** 10.1183/13993003.01402-2021


Features of a Cross-Sectional Study
Takes place at a single point in time
Does not involve manipulating variables
Considers several characteristics at once
Analyzes the prevailing characteristics in a given population
verywell

Background

assessed primary health data across **24 countries** in five continents.

To gain a **global perspective on short-acting β_2-agonist** (SABA)

prescriptions and associated **asthma-related clinical outcomes** in patients with asthma .

Methods

SABINA III was a cross-sectional study that employed
electronic case report forms at a study visit (in primary or specialist care)

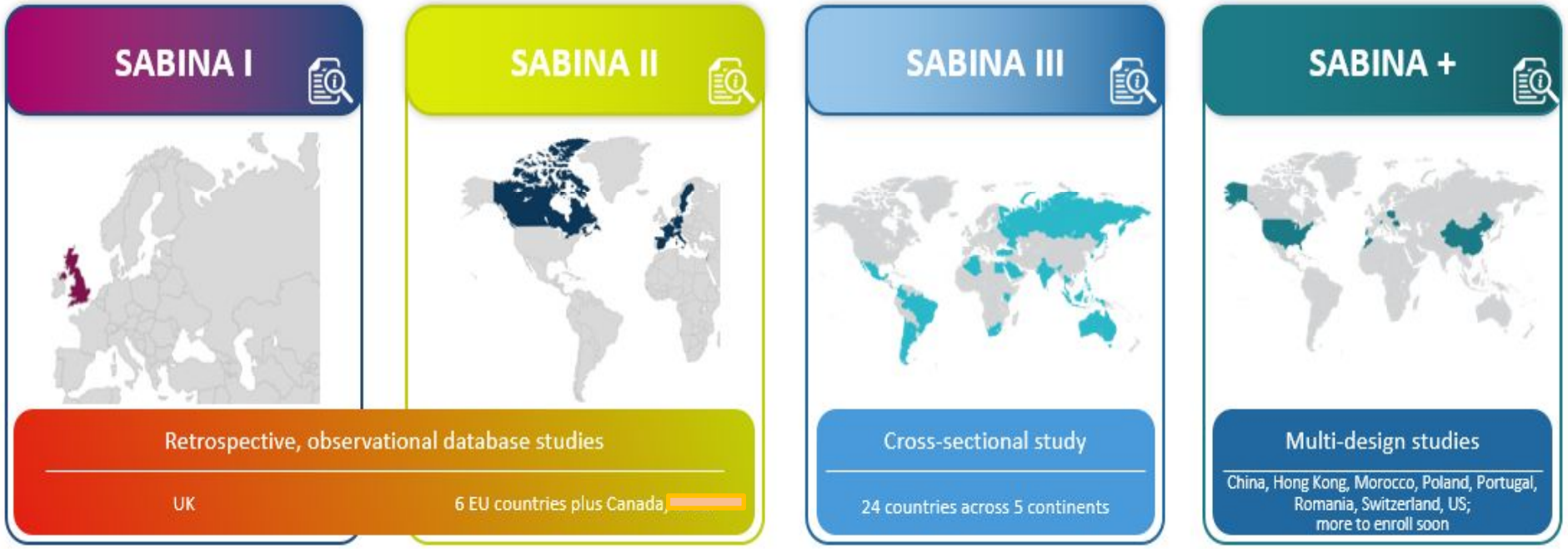
to record
patients (≥12 years old)
-prescribed medication(s) .
-over-the-counter (OTC) SABA purchases and
-clinical outcomes in asthma
during the past 12 months.

in patients with ≥1 SABA prescriptions,
associations of SABA with asthma symptom control and
severe exacerbations were analysed using multivariable regression models.

SABINA Programme: To establish global patterns of SABA and maintenance therapy use in asthma, and their relation to asthma outcomes

Largest real-world data analysis on SABA and maintenance therapy globally

Flexible framework with one core protocol and core requirements across pillars to ensure scientific alignment[1]

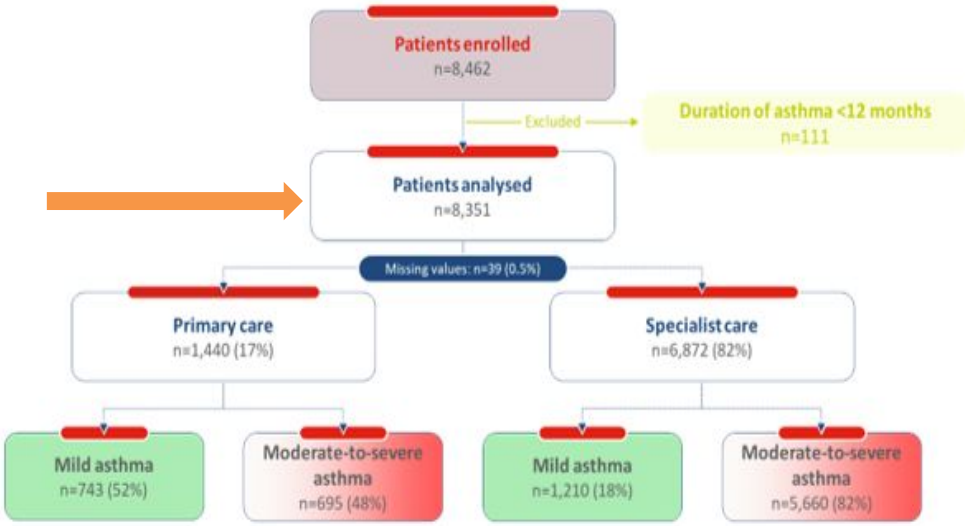


EU, European Union; SABA, short-acting β_2-agonists; SABINA, SABA use IN Asthma; UK, United Kingdom; US, United States.

1. Cabrera CS, Nan C, Lindarck N, Beekman MJ, Arnetorp S, van der Valk RJ. SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β2-agonist use in asthma. European Respiratory Journal. 2020 Feb 1;55(2).

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

- Aim: To assess SABA prescriptions and associated outcomes in countries most of which lacked national healthcare databases
- Real-world primary data was collected in local health care settings through eCRFs
- Unlike in database studies, this enabled assessment of additional parameters, such as asthma control and SABA purchase without a prescription



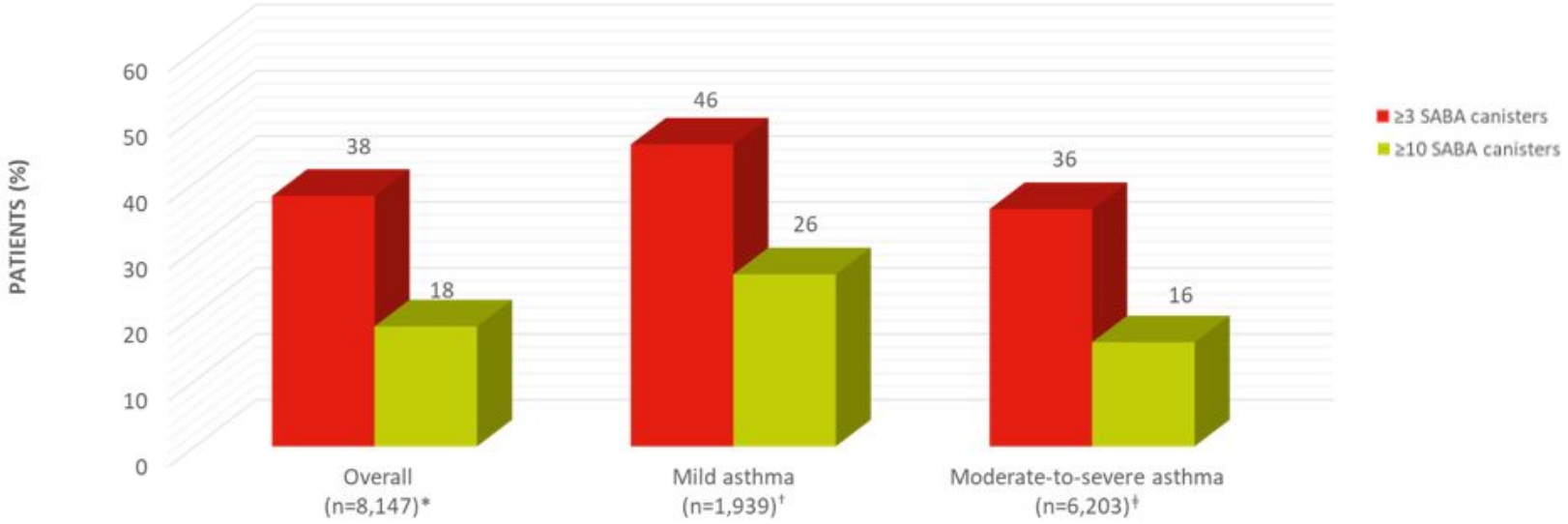
Of the patients included, 37% were from Asia, 21% from Africa, 17% from the Middle East, 13% from Latin America, 7% from Russia and 5% from Australia

Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

- 63% of patients were prescribed SABA, either as monotherapy or in addition to maintenance therapy
- Overall, 38% of patients had SABA over-prescriptions in the previous year and almost one-fifth were prescribed ≥10 SABA canisters

61% of the patients who were prescribed SABA had used more than 3 canister per year (overuse)

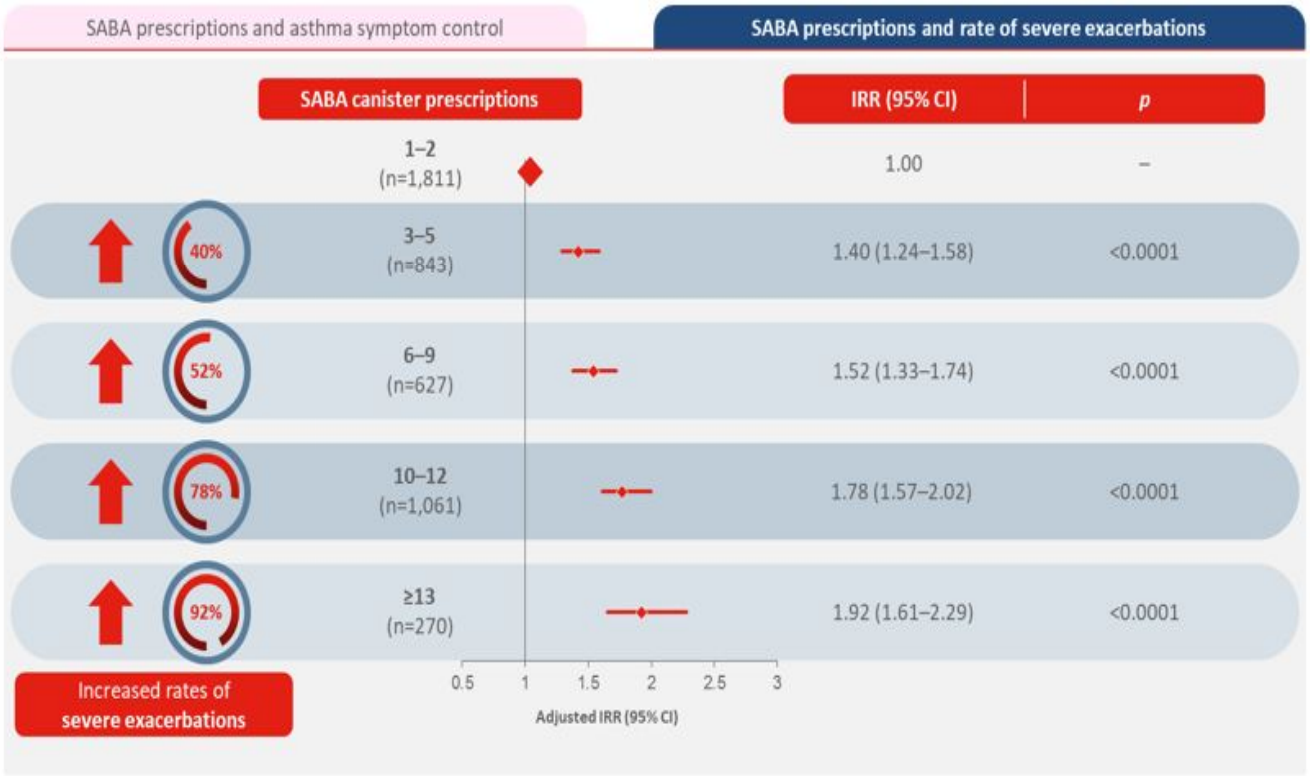


Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

SABINA III – An observational, cross-sectional study carried out in 24 countries[1]

Association of SABA prescriptions with severe exacerbations (n=4,612)

The rate of severe exacerbations significantly increased with the number of SABA prescriptions (vs. 1–2 SABA prescriptions)



Analyses were adjusted for the following covariates: country, age, sex, BMI, smoking history, GINA step, and education level. Severe exacerbations were defined as per American Thoracic Society/European Respiratory Society recommendations.
BMI, body mass index; GINA, Global Initiative for Asthma; IRR, incidence rate ratio; SABA, short-acting β_2-agonists.

Bateman ED, Price DB, Wang HC, Khattab A, Schonffeldt P, Catanzariti A, van der Valk RJ, Beekman MJ. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. European Respiratory Journal. 2021 Jan 1.

Conclusions:

This study indicates **an association** between
high SABA prescriptions and poor clinical outcomes
across a broad range of countries,
healthcare settings and
asthma severities,

providing support for initiatives to improve asthma morbidity by reducing SABA overreliance.

2022 GINA Main Report - Global Initiative for Asthma

PART B. MEDICATIONS AND STRATEGIES FOR SYMPTOM CONTROL AND RISK REDUCTION

KEY POINTS

- For safety, GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone. All adults and adolescents with asthma should receive ICS-containing controller treatment to reduce their risk of serious exacerbations and to control symptoms. ICS-containing controller can be delivered either with regular daily treatment or, in mild asthma, with as-needed ICS-formoterol taken whenever needed for symptom relief.

Box 3-4A. Initial asthma treatment - recommended options for adults and adolescents

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g. less than twice a month and no risk factors for exacerbations, including no exacerbations in the last 12 months (Box 2-2B, p.36)	**As-needed low dose ICS-formoterol** (Evidence B)	**Low dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B)
Asthma symptoms or need for reliever twice a month or more	**As-needed low dose ICS-formoterol** (Evidence A)	**Low dose ICS with as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Troublesome asthma symptoms most days (e.g. 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B, p.36)	**Low dose ICS-formoterol maintenance and reliever therapy** (Evidence A)	**Low dose ICS-LABA with as-needed SABA** (Evidence A), OR Medium dose ICS with as-needed SABA (Evidence A). Consider likely adherence with daily controller.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	**Medium dose ICS-formoterol maintenance and reliever therapy** (Evidence D). A short course of oral corticosteroids may also be needed.	**Medium or high dose ICS-LABA** (Evidence D) with as-needed SABA. Consider likely adherence with daily controller. A short course of oral corticosteroids may also be needed. High dose ICS with as-needed SABA is another option (Evidence A) but adherence is poor compared with combination ICS-LABA.

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Box 3-8. Treating potentially 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 an ICS-containing controller. • Maintenance and reliever therapy (MART) with ICS-formoterol reduces risk of severe exacerbations compared with if the reliever is SABA. • 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, p.36).	A A A A A D
≥1 severe exacerbation in last year	• ICS-formoterol maintenance and reliever regimen reduces risk of severe exacerbations compared with if the reliever is SABA. • 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. • Consider 2 weeks' OCS, but take short- and long-term risks into account • Exclude other lung disease, e.g. COPD. • Refer for expert advice if no improvement.	B B D D
Obesity	• Strategies for weight reduction • Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea.	B D

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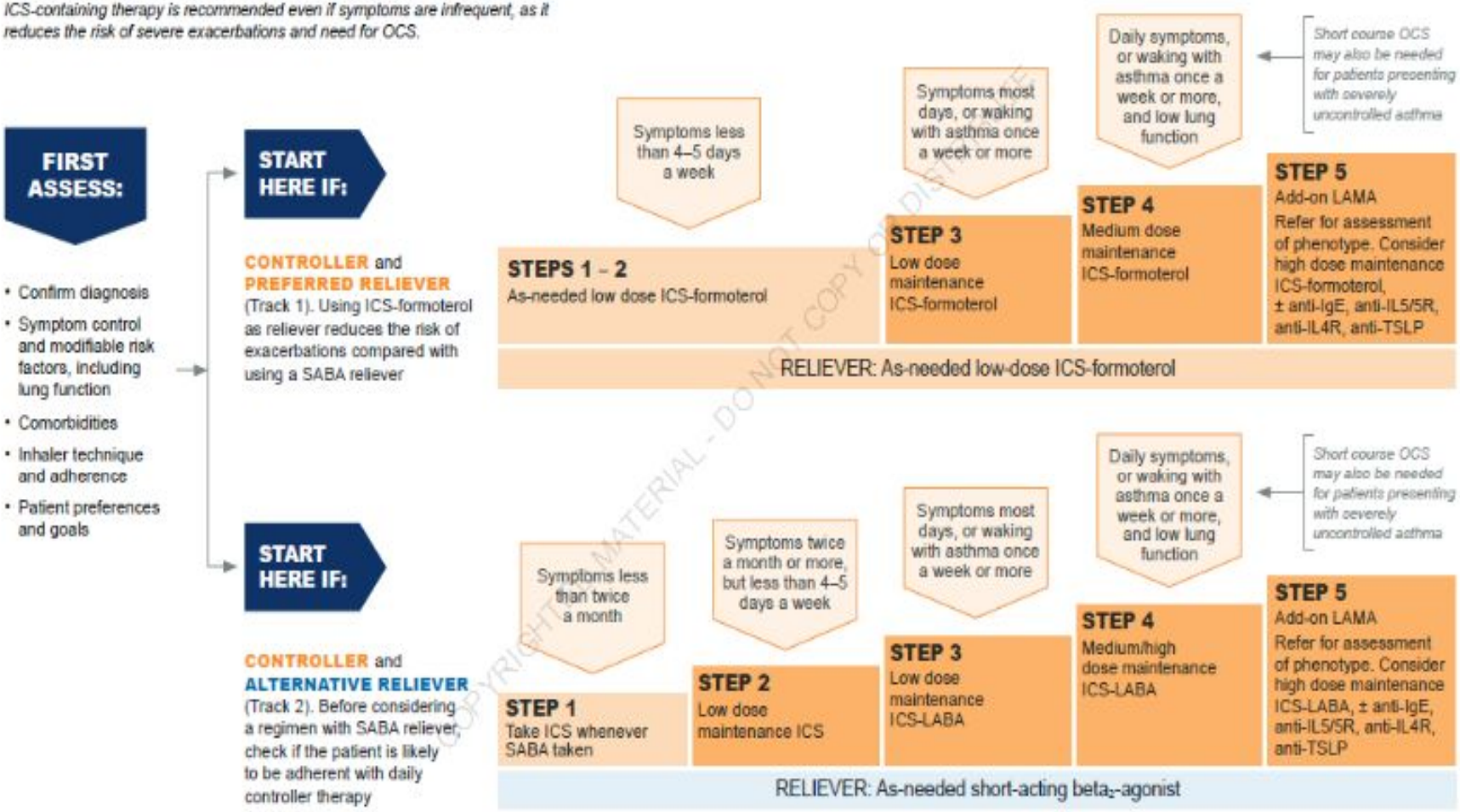
Obesity	• Strategies for weight reduction • Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea.	B D
Major psychological problems	• Arrange mental health assessment. • Help patient to distinguish between symptoms of anxiety and asthma; provide advice 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. • Consider adding SLIT in symptomatic adult HDM-sensitive patients with allergic rhinitis despite ICS, provided FEV_1 is >70% predicted.	C D B
Sputum eosinophilia (limited centers)	• Increase ICS dose independent of level of symptom control.	A*

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. * Based on evidence from relatively small studies in selected populations. Also see Box 3-9 and p.79 for more information about non-pharmacological interventions.

STARTING TREATMENT

in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller. ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.



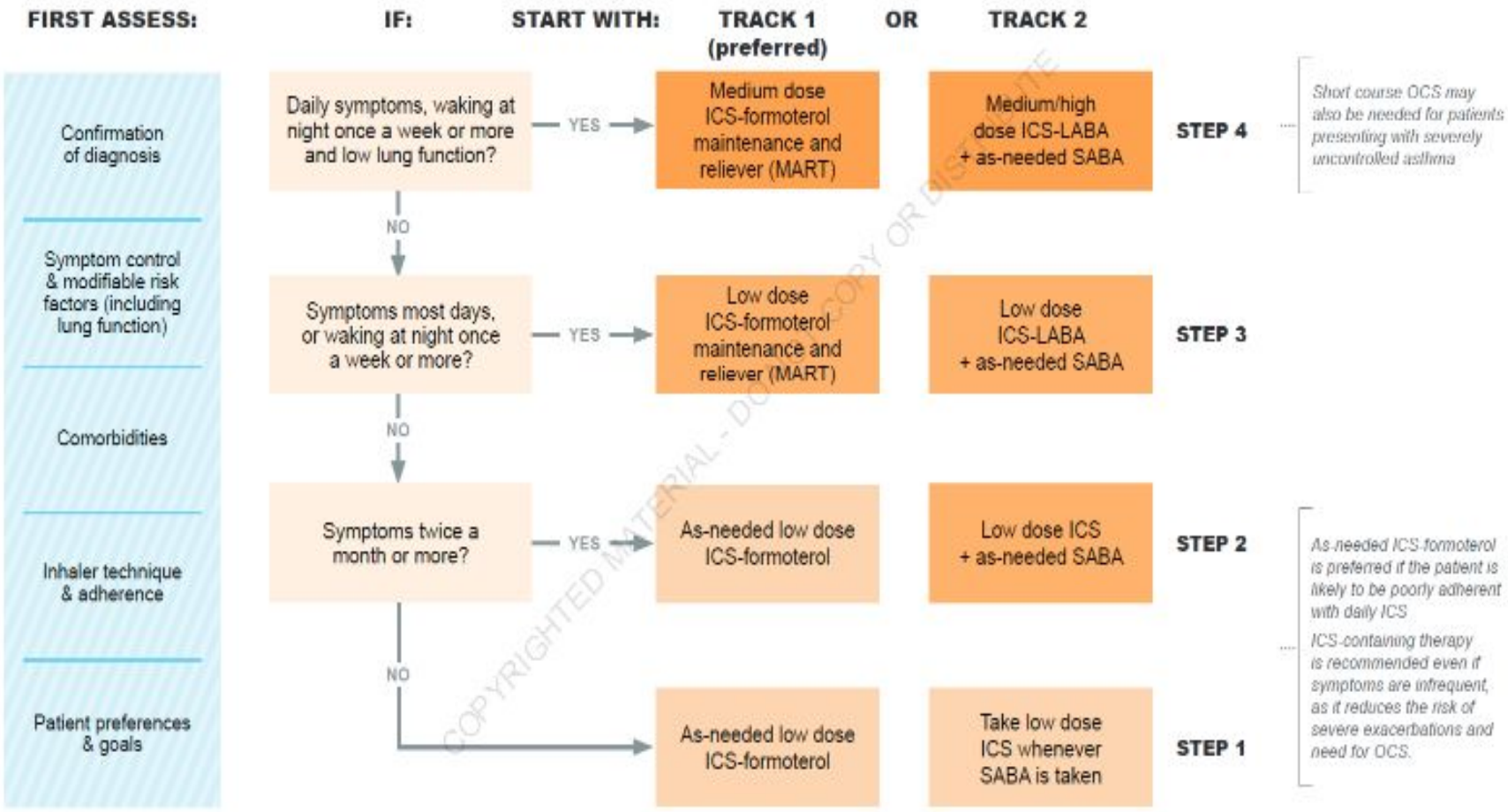
COPYRIGHT MATERIAL - DO NOT COPY OR DISTRIBUTE

ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting $beta_2$-agonist. See Box 3-6, p.83 for low, medium and high ICS doses for adults and adolescents.

Box 3-4Bii. Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma (V2)

STARTING TREATMENT

in adults and adolescents 12+ years with a diagnosis of asthma



COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE

ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; MART: maintenance and reliever therapywith ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

See Box 3-6, p.63 for low, medium and high ICS doses for adults and adolescents.

ASSESSING ASTHMA SEVERITY

The currently accepted definition of asthma severity is based on 'difficulty to treat'

The current definition of asthma severity, recommended by an ATS/ERS Task Force[24,65] and included in most asthma guidelines, is that severity should be assessed retrospectively from the level of treatment required to control the patient's symptoms and exacerbations, i.e. after at least several months of treatment.[24,65,155] Hence:

- *Severe asthma* is defined as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity,[155] as there are very different treatment implications compared with if asthma is relatively refractory to high dose ICS-LABA or even OCS.[155] See Box 2-4 (p.43) for how to distinguish difficult-to-treat and severe asthma, and Chapter 3E (p.104) for more detail about assessment, referral and treatment.
- *Moderate asthma* is currently defined as asthma that is well controlled with Step 3 or Step 4 treatment e.g. with low or medium dose ICS-LABA in either treatment track.
- *Mild asthma* is currently defined as asthma that is well controlled with as-needed ICS-formoterol, or with low dose ICS plus as-needed SABA.

By this retrospective definition, asthma severity can only be assessed after good asthma control has been achieved and treatment stepped down to find the patient's minimum effective dose (p.75), or if asthma remains uncontrolled despite at least several months of optimized maximal therapy.

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Why Symbicort® Turbuhaler® is different?

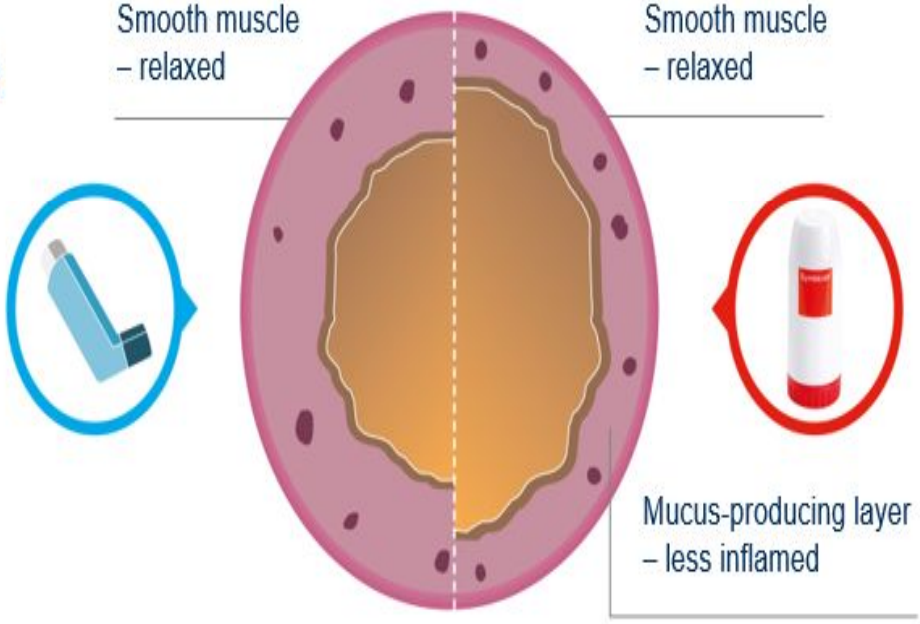
Symbicort®

Symbicort® – Efficacy Data: Exacerbations

Symbicort®* – anti-inflammatory relief from a single inhaler to reduce exacerbations[1,2] and provide 24-hour symptom control[3]

Worsening symptoms are due to bronchoconstriction and inflammation[3]

SABAs provide only bronchodilation, without inflammatory control[3]



When Symbicort®* is used as an anti-inflammatory reliever as needed on top of maintenance therapy it provides:

bronchodilation and additional **inflammatory control**

to reduce exacerbations[1,2] and provide 24-hour symptom control[3]

*Symbicort® Maintenance and Reliever

Ref 3: Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). Symbicort® Maintenance and Reliever 160/4.5 µg one inhalation bd + additional inhalations as needed. Symbicort® Maintenance and Reliever prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone and budesonide/formoterol (p=0.0034 and p=0.023 respectively). Symbicort had 7x more asthma control days (defined as no day-time symptoms, no night-time symptoms, no night awakenings caused by asthma, no as-needed medication use) vs baseline: Baseline 5.8% vs Treatment 41.3%. Study results also showed salmeterol/fluticasone 25/125 µg two inhalations bd + terbutaline as needed has similar asthma control days results: Baseline 5.7% vs Treatment 43.7%.

The formoterol component of Symbicort® produces as rapid bronchodilation as salbutamol

- Improvement in FEV_1 is as rapid and effective with formoterol 4.5 or 9 µg as with salbutamol 100 or 200 µg

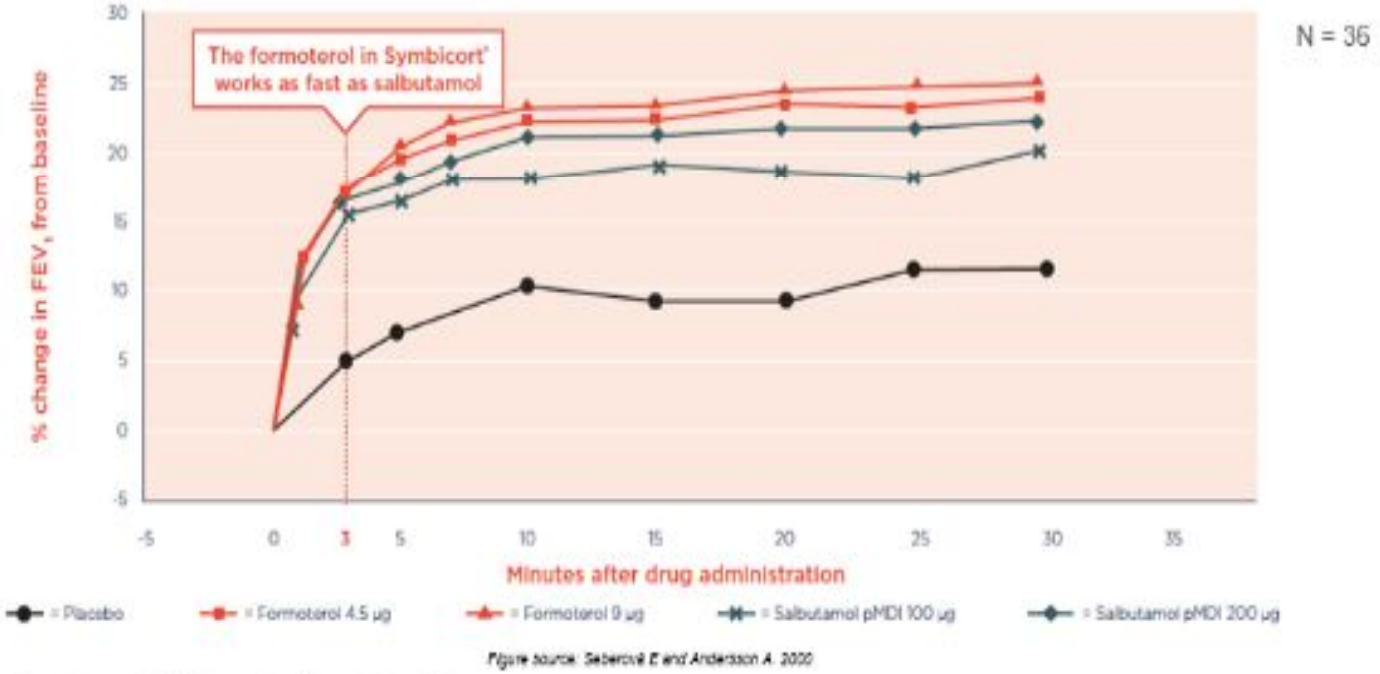
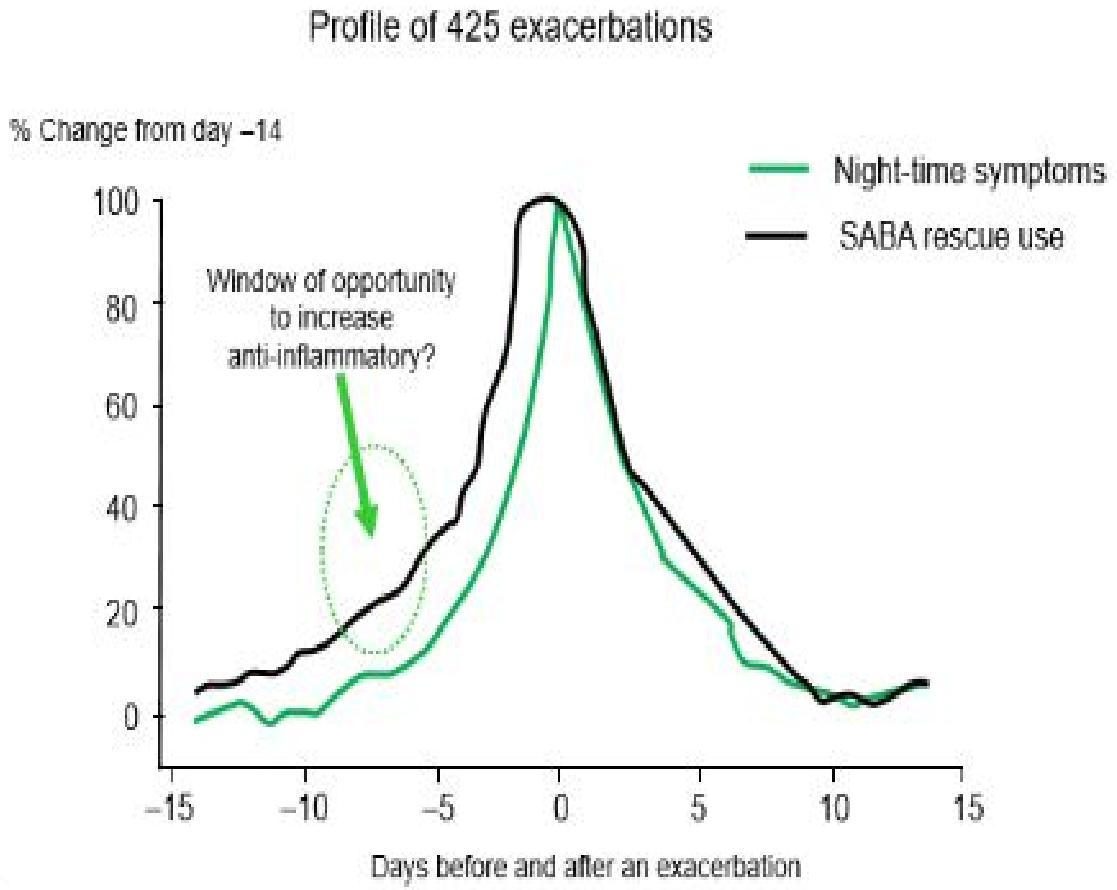


Figure source: Sebercvá E and Andersson A. 2000

FEV_1, forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler

Sebercva E, Andersson A. Oxis®(formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by a pMDI. Respiratory medicine. 2000 Jun 1;94(6):607-11.

Window of opportunity for Symbicort® anti-inflammatory reliever to prevent exacerbations?

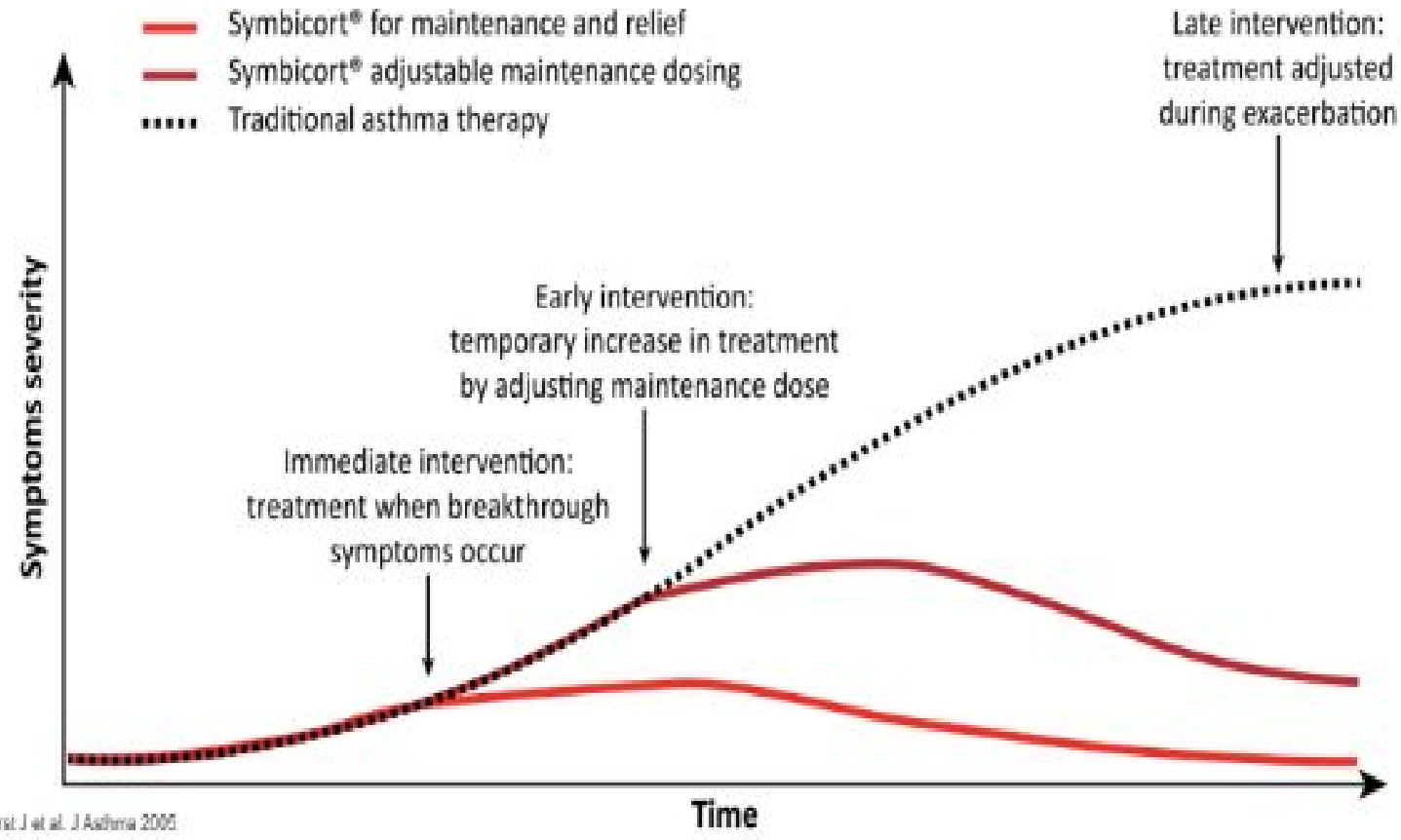


SABA, short-acting β_2-agonist.

Adapted from Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, Lofdahl CG, Pauwels RA, Ullman A. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. American journal of respiratory and critical care medicine. 1999 Aug 1;160(2):594-9.

Early intervention with Symbicort® as part of a reliever regimen can prevent exacerbations[1,2]

Potential outcomes with different asthma treatment regimens in response to worsening symptoms[1]



Adapted from Ankerst J et al. J Asthma 2005

1. Ankerst J. Combination inhalers containing inhaled corticosteroids and long-acting β2-agonists: improved clinical efficacy and dosing options in patients with asthma. Journal of Asthma. 2005 Jan 1;42(9):715-24. 2. Global Initiative For Asthma (GINA). Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed Dec 2010

Recommended doses for Adults (18 years & older)*

- ✓ The recommended maintenance dose is 2 inhalations per day (160/4.5), given either as one inhalation in the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate.
- ✓ Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.
- ✓ **Not more than 6 inhalations should be taken on any single occasion.**
- ✓ **A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period.**

*Symbicort Prescribing Information, last reviewed 2017

As-needed budesonide/formoterol use in a real-life observational study of budesonide/formoterol as-needed on top of maintenance therapy

- As-needed medication was generally low for the majority of the 12-month follow-up (mean 61–66% of reliever-free days)
- High as-needed use (>4 inhalations) was observed for a mean of 1–3% of days
- Budesonide/formoterol as-needed on top of maintenance therapy provided appropriate levels of asthma control in normal clinical practice

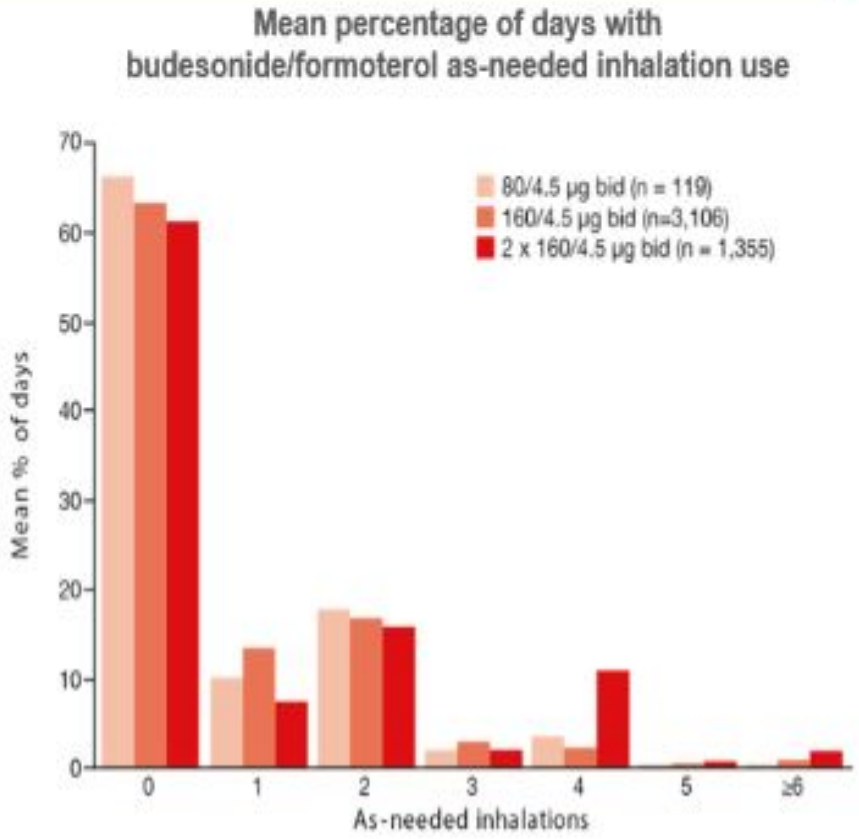


Figure adapted from Stahlberg et al, 2015.

bid, twice per day.

Ställberg B, Naya I, Ekelund J, Eckerwall G. Real-life use of budesonide/formoterol in clinical practice: a 12-month follow-up assessment in a multi-national study of asthma patients established on single-inhaler maintenance and reliever therapy. International journal of clinical pharmacology and therapeutics. 2015 Jun;53(6):447.

observational study

A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given).

Symbicort® as-needed use in a real-life observational study is lower than in RCTs, suggesting Symbicort®* may be associated with lower treatment costs than expected[1–5]

- Patients on the most common regimen used a mean of 2.53 inhalations per day in total,[1] compared with an assumption of 3 inhalations per day (two maintenance, one as-needed) based on previous clinical trials[2–5]
- This reduction suggests mean medication costs with Symbicort® (160/4.5 µg bid plus as-needed) may be 15% lower in real-life practice than previous clinical trials have suggested

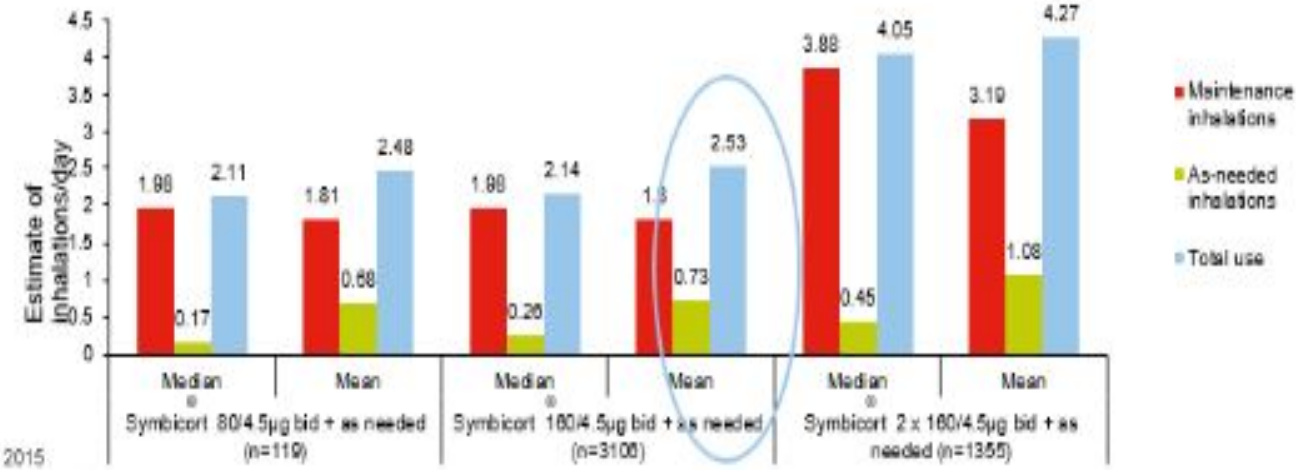


Figure source: Ställberg et al. 2015

*Symbicort® maintenance and reliever therapy

bid, twice per day; RCT, randomised controlled trial

1. Ställberg B, Naya I, Ekelund J, Eckerwall G. Real-life use of budesonide/formoterol in clinical practice: a 12-month follow-up assessment in a multi-national study of asthma patients established on single-inhaler maintenance and reliever therapy. International journal of clinical pharmacology and therapeutics. 2015 Jun;53(6):447. 2. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martínez-Jimenez NE, Buhl R. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC public health. 2012 Dec;12(1):204. 3. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. European Respiratory Journal. 2000 Nov 1;16(5):802-7. 4. Bousquet J, Boulet LP, Peters MJ et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007; **101**: 2437-46. 5. Scichilone R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Opin Curr Med Res.* 004; **20**: 1403-18

GINA Recommendation For Maintenance And Reliever Therapy *

1

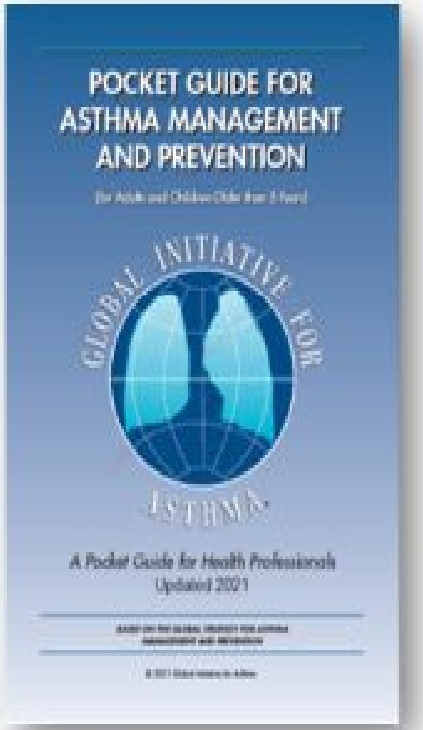
Track 1: The reliever is as-needed low dose ICS-formoterol.
This is the preferred approach recommended by GINA for adults and adolescents. Using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control. With this approach:

- When a patient at any treatment step has asthma symptoms, they use low dose ICS-formoterol in a single inhaler for symptom relief.
- In Steps 3–5, patients also take ICS-formoterol as their regular daily treatment. This is called 'maintenance and reliever therapy' (MART).

2

ICS-formoterol should not be used as the reliever by patients taking any other ICS-LABA.

Track 2: The reliever is as-needed SABA. This is an alternative approach when Track 1 is not possible or is not preferred by a patient who has no exacerbations on their current therapy.



ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist.

Disclaimer : (Budesonide/Formoterol is indicated only in management of Moderate to Severe Asthma (GINA Stage 3 to 5) as per label in Jordan , Iraq, Syria ,Sudan & Libya

* Global Initiative For Asthma (GINA), Global strategy for asthma management and prevention, http://ginasthma.org. Last accessed May 2021.

Treatment tracks for adults and adolescents

- For clarity, the treatment figure for adults and adolescents now shows two 'tracks', based on the choice of reliever. Treatment may be stepped up or down within a track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs.
- ***Track 1***, in which the reliever is low dose ICS-formoterol, is the preferred approach recommended by GINA. When a patient at any step has asthma symptoms, they use low dose ICS-formoterol as needed for symptom relief. In Steps 3–5, they also take ICS-formoterol as regular daily treatment. This approach is preferred because it reduces the risk of severe exacerbations compared with using a SABA reliever, with similar symptom control.
- ***Track 2***, in which the reliever is a SABA, is an alternative if Track 1 is not possible, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy. In Step 1, the patient takes a SABA and a low dose ICS together for symptom relief (in combination, or with the ICS taken right after the SABA). In Steps 2–5, the reliever is a SABA. Before considering a SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they would be at higher risk of exacerbations.

Steps 1 and 2

- In adults and adolescents with mild asthma, treatment with as-needed-only low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. The risk of emergency department visits and hospitalizations is reduced with as-needed ICS-formoterol compared with daily ICS. In patients previously using SABA alone, as-needed ICS-formoterol significantly reduced the risk of severe exacerbations compared with daily ICS.
- Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death. However, adherence with ICS in the community is poor, leaving patients taking SABA alone and at increased risk of exacerbations.

Low, Medium And High ICS Doses: Adults/Adolescents

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; CFC: chlorofluorocarbon; DPI: dry powder inhaler; HFA: hydrofluoroalkane

Global Initiative For Asthma (GINA). Global strategy for asthma management and prevention. http://ginasthma.org. Last accessed May 2007

A study of 3335 patients demonstrated Symbicort®* reduces the risk of exacerbations vs salmeterol/fluticasone + SABA[1]

fewer severe exacerbations**

with Symbicort®* 160/4.5 µg bd + additional inhalations as needed vs salmeterol/fluticasone 50/250 µg bd + SABA as needed[1]

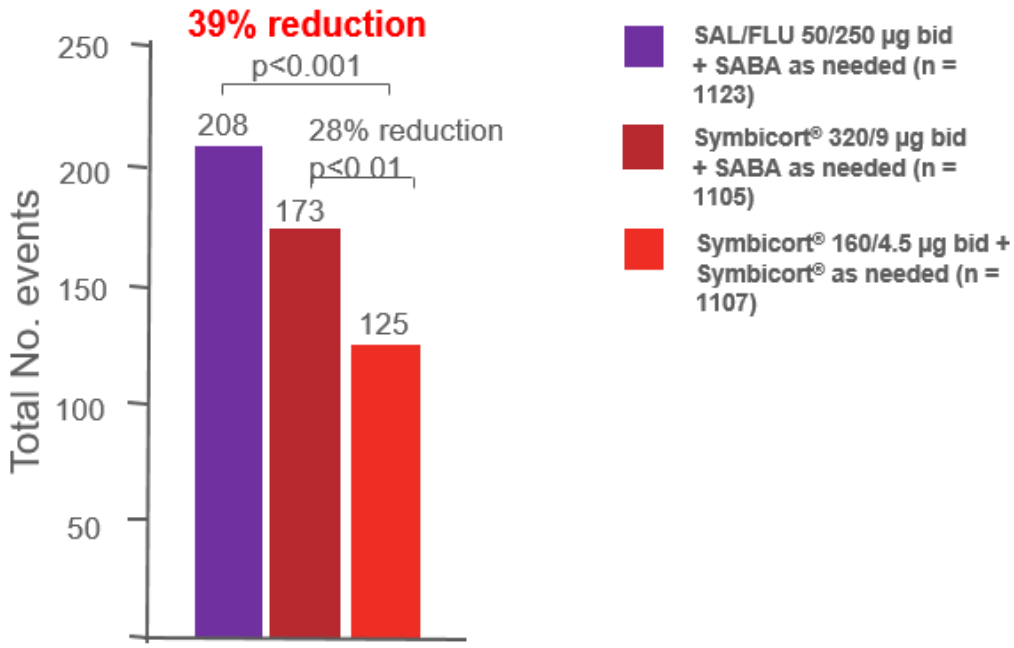
- 19 and 12 events/100 patients/6 months for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]
- Total number of severe exacerbations = 208 vs 125 for salmeterol/fluticasone + SABA and Symbicort®*, respectively[1]

*Symbicort® Maintenance and Reliever

**Severe exacerbations defined as deterioration in asthma requiring hospitalization or ER treatment, or the need for oral steroids for ≥ 3 days (as judged by the investigator).
Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV_1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). Symbicort® Maintenance and Reliever prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone (p=0.0034). Rate reduction for severe exacerbations: 0.61; 95% CI 0.49-0.76.[1]

Symbicort®* reduces severe exacerbations by 39% vs salmeterol/fluticasone over 6 months

- As well as meeting its primary endpoint (time to first severe exacerbation), in this study, Symbicort®* reduced the number of severe exacerbations over 6 months



*Symbicort® maintenance and reliever therapy.

Severe exacerbations were defined as exacerbations requiring either **A.** hospitalisation, **B.** emergency room treatment or **C.** treatment with oral steroids

bid, twice per day; SABA, short-acting β_2-agonist; SAL/FLU, salmeterol/fluticasone.

Why Symbicort® Turbuhaler® is different?

Symbicort®

Symbicort® – Efficacy data: Symptoms and asthma control

Symbicort®* – standard of care 24-hour symptom control

Asthma control days

Asthma control days defined as:

- no day-time symptoms
- no night-time symptoms
- no night awakenings caused by asthma
- no as-needed medication use

Symbicort®*: Baseline 5.8% vs Treatment 41.3%

*Symbicort® maintenance and reliever therapy

Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). Symbicort® Maintenance and Reliever 160/4.5 µg one inhalation bd + additional inhalations as needed. Symbicort® Maintenance and Reliever prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone (p=0.0034). Study results also showed salmeterol/fluticasone 25/125 µg two inhalations bd + terbutaline as needed has similar asthma control days results: Baseline 5.7% vs Treatment 43.7%.[1]

1. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NR, Rutt R. Effect of budesonide formoterol maintenance and reliever therapy on asthma exacerbations. International journal of clinical practice. 2007 May;61(5):725-36.

The formoterol component of Symbicort® produces as rapid bronchodilation as salbutamol

- Improvement in FEV_1 is as rapid and effective with formoterol 4.5 or 9 µg as with salbutamol 100 or 200 µg

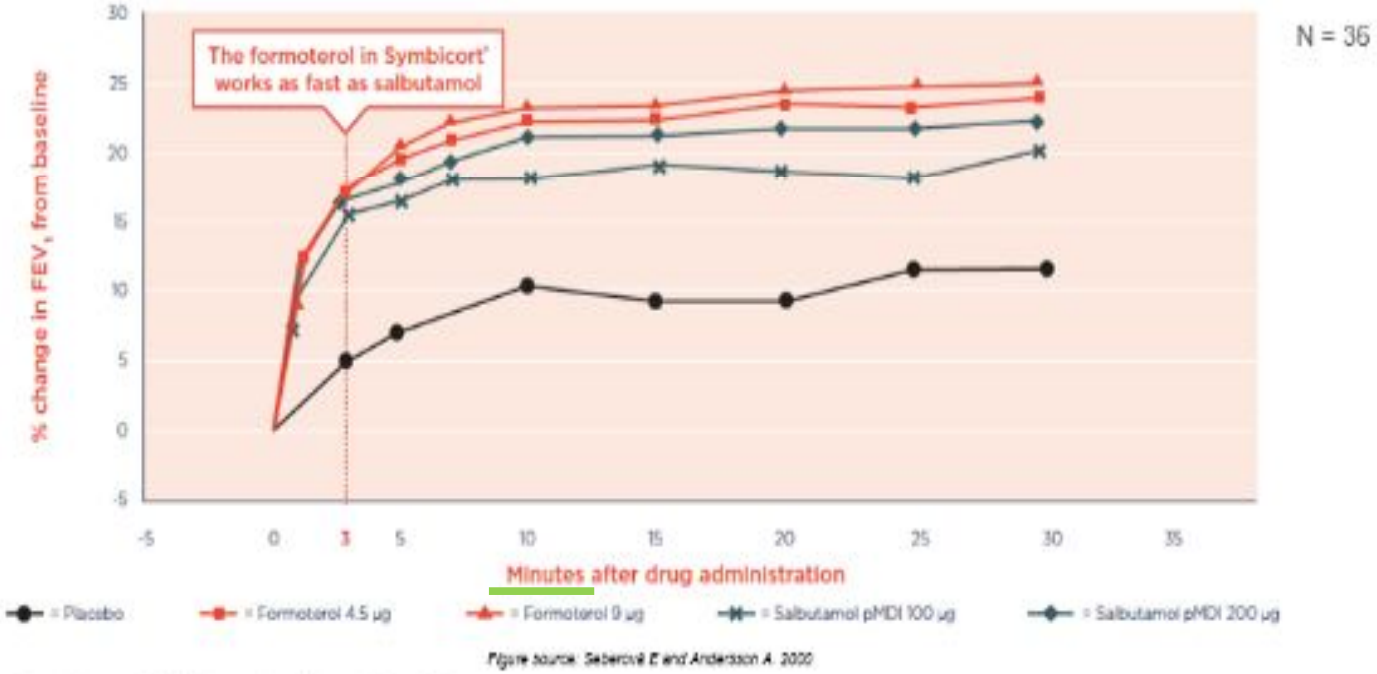


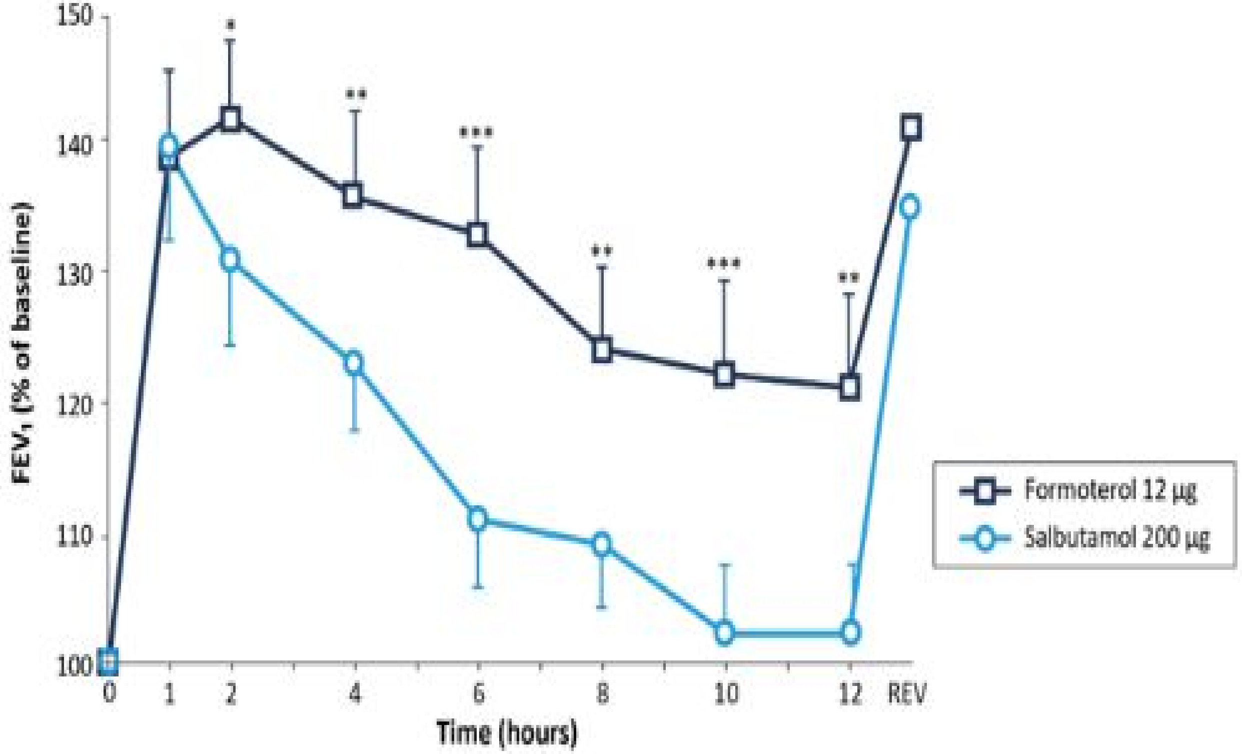
Figure source: Sebercvá E and Andersson A. 2000

FEV_1, forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler

Sebercva E, Andersson A. Oxis®(formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by a pMDI. Respiratory medicine. 2000 Jun 1;94(6):607-11.

Symbicort® provides sustained bronchodilation over 12 hours, compared to salbutamol

- The formoterol component of Symbicort® provides greater bronchodilation than salbutamol over 12 hours in patients with asthma



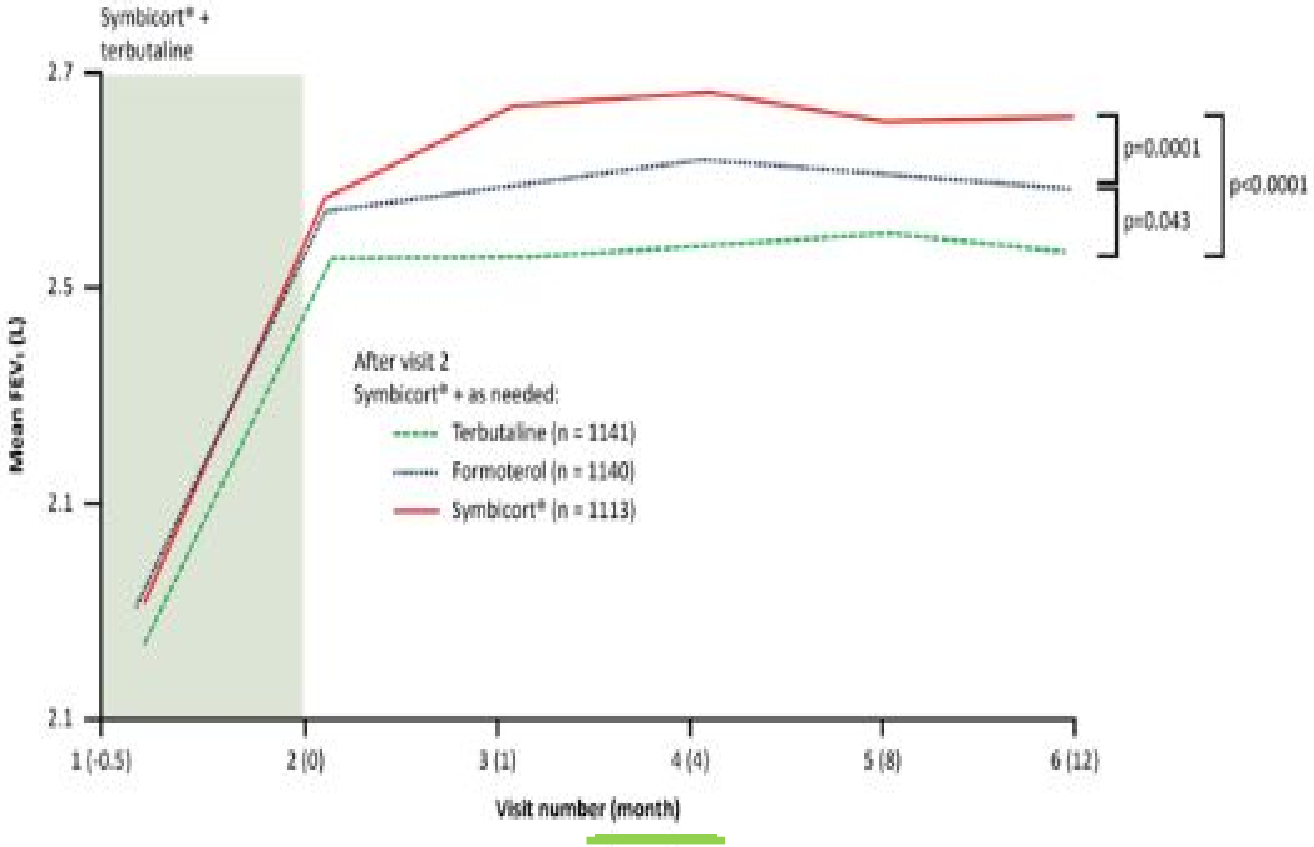
*p<0.05; **p<0.01; p<0.001

FEV_1, forced expiratory flow in 1 second; REV, reversibility

Maesen FP, Smeets JJ, Gubbelmans HL, Zweers PG. Bronchodilator effect of inhaled formoterol vs salbutamol over 12 hours. Chest. 1990 Mar 1;97(3):590-4.

Symbicort® gives additional increase in FEV_1 and sustained bronchodilation over 6 months when used as-needed vs terbutaline or formoterol as-needed

- Increases in FEV_1 occurred in each treatment group during run-in when all patients used budesonide/formoterol maintenance plus SABA, but additional increases in FEV_1 were also seen with as-needed budesonide/formoterol vs formoterol and terbutaline



FEV_1, forced expiratory volume in 1 second; SABA, short-acting β_2-agonist.

Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for relever therapy in asthma exacerbations: a randomised controlled, double-blind study. The Lancet 2006 Aug 26;368(9537):744-53; 744-753

Why Symbicort® Turbuhaler® is different?

Symbicort®

Symbicort® – Safety profile

Undesirable effects

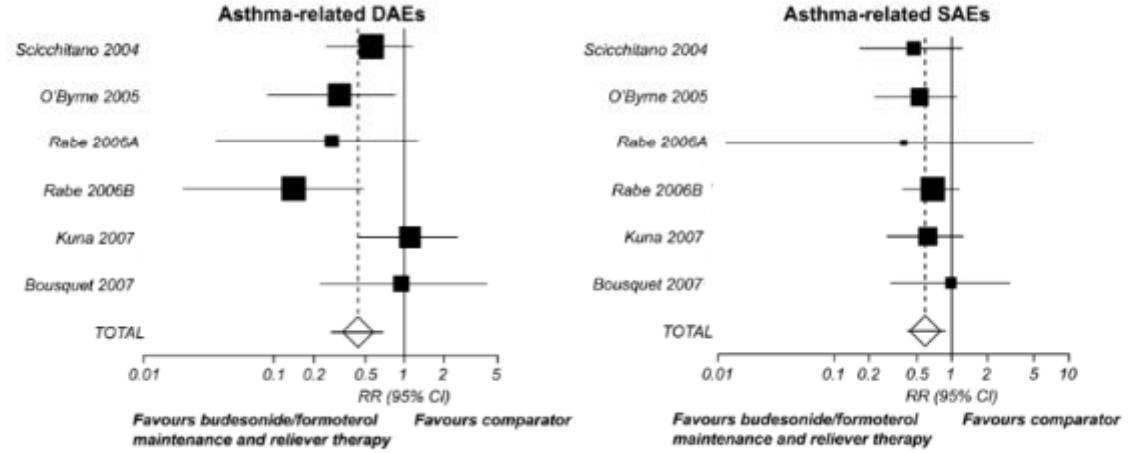
The most common drug related adverse reactions are pharmacologically predictable side-effects of beta2-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequency are defined as: common (≥1/100)		
Cardiac disorders	Common	Palpitations
Infections and infestations		Candida infections in the oropharynx
Nervous system disorders		Headache, tremor

Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Treatment with beta2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Lower risk of asthma-related DAEs and SAEs with Symbicort® anti-inflammatory reliever on top of maintenance compared to FD regimens

- Pooled analysis of safety data from six double RCTs found that asthma-related DAEs and SAEs were significantly reduced with Symbicort®* vs comparator therapy



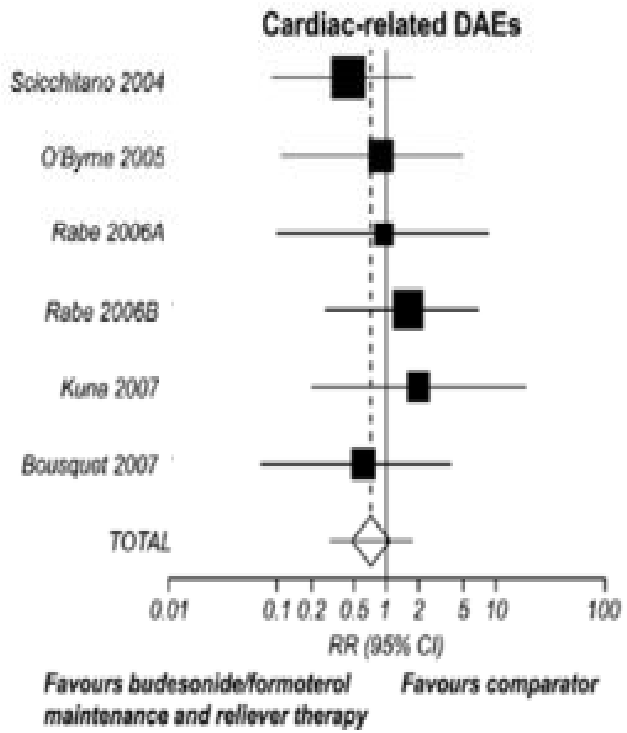
*Symbicort® maintenance and reliever therapy

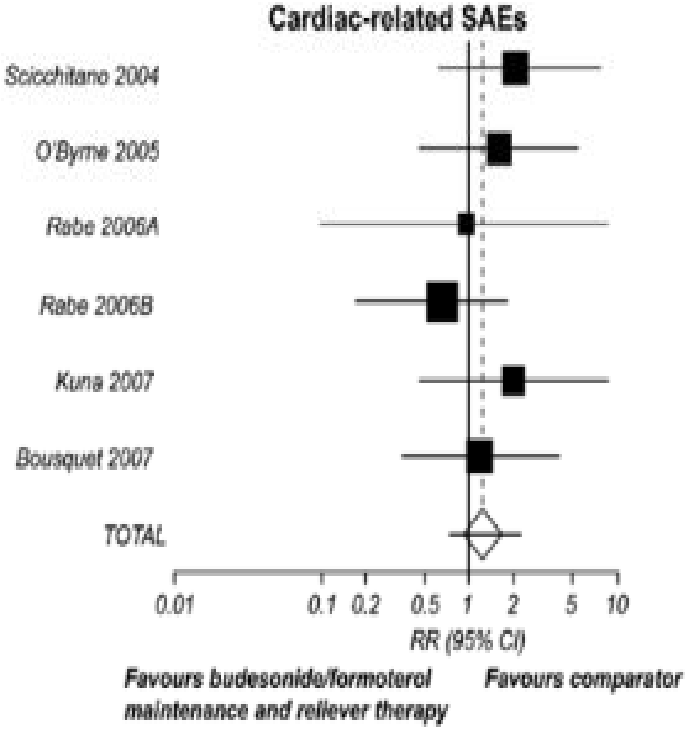
CI, confidence interval; DAE, discontinuation due to adverse events; FD, fixed dose; RCT, randomised clinical trials; RR, relative risk; SAE, serious adverse event..

Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1960-8.

Symbicort® anti-inflammatory reliever on top of maintenance is not associated with an increased risk of cardiac-related DAEs or SAEs

- In the pooled analysis of safety data from six RCTs, Symbicort®* was not associated with any increased risk of cardiac-related DAEs or SAEs





*Symbicort® maintenance and reliever therapy.

CI, confidence interval; DAE, discontinuation due to adverse events; RCT, randomised clinical trials; RR, relative risk; SAE, serious adverse event.

Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine. 2009 Dec 1;103(12):1860-8.

Contraindications and Interactions

Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or lactose (which contains small amounts of milk proteins).

Interactions

The metabolic conversion of budesonide is impeded by substances metabolized by CYP P450 3A4 (e.g. itraconazole, ritonavir). The concomitant administration of these potent inhibitors of CYP P450 3A4 may increase plasma levels of budesonide. The concomitant use of these drugs should be avoided unless the benefit outweighs the increased risk of systemic side effects.

Special warning and precautions for use

- It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly.

- Symbicort should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

- Potentially serious hypokalaemia may result from high doses of beta2- agonists. Concomitant treatment of beta2-agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta2-agonist.


THANK YOU