Update on Adult Asthma Management

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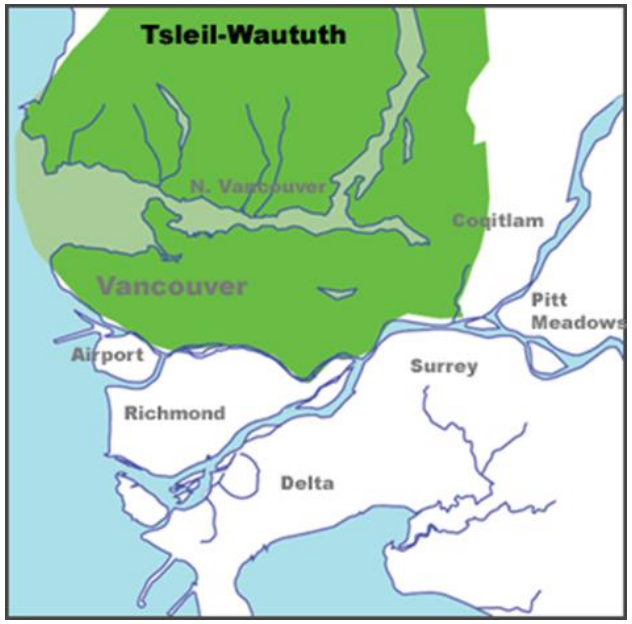
Vancouver, 7 February 2024

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Speaker Disclosures

- **Employer**: British Columbia Health Services
- **Advisory Boards:** Sanofi-Regeneron, Astra-Zeneca, ValeoPharma, Takeda
- **Speaker fees/honoraria:** Astra-Zeneca-Amgen, GlaxoSmithKline, Grifols, ValeoPharma, Sanofi-Regeneron
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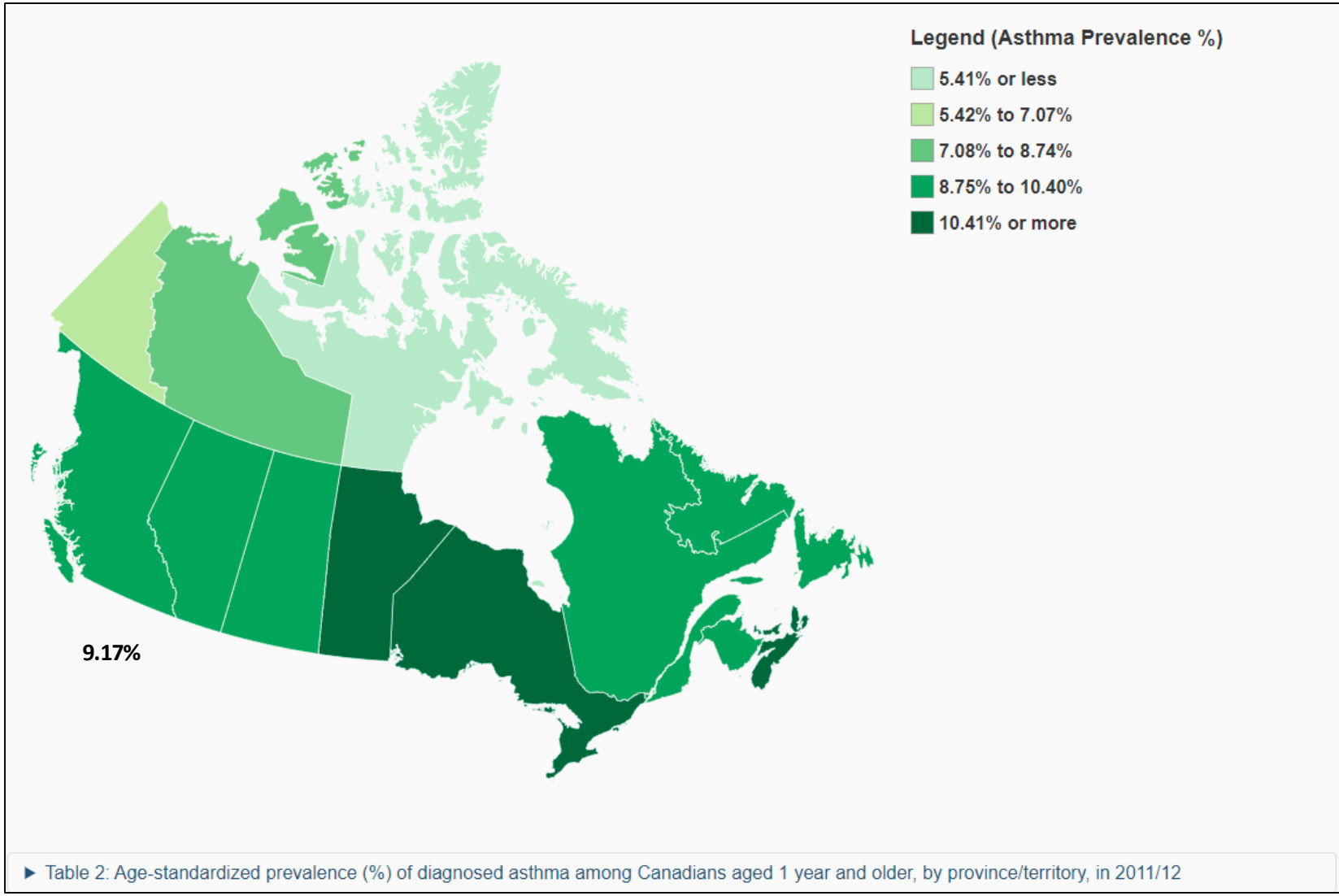
Objectives

1. Review the mild adult asthma management in 2024
2. Understand the management of moderate to severe adult asthma
3. Overview of available biological therapy for severe asthma
4. Recognize the risk factors of exacerbations and mortality in adult asthma
5. Discuss the ISAR data on socioeconomic disparity in severe asthma

Asthma - prevalence

- Worldwide
  - Prevalence 1-18%
  - 346,000 deaths/year
- In Canada
  - Affects 8.4% of Canadians
    - 9.8% Females
    - 7.0% Males
- 35th cause of death worldwide
  - Rate of asthma deaths 1.5-2.0 / 10,000

Risk factors of mortality
- Poorly controlled asthma
- Prior history of near-fatal asthma
- In all severity of asthma



▶ Table 2: Age-standardized prevalence (%) of diagnosed asthma among Canadians aged 1 year and older, by province/territory, in 2011/12

GINA 2017

Statistics Canada and Public Health Agency of Canada

Mild Adult Asthma Management

Objective 1

NEW

Change to criteria for well-controlled asthma

Characteristic	Frequency or value
Daytime symptoms	≤ 2 days/week
Nighttime symptoms	< 1 night/week and mild
Physical activity	Normal
Exacerbations	Mild and infrequent*
Absence from work or school due to asthma	None
Need for a reliever (SABA or bud/form)†	≤ 2 doses per week
FEV_1 or PEF	≥ 90% of personal best
PEF diurnal variation	< 10-15%#
Sputum eosinophils	< 2-3%●

A patient who meets all of the above criteria would be considered to have well-controlled asthma

* A mild exacerbation is an increase in asthma symptoms from baseline that does not require systemic steroids, an ED visit, or a hospitalization. "Infrequent" is not specifically defined, since the frequency of mild exacerbations that patients consider an impairment to quality of life varies. If the patient feels that the frequency of mild exacerbations is impairing their quality of life, then their asthma should be considered poorly-controlled. If a patient is having frequent mild exacerbations, they should be assessed to determine if at baseline, they have poorly-controlled asthma.

† There are no established criteria for control when using bud/form as a reliever, however, use of a reliever often indicates that a patient is having symptoms and is a criterion that can be objectively assessed.

\# Diurnal variation is calculated as the highest peak expiratory flow (PEF) minus the lowest divided by the highest peak flow multiplied by 100, for morning and night (determined over a two-week period).

● Consider in adults ≥ 18 years of age with uncontrolled moderate to severe asthma who are assessed in specialist centres.

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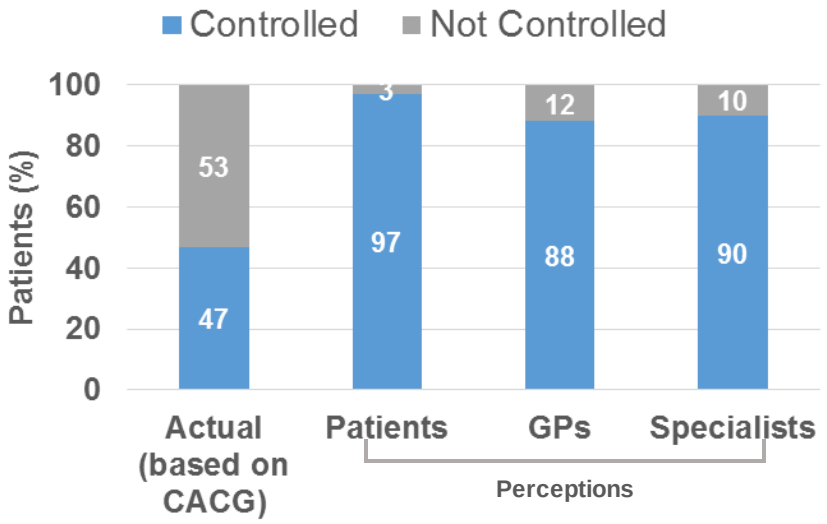
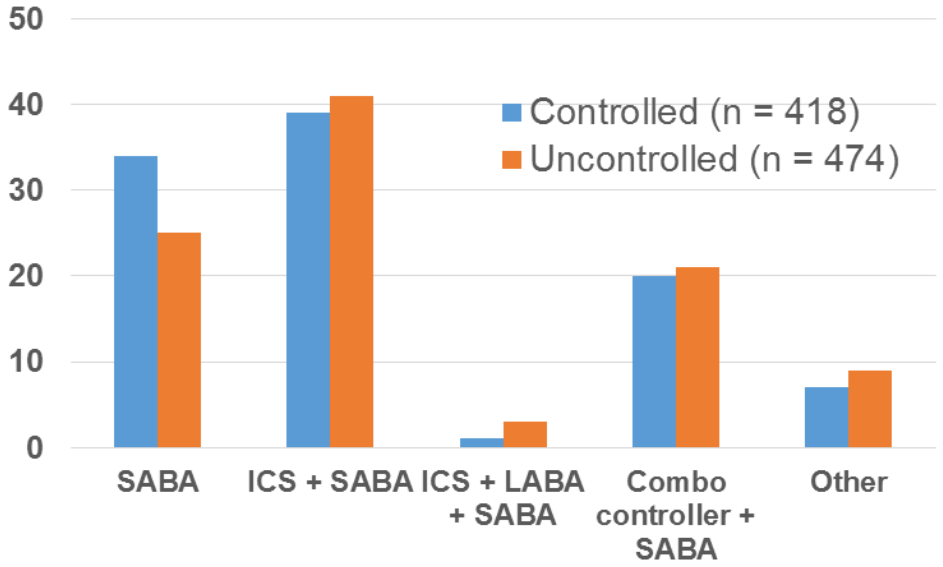
THE MAJORITY OF CANADIANS WITH ASTHMA ARE INADEQUATELY CONTROLLED

The Reality of Asthma Control (TRAC) study (N = 893)[1]



53%

of Canadian adult patients with asthma had uncontrolled disease



- FitzGerald, JM, *et al*. *Can Resp J* 2006;13(5):253-259.

Importance to achieve good control of asthma

- **Population**
- Economic burden of asthma In British-Columbia:
  - $46.3 to $62 millions per year related tc direct costs of asthma
- Sub-optimal asthma control is responsible for significant cost
  - 10% prevalence reduction in suboptima control = 18% reduction in cost

Sadatsafavi, M. et al. 2010: CRJ. 74-80
Zafari, Z. et al. 2018: Resp Med. 138: 7-12

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- **Individual**

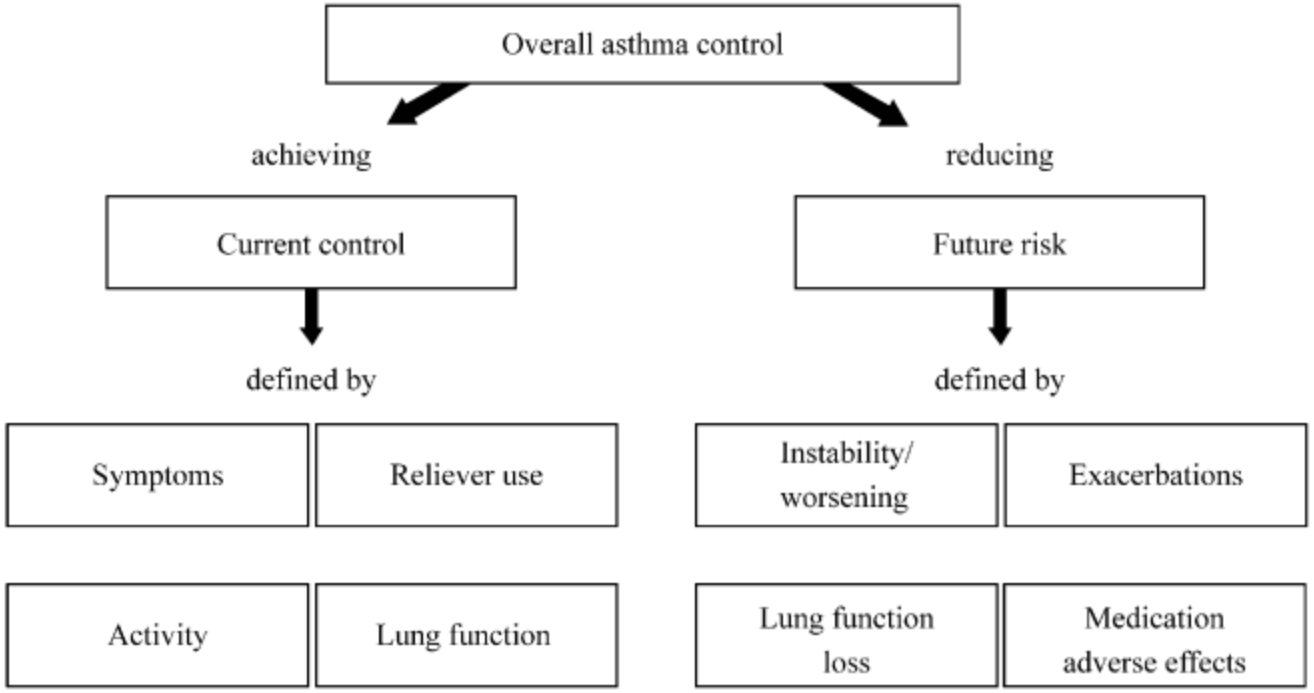

FIG 1. Goals of asthma management.

Bateman E. Et al. J Allergy Clin Immunol 2010;125:600-8

Goals of asthma treatment

- Few asthma symptoms
- No sleep disturbance
- No exercise limitation

} Symptom control (e.g. ACT, ACQ)

- Maintain normal lung function
- Prevent flare-ups (exacerbations)
- Prevent asthma deaths
- Minimize medication side-effects (including OCS)

} Risk reduction

- The patient's goals may be different
- Symptom control and risk may be discordant
  - Patients with few symptoms can still have severe exacerbations

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroids

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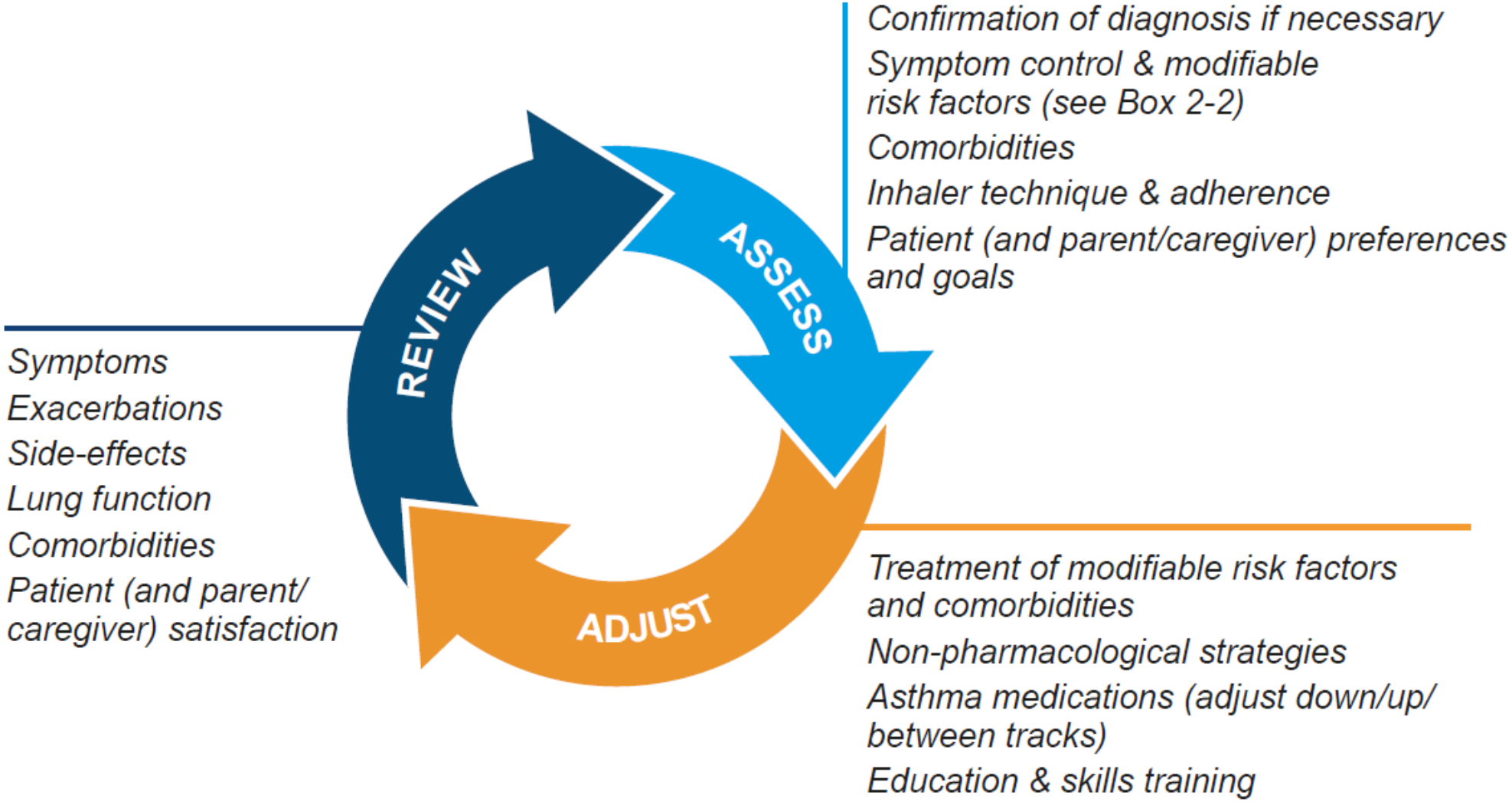

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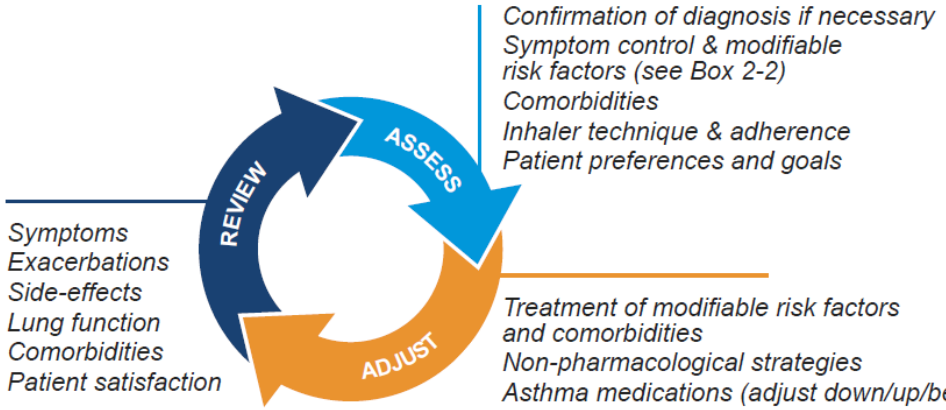
GINA 2023 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol*			

See GINA severe asthma guide

TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: as-needed ICS-SABA*, or as-needed SABA				

Other controller options (limited indications, or less evidence for efficacy or safety – see text)	*Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever (AIR)

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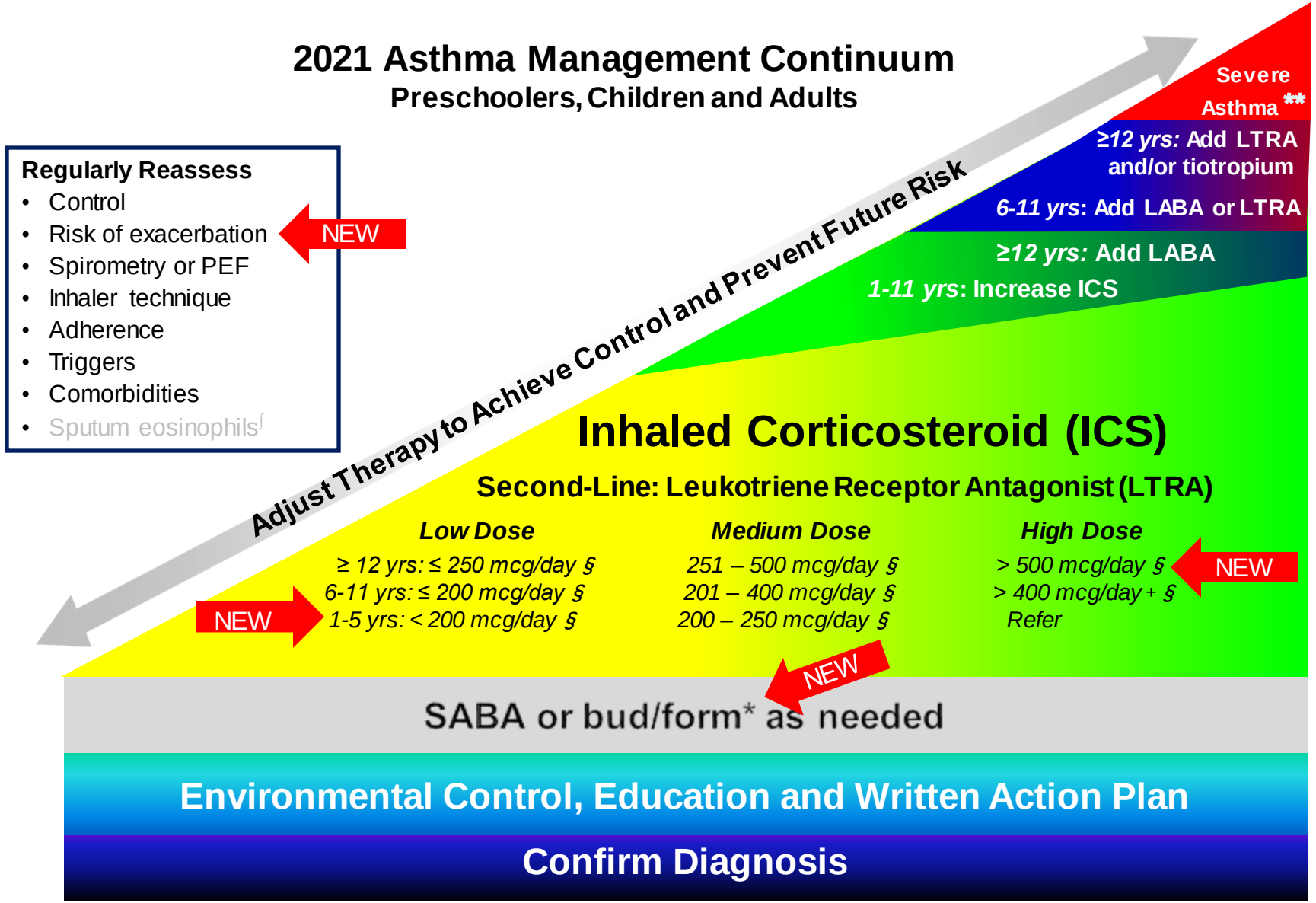
2021 Asthma Management Continuum

Preschoolers, Children and Adults



* Or an alternative ICS/form preparation if another is approved for use as a reliever in the future. Bud/form is approved as a reliever for ≥12 years of age and should only be used as a reliever in individuals using it as monotherapy or in conjunction with bud/form maintenance therapy

§ HFA Fluticasone propionate or equivalent

\+ Not approved for use in Canada

∫ In adults, 18 years old and over with moderate to severe asthma assessed in specialist centres

** For severe asthma refer to CTS 2017 Recognition and management of Severe Asthma Position Statement

NEW

Assessing risk of exacerbations in addition to asthma control

- When deciding on optimal treatment, in addition to evaluating asthma control, risk of asthma exacerbation should be assessed.
- A higher risk for an exacerbation is defined by any of the following criteria:

History of a previous severe asthma exacerbation (requiring any of: systemic steroids; ED visit; or hospitalization)
Poorly-controlled asthma as per CTS criteria
Overuse of SABA (defined as use of more than 2 inhalers of SABA in a year[1]); or
Current smoker

Risk factors chosen based on: OR >1.5, certainty of the effect of the risk factor, ease of use in clinical practice

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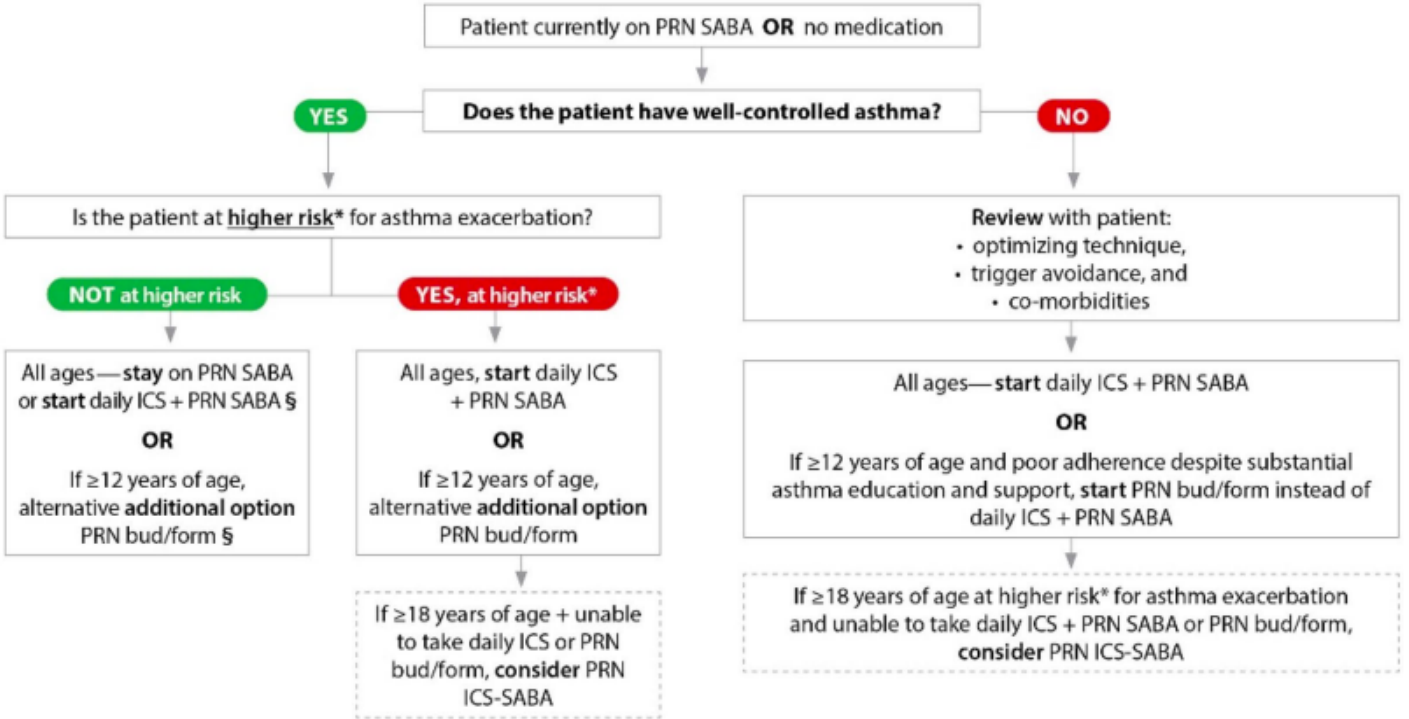
(1) Nwaru BI et al. ERJ, 2020; 55(4).



***Higher risk if a patient had any of the following:**

1) any history of a previous severe asthma exacerbation requiring:
   - systemic steroids,
   - ED visit, or
   - hospitalization
2) poorly-controlled asthma as per CTS criteria
3) overuse of short-acting beta-agonist (defined as use of more than two inhalers of SABA in a year)
4) current smoker

§ Based on patient preference—the decision to switch from PRN SABA to daily ICS + PRN SABA or PRN bud/form is for those that want better asthma control and to decrease their risk of exacerbation

⬚ Dash boxes represent harm reduction strategy

SABA: short-acting beta-agonist; **ICS**: inhaled corticosteroids; **bud/form**: budesonide-formoterol in a single inhaler; **ED**: emergency department

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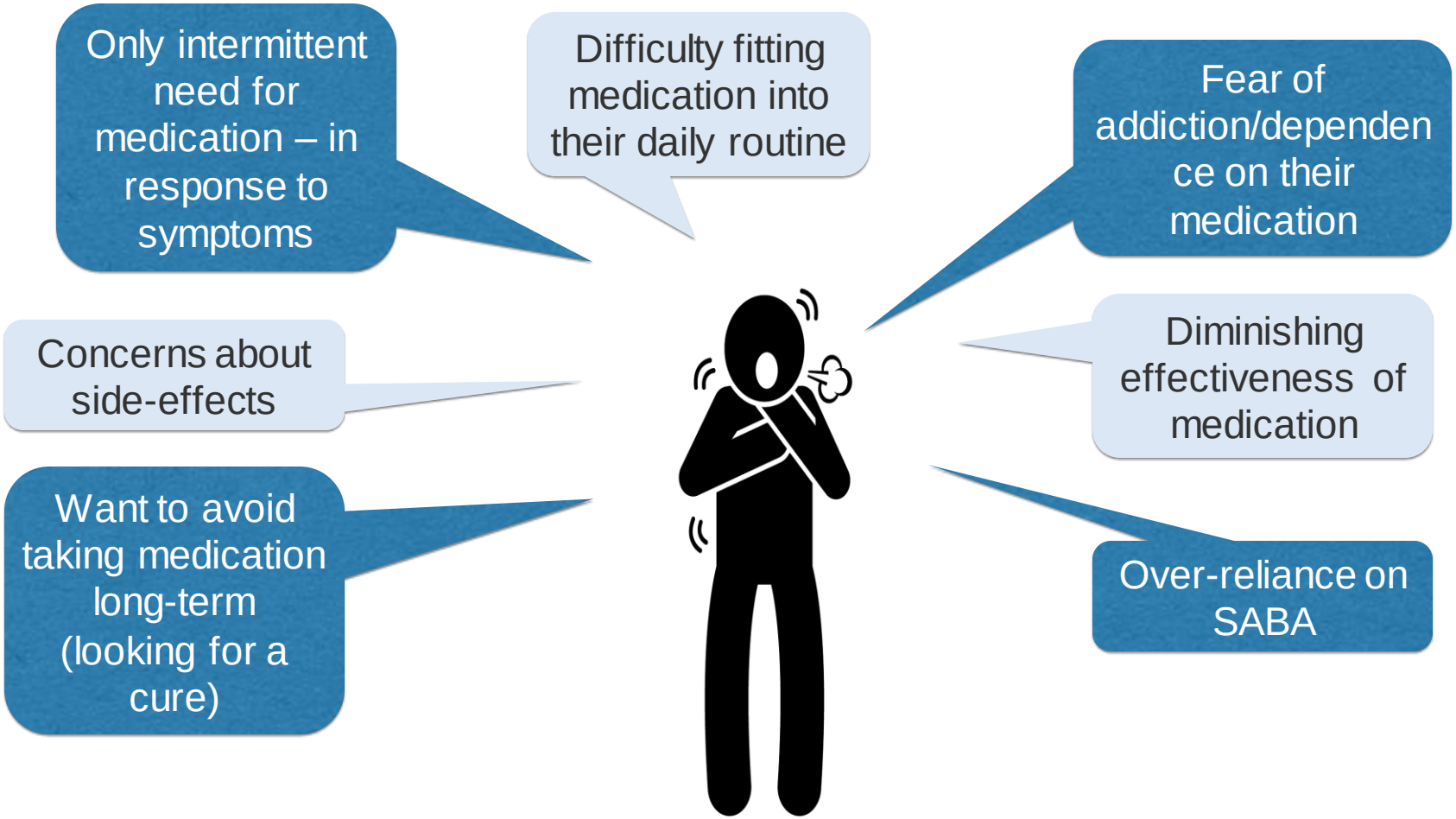
Mild asthma management
– Education, Action Plan and Self-Management

- **Essential component of management**
- Reduction
    - Hospitalizations
    - Emergency visits
    - Urgent physician visits
    - Missed days at work or school
    - Days of restricted activity
- Improvement in pulmonary function
- Non-compliance with medication is common
    - Assessing individual barriers with patients is important

My patient isn't taking her/his inhalers….



Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available from: www.ginasthma.org;
Peláez et al. BMC Pulmonary Medicine (2015) 15:42
Partridge MR, *et al. BMC Pulm Med 2006;6 13)*

Components of an asthma education program

1. Written action plan: Provision and explanation of a written action plan comprising:
   - How and how often to assess asthma control (self-monitoring)
   - Instructions to maintain good control using controller medication and making specific environmental changes
   - Signs and symptoms indicating uncontrolled asthma, with instructions on what to do during loss of control (medication to add or increase, how much and how long; when and how to seek additional help (eg, when to go to the hospital or call the health care provider)
2. What is asthma?: A chronic inflammatory condition in which airways are hyper-reactive (sensitive) to environmental (allergenic, irritants or infectious) and/or intrinsic factors
3. Asthma control for all patients: Asthma can be controlled and all patients with asthma can lead a normal life. Regular symptoms and asthma exacerbations indicate treatment failure
4. Reliever versus controller: The difference between reliever and controller medications and their use in the written action plan
5. Identify triggers: Identification and avoidance of environmental triggers specific to the patients
6. Inhaler technique: Teaching and verification of the inhalation technique specific to the inhalation devices prescribed for the patient
7. Medication safety and side effects: Expected onset of action and potential side effects of medications

Carbon footprint of inhalers

House of Commons

Environmental Audit Committee

UK Progress on reducing F-gas Emissions

Fifth Report of Session 2017–19

Report, together with formal minutes relating to the report

Ordered by the House of Commons to be printed 18 April 2018

Contents

Carbon footprint of inhalers

- 1 salbutamol MDI = 24 turbuhalers

Health

Asthma carbon footprint 'as big as eating meat'

By Michelle Roberts
Health editor, BBC News online

30 October 2019 | Share

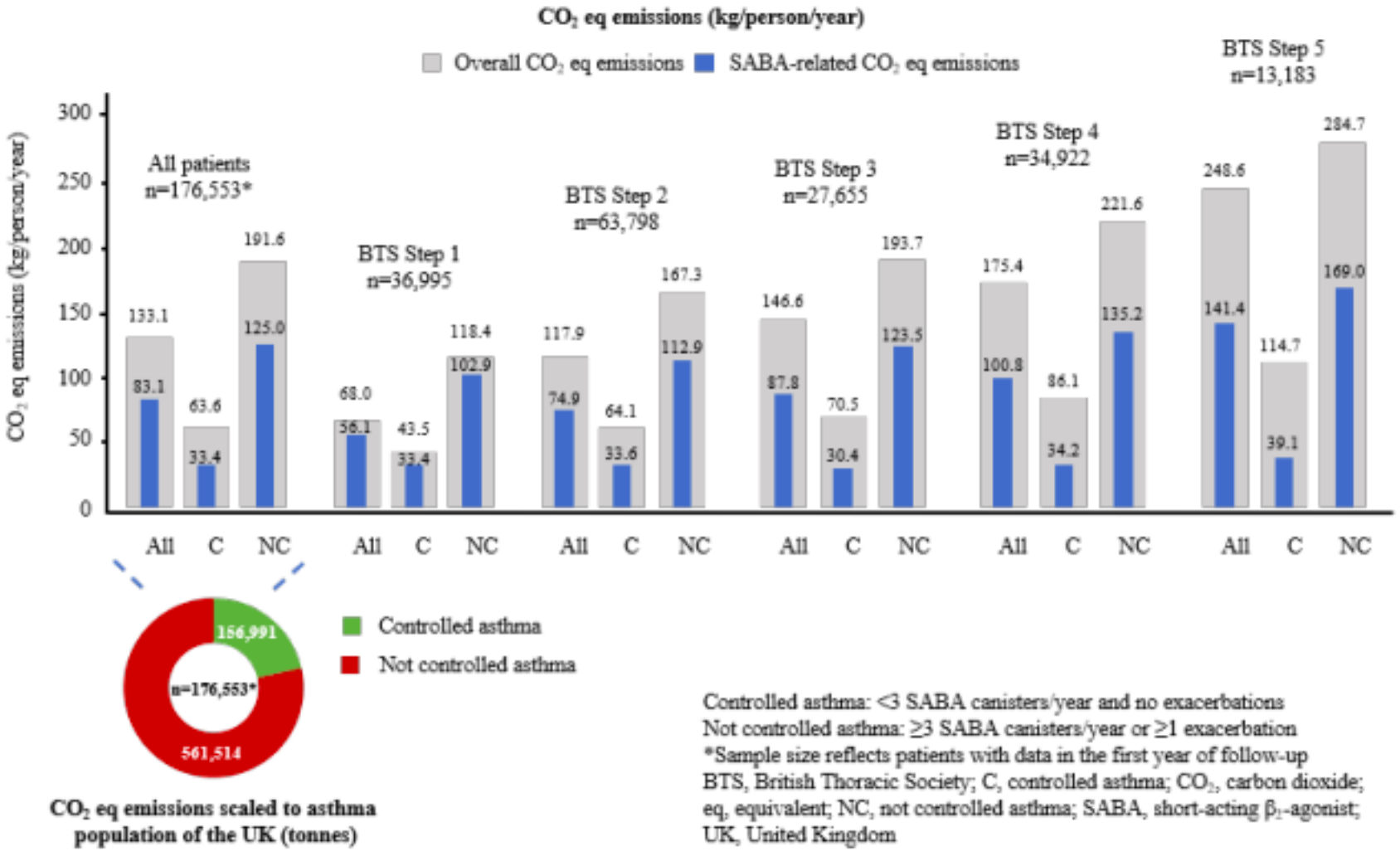
Climate change

Many people with asthma could cut their carbon footprint and help save the environment by switching to "greener" medications, UK researchers say.

1 aerosol inhaler, depending on the type, can have the same carbon footprint as driving up to **170km** in a gas car.*

- In UK, 70% MDI, 30% DPI
- Some inhalers release greenhouse gases linked to global warming:
  - gas – hydrofluoroalkane (HFA) ; (Global Warming Potential)
    - Mainly HFA 134a as propellant, which has a GWP of 1,480,
    - minority use HFA 227, which has a GWP of 2,800
- In UK, MDI account for nearly **4%** of NHS greenhouse gas emissions
- Replacing 1 in every 10 of MDI inhalers with a more environmentally friendly type (dry powder inhalers)
  - Reduction in carbon dioxide equivalent emissions by **58 kilotonnes** (similar to the carbon footprint of 180,000 return car journeys from London to Edinburgh; 666km x2)
- Making the swap would have as big an "eco" impact as turning vegetarian or becoming an avid recycler
- At the individual level, each MDI replaced by DPI could save the equivalent of between 150kg and 400kg (63 stone) of carbon dioxide a year - similar to the carbon footprint reduction of cutting meat from your diet.

Fig 1. Annual greenhouse gas emissions associated with asthma care in the UK



Controlled asthma: <3 SABA canisters/year and no exacerbations
Not controlled asthma: ≥3 SABA canisters/year or ≥1 exacerbation
*Sample size reflects patients with data in the first year of follow-up
BTS, British Thoracic Society; C, controlled asthma; CO_2, carbon dioxide; eq, equivalent; NC, not controlled asthma; SABA, short-acting β_2-agonist; UK, United Kingdom

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Greenhouse gas emissions associated with asthma care in the UK: results from SABINA CARBON
A. Wilkinson et al. ERS 2021

Check for updates

Canadian Thoracic Society Position Statement on Climate Change and Choice of Inhalers for Patients with Respiratory Disease

Samir Gupta[a,b], Simon Couillard[c], Geneviève Digby[d], Sze Man Tse[e,f], Samantha Green[g], Raymond Aceron[h], Chris Carlsten[i], Jill Hubick[j] and Erika Penz[k]

Table 1. Overview of inhaler form, carbon footprint and considerations for inhaler choice.

Inhaler format	 SMI	 DPI[a]	 pMDI (current)	 pMDI (future)
Relative carbon footprint[b]	<1 (LOW)	1 (LOW)	15–30 (HIGH)	<1[c]–2[d] (LO
Requirements	• Age ≥ 4 • Teaching and demonstration required to minimize critical errors	• Age ≥ 4[e] • Adequate inspiratory flow rate/pressure • Teaching and demonstration required to minimize critical errors	• Any age • Spacer (or VHC/facemask in early life) • Teaching and demonstration required to minimize critical errors	• Any age • Spacer (or VHC/facemas early life) • Teaching and demonstration required minimize critical errors
Advantages	• Lack of propellent decreases carbon footprint • Propellant-free solution under mechanical pressure requires a low inspiratory flow rate/pressure • May be used with a spacer (or VHC/facemask in early life) • Amenable to caregiver administration • Often has a dose indicator	• Lack of propellent decreases carbon footprint • Often has a dose counter	• Often less expensive than DPI alternative • Amenable to caregiver administration	• Newer propellants have much lower to no GHGs emissions • Am ad
Limitations	• Coordination may be difficult when no spacer used • Dose cannister must be loaded in device • Priming required	• Younger, older patients and some patients with acute / chronic respiratory disease may lack sufficient inspiratory flow rate/ pressure for adequate administration	• Propellent generally carbon-intensive • Dose counter not often available • Need to shake and prime	• Ne to yet inh • Co

Abbreviations: DPI, dry powder inhaler; GHG, greenhouse gas; pMDI, pressurized multi-dose inhaler; SMI, soft-mist inhaler; VHC, valved h
[a]Other DPI devices include: respiclick™, inhub™, genuair™, aerolizer™, handihaler™
[b]For specific inhaler carbon footprint estimations, see PrescQIPP resource: https://www.prescqipp.info/our-resources/bulletins/bulletin-295-
[c]Relative estimate for HFO-1234ze molecule.[14]
[d]Relative estimate for HFA-152a molecule.[67]
[e]DPI devices are approved for children aged ≥ 4 years but preschool aged children may not be able to consistently achieve adequate pressures, nor form a tight seal around the mouthpiece of the device and require extensive teaching and verification.
Note. Inhaler images in Table 1 are from the Electronic Asthma Management System (eAMS), reproduced with permission from Dr. Samir Gupta.

Box 1. Practical considerations when selecting an inhaler device.

- Patient preference
- Impact of inhaler device on adherence
- Inhalation technique (patient ability)
- Inspiratory flow rate/pressure required for adequate medication delivery (patient ability)
- Patient age
- Cost for patient and/or public healthcare system
- Side effect profile
- Environmental footprint

Don't prescribe greenhouse gas-intensive metered-dose inhalers (MDIs) for asthma and/or COPD where an alternative inhaler with a lower carbon footprint (e.g. dry power inhaler (DPI), soft-mist inhaler, or MDI with a low greenhouse gas potential propellant) containing medications with comparable efficacy is available, and where the patient has demonstrated adequate technique and patient preference has been considered.

CANADIAN JOURNAL OF RESPIRATORY, CRITICAL CARE, AND SLEEP MEDICINE
2023, VOL. 7, NO. 5, 232–239
https://doi.org/10.1080/24745332.2023.2254283

What we can do as HCP for the environment

- Awareness of carbon footprint of inhalers
  - Choice of dry powder over metered dose inhaler

- Aim for good asthma control
  - Acceptable asthma control (< 3 SABA cannister/year) is one third of uncontrolled asthma (> = 3 SABA cannister/y or 1 exacerbation)
  - Severe asthma exacerbation increased the Carbon footprint via use of ambulance, car, ER visits and hospitalisations.
  - Reduction in CO2 emission by prevention severe exacerbation equal to use a low carbon DPI (Breezhaler®) for ~74 patient years.

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Wilkinson et al. ERS 2021
Beeh et al. ERS 2021

bcinhalers.ca

Relaunch to up

BC Inhalers

A guide to green inhalers in British Columbia, Canada

Inhaler Carbon Emissions:

Low	Moderate	High

Instructions

1. Select indication:*

Asthma

2. Add criteria:

- Green inhalers only
- PharmaCare covered (Special Authority NOT required)
- Available in hospital

Patient's Age:

Years Old

Updated: November 2023

Disclaimer & About Us

Quick Guide to Inhaler Switches

SABA

Bricanyl Turbuhaler
terbutaline

Ventolin Diskus
salbutamol

Teva-Salbutamol MDI
salbutamol

Ventolin MDI
salbutamol

ICS

Pulmicort Turbuhaler
budesonide

Arnuity Ellipta
fluticasone furoate

Flovent Diskus
fluticasone propionate

Aermony Respiclick
fluticasone propionate

Asmanex Twisthaler
mometasone furoate

Flovent MDI
fluticasone propionate

Alvesco MDI
ciclesonide

Qvar MDI
beclomethasone dipropionate

ICS/LABA

Symbicort Turbuhaler
budesonide + formoterol

Breo Ellipta
fluticasone furoate + vilanterol

Wixela Inhub
fluticasone propionate + salmeterol

Advair Diskus
fluticasone propionate + salmeterol

Atectura Breezhaler
indacaterol + mometasone

Advair MDI
fluticasone propionate + salmeterol

Zenhale MDI
mometasone + formoterol fumarate

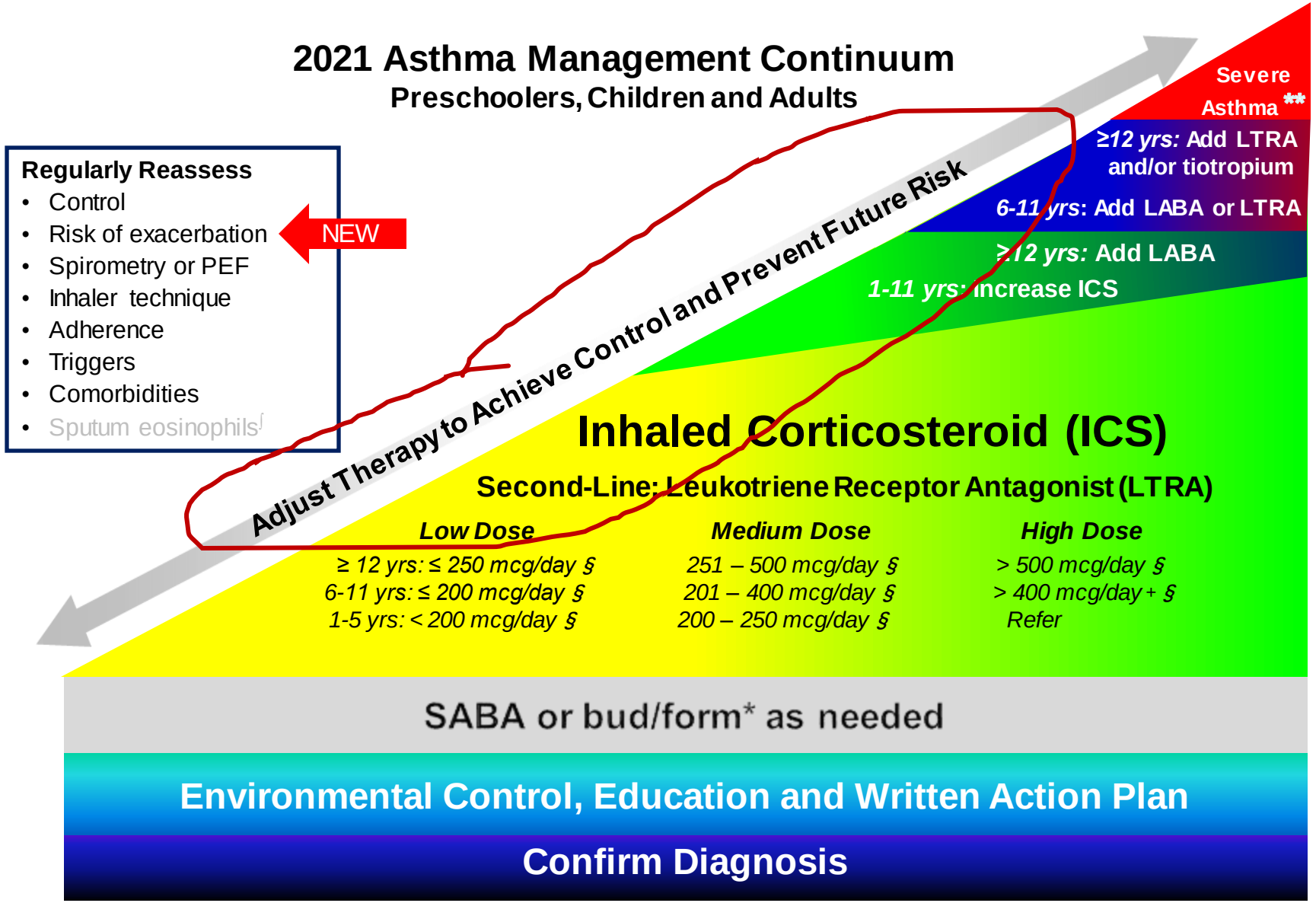
ICS/LAMA/LABA

Trelegy

Enerzair

2021 Asthma Management Continuum

Preschoolers, Children and Adults



* Or an alternative ICS/form preparation if another is approved for use as a reliever in the future. Bud/form is approved as a reliever for ≥12 years of age and should only be used as a reliever in individuals using it as monotherapy or in conjunction with bud/form maintenance therapy

§ HFA Fluticasone propionate or equivalent

\+ Not approved for use in Canada

∫ In adults, 18 years old and over with moderate to severe asthma assessed in specialist centres

** For severe asthma refer to CTS 2017 Recognition and management of Severe Asthma Position Statement

Mild asthma

- Control to optimize
  - Symptoms control and risk reduction
- Education
- Risks factors: prior severe exacerbation, poorly control, overuse SABA, smoker
- ICS/formoterol as needed
- Low carbon footprint inhalers

Why is GINA Track 1 with ICS-formoterol preferred?

- **Steps 1–2**: weight of evidence for effectiveness and safety compared with SABA alone, or low-dose ICS plus as-needed SABA (4x12 month studies, n~10,000) *(Crossingham et al, Cochrane 2021)*
  - As-needed ICS-SABA: only one 6-month RCT (n=455) *(Papi et al, NEJMed 2007)*
- **Steps 3–5**: weight of evidence for effectiveness and safety of MART versus regimens with as-needed SABA (n~30,000) *(Sobieraj et al, JAMA 2018; Cates et al, Cochrane 2013)*
  - As-needed ICS-SABA: only one RCT (n=3,132) vs as-needed SABA *(Papi et al, NEJMed 2022);* cannot be used for maintenance and reliever therapy
- Both the ICS and the formoterol contribute to reduction in severe exacerbations *(Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003; Rabe et al, Lancet 2006)*
  - Safety established up to total 12 inhalations in any day, in large studies
- **Simplicity of approach** for patients and clinicians
  - A single medication for both symptom relief and maintenance treatment (if needed) from diagnosis
  - Avoids confusion about inhaler technique with different devices
  - Short-term increase in symptoms à patient increases the number of **as-needed** doses
  - Step treatment down or up by changing the number of maintenance doses

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Reliever doses of ICS-formoterol - how much can be taken?

- For ICS-formoterol with 6 mcg (4.5 mcg delivered dose) of formoterol, take **1 inhalation** whenever needed for symptom relief
- Another inhalation can be taken after a few minutes if needed
- Maximum total number of inhalations in any single day (as-needed + maintenance)
  - **Budesonide-formoterol**: maximum 12 inhalations* for adults, 8 inhalations for children, based on extensive safety data *(Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003)*
  - **Beclometasone-formoterol**: maximum total 8 inhalations in any day *(Papi et al, Lancet Respir Med 2013)*
- Emphasize that most patients need far fewer doses than this!

- For pMDIs containing 3 mcg formoterol (2.25 mcg delivered dose), take 2 inhalations each time

**For budesonide-formoterol 200/6 [delivered dose 160/4.5 mcg], 12 inhalations gives 72 mcg formoterol (54 mcg delivered dose)*

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Practical advice for GINA Track 1

- At first, patients may be unsure whether ICS-formoterol will work as well as their previous SABA reliever
  - In the PRACTICAL study, 69% patients said ICS-formoterol worked as fast as, or faster than, their previous SABA *(Baggott et al, ERJ 2020)*
  - Suggest to the patient that they try out the new reliever at a convenient time
  - Emphasise that they should use the ICS-formoterol **instead of** their previous SABA, and that they should take an additional inhalation when they have more symptoms
- Advise patients to have two inhalers (if possible), 1 at home, 1 in bag/pocket
- Advise patients to rinse and spit out after maintenance doses, but this is not needed with reliever doses
  - No increased incidence of candidiasis in RCTs with this recommendation (n~40,000)
- Use an action plan customised to MART
  - The patient continues their usual maintenance ICS-formoterol inhalations, but takes more **as-needed** ICS-formoterol inhalations
  - Taking extra as-needed inhalations reduces the risk of progressing to a severe exacerbation needing oral corticosteroids *(Bousquet et al, Respir Med 2007; Buhl et al, Respir Res 2012; O'Byrne et al, Lancet Respir Med 2021)*
- Additional practical advice for MART *(Reddel et al, JACI in Practice 2022)*

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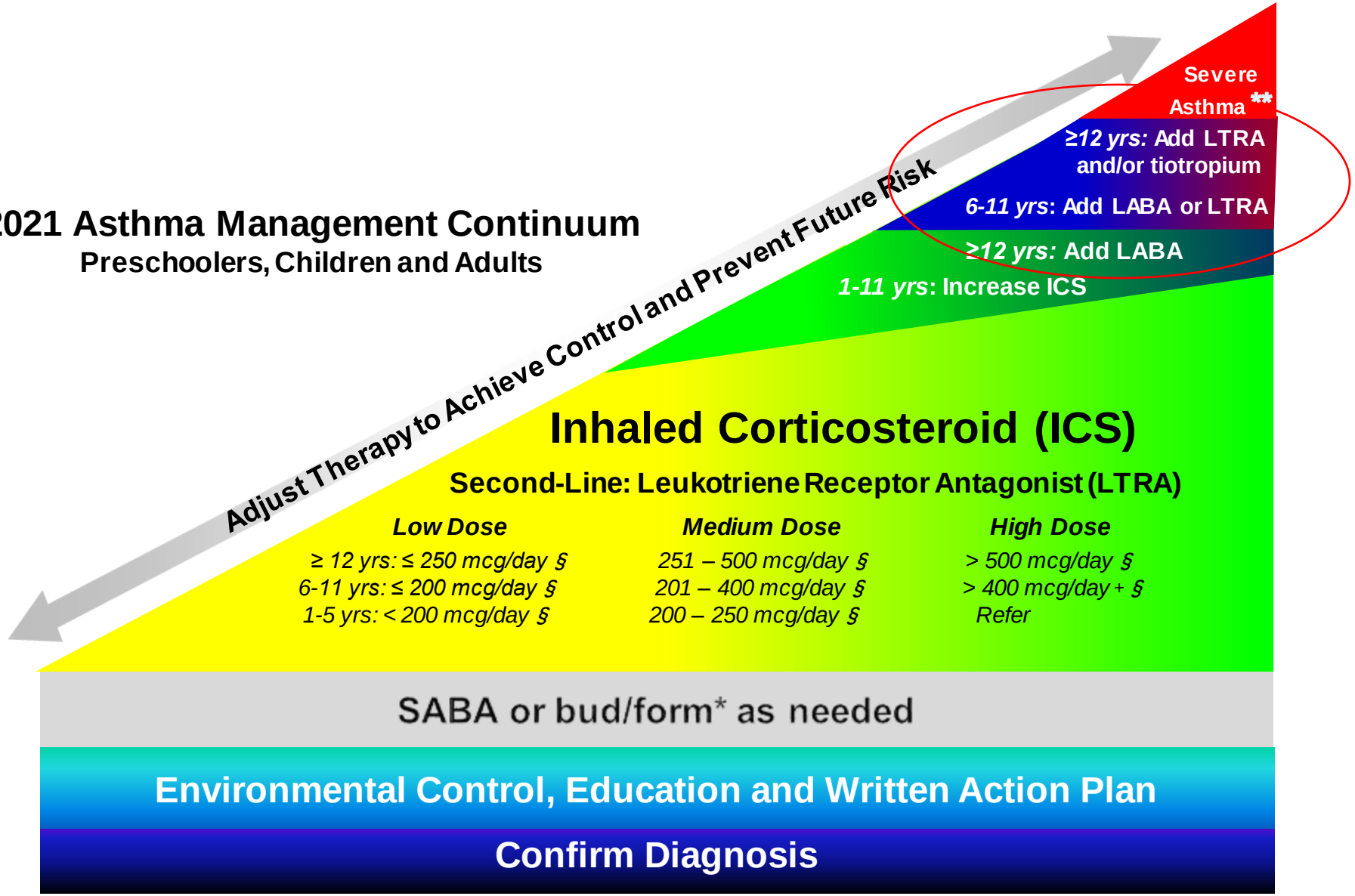
Moderate to severe asthma management

Objective 2

2021 Asthma Management Continuum

Preschoolers, Children and Adults



Reference: Connie L. Yang, Elizabeth Anne Hicks, Patrick Mitchell, Joe Reisman, Delanya Podgers, Kathleen M. Hayward, Mark Waite & Clare D. Ramsey (2021): Canadian Thoracic Society 2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine,

* Or an alternative ICS/form preparation if another is approved for use as a reliever in the future. Bud/form is approved as a reliever for ≥12 years of age and should only be used as a reliever in individuals using it as monotherapy or in conjunction with bud/form maintenance therapy

§ HFA Fluticasone propionate or equivalent

\+ Not approved for use in Canada

∫ In adults, 18 years old and over with moderate to severe asthma assessed in specialist centres

** For severe asthma refer to CTS 2017 Recognition and management of Severe Asthma Position Statement

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ICS/LABA options

Inhaled Respiratory Medication for Patients with Poor Asthma Control treated with ICS/LABA

Single Inhaler Triple Therapies (SITTs)

Mometasone furoate /Indacaterol/Glycopyrronium

ENERZAIR
Breezhaler
160/50/150 mcg

Fluticasone furoate/ Vilanterol/Umeclidinium

TRELEGY
Ellipta
100/62,5/25 mcg

TRELEGY
Ellipta
200/62,5/25 mcg

One inhalation once daily

Open Triple Therapy

ICS/LABA + Tiotropium

ICS/LABA

\+

SPIRIVA
Respimat
2,5 mcg

Two inhalations once daily (plus dosing schedule for existing ICS/LABA regimen)

There are two closed SITTs and one open triple therapy available in Canada.

ICS: inhaled corticosteroids, LABA: long-acting beta-agonist

CANADIAN JOURNAL OF RESPIRATORY, CRITICAL CARE, AND SLEEP MEDICINE
https://doi.org/10.1080/24745332.2023.2237972

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CLINICAL RESPIRATORY REVIEW

OPEN ACCESS Check for updates

Triple inhaled therapy for asthma in Canada

Kenneth R. Chapman[a], Meyer Balter[b], Sacha Bhinder[c], Alan Kaplan[d], Andrew McIvor[e], Panayiota Papadopoulos[f] and Krystelle Godbout[g]

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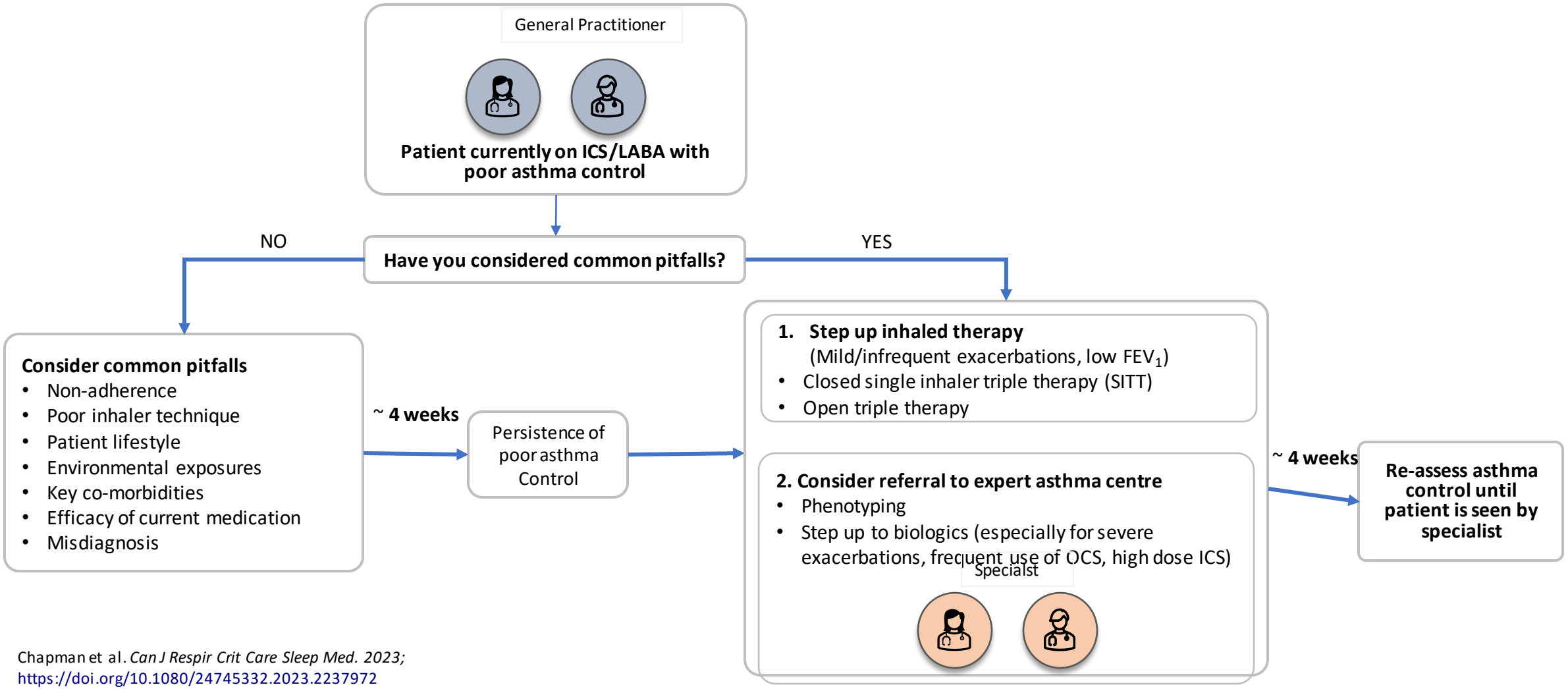
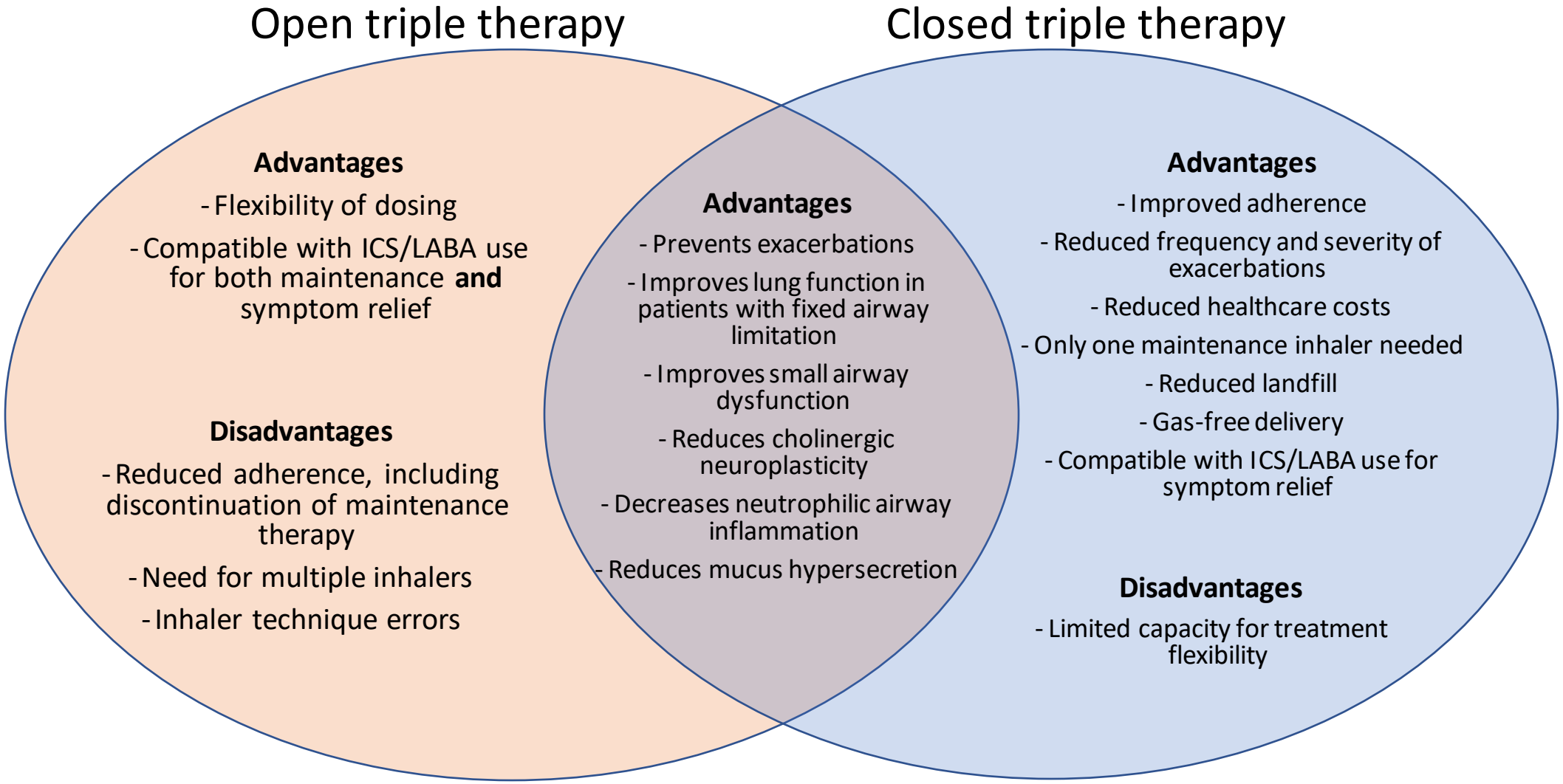
Schematic to assist decisions to initiate triple inhaled therapy



Chapman et al. *Can J Respir Crit Care Sleep Med. 2023;*
https://doi.org/10.1080/24745332.2023.2237972

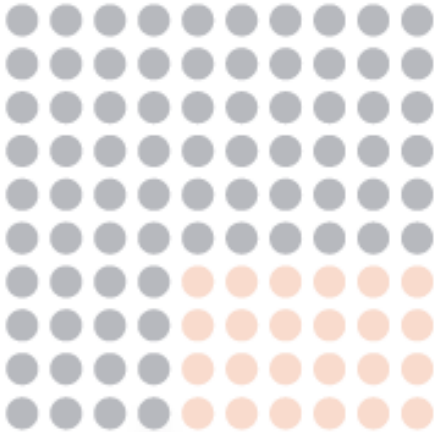
Potential advantages and disadvantages of open and closed triple inhaled therapies



Chapman et al. *Can J Respir Crit Care Sleep Med. 2023;*
https://doi.org/10.1080/24745332.2023.2237972

How common is severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



24%

GINA Step 4-5 treatment

17%

difficult-to-treat asthma

= GINA Step 4-5 treatment
+ poor symptom control

3.7%

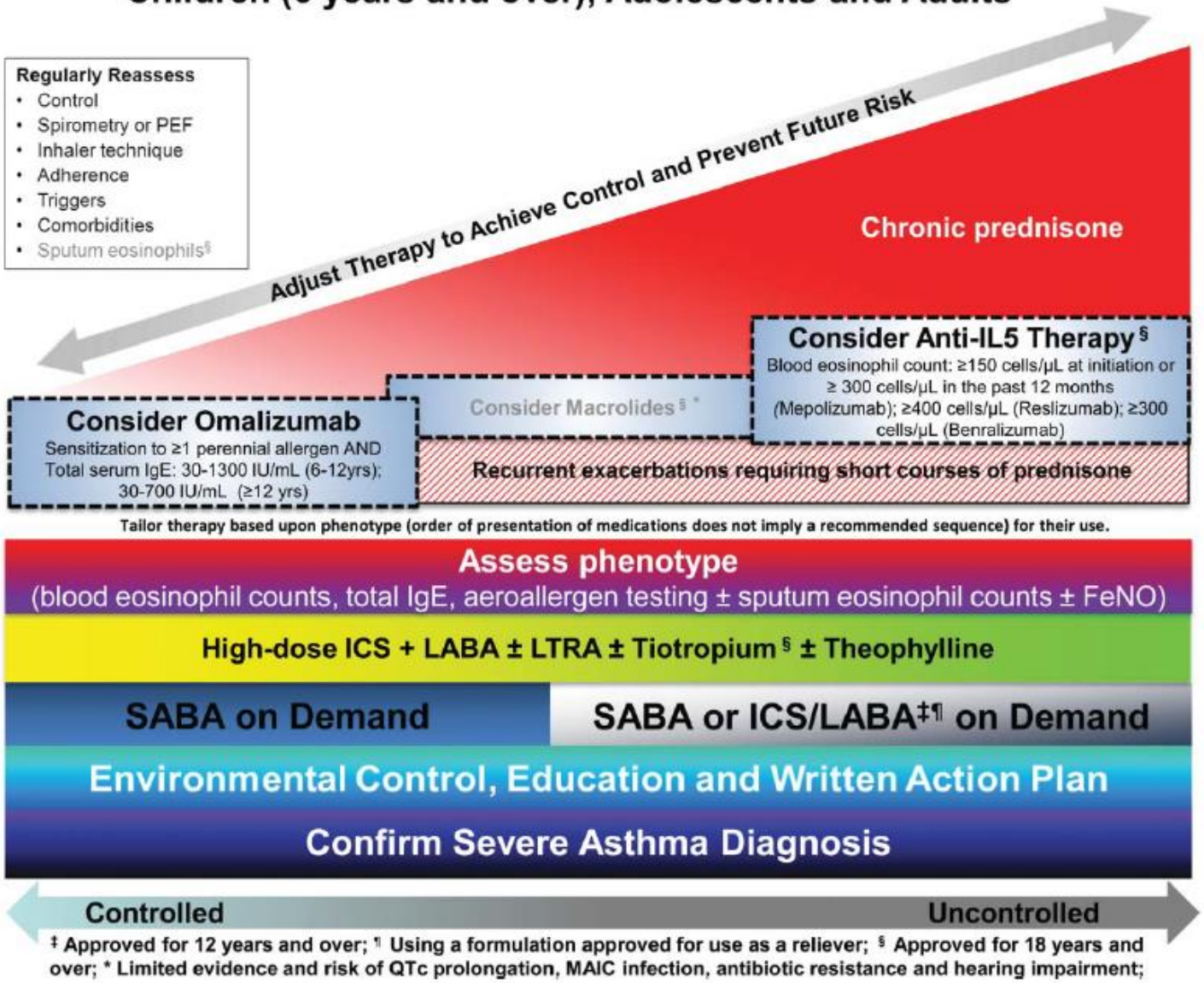
severe asthma

= GINA Step 4-5 treatment
+ poor symptom control
+ good adherence and inhaler technique

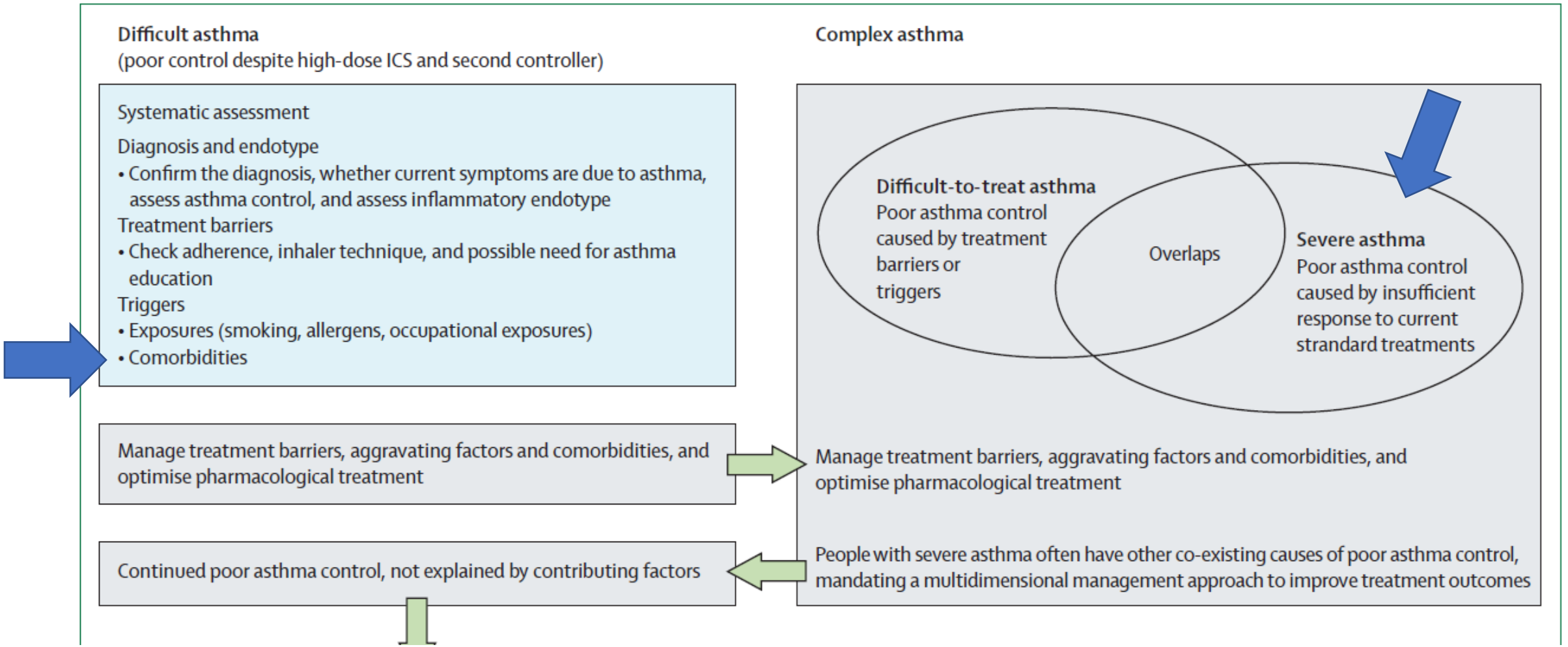
These data are from a Dutch population survey of people ≥18 years with asthma[2]

Hekking et al, JACI 2015

© Global Initiative for Asthma, www.ginasthma.org



Fitzgerald et al. CANADIAN JOURNAL OF RESPIRATORY, CRITICAL CARE, AND SLEEP MEDICINE 2017, VOL. 1, NO. 4, 199–221



Lancet 2023; 401: 858–73

Prevalence of Comorbidities in Adults with Severe Asthma: Results from the International Severe Asthma Registry (ISAR)G. Scelo et al. ATS 2022

Table. Prevalence of 33 comorbid conditions in adults with severe asthma enrolled in the

Potentially oral corticosteroid (OCS)-related			
Obesity	44%	4 646	10 715
Hypertension	22%	2 176	9 729
Sleep apnea	21%	2 078	9 698
Dyslipidemia	18%	1 109	6 280
Diabetes	11%	1 048	9 801
Coronary heart disease	9.5%	777	8 160
Pneumonia	9.0%	815	9 091
Osteoporosis	7.1%	708	9 922
Pulmonary embolism/venous thromboembolism	2.8%	246	8 867
Cataract	2.2%	201	8 981
Peptic ulcer	2.2%	183	8 330
Renal failure	1.7%	157	9 031
Glaucoma	1.4%	129	8 975
Adrenal insufficiency	1.4%	82	5 765
Cerebrovascular accident	0.71%	58	8 152
Aspirin sensitivity	0.96%	62	6 464
Eosinophilic esophagitis	0.65%	33	5 064

level.

Comorbidities- ISAR PRISM

Figure 1. Co-occurrence of comorbidities across three categories in patients with complete data (N=7,561 patients; 7 countries).

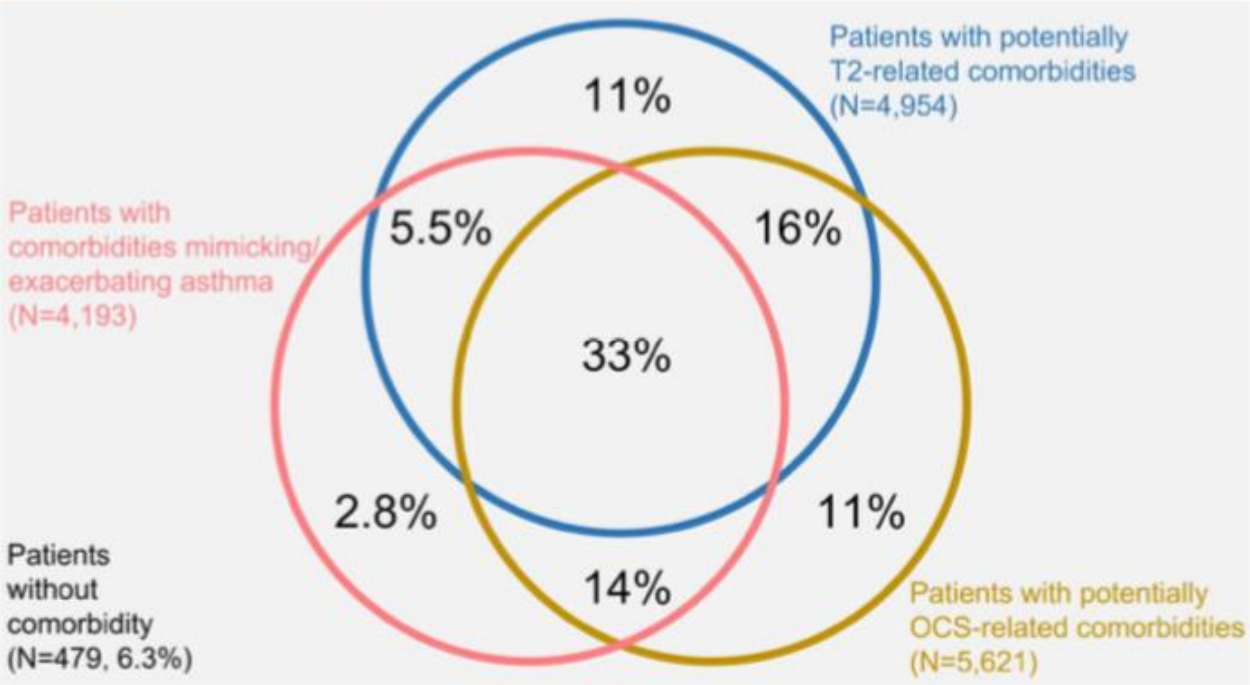
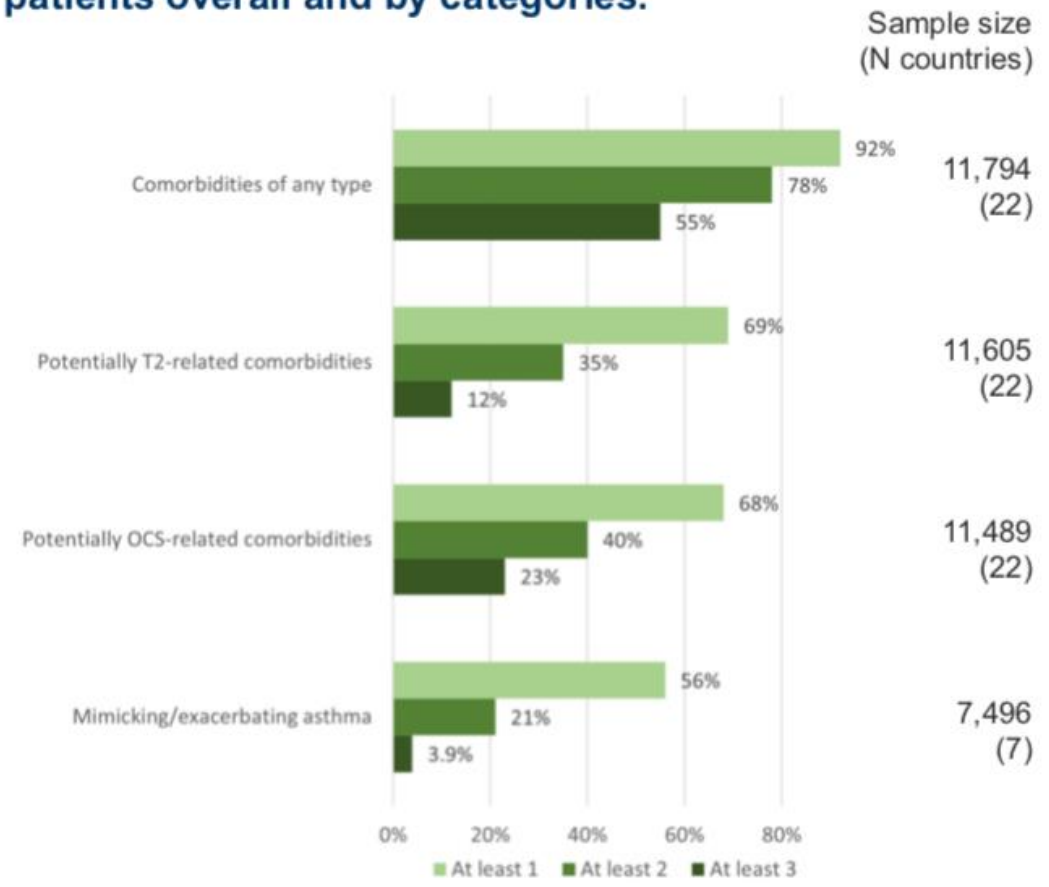


Figure 2. For those with data on at least 3 comorbidities of any type, number of comorbidities reported in ISAR patients overall and by categories.



ATS 2022

Optimisation of severe asthma control

- Reduction of exacerbations
- Limit OCS exposure
- Optimize lung function

} Reduction in mortality

- **Comorbidities** are highly prevalent and need to be treated
  - T2 related
  - OCS related
  - Mimicking/exacerbating asthma

CENTRE FOR LUNG HEALTH

Risk factors of exacerbations and mortality in adult asthma

Objective 4

Uncontrolled Asthma Poses a Cumulative Burden on Patients

Low FEV_1 is a strong independent predictor of risk of exacerbations, regardless of symptom frequency[1,2]

Uncontrolled persistent asthma results in exacerbations[1]

Recent exacerbations increase risk of future exacerbations by nearly 6-fold[3]

- Exacerbation prone[4]
- Leading to hospitalizations and/or ED visits[5,6]
- Necessitating frequent OCS use[4–6]

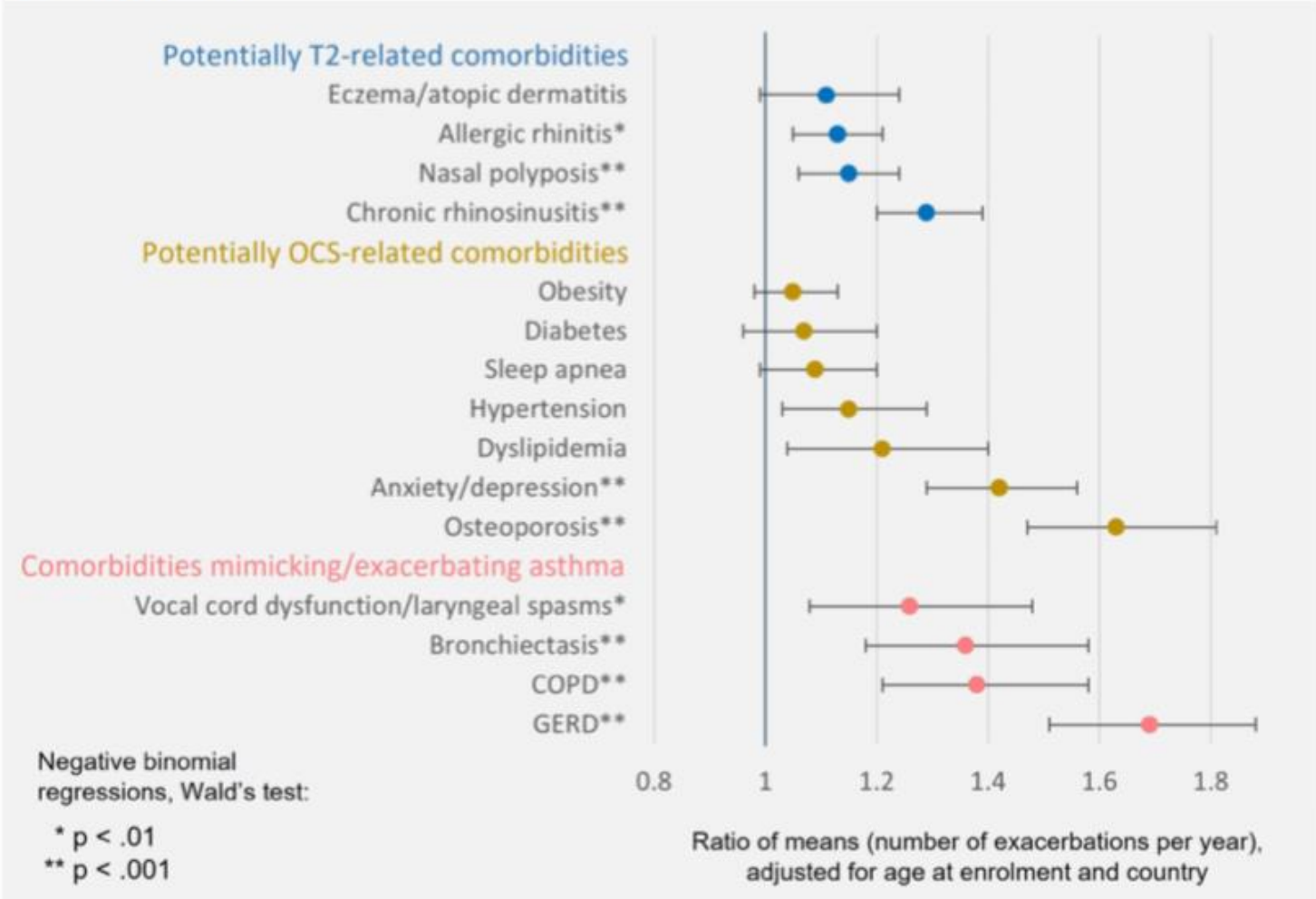
Frequent exacerbations lead to long-term complications

- Medication AEs (eg OCS)[1]
- Greater annual decline in lung function[7]
- Significant decreases in HRQoL[8]
- Mortality[9]

AE, adverse event; ED, emergency department; FEV_1, forced expiratory volume in 1 second; HRQoL, health-related quality of life

1. GINA. Pocket guide for asthma management and prevention. 2019. Available at: https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf. Accessed June 2019; 2. Khan A, et al. *Ann Allergy Asthma Immunol*. 2018;121:S44. Abstract no. P220; 3. Miller MW, et al. *Respir Med*. 2007;101:481–489; 4. Dougherty RH, et al. *Clin Exp Allergy*. 2009;39:193–202; 5. Haselkorn T, et al. *J Allergy Clin Immunol*. 2009;124:895–902; 6. Pola-Bibian B, et al. *J Investig Allergol Clin Immunol*. 2017;27:238–245; 7. Bai TR, et al. *Eur Respir J*. 2007;30:452–456; 8. Lee LK, et al. *J Asthma*. 2018;55:208–219; 9. Sears M. *J Allergy Clin Immunol*. 2008;122:662–668

Figure 3. Association between comorbidities and exacerbation rates at enrolment.



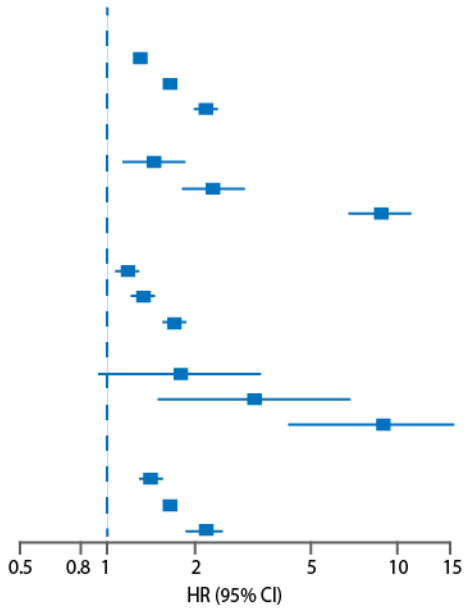
Note: Pre-biologic exacerbation rates for patients undergoing biologic therapy.

ISAR PRISM

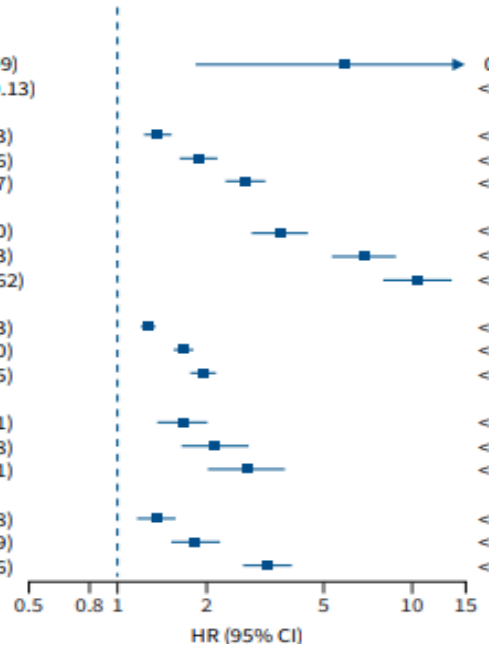
Oral Corticosteroid (OCS) Use Associated with Increased Risk of Comorbidities among Adults with Asthma

- Danish registers during 1999–2018 and followed prospectively in an open-cohort design
- Even at low cumulative exposure over the course of 20 years, OCS use was associated with increased risk of comorbidities, mortality and unscheduled hospital visits

Outcome	n	HR (95% CI)	p-value
Any OCS-related comorbidity			
Low use	3391	1.26 (1.21-1.31)	<0.001
Medium use	1283	1.59 (1.50-1.69)	<0.001
High use	742	2.07 (1.92-2.23)	<0.001
Osteoporosis			
Low use	173	1.41 (1.18-1.69)	<0.001
Medium use	116	2.22 (1.80-2.74)	<0.001
High use	235	7.79 (6.56-9.26)	<0.001
Fractures			
Low use	1762	1.16 (1.10-1.22)	<0.001
Medium use	673	1.29 (1.19-1.40)	<0.001
High use	430	1.62 (1.47-1.79)	<0.001
Osteonecrosis			
Low use	15	1.72 (0.93-3.17)	0.083
Medium use	9	2.99 (1.43-6.27)	0.004
High use	12	7.86 (3.99-15.50)	<0.001
Diabetes mellitus type 2			
Low use	849	1.37 (1.27-1.49)	<0.001
Medium use	375	1.60 (1.43-1.79)	<0.001
High use	259	2.08 (1.82-2.37)	<0.001



Outcome	n	HR (95% CI)	p-value
Adrenal insufficiency			
Low use	<5	NA	NA
Medium use	5	5.85 (1.80–18.99)	0.003
High use	26	55.91 (24.02–130.13)	<0.001
Ischaemic heart disease			
Low use	443	1.37 (1.23–1.53)	<0.001
Medium use	234	1.87 (1.62–2.16)	<0.001
High use	192	2.71 (2.32–3.17)	<0.001
Heart failure			
Low use	160	3.53 (2.84–4.40)	<0.001
Medium use	109	6.84 (5.31–8.83)	<0.001
High use	97	10.40 (7.95–13.62)	<0.001
Depression/anxiety			
Low use	2133	1.27 (1.21–1.33)	<0.001
Medium use	805	1.67 (1.55–1.80)	<0.001
High use	421	1.94 (1.76–2.15)	<0.001
Peptic ulcer disease			
Low use	153	1.65 (1.36–2.01)	<0.001
Medium use	71	2.14 (1.64–2.78)	<0.001
High use	49	2.72 (2.00–3.71)	<0.001
Cataract			
Low use	227	1.36 (1.16–1.58)	<0.001
Medium use	135	1.82 (1.50–2.19)	<0.001
High use	147	3.20 (2.66–3.86)	<0.001

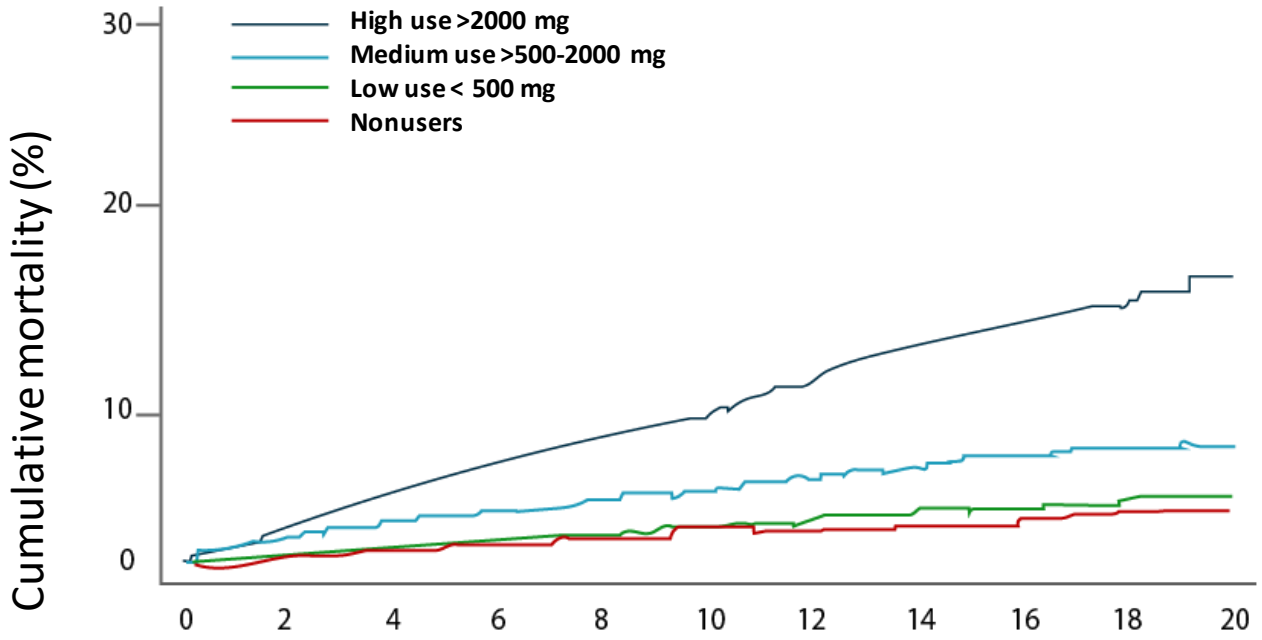


Use stratified: low use ⩽500 mg, medium use >500–2000 mg and high use >2000 mg)

Reducing the need for OCS use is pivotal in asthma management.

Skov IR, et al. Eur Respir J 2022; 60: 2103054

Twenty-Year Cumulative OCS Use Associated with increased Risk of Mortality among Adults with Asthma



Nationwide Danish asthma population

- OCS users (n=30,352)
- OCS nonusers (n=121,408)

OCS users have 2.2X higher mortality than nonusers.
High users=5.58X

At risk (n):

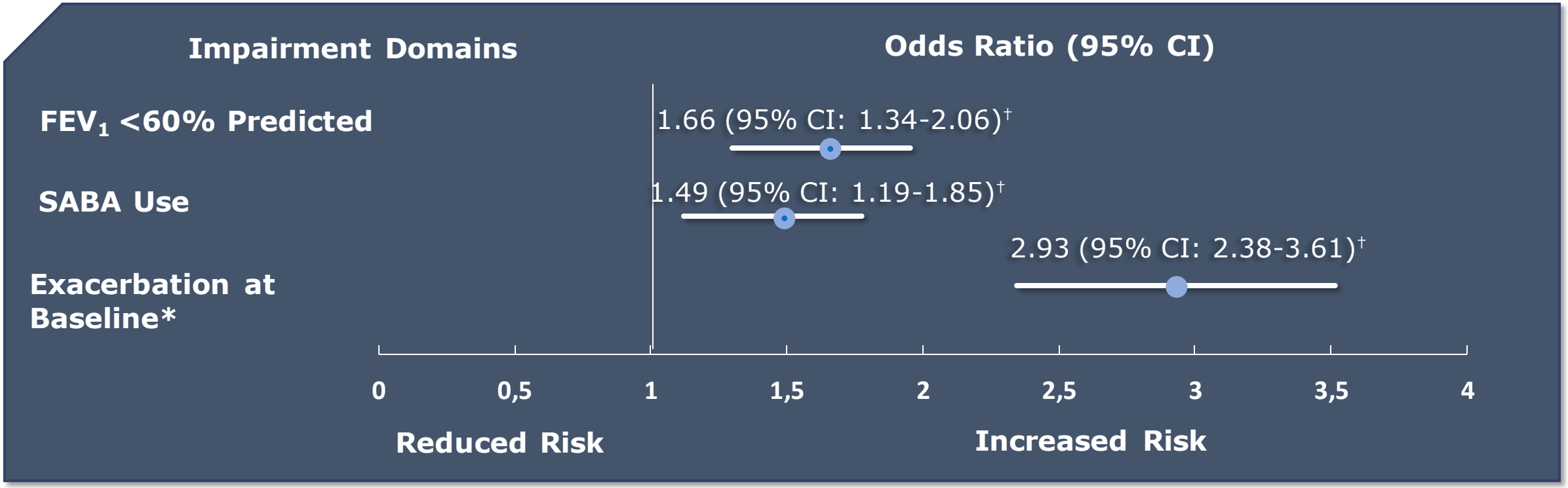
Nonusers	121408	121408	55442	38565	26835	18587	12623	7974	4565	1873
Low use < 500 mg	2885	19550	14953	11693	8905	6569	4712	3116	1836	739
Medium use >500-2000 mg	487	4549	5000	4748	4189	3447	2719	1928	1195	549
High use >2000 mg	980	1745	2071	2196	2123	1941	1659	1303	881	437

Causes of mortality: respiratory specific (1/3), mostly dying from comorbid conditions/treatment side effects (CVD (20%), endo, neuro, mental disorders)

Skov IR, et al. Eur Respir J 2022; 60: 2103054; OCS: oral corticosteroids

Poor Lung Function Is a Significant Predictor of Future Severe Asthma Exacerbations

Predictor of Severe Exacerbation Risk at Month 12 in Patients Aged ≥12 Years With Severe or Difficult-to-Treat Asthma From TENOR Study (N=2,094)

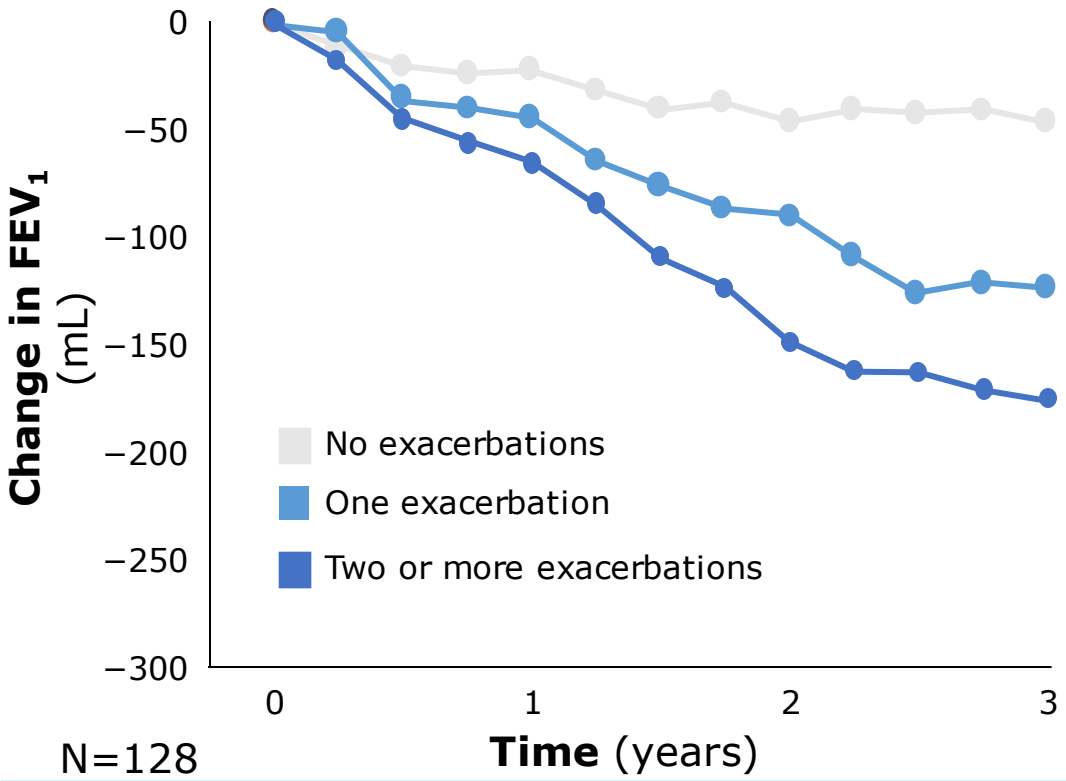


CI=confidence interval; FEV_1=forced expiratory volume in 1 second; SABA=short-acting beta-agonist.
*Defined as a hospitalization, emergency department visit, or a course of corticosteroids at 12 months. †P<0.001
Data from analysis included patients from TENOR study with baseline and month 12 study visits and those with complete baseline data to classify asthma control based on the impairment domain of the 2007 NHLBI guidelines.

References located in the speaker notes

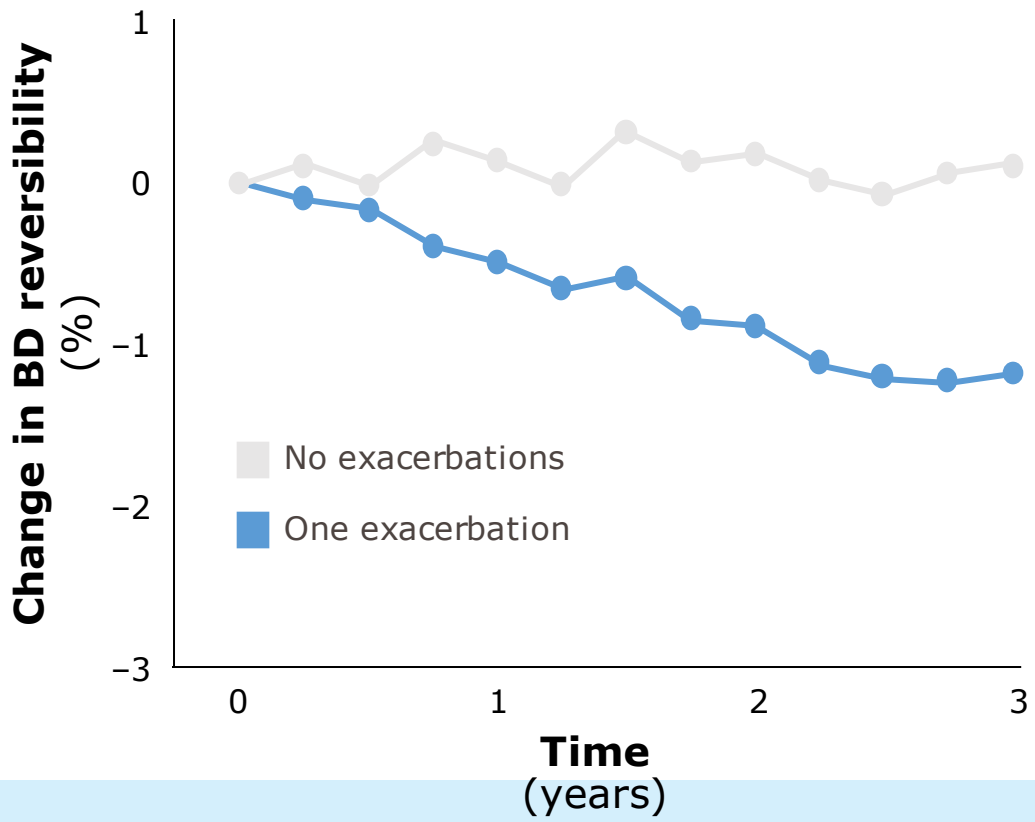
Asthma Exacerbations Correlate With Progression of Irreversible Airflow Limitation

Change in Lung Function Over Time in Patients With Controlled and Uncontrolled Asthma



N=128

BD Reversibility Over Time in Patients With Controlled and Uncontrolled Asthma

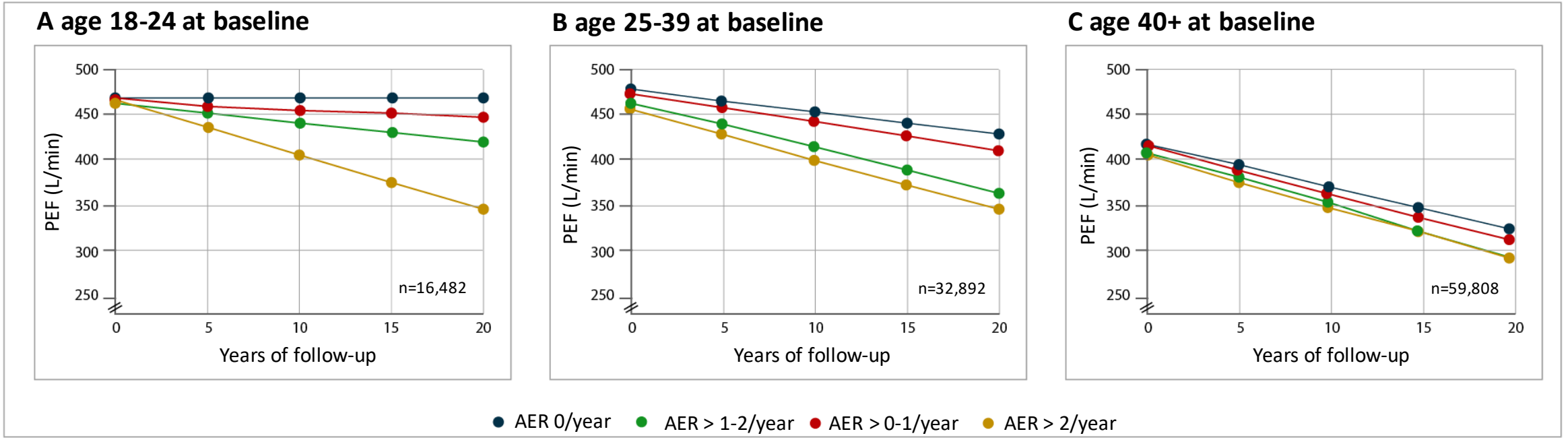


BD=bronchodilator; FEV1=forced expiratory volume in 1 second.

Reprinted from The Journal of Allergy and Clinical Immunology: In Practice, volume 3/issue 5, Matsunaga K, et al. Progression of Irreversible Airflow Limitation in Asthma: Correlation with Severe Exacerbations, pp 759-764.e1. Copyright © 2015, with permission from Elsevier.

Exacerbations defined as events outside the patient's usual range of day-to-day asthma variation, requiring a change in controller therapy.

Asthma Exacerbations Associated with Faster Lung Function Decline



Adjusted 20-year Peak Expiratory Flow (PEF) Trajectories (L/Year) by Annual Exacerbation Rate (AER) Stratified by Patient Age at Baseline

- This 20-year-long, UK-wide observational study of patients with active asthma managed in primary care demonstrates that asthma exacerbations are associated with faster lung function decline.
- Achieving better control decreases the likelihood of lung function decline in any age.

Early identification and intervention of patients with asthma is of value.

Soremekun S, et al. Thorax 2022;0:1–10.

Risk factors for asthma exacerbations

a. Risk factors for exacerbations

Uncontrolled asthma symptoms	Having uncontrolled asthma symptoms is an important risk factor for exacerbations.[98]	
Factors that increase the risk of exacerbations *even if the patient has few asthma symptoms*†	*Medications*	High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)[74,75,99,100]
		Inadequate ICS: not prescribed ICS, poor adherence,[101] or incorrect inhaler technique[102]
	Other medical conditions	Obesity,[103,104] chronic rhinosinusitis,[104] GERD,[104] confirmed food allergy,[105] pregnancy[106]
	Exposures	Smoking,[107] e-cigarettes,[108] allergen exposure if sensitized,[107] air pollution[109-112]
	Psychosocial	Major psychological or socioeconomic problems[113,114]
	Lung function	Low FEV1 (especially <60% predicted),[107,115] high bronchodilator responsiveness[104,116,117]
	Type 2 inflammatory markers	Higher blood eosinophils,[104,118,119] elevated FeNO (in adults with allergic asthma taking ICS)[120]
	Exacerbation history	Ever intubated or in intensive care unit for asthma,[121] ≥1 severe exacerbation in last 12 months[122,123]

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GINA 2023

Risk factors for asthma death

Box 4-1. Factors that increase the risk of asthma-related death

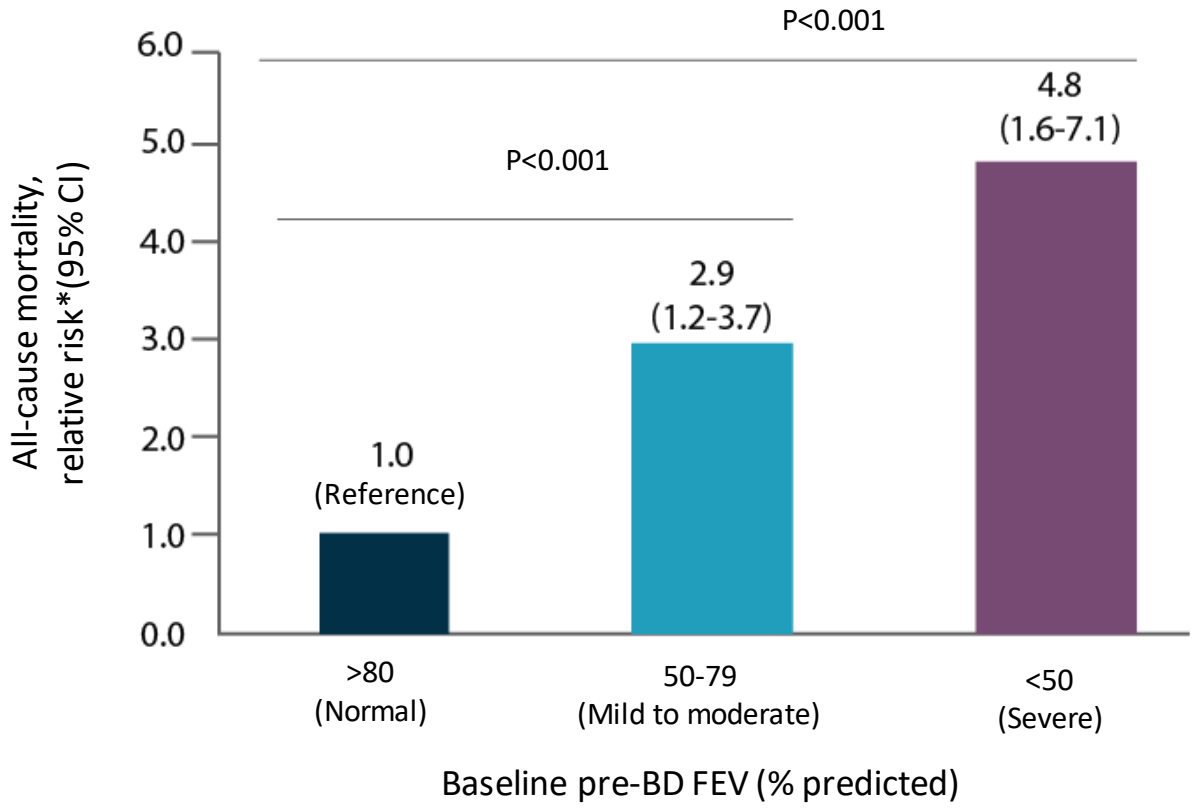
- A history of near-fatal asthma requiring intubation and mechanical ventilation[636]
- Hospitalization[636,637] or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)[636]
- Not currently using inhaled corticosteroids[101,636]
- Over-use of short-acting beta$_2$-agonists (SABAs), especially use of more than one canister of salbutamol (or equivalent) monthly[75,121,638]
- Poor adherence with ICS-containing medications and/or poor adherence with (or lack of) a written asthma action plan[113]
- A history of psychiatric disease or psychosocial problems[113]
- Food allergy in a patient with asthma[499,639]
- Several comorbidities including pneumonia, diabetes and arrhythmias were independently associated with an increased risk of death after hospitalization for an asthma exacerbation.[637]

See list of abbreviations (p.10).

GINA 2023

Lung Function Decline is Associated with an Increased Mortality Risk

25-year follow up in adult patients with asthma (n=1075)



This 25-year prospective study of adult patients with well-characterized asthma showed a significant increase in mortality mainly due to obstructive lung disease in comparison to matched controls.

Variable	RR	95% CI	*P* Value
Age			< .001
< 39 y	1.0	…	
40-69 y	3.2	1.1-5.2	
> 70 y	4.8	2.2-6.7	
FEV_1 % predicted			< .001
> 80	1.0	…	
50-79	2.9	1.2-3.7	
< 50	4.8	1.6-7.1	
Reversibility[a]			< .01
15%-24%	1.0	…	
25%-49%	3.2	1.4-5.1	
> 50%	4.8	1.6-7.1	
Acute hospital contacts			.002
No	1.0	…	
Yes	2.9	…	
B-eosinophils		1.5-3.7	< .0001
< .45 mia/L	1.0	…	
> .45 mia/L	4.3	2.5-6.6	

RR = relative risk.
[a]Defined as (FEV_1after − FEV_1before) × 100)/FEV_1before.

The importance of timely identification and appropriate treatment of patients with asthma is of value.

Ali Z, et al. Chest 2013;143:1649-1655; pre-BD FEV: pre-bronchodilator forced expiratory volume

Therapy for severe asthma -biologics

Objective 3

Beyond inhalers…

Possible specialised treatments for uncontrolled severe asthma						
	Anti-IgE	Anti-IL-5/5R	Anti-IL-4/13	Anti-TSLP	Azithromycin	Bronchial thermoplasty
Eligibility	• Sensitised to perennial allergens, allergen driven disease and • Exacerbations or • mOCS use	• Blood eosinophilia (>0·15 or 0·3) and •Exacerbations or • mOCS use	B-eos 0·15–1·5, or FeNO >25 ppb and •Exacerbations or • mOCS use	• No phenotype requirements • Exacerbations or • mOCS use	• Exacerbations	• Exacerbations • mOCS at most 10 mg of prednisolone per day • Adults only • FEV_1 >60%
Possible predictors of good response	• B-eos >0·26 • FeNO >20 ppb • Allergen driven asthma	• Higher blood eosinophils • More exacerbations • CRSwNP	• Higher blood eosinophils • Higher FeNO • CRSwNP	• Higher blood eosinophils • Higher FeNO	• Colonisation with *Haemophilus influenzae*	NA
Effective also in	• Chronic spontaneous urticaria • CRSwNP	• CRSwNP • EGPA • HES	• CRSwNP • Atopic dermatitis	NA	• Bronchiectasis	NA

Figure 5: Assessment and treatment of severe asthma

***Lancet* 2023; 401: 858–73**

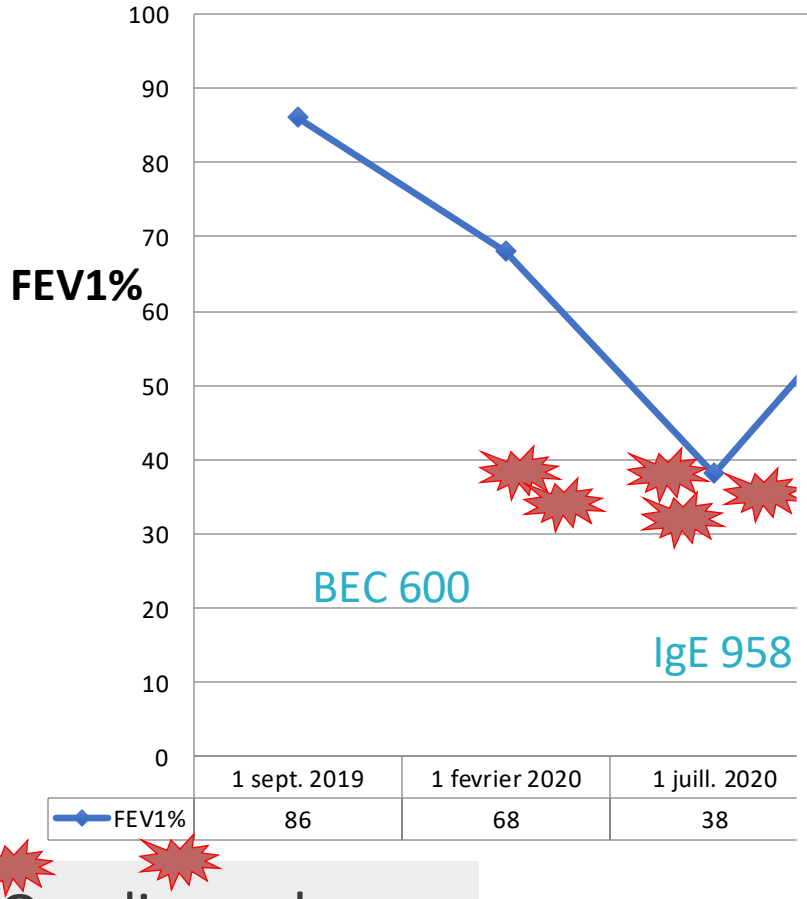
Mr. D 66 y-o, mechanic

- Severe asthma
  - Adult onset at age 58 y-o
  - Possible initial trigger: ASA/NSAID
  - No admission, no ICU
- CRS without NP
- Mild atopic dermatitis
- GERD
- OSA on CPAP
- Stroke in 2019
- Ex smoker, 35 p-y, discontinue at age 40
- Allergy: ASA/NSAID causing urticaria

BEC 600
IgE 958
FEV1 38-87%
ANCA neg
Asp ppt neg
Sinus CT: chronic pansinusitis
Chest CT: small airway disease

Mr. D- Adult onset eosinophilic/T2

Prednisone



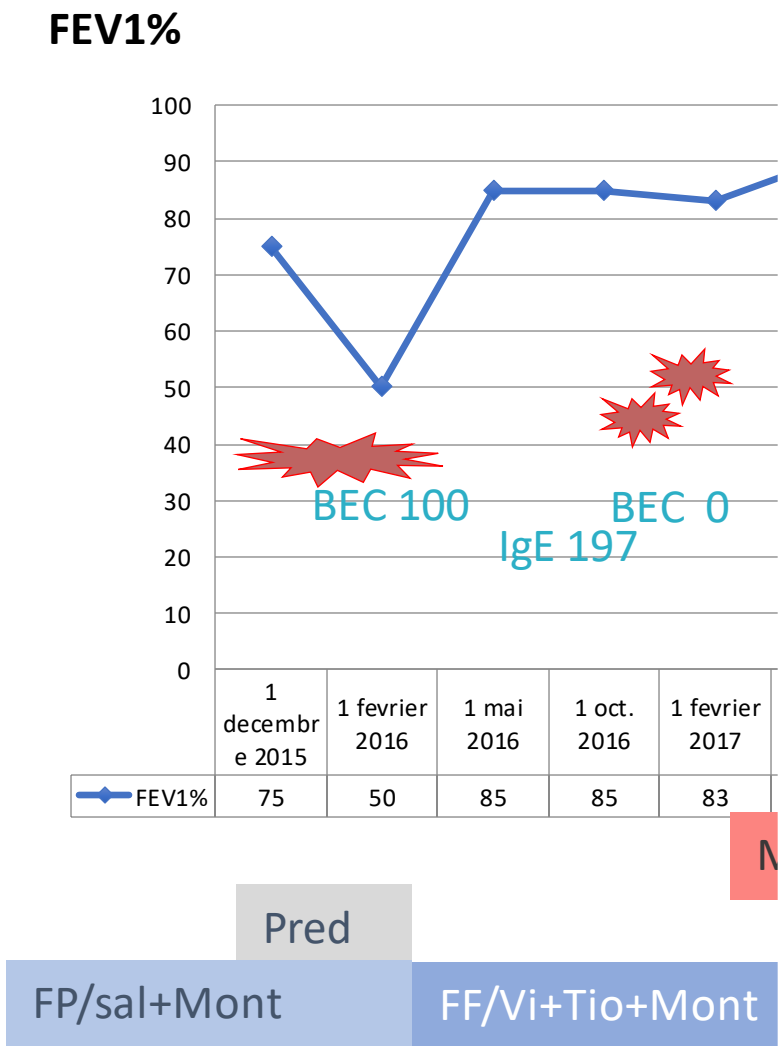
Omalizumab

Budesonide/Formoterol + tiotropi

Montelukast, pantoprazole, SR+budeso

Prednisone

Mrs. H – allergic asthma

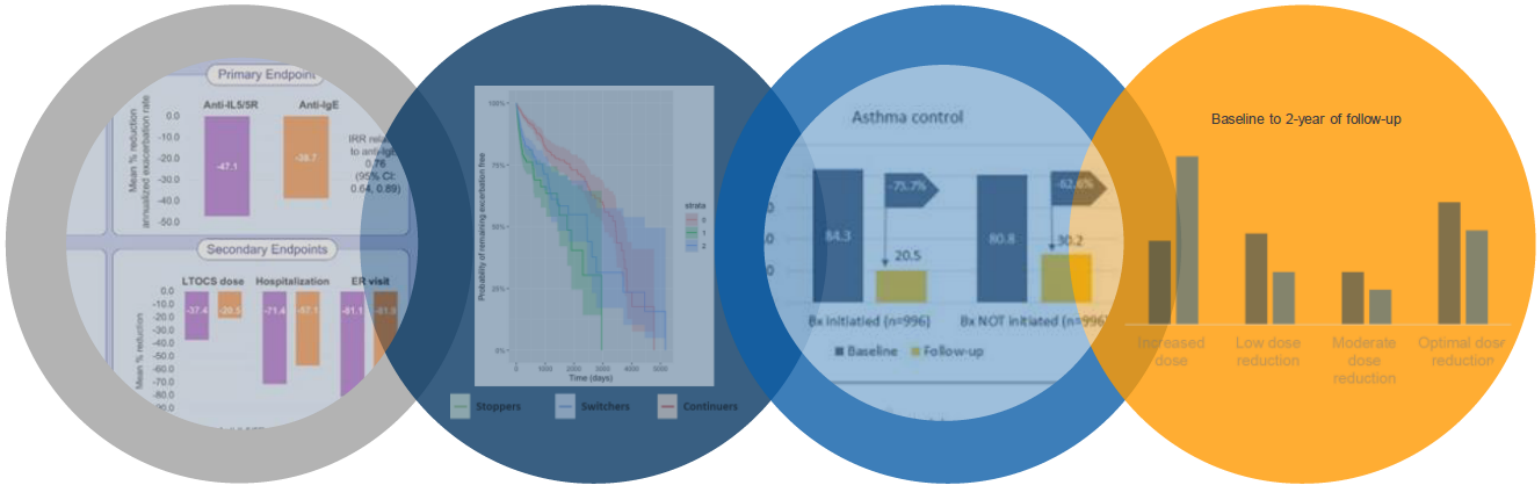


ACQ 0
FeNO 38

Mepolizumab

- Good asthma and CRS control
- Discontinue Sep 2017 for lightheadness
- Rapid recurrence of sinus symptoms

Research that impacts clinical practice
2. How biologics can change the trajectory



01

A need to determine the 'right' biologic when eligible for both

Anti-IL5/5R was superior to anit-IgE in reducing asthma exacerbations and LTOCS use[1]

02

Switchers (compared to continuers) had increased exacerbation rates, a higher LTOCS dose and higher chance of uncontrolled asthma

Receiving and continuing the right biologic leads to better outcomes[2]

03

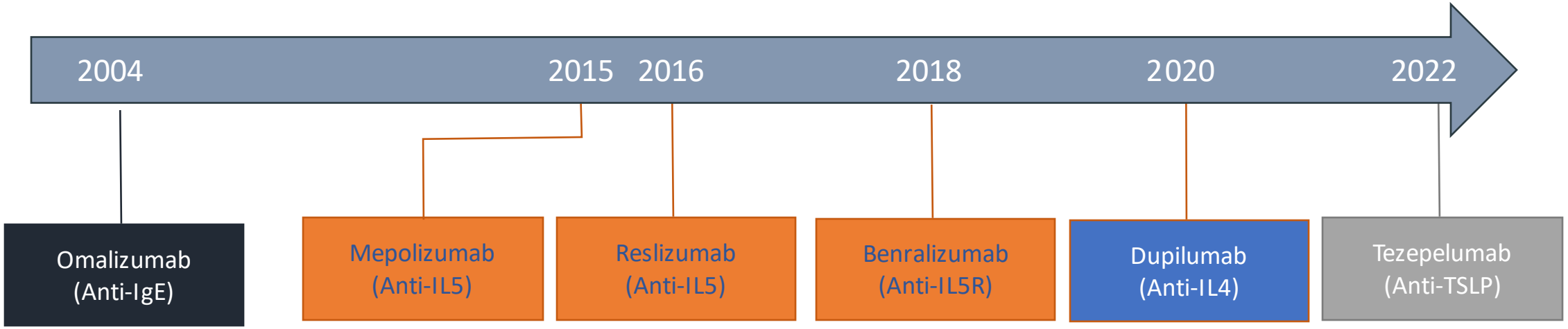
Biologics reduce exacerbations, improve asthma control and reduce OCS use in patients with high steroid exposure[3]

04

SOLAR:
Continues to examine biologic impact on OCS exposure
Asks: will this lower likelihood of OCS reduce related adverse outcomes?

1.FIRE, Comparative effectiveness of Anti- IL5 and Anti- IgE biologic classes in patients with severe asthma eligible for both Pfeffer, P. et al, Allergy. 78. 10.1111/all.15711.
2.CLEAR, clinical outcomes and emergency health care utilization in patients with severe asthma who continued, switched or stopped biologic therapy, Ali N et al. Allergy and Airway 2022;162(4) Suppl A28-32; doi: 10.1016/j.chest.2022.08.020
3. GLITTER II, Impact of initiating biologics in patients with severe asthma on long term or frequent rescue steroids, Chen W et al. J Allergy Clin Immunol Pract 2023, available online June 8 2023
LTOCS: Long Term Oral Corticosteroids, OCS: Oral Corticosteroids, Anti-IL5/5R: Anti- Interleukin 5/5R

Timeline of approvals for biologics for severe asthma in Canada

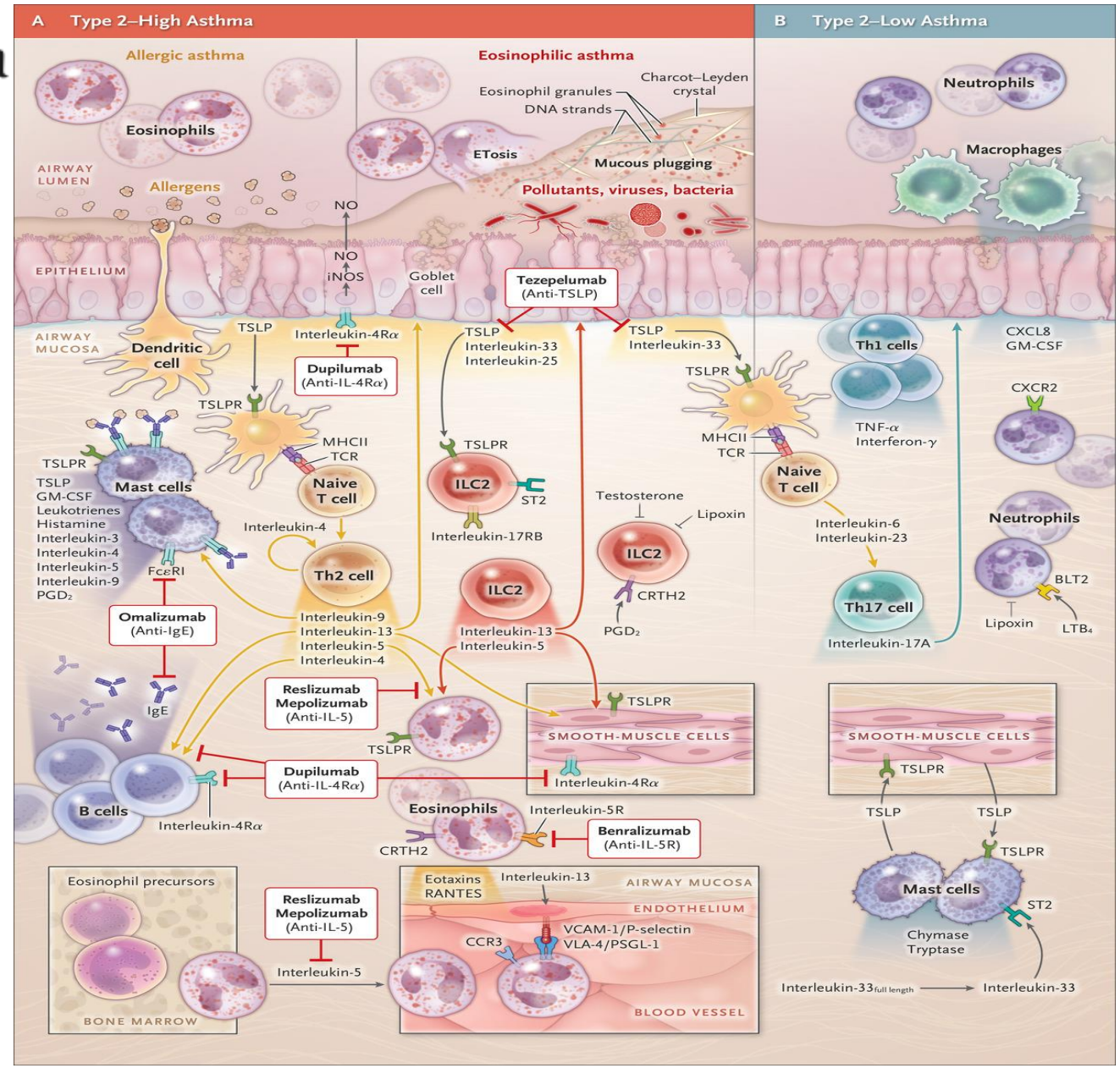


All categories accessible under Pharmacare

REVIEW ARTICLE

Biologic Therapies for Severe Asthma

Guy G. Brusselle, M.D., Ph.D., and Gerard H. Koppelman, M.D., Ph.D.



January 13, 2022 N Engl J Med 2022; 386:157-171
DOI: 10.1056/NEJMra2032506

Table 1. Biologic Agents Approved by the Food and Drug Administration for the Treatment of Severe Asthma.*

Biologic Agent (Therapeutic Target and Mechanism of Action)	Route of Administration and Dose†	Forms	Indication	Patient Yr of Age†	Efficacy	Safety Concerns
Benralizumab (interleukin-5Rα; antibody binds to interleukin-5Rα on eosinophils and basophils, depleting them through antibody-dependent, cell-mediated cytotoxicity)	SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma	≥12	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs
Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, inhibiting interleukin-4 and interleukin-13 signaling in hematopoietic cells [e.g., B cells, CD4+ helper T cells, and eosinophils], epithelial cells, and airway smooth-muscle cells)	Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-to-severe atopic dermatitis, initial dose of 600 mg, followed by 300 mg every 2 wk Children, ages 6–11 yr: SC; dose depends on body weight‡	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis	≥6	Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis
Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5)	Adults and adolescents: SC; 100 mg every 4 wk Children, ages 6–11 yr: SC; 40 mg every 4 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome	≥6	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare)
Omalizumab (IgE; antibody binds to Fc part of free IgE, inhibiting binding of IgE to FcεRI on mast cells and basophils and FcεRII on dendritic cells and eosinophils)	SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE	Prefilled syringe	Severe allergic asthma; other indication: chronic idiopathic urticaria	≥6	Reduced exacerbations, reduced symptoms, small effect on FEV_1; improved quality of life	Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients)
Reslizumab (interleukin-5; antibody binds to circulating interleukin-5)	IV; 3 mg/kg every 4 wk	IV infusion	Severe eosinophilic asthma	≥18	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; improved quality of life	Helminthic infections, abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.3% of patients)
Tezepelumab (TSLP)	SC; 210 mg every 4 wk	Prefilled syringe	Severe asthma	≥12	Reduced exacerbations, reduced symptoms, improved lung function; improved quality of life	Pharyngitis, arthralgia, back pain

* CRS denotes chronic rhinosinusitis, EGPA eosinophilic granulomatosis with polyangiitis, EMA European Medicines Agency, FcεRI high-affinity receptor for the Fc region of IgE, FcεRII low-affinity receptor for the Fc region of IgE, FDA Food and Drug Administration, FEV_1 forced expiratory volume in 1 second, interleukin-4Rα interleukin-4 receptor α, interleukin-5Rα interleukin-5 receptor α, IV intravenous, OGs oral glucocorticoids, SC subcutaneous, and TSLP thymic stromal lymphopoietin.
† Information on dose and age is for patients with severe asthma as the main indication.
‡ For pediatric patients, ages 6 to 11 yr, with a body weight of 15 kg to less than 30 kg, the recommended dose of dupilumab is 100 mg every 2 wk or 300 mg every 4 wk; for children with a body weight of 30 kg or more, the dose is 200 mg every 2 wk.

January 13, 2022 N Engl J Med 2022; 386:157-171
DOI: 10.1056/NEJMra2032506

ADA

25-60%

12%

9%

50-70%

6%

50%

CRSwNP

<0.1%

~25%

5%

50-60%

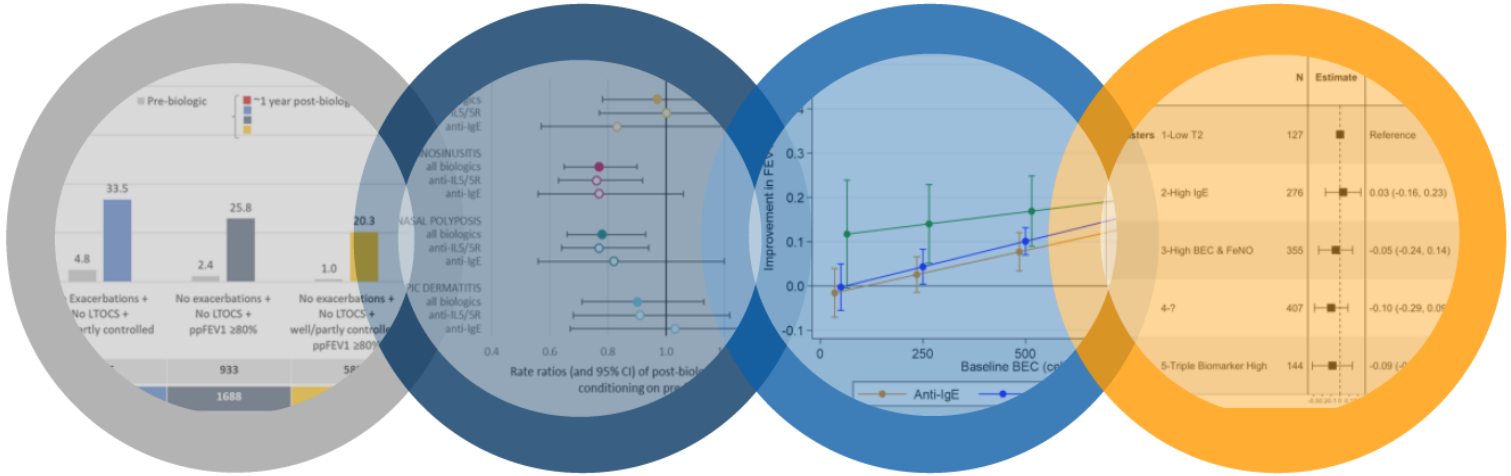
4.9%

40-71%

Biologics	Indications in Canada	Formulations available
Omalizumab (Xolair) $8,137-$48,824/year depending on dose	**Allergic asthma either moderate or severe** – has one or more of the following: Asthma symptoms every day Daily need for a rescue inhaler 2 or more asthma attacks a week 1 or more nights a week waking up with asthma symptoms Below normal readings (less than 80%) peak flows **IgE level** must be between **72-1680mcg/L** **Positive skin prick test** or **in vitro reactivity allergen** test results	Subcu: vial, pre-filled
Mepolizumab (Nucala) $25,269/year	**severe eosinophilic asthma -** inadequately controlled with high-dose corticosteroids and an additional asthma controller *(e.g. long acting beta$_2$-adrenergic agonist (LABA)* **blood eosinophils count ≥ 0.15GI/L** at initiation of treatment and on **maintenance OCS** for > 6 months **OR blood eosinophils count ≥ 0.3GI/L** in the previous 12 months **+ ≥ 2 exacerbations in the previous 12 months**	Subcu: vial, pre-filled, auto-injector
Benralizumab (Fasenra) $31,015 for the first year and then $25,200 for subsequent years	**severe eosinophilic asthma** and is 18 years or older on maintenance add on treatment **blood eosinophil** count **≥ 0.3GI/L** *and* experienced **≥ 2 clinically significant exacerbations in the past 12 months** OR **blood eosinophil count ≥ 0.15GI/L** and treated chronically with **OCS**	Subcu: vial or pre-filled
Reslizumab (Cinqair) $8,349-$33,394/year	**severe eosinophilic asthma** and is 18 years or older **inadequately controlled** with medium to high dose of inhaled corticosteroids and an additional asthma controller(s) (e.g. LABA) **blood eosinophil** level count of **≥ 0.4 GI/L** at initiation of treatment	IV
Dupilumab (Dupixent) $25,000/year	**severe eosinophilic asthma** or OCS dependent asthma **inadequately controlled** with medium to high dose of inhaled corticosteroids and an additional asthma controller **AND for Fast start program** Blood EOS ≥300 cell/uL, and ≥2 exacerbations, **OR** OCS dependence and blood EOS ≥150 cell/uL	Subcu: Pre-filled syringes SA : 400 mg initial dosem then 200 mg q2w SA+OCS, AD or CRSwNP: 600 mg inititial dose then 300 mg q2w
Tezepelumab (Tezspire) $26 000/year	**Severe asthma and is 12 years or older** Inadequately controlled with high dose ICS (minimum 500 mcg fluticasone proprionate or equivalent) and an additional asthma controller(s) (e.g. LABA) Has experienced two or more clinically significant asthma exacerbations in the past 12 months (Systemic corticosteroids for at least three days, emergency room visit, or hospitalization)	Subcu 210 mg Q 4 weeks

Research that impacts clinical practice

3. What is possible in response and remission?



01

Data suggests earlier intervention predicts greater likelihood of remission[1]

02

T2 comorbidities may predict biologic effectiveness

Important to proactively assess for T2 comorbidities[2]

03

Baseline BEC and FeNO associated with greater improvement in FEV1[3]

04

Less improvement in exacerbations with biologic therapy in Low T2 cluster[4]

1. FULL BEAM: Defining and characterizing responders and non-responders to biologic treatment in severe asthma
2 .PRISM II: ImPact of comoRbidity In Severe asthMa patients
3. IGNITE: Association between post-treatment outcomes and pre-biologic BEC
4. EMBER Objective 3: Investigate non T2 and T2 asthma group responses to intervention with biologics

T2: Type 2, FEV1: Forced Expiratory Volume 1 second, BEC: Blood eosinophil count

LUMINANT: assessing response in severe asthma

Biologic Responders And Super-responders in the International Severe Asthma Registry ATS 2023

Table 1. Single domain definition of response and super-response in patients with severe asthma between baseline and month 12 visit

Domain	Definition of responders	Definition of super-responders	Excluded from analysis
Asthma exacerbations	≥ 50% reduction in annualised exacerbation rate	Exacerbation elimination	Zero annualised exacerbations at baseline
FEV_1	≥ 100 mL improvement in post bronchodilator FEV_1	≥ 500 mL improvement in post bronchodilator FEV_1	Not applicable
Asthma control	Improved asthma control by category (controlled, partial, poor)	New attainment of well-controlled asthma	Well-controlled asthma at baseline
Long-term oral corticosteroid (LTOCS) burden	Reduction in LTOCS (mg)	Cessation of LTOCS or weaning to adrenal insufficiency dose ≥ 5 mg	Not on LTOCS at baseline

Table 2: Baseline characteristics of the total LUMINANT cohort, those who were initiated on biologics and those who were not

	Biologic n = 2116	Non-biologic n = 6330	P-value
DEMOGRAPHICS			
Sex (female), % (n/N)	62% (1311 / 2116)	62% (3893 / 6330)	0.71
White race, % (n/N)	78% (1471 / 1876)	79% (4380 / 5573)	
Age (years), mean ± SD (n)	53 ± 15 (2115)	58 ± 17 (6335)	<0.001
BMI, mean ± SD (n)	29.1 ± 7 (1862)	29.6 ± 8 (4995)	0.03
Smoking status never smoker, % (n/N)	62% (1309 / 2116)	45% (2858 / 6335)	<0.001
Asthma onset, mean ± SD (n)	29 ± 19 (1449)	31 ± 20 (2126)	<0.001
ASTHMA STATUS			
Baseline FEV_1 pre-bronchodilator, mean ± SD (n)	1.9 ± 0.8 (1516)	2.1 ± 0.8 (3678)	<0.001
FEV_1 reversibility, % (n)	16% (178)	12% (346)	<0.001
Poor asthma control, % (n/N)	75% (973 / 1299)	56% (1277 / 2268)	<0.001
Baseline annualised exacerbations, mean ± SD (n)	3.8 ± 4 (1711)	1.6 ± 2 (2688)	<0.001
Baseline annualised exacerbations (categorical), %			
0	11%	30%	<0.001
1–3	48%	58%	
4–5	20%	7%	
≥ 6	21%	5%	
LTOCS, % (n/N)	43% (901 / 2116)	14% (878 / 6335)	<0.001
Anti-IgE, % (n)	38% (809)	N/A	
Anti–IL-5/5R, % (n)	59% (1242)	N/A	
Anti–IL-4/13, % (n)	3% (63)	N/A	
BIOMARKERS			
Blood eosinophil count, mean ± SD (n)	598 ± 893 (504)	617 ± 820 (954)	0.7
FeNO (ppb), mean ± SD (n)	49 ± 46 (800)	47 ± 46 (1532)	0.3
IgE, mean ± SD (n)	443 ± 1003 (1273)	417 ± 1306 (2441)	0.5
Sensitised to perennial allergens, % (n/N)	39% (671 / 1724)	44% (1844 / 4177)	0.001

- Response was more frequently achieved among participants initiating biologics versus

LUMINANT: assessing response in severe asthma

Figure 1. Proportion of responders (orange), super-responders (yellow) and non-responders (blue) across single domains in those initiated on biologics, with ≥ 24 weeks follow up, and those who were not initiated on biologics

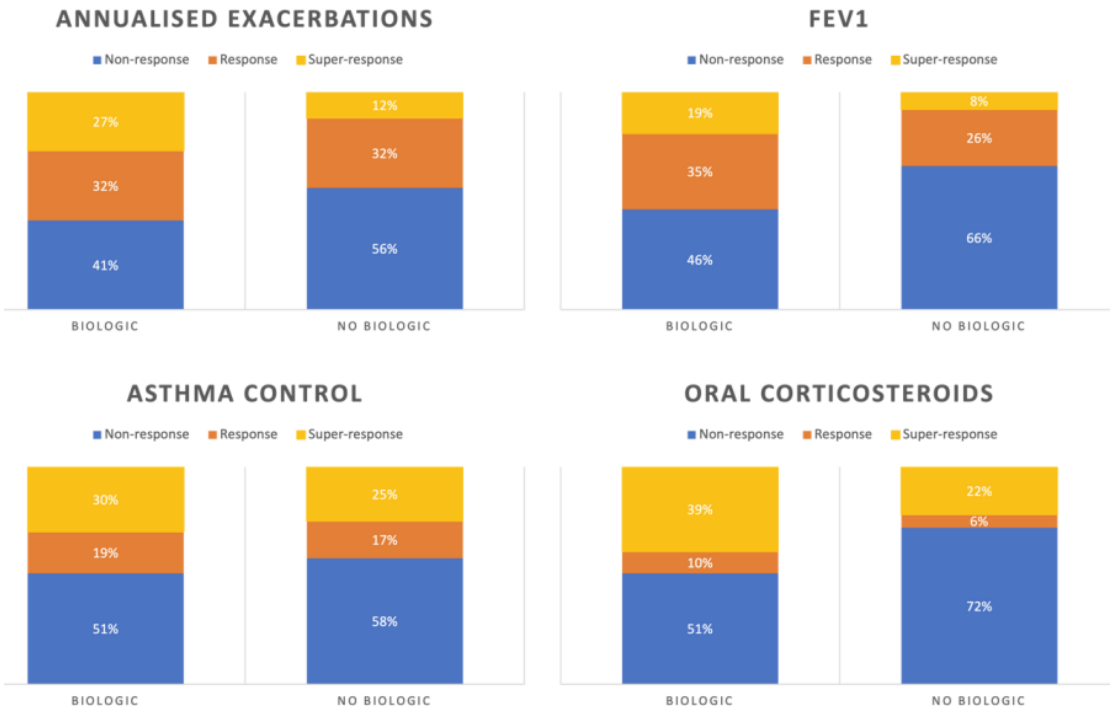


Table 3. Proportion of patients that met the criteria of a single domain of response among those who did and did not initiate a biologic medication between the baseline and follow-up visit

	Biologic	Non-biologic	p-value
RESPONSE, % (n/N)			
Exacerbation reduced ≥ 50%	59% (806 / 1375)	44% (359 / 814)	<0.001
FEV_1 improved ≥ 100 mL	54% (358 / 665)	34% (354 / 1048)	<0.001
Asthma control improved	49% (524 / 1072)	42% (299 / 706)	0.007
LTOCS dose reduced	49% (255 / 517)	28% (32 / 112)	<0.001
SUPER-RESPONSE, % (n/N)			
Exacerbation elimination	27% (442 / 1620)	12% (242 / 1967)	<0.001
FEV_1 improved ≥ 500 mL	19% (124 / 665)	8% (86 / 1048)	<0.001
New good asthma control	30% (318 1072)	25% (196 / 706)	0.016
LTOCS super-response	39% (200 / 517)	22% (25 / 112)	<0.001

Conclusions

- Patients with severe asthma who initiated biologics had greater disease severity at baseline than those who did not initiate biologics, but biomarker levels were similar
- Only 5.3% of study participants met even basic criteria for clinical trials
- Clinical response and super-response to biologics was observed in all four domains
- Super-response was more frequent amongst biologic initiators than non-initiators
- In the context of differing baseline impairment, response to biologics may differ by biologic class

An expert consensus framework for asthma remission as a treatment goal

Check for updates

Andrew Menzies-Gow, PhD,[a] Mona Bafadhel, PhD,[b] William W. Busse, MD,[c] Thomas B. Casale, MD,[d] Janwillem W. H. Kocks, MD, PhD,[e,f,g] Ian D. Pavord, MD,[b] Stanley J. Szefler, MD,[h] Prescott G. Woodruff, MD,[i] Alexander de Giorgio-Miller, PhD,[j] Frank Trudo, MD,[k] Malin Fageras, PhD,[l] and Christopher S. Ambrose, MD[m]

London, Oxford, and Cambridge, United Kingdom; Madison, Wis; Tampa, Fla; Groningen, The Netherlands; Singapore; Aurora, Colo; San Francisco, Calif; Wilmington, Del; Gothenburg, Sweden; and Gaithersburg, Md

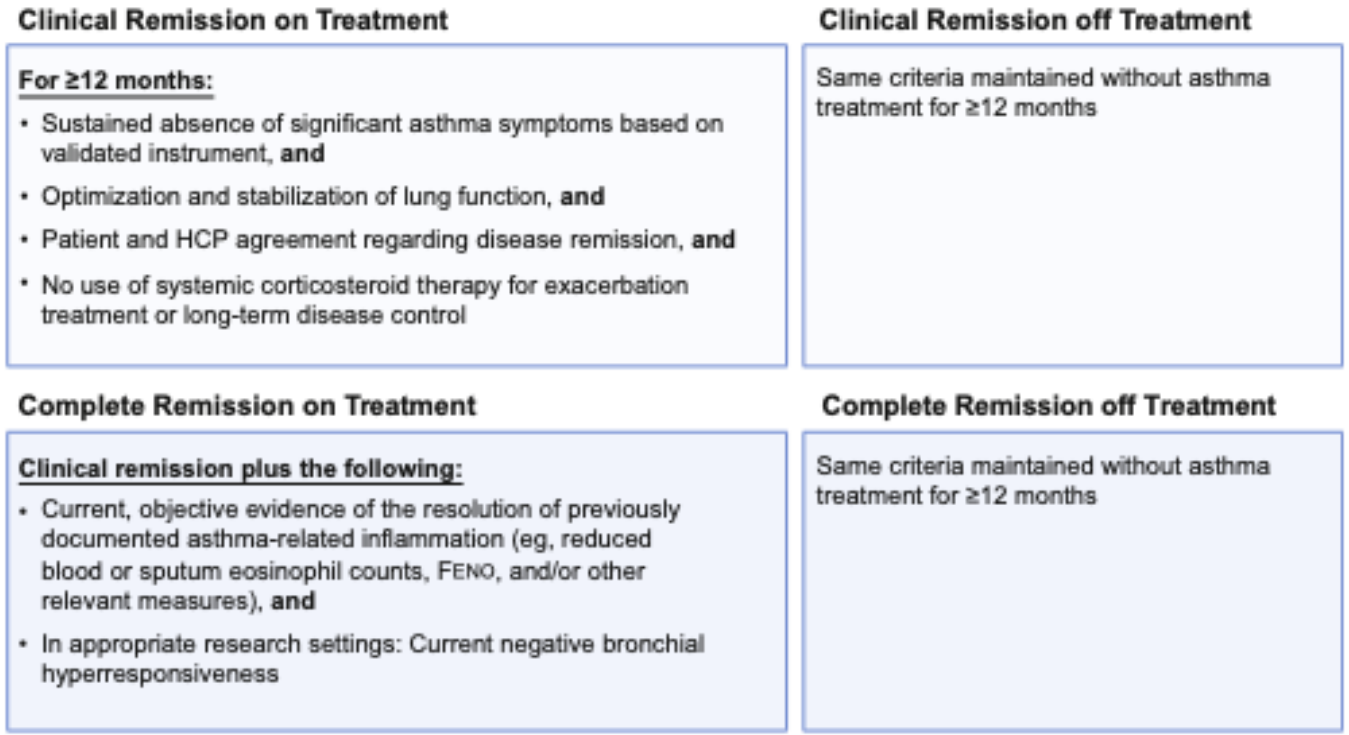


FIG 1. Generalized framework for remission in asthma. Criteria for clinical and complete remission, on and off treatment, were identified by consensus among clinical experts. *FENO*, Fractional exhaled nitric oxide. *Blood eosinophil counts and FENO are less relevant for T2-low asthma.

J Allergy Clin Immunol 2020;145:757-65.

BEAM - remission

Clinical remission following biologic initiation in severe asthma: results of the International Severe Asthma Registry (ISAR)

G. Scelo,[1] T. N. Tran,[2] T. T. Le,[2] M. Faregås,[3] N. Martin,[4] A. N. Menzies-Gow,[4] E. Wang,[5] M. E. Wechsler,[6] G. W. Canonica,[7] E. Heffler,[8] L. G. Heaney,[9] D. J. Jackson,[10] P. E. Pfeffer,[11] J. Busby,[12] C. M. Porsbjerg,[13] M. Hew,[14] M. Peters,[15] P. G. Gibson,[16] M. Al-Ahmad,[17] C. Bergeron,[18] M. Sadatsafavi,[19] L. Perez-De-Llano,[20] B. G. Cosio,[21] P. Kuna,[22] D. W. Perng,[23] T. Iwanaga,[24] C. A. Torres-Duque,[25] D. Larenas-Linnemann,[26] B. Mahboub,[27] R. Al- Lehebi,[28] J. A. Fonseca,[29] C. K. Rhee,[30] J. Máspero,[31] M. S. Koh,[32] G. C. Christoff,[33] T. A. Popov,[34] J. Kwiatek,[35] V. Carter,[1] C. Goh,[1] L. Bulathsinhala,[1] A. Beastall,[1] D. Price[36]

[1]Observational and Pragmatic Research Institute, Singapore; Optimum Patient Care Global Cambridge (UK); [2]BioPharmaceuticals Medical, AstraZeneca - Gaithersburg, MD (USA); [3]BioPharmaceuticals Medical, AstraZeneca - Gothenburg (Sweden); [4]BioPharmaceuticals Medical, AstraZeneca - Cambridge (UK); See QrC for all affiliations

ISAR

1891

Why did we perform this research?

- Despite the emergence of common domains of asthma remission, there is little agreement on clinically useful criteria for identifying remission in real-life.
- Our aim was to explore different definitions of remission using multiple asthma outcome domains, and to quantify the prevalence of remission when treated with biologics using these definitions in adults with severe asthma.

How did we perform this research?

Methods

- This was a registry-based cohort study including data from 23 countries sharing data with ISAR between May 1st 2017 and Dec 5th 2022.
- Pre and post-biologic outcomes were described across 4 domains: exacerbation rate, LTOCS daily dose, asthma control status and $ppFEV_1$, and remission defined using various combinations of these domains using strict and alternate criteria (**See Figure 1**).
- Patients were aged ≥18 years with severe asthma, with pre- and post-biologic data for ≥1 domain.

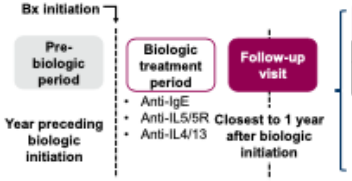


Figure 1: study design

Remission definitions	Exacerbations	LTOCS daily dose	Asthma control	$ppFEV_1$
Strict	0	0	Partly or well controlled	≥ 80%
Alternate	≤1	≤5 mg		
2 domains				
3 domains				
3 domains				
4 domains				

See **Supplementary Table 1** for outcome definitions and timing of assessments.

E-poster · Supplementary material · Audio/video narration

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Corresponding author email address: : David@opri.sg

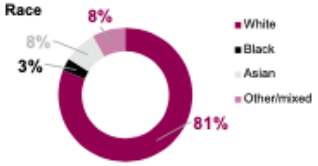
Poster presented at ERS International Congress, Milan, Italy, 9-13 Sept 2023

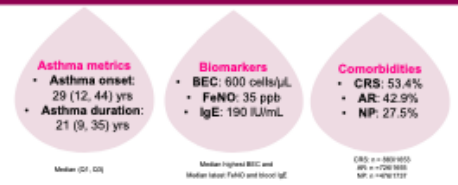
What did we find?

Up to 2,031 eligible adults were included

Median (Q1, Q3) age: 54 (44, 63) years

60% female · 40% male





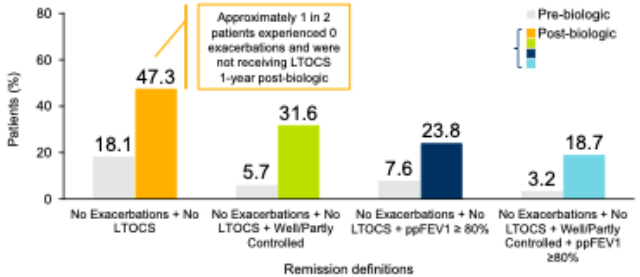
See **Supplementary Tables 2A & 2B** for full demographics and pre-biologic clinical characteristics.

Table 1. Patient pre-biologic clinical characteristics

Pre-biologic asthma outcome domain	
Exacerbations,[a] N n (%)	1499 673 (44.9)
LTOCS user, N n (%)	1769 580 (32.8)
Uncontrolled, N n (%)	1082 794 (73.4)
$ppFEV_1$ < 80%, N n (%)	1207 698 (57.8)

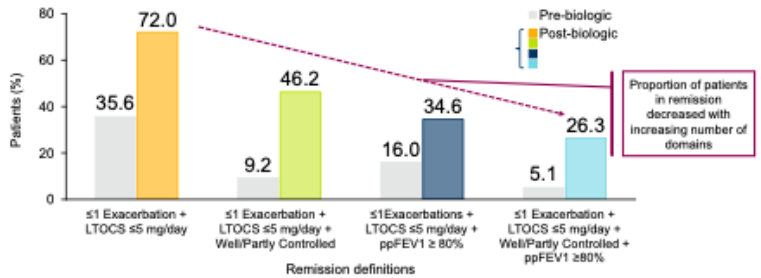
[a]≥ 1 hospitalized or ≥3 exacerbations in total

Figure 2. Proportion of patients with severe asthma in multi-domain remission pre- and ~1-year post-biologic initiation (Strict Criteria)



Sample size				
	1470	771	537	251
	2031	1218	1235	831

Figure 3. Proportion of patients with severe asthma in multi-domain remission pre- and ~1 year post-biologic initiation (Alternate Criteria)



Sample size				
	1364	703	518	237
	1959	1167	1184	790

How might this impact current clinical practice?

- **Almost 1 in 5 adults with severe asthma met criteria for clinical remission in all 4 domains 1 year following biologic initiation**
- **Our results may be useful in informing physicians of the likelihood of remission 1-year post biologic, specific to domains of interest to patients**
- **Identification of a continuum of remission according to type and number of domains highlights the need for a universal approach to assess remission**

Abbreviations

AR: allergic rhinitis; BEC: blood eosinophil count; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; ISAR: International Severe Asthma Registry; LTOCS: long-term oral corticosteroid; NP: nasal polyposis; OPRI: Observational & Pragmatic Research Institute; $ppFEV_1$: percent predicted forced expiratory flow in one second

Acknowledgments

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by OPRI for its contribution.

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Disclosures

GS, VC, CG, LB, and AB are employees of OPRI. TNT, TTL, MF, NM and ANM-G are employees of AstraZeneca; DP: has consultancy agreements with Amgen, AZ, Boehringer Ingelheim, Chiesi, GSK, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance. All other disclosures available on QrC

Responders/Remission

- Similar biomarkers in patients initiating biologics or not
  - But less LTOCS and exacerbations in non initiators
- 5.3% of biologic initiators would have met basic criteria for clinical trial
- More chance to have super responders if initiated on biologics
- Remission:
  - 1 out of 5 patients initiated on biologics
  - Less likely of higher exacerbations and longer asthma duration

Severe asthma

- Importance of SA diagnosis and co-existing diseases – adherence/education/interdisciplinary approach/Phenotype
- Significant overlap in biologic eligibility
  - T2 high asthma phenotype
  - reassess periodically and switch as needed
- Biologics:
  - Reduction in exacerbation ~ 50-70%
  - Weaning OCS ~ 50%
  - Stabilize or improve lung function (~150 ml)
  - Decrease symptoms/disease burden
  - Remission in 10-40%
- OCS life long: target < 2g (ideally < 0.5g) as risks++
- Lung function: influence on exacerbations and mortality

ISAR- Socioeconomy disparity in severe asthma

Objective 5

ISAR Global Reach – 28 Countries across 5 Continents

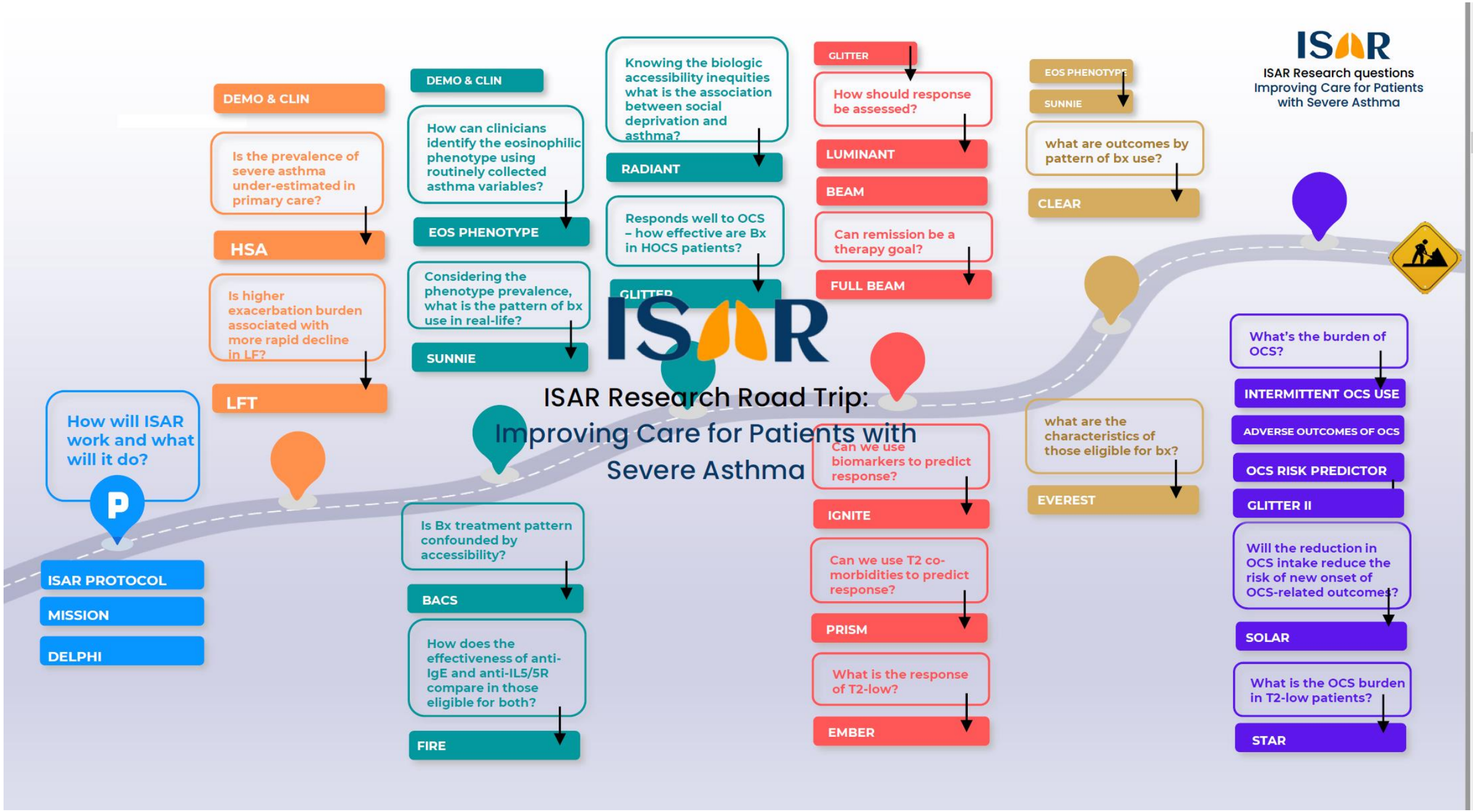
Total number of patients worldwide: **17,582**

Total number of Canadian patients: **442**

Canada - Demographics

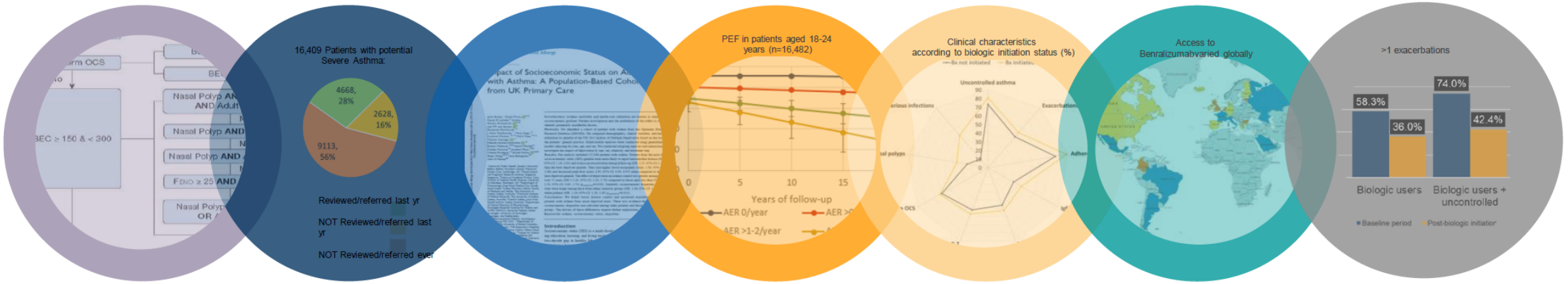
Date of last extraction: 25 October 2023

468	Patients
1384	Visits
20 October 2023	Latest visit date
361	Biologic patients
107	Non-biologic patients
1.59K	Total patient years
3.39	Average patient years


ISAR Research questions
Improving Care for Patients with Severe Asthma
ISAR Research Road Trip:
Improving Care for Patients with Severe Asthma
How will ISAR work and what will it do?
ISAR PROTOCOL
MISSION
DELPHI
DEMO & CLIN
Is the prevalence of severe asthma under-estimated in primary care?
HSA
Is higher exacerbation burden associated with more rapid decline in LF?
LFT
DEMO & CLIN
How can clinicians identify the eosinophilic phenotype using routinely collected asthma variables?
EOS PHENOTYPE
Considering the phenotype prevalence, what is the pattern of bx use in real-life?
SUNNIE
Is Bx treatment pattern confounded by accessibility?
BACS
How does the effectiveness of anti-IgE and anti-IL5/5R compare in those eligible for both?
FIRE
Knowing the biologic accessibility inequities what is the association between social deprivation and asthma?
RADIANT
Responds well to OCS – how effective are Bx in HOCS patients?
GLITTER
GLITTER
How should response be assessed?
LUMINANT
BEAM
Can remission be a therapy goal?
FULL BEAM
Can we use biomarkers to predict response?
IGNITE
Can we use T2 co-morbidities to predict response?
PRISM
What is the response of T2-low?
EMBER
EOS PHENOTYPE
SUNNIE
what are outcomes by pattern of bx use?
CLEAR
what are the characteristics of those eligible for bx?
EVEREST
What's the burden of OCS?
INTERMITTENT OCS USE
ADVERSE OUTCOMES OF OCS
OCS RISK PREDICTOR
GLITTER II
Will the reduction in OCS intake reduce the risk of new onset of OCS-related outcomes?
SOLAR
What is the OCS burden in T2-low patients?
STAR

Research that impacts clinical practice

1. Who, what and when of severe and high risk asthma



01 Eosinophilic phenotype is common in severe asthma[1]

02 Patients with severe asthma may be missed in primary care[2]

03 Worse disease control and increased exacerbation rates among patients with asthma from more deprived areas[3]

04 Asthma exacerbations are associated with faster lung function decline, more pronounced in younger patients[4]

05 Nearly one-third of severe asthma patients with high OCS exposure did not receive biologics[5]

06 Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy: Standardization of biologic prescription and access criteria are needed[6]

07 Substantial baseline disease burden, reduced post-biologic, but remained high[7]

1.Eosinophilic and non-eosinophilic asthma: A consensus framework, Heaney L, et al. Chest 2021;160(3):814-30. 2. Hidden severe asthma (HSA) patients in UK primary care, Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9 3. RADIANT: Differences in asthma disease severity by socioeconomic status and ethnicity, Busby, J. et al. J Asthma Allergy. 2021 Nov 10;14:1375-1388, 4. Lung Function Trajectory (LFT), Soremekun S et al. Thorax 2022;0:1–10. doi:10.1136/thoraxjnl-2021-217032, 5. GLITTER I: Chen W et al. *J Asthma Allergy*, 2022;15:1491-1510, 6. BACS, Chen W et al. J Asthma Allergy, 2022;15:1491-1510 7. EVEREST study, Burden of severe asthma by biologic use and eligibility: an analysis of the International Severe Asthma Registry, T. Le, 2022 60: 2143

OCS: Oral Corticosteroids

Journal of Asthma and Allergy

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ORIGINAL RESEARCH

Impact of Socioeconomic Status on Adult Patients with Asthma: A Population-Based Cohort Study from UK Primary Care

Journal of Asthma and Allergy 2021:14 1375–1388

Cohort of 127 040 patients with asthma

Socioeconomic status :

- UK 2011 Indices of Multiple Deprivation (IMD)

- IMD score calculates the relative deprivation of small areas by taking a weighted average across seven domains (income, employment, health, education, housing, crime, and living environment).

Table 1 Comparison of Demographic and Clinical Information by Indices of Multiple Deprivation Quintile

	5 (Least Deprived)	4	3	2	1 (Most Deprived)	P-value
Number Patients	28,215	26,900	24,332	31,059	16,534	
Age (years)	51.8 (16.7)	51.1 (17.0)	52.1 (17.1)	50.8 (17.0)	50.0 (16.9)	<0.001
<35	4911 (17.4%)	5234 (19.5%)	4453 (18.3%)	6330 (20.4%)	3708 (22.4%)	
35–54	11,553 (40.9%)	10,795 (40.1%)	9369 (38.5%)	12,350 (39.8%)	6487 (39.2%)	
55–74	8981 (31.8%)	8286 (30.8%)	7994 (32.9%)	9556 (30.8%)	4911 (29.7%)	
75+	2770 (9.8%)	2585 (9.6%)	2516 (10.3%)	2823 (9.1%)	1428 (8.6%)	
Sex						<0.001
Female	16,362 (58.0%)	15,780 (58.7%)	14,388 (59.1%)	18,617 (59.9%)	9961 (60.2%)	
Male	11,853 (42.0%)	11,120 (41.3%)	9944 (40.9%)	12,442 (40.1%)	6573 (39.8%)	
Ethnicity						<0.001
White	18,268 (97.5%)	16,960 (94.7%)	15,777 (96.2%)	20,517 (95.3%)	9737 (88.3%)	
Asian	304 (1.6%)	710 (4.0%)	449 (2.7%)	769 (3.6%)	933 (8.5%)	
Black	45 (0.2%)	104 (0.6%)	61 (0.4%)	143 (0.7%)	185 (1.7%)	
Mixed	48 (0.3%)	78 (0.4%)	59 (0.4%)	57 (0.3%)	55 (0.5%)	
Other	79 (0.4%)	66 (0.4%)	50 (0.3%)	47 (0.2%)	115 (1.0%)	
BMI (kg/m^2)	27.8 (5.8)	27.9 (5.9)	28.2 (6.1)	28.6 (6.1)	28.9 (6.4)	<0.001
Alcohol Consumption (Weekly Units)	4.0 (0.0, 10.0)	3.0 (0.0,10.0)	2.0 (0.0,10.0)	2.0 (0.0,10.0)	2.0 (0.0,10.0)	<0.001
Smoking Status						<0.001
Never-Smoker	16,376 (59.2%)	14,977 (57.3%)	12,492 (55.0%)	16,135 (53.1%)	7929 (50.8%)	
Ex-Smoker	7672 (27.7%)	7483 (28.6%)	6549 (28.9%)	8744 (28.8%)	4206 (26.9%)	
Current Smoker	3633 (13.1%)	3690 (14.1%)	3657 (16.1%)	5511 (18.1%)	3473 (22.3%)	
Any Exacerba						
Respiratory Referral	1226 (4.3%)	619 (2.3%)	767 (3.2%)	1094 (3.5%)	665 (4.0%)	<0.001

(*Continued*)

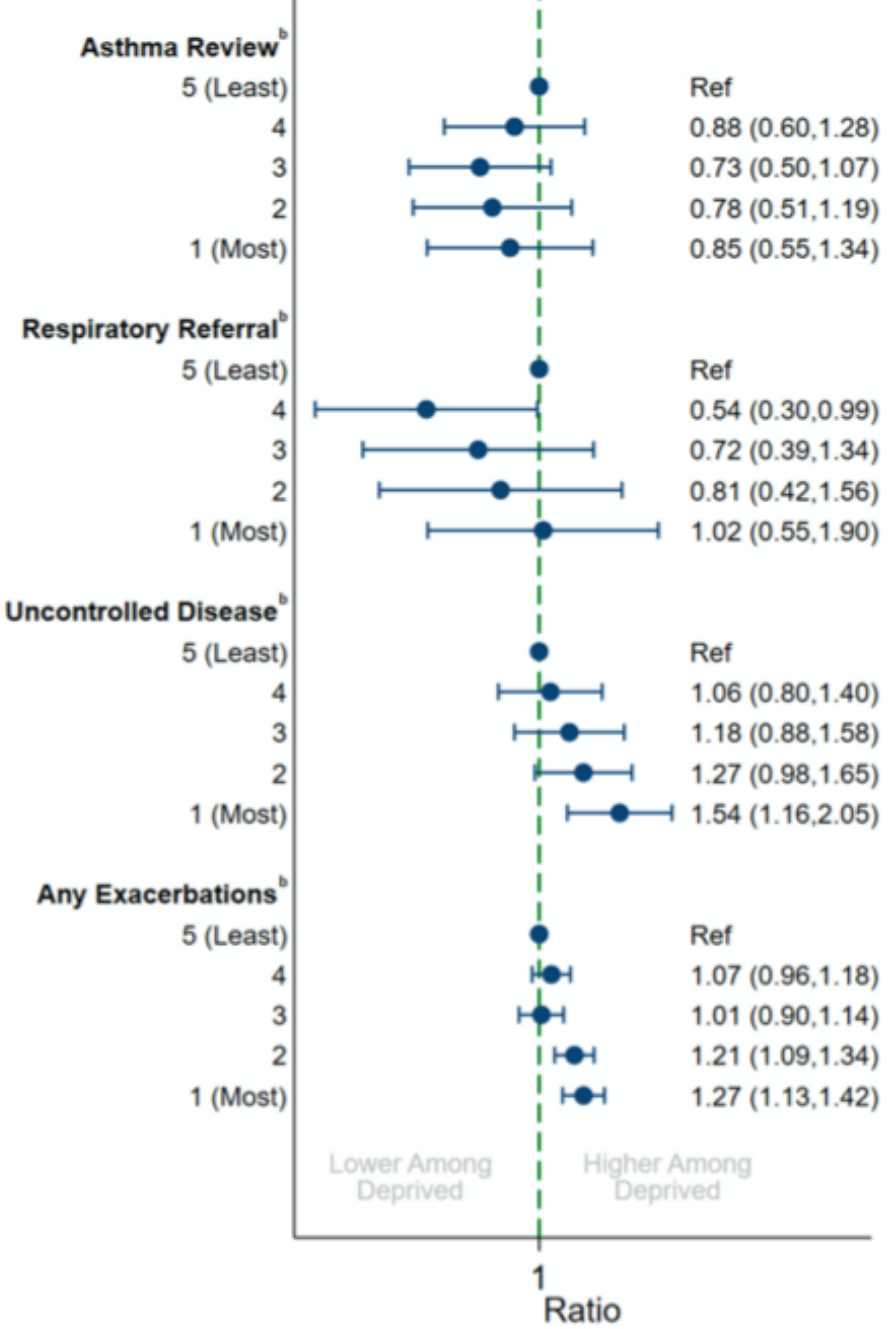

Figure 1 Multivariable association between indices of multiple deprivation quintile and clinical variables[a]. [a]Adjusted for year, age (5-year groups) and sex, [b]Odds ratio.

Patients from more deprived areas had:

- poorer asthma disease control,
- lower peak flow, and
- increased exacerbations.

There was evidence that the magnitude of socio-economic disparities were elevated among

- older patients and
- ethnic minority groups.

Conclusions

- Education
- Optimization of control and prevention of future risks
- Comorbidities highly prevalent
- Environment friendly inhalers if appropriate
- OCS burden: comorbidities and mortality
- Lung function to maintain to prevent exacerbations and mortality

- Mild asthma
  - Consider ICS/Form as needed
- Moderate to Severe:
  - Consider SITT
- Severe asthma:
  - Referral for phenotyping and consideration of biologics
- Remission:
  - Target for more severe asthma patients with biologics
- Deprived area: lower asthma control, lower lung function and higher exacerbations rate

Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma

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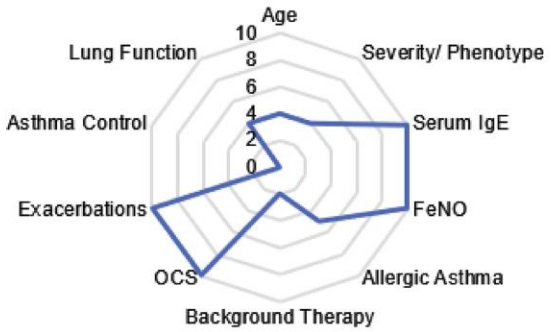
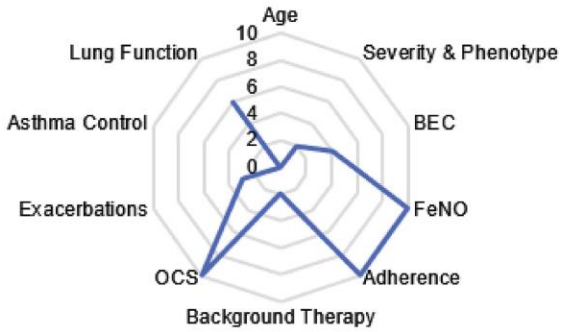
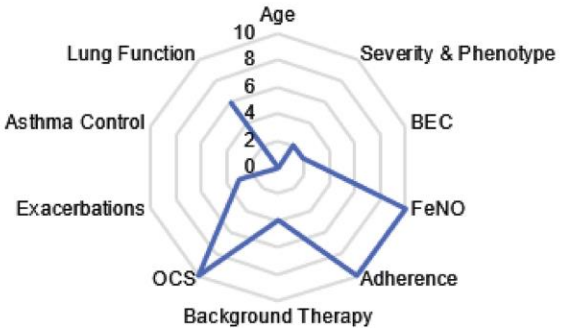
Omalizumab: Canada - BACS 40



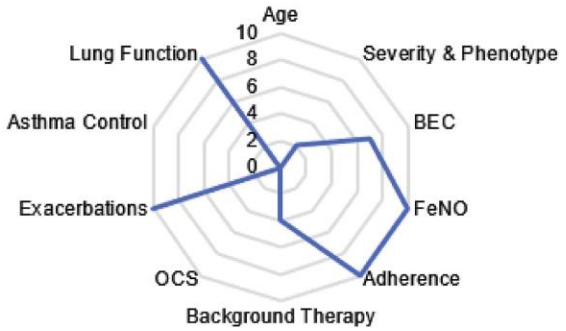
Mepolizumab: Canada - BACS 47



Reslizumab: Canada - BACS 47



Benralizumab: Canada - BACS 53



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Biologic prescription criteria differed substantially across 28 countries from five continents. Blood eosinophil count thresholds (usually ‡300 cells/mL) and exacerbations were key requirements for anti-IgE/antieIL-5/5R prescriptions in around 80% of licensed countries. Most countries (40% for dupilumab to 54% for mepolizumab) require two or more moderate or severe exacerbations, whereas numbers ranged from none to four. Moreover, 0% (for reslizumab) to 21% (for omalizumab) of countries required long-term oral corticosteroid use. The BACS highlighted marked between-country differences in ease of access. For omalizumab, mepolizumab, benralizumab, and dupilumab, only two, one, four, and seven countries, respectively, scored equal

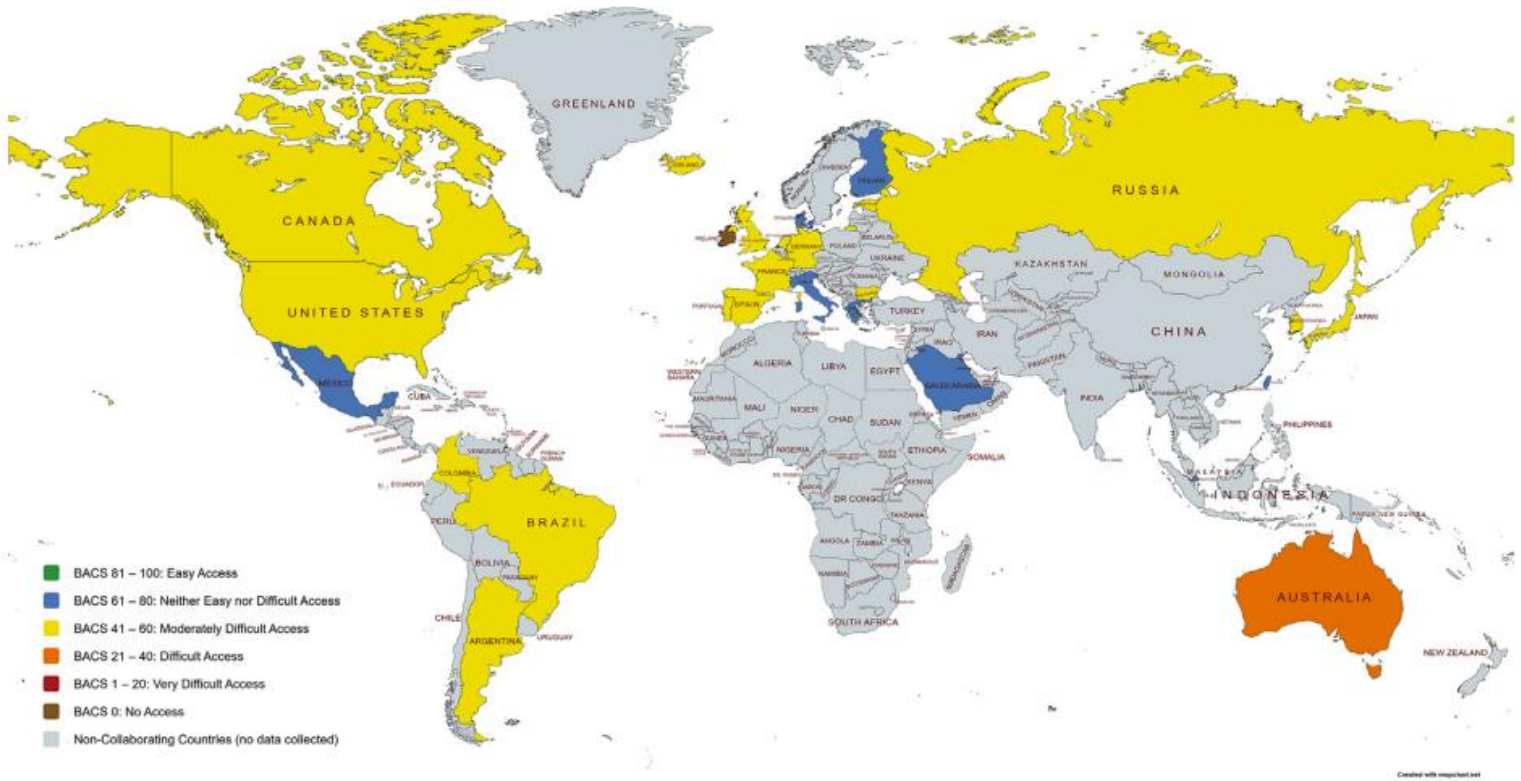
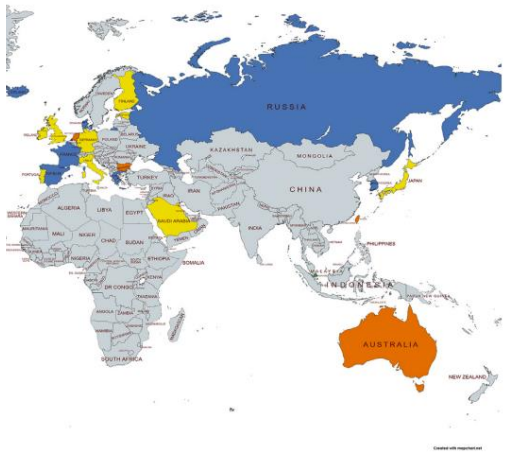


FIGURE 1. Omalizumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.



e (BACS) for International Severe Asthma Registry (ISAR) countries.

MAY 2022

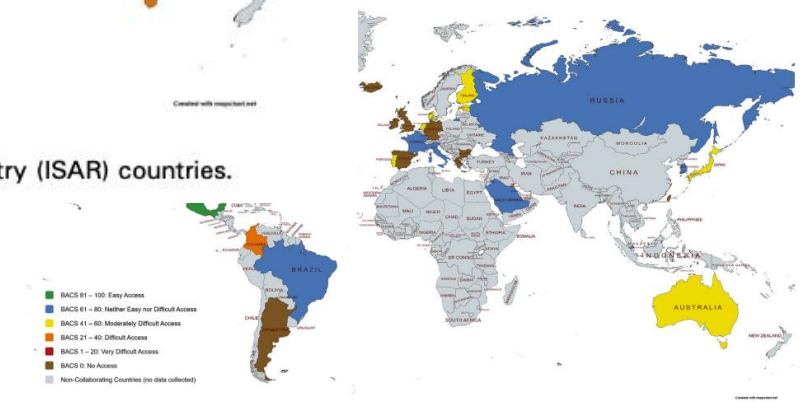


FIGURE 5. Dupilumab Biologic Accessibility Score (BACS) for International Severe Asthma Registry (ISAR) countries.