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Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study

Lakmini Bulathsinhala et al, *J Allergy Clin Immunol Pract* 2019;7(2):578-588.e2

Background and aims

Original Article

Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study

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Cambridge, London, Aberdeen, Manchester, UK; Belfast, Northern Ireland; Newcastle, New Lambton Heights, Sydney, Melbourne, Australia; Groningen, Amsterdam, The Netherlands; Tampere, Finland; Lyon, France; Madrid, Mallorca, Spain; Athens, Greece; Vancouver, Canada; Copenhagen, Denmark; Milan, Italy; Seoul, South Korea; Gent, Belgium; Mainz, Germany; Singapore; and Gaithersburg, Md

What is already known about this topic? All existing severe asthma registries in the world were either country or region specific. Most importantly, none shared a common set of variables for data collection. This impedes data sharing and subsequently disallows data pooling to conduct research with robust sample size.

What does this article add to our knowledge? This paper depicts a systematic method of soliciting group consensus on a topic that entails a spectrum of choices and viewpoints.

How does this study impact our current management guidelines? Using the standardized minimal list of variables identified by our study, we hope to achieve data interoperability between severe asthma registries across the globe and subsequently improve patient management guidelines in severe asthma.

BACKGROUND: The lack of centralized data on severe asthma has resulted in a scarcity of information about the disease and its management. The development of a common data collection tool for the International Severe Asthma Registry (ISAR) will enable standardized data collection, subsequently enabling data interoperability.

OBJECTIVES: To create a standardized list of variables for the first international registry for severe asthma via expert consensus.

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This study is cofunded by Optimum Patient Care Global and AstraZeneca.

Conflicts of interest: L. Bulathsinhala, N. Eleangovan, V. Carter, C. Price, T. Le, and M. S. d'Alcontres are employees of Optimum Patient Care, a cofunder of the International Severe Asthma Registry. L. G. Heaney has taken part in advisory boards and given lectures at meetings supported by GlaxoSmithKline, Respivert, Merck Sharpe & Dohme, Nycomed, Boehringer Ingelheim, Teva Pharmaceuticals, Vectura, Novartis, and AstraZeneca. He declares sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Napp Pharmaceuticals; and speaker fees from AstraZeneca, Aerocrine, Hoffman-La Roche, and Teva Pharmaceuticals. A. Menzies-Gow declares grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Hoffman La Roche; consultancy agreements with AstraZeneca and Vectura;

Background

- Registries are well-established and valuable tools for disease surveillance, and the current registry landscape for severe asthma is viewed as a collection of **divergent, national and regional registries**.
- The **lack of centralized data on severe asthma** has resulted in a scarcity of information about the disease and its management.
  - Hence, the **development of a common data collection tool** for the International Severe Asthma Registry (ISAR) will **enable standardized data collection, subsequently enabling data interoperability**.

Aim

- To **create a standardised list of variables** for the first international registry for severe asthma via expert consensus.

Full Text available here.

ISAR: International Severe Asthma Registry

Methods:
Delphi panel, panel selection and consensus criteria

- Delphi panel
  - **27 international experts** in the field of severe asthma research, representing **16 countries.**

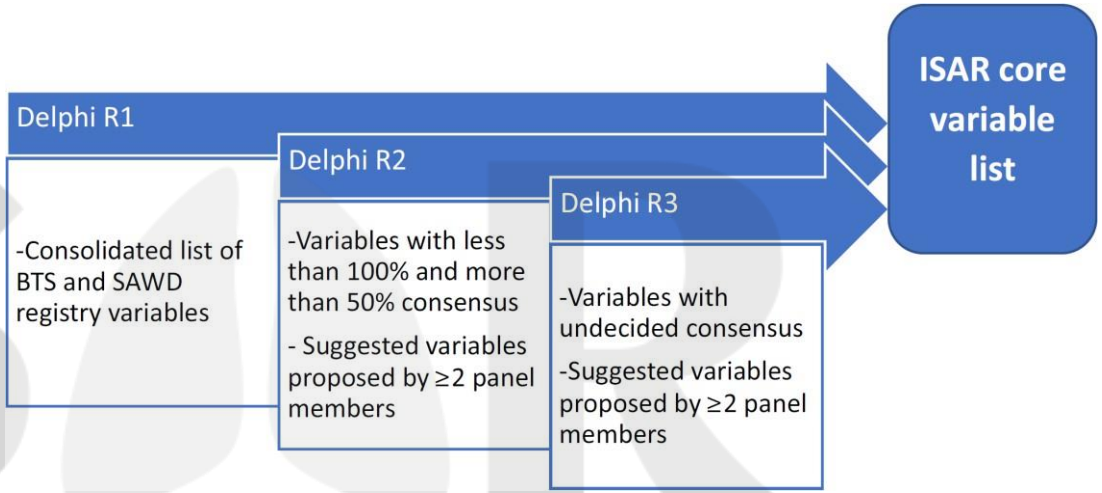
- Panel selection criteria – **2 or more** of the following:
  1. **Evidence of relevant asthma research** published in high-ranking peer-reviewed journals.
  2. A **history of participation** in:
     - The development and/or management of one or more severe asthma registries
     - Epidemiological databases, and
     - Scientific congress committees in a particular country and/or internationally.
  3. Experience as a medical provider with **interest in advancing asthma management** in clinical practice.

- Criteria for consensus
  - Variables receiving **≥66.6%** consensus were selected as **ISAR core variables**.
  - Variables receiving **50%-66.6%** consensus ("undecided") were **circulated for another round of review**.
  - Variables receiving **<50%** consensus were **removed**.

ISAR: International Severe Asthma Registry

Methods: A 3-round modified Delphi process

- In each round:
  - Panel members were issued an **electronic ISAR Delphi workbook** to vote and comment for the inclusion of variables.
    - Experts were encouraged to **provide comments** for excluding or including variables, to **nominate variables** from the "suggest" variable list, and/or **propose new variables**.
  - These workbooks were returned to the ISAR Delphi administrator anonymously.
  - Variables with 'undecided' consensus for inclusion/exclusion ➔ **submitted for evaluation in the subsequent round.**
  - Finalisation of the core variable list was facilitated by **2 face-to-face meetings**.



The modified Delphi process consisted of 3 iterative rounds (R1, R2, and R3).

BTS: British Thoracic Society; SAWD: Severe Asthma Web-based Database

ISAR: International Severe Asthma Registry

Methods:

Samples of the variable list from Delphi R1

Page	Potential core variables	Field format	Response option (where applicable)	Unit (where applicable)	Place in core list?	Reason for choice (if "no")
Patient details	Date of visit	Date		DDMMYY		
	Date of birth	Date		DDMMYY		
	Gender	Radio button	Female/Male			
	Ethnicity	Drop-down menu	Caucasian/South-East Asian/North-East Asian/African /Mixed/ Other			
	Height	Decimal		m		
	Weight	Number		kg		
	Bronchial thermo-plasty	Radio button				

Sample of the "Potential Core" variable list from the ISAR Delphi workbook R1.

Page	Suggest variables	Field format	Response option (where applicable)	Unit (where applicable)	Propose for core list?	Reason for choice (if "yes")
Sputum	Neutrophils	Decimal		%		
	Eosinophils	Decimal		%		
	Date of sputum	Date		DDMMYY		
	Sputum processing protocol	Text				
	Bronchial epithelial cells	Decimal		%		
	Bronchial epithelial cells	Decimal		109/L		
	Macrophages	Decimal				
	Lymphocytes	Decimal				
	Samples stored locally for biobanking	Radio button	No/Yes			

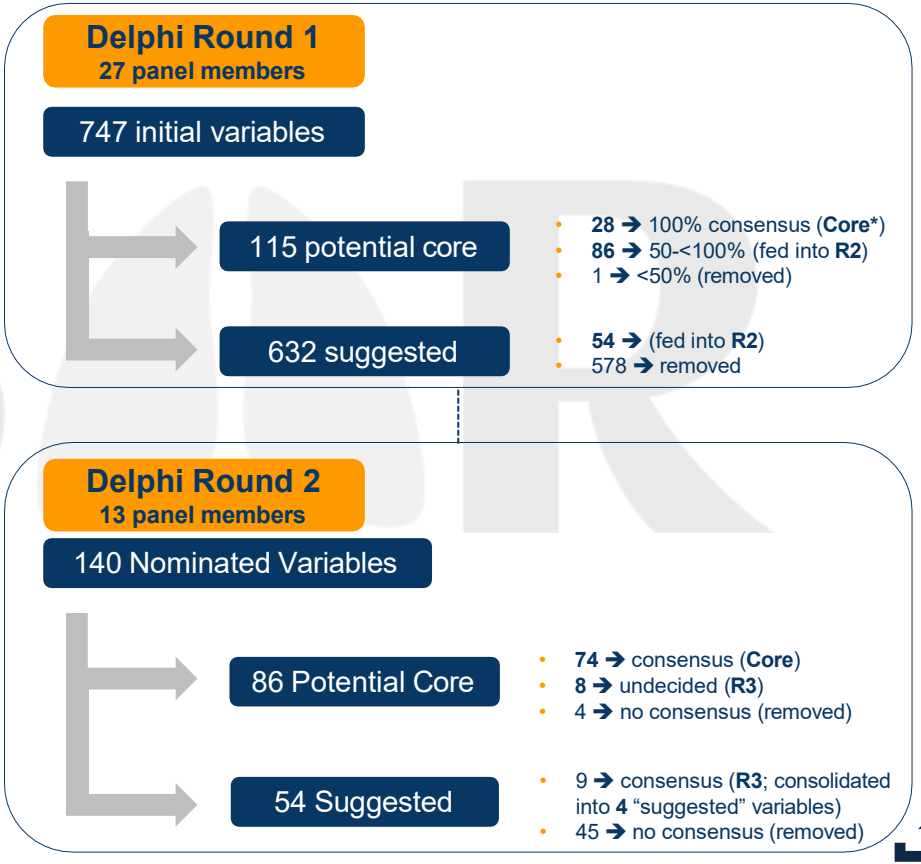
Sample of the "Suggest" variable list from the ISAR Delphi workbook R1.

R1: Round 1

ISAR: International Severe Asthma Registry

Results: Delphi R1 and R2

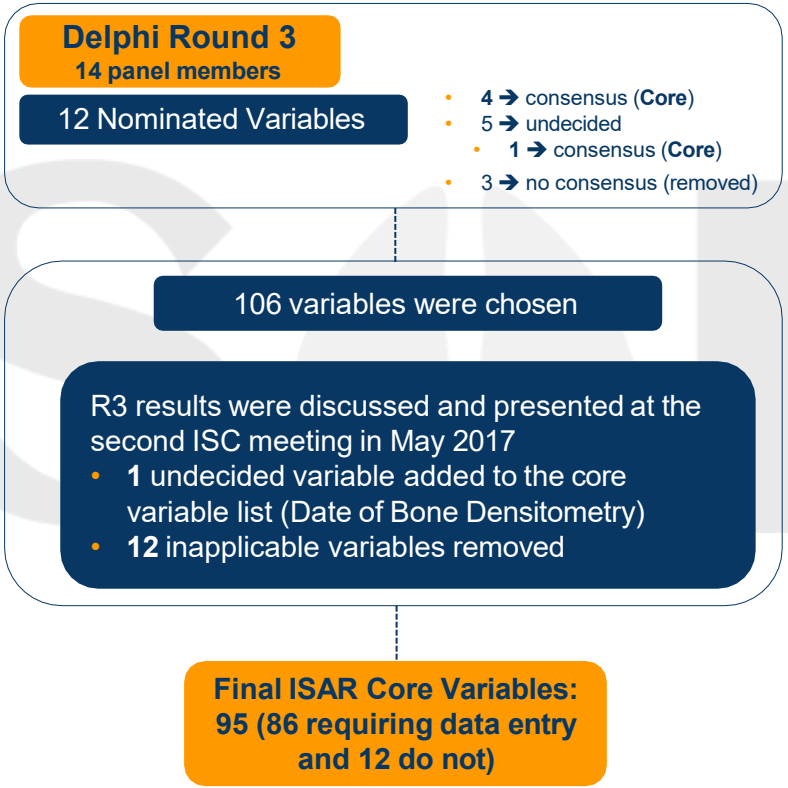
- A total of **747 variables** were identified and compiled from longstanding severe asthma registries (**UK** and **Australia**).
- The **Delphi workbook** comprises:
  - **115** potential core variables, **common** to UK and Australia, and
  - **632** suggested variables **unique** for either registry.



*Core Variable: Set of standardized variables that will be captured by ALL countries participating in the ISAR.

ISAR: International Severe Asthma Registry

Results: Delphi R2 and R3



ISAR: International Severe Asthma Registry

Results: Consensus on 95 core variables

- Of the initial 747 selected variables, the Delphi panel **reached a consensus on 95**.
- The chosen variables will allow severe asthma to be assessed against:
  - Patient demographics
  - Medical history and diagnostics
  - Clinical characteristics
  - Patient-reported outcomes
- Physician-reported outcomes such as **nonadherence** and information about **treatment and management strategies** will also be recorded.

Patient details and medical history

- Patient demographic and medical history data fields will allow patients to be **categorised**.
- The panel-approved variables were chosen to ensure that a **comprehensive set** of patient characteristics are collected for patient aggregation.
- Previous literature has shown that many patients **overestimate their level of asthma control** and **underestimate the severity of their condition**, indicating that they tolerate symptoms and lifestyle limitations.
- Thus, the **GINA Assessment for Asthma Control** was the preferred tool for this assessment because it:
  - does not overestimate the proportion of patients with controlled asthma, and
  - is therefore more likely to give a less exaggerated score compared with other available questionnaires.

ISAR: International Severe Asthma Registry

Diagnostics, adherence, and comorbidities

- The Delphi panel agreed to collect **screening and diagnostic results** to help identify the **care requirements** of individual patients.
- **Biomarkers** such as peripheral blood and sputum eosinophils, and fractional exhaled nitric oxide have been shown to be:
  - Useful for the **management of asthma**, and
  - May help identify specific subtypes of severe asthma **likely to benefit from treatment with novel biological agents**.
- Nonadherence to therapy is approximately **50%** in adults with severe asthma.
- Physicians need to ensure that patients are **satisfied** with their medication to increase adherence and optimise disease control.
- There is a potential for ISAR to investigate nonadherence across **different geographical regions**, which comes with different health care systems, availability of medications, access to specialists, and asthma education.

ISAR: International Severe Asthma Registry

Treatment management plan

- **Asthma patient management practices** among adults have been found to be **inadequate** in many practices in Europe.
- Along with the information that ISAR will collect on clinical outcomes and demographic characteristics, the **best treatment management plan by patient group** will be assessed.
- Moreover, the Delphi panel agreed to collect **broad treatment options** to ensure that all participating countries will be able to contribute without subjection to individual country specifications.

ISAR: International Severe Asthma Registry

Main strengths and weaknesses

Strengths

- Global panel of international severe asthma experts and professionals allowed **broad consensus** to be obtained
- Consistent number of experts participating in each Delphi round conserved possibility **of reaching consensus**
- **Efficient**, **economically viable**, and **rapid communication**
- Decreased bias and maximised diversity within the Delphi panel, resulting in a **decreased possibility of overlooking** the obvious facets of the questions

Weaknesses

- **Not fully representative** of the diversity amongst stakeholders of respiratory health
- Response rate was **not 100%**

ISAR: International Severe Asthma Registry

Conclusion, implications, and future work

- The Delphi process was utilised to **gain anonymized international consensus on 95 core variables** among **27 severe asthma experts** across **16 countries**.
  - **Less than 100 core variables** offers relatively **small data entry burden** for healthcare professionals.
- The first international severe asthma registry (ISAR) now allows for **exchange of data** across registries worldwide.
  - The international scientific community will have access to **larger databases** to conduct research with **improved power**, which further increases the **precision** of research results.
  - Ultimately, the ability to identify severe asthma **phenotypes** and **best clinical management** practices will be heightened.
- This is the first attempt to develop such a registry on a global scale within the severe asthma setting, using a **common set of core variables**, ensuring that data collected across all participating countries are **standardised**.
- The next step is to enroll patients and collect data that will allow **gaps in diagnosis and treatment** to be identified and **solutions to be found**, which will help bridge these gaps and thus bring us one step closer to controlling severe asthma.

ISAR: International Severe Asthma Registry

ISAR Mission Statement: Key statements

Sept 2019

The need for ISAR

Pre ISAR

- Local national registries may be limited in scope, have insufficient statistical power to answer many research questions, lack intra-operability to share lessons learned and collect different data, making cross comparisons difficult

What was needed?

- A worldwide registry which brings all severe asthma data together in a cohesive way, under a single umbrella, based on standardized data and collection protocols, permitting data to be shared seamlessly.

What ISAR brings

- ISAR is the first global adult severe asthma registry. Its strength comes from collection of patient level, anonymous, longitudinal, real-life, standardized, high quality data from countries across the world, combined with organizational structure, database experience, inclusivity/openness and clinical, academic and data base expertise

ISAR: International Severe Asthma Registry; http://isaregistries.org/

It’s a partnership

- ISAR is a **joint initiative** and would not exist without the data provided by local registries.
- **ISAR acts as a data custodian**, collecting, collating, exploring, and analyzing standardized data provided by these local registries.
- **Local registries retain ownership** of their own data, but benefit from ISAR in terms of the analytical power it provides and cross comparisons with data from other countries
- **ISAR already partners with 20 national or regional registries** in: Europe, The Americas, Asia Pacific, and the Middle East, with planned expansion to other regions of the world – including Africa.

ISAR: International Severe Asthma Registry; http://isaregistries.org/

What makes ISAR unique?

- ISAR has **sufficient statistical power** to answer important research questions in the field of severe asthma, **sufficient data standardization t**o compare across countries and regions, and the **structure and expertise** necessary to ensure its continuance as well as the **scientific integrity and clinical applicability** of its research.
- ISAR offers a **unique opportunity** to implement existing knowledge, generate new knowledge, and identify the unknown, therefore promoting new research in severe asthma.
- ISAR has a **strong academic focus**. Research projects are prioritized each year, with ethical oversight provided by REG and ADEPT committee,

ISAR: International Severe Asthma Registry; http://isaregistries.org/; REG: Respiratory Effectiveness Group; ADEPT; Anonymized Data Ethics & Protocol Transparency

ISAR: something for everyone!

- **Clinicians** may gain information on patient presentation, knowledge of predictors of treatment success in the era of personalized medicine and predicted outcomes of personalized therapies.
- **Patients** may gain a better understanding of the natural history of their disease, with their collective data used to inform treatment guidelines.
- **Payers** may get evidence on how treatments are used and their effectiveness (both clinical and economic) in different patient populations.
- **The pharmaceutical industry** may assess the effectiveness and long-term safety of therapeutic agents in real-life.

ISAR: International Severe Asthma Registry; http://isaregistries.org/

5 reasons why ISAR is the go-to severe asthma registry

1. ISAR is a **global registry**; large enough to ensure **sufficient power** to answer numerous important clinical questions.
2. The **data collected** by ISAR are standardized, individualized, and comprehensive
3. ISAR has **scientific, academic, and ethical oversight** providing confidence in data collection, analysis and dissemination, and extensive experience in large data collection and management
4. ISAR operates on the principle of **inclusivity and collaboration**, continually seeking new partners and prioritizing relevant research pertinent to severe asthma.
5. ISAR is a **cross-disciplinary initiative**, holding within it the combined experience of key thought leaders in severe asthma (clinicians & epidemiologists) as well as basic scientists, data analysts, and experts in database management and communication.

ISAR: International Severe Asthma Registry; http://isaregistries.org/

Aiming high

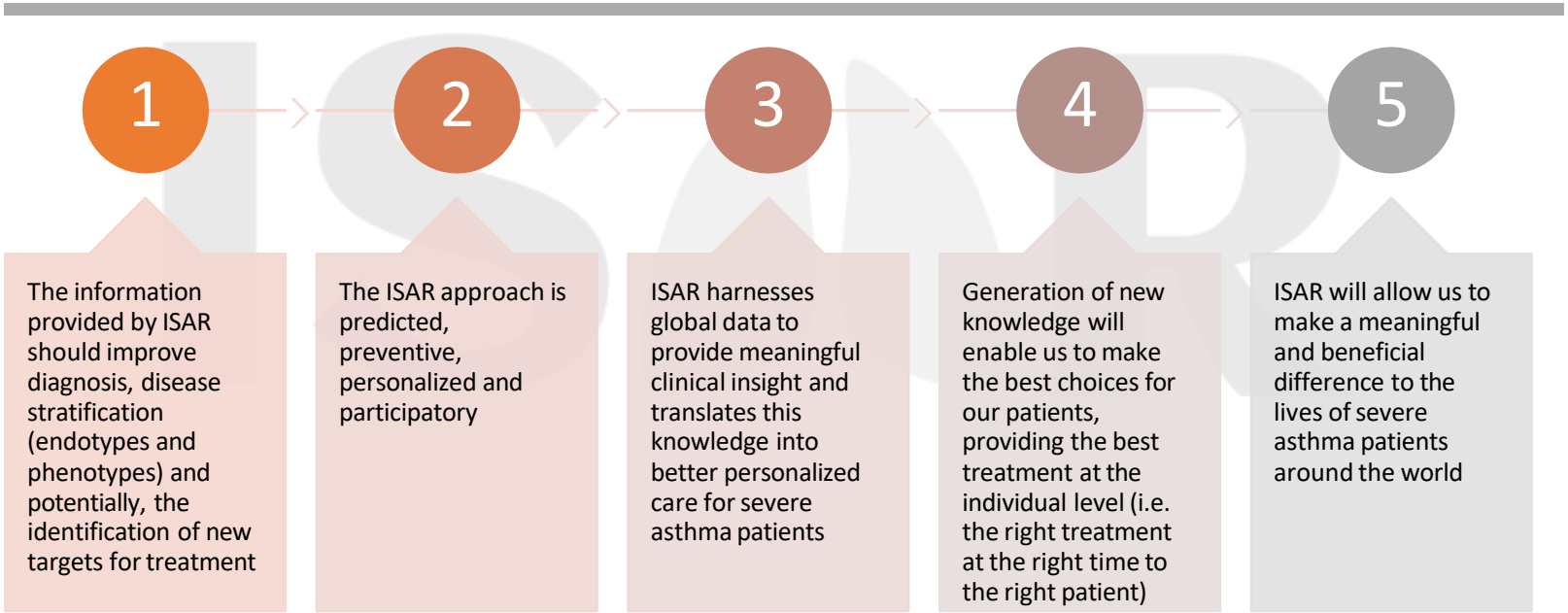
- The aim of ISAR is to **improve the care** of adults with severe asthma globally (both in primary and secondary care).
- This aim will be achieved via provision of a rich source of real-life data for scientific research which will enable:
  - A **better understanding** of the epidemiology, burden and clinical evolution of severe asthma
  - An **assessment of the real-world efficacy and safety** of new treatments and patient outcomes for severe asthma
  - The **exploration of management patterns** of severe asthma (exploring differences across healthcare systems)

ISAR: International Severe Asthma Registry; http://isaregistries.org/

The ISAR vision

- ISAR permits the **implementation** of existing knowledge in the severe asthma patient population, **generation** of new knowledge, and identification of the unknown, **promoting** new research
- By combining data from small registries into one large standardized registry, ISAR is able to **compare and contrast differences** between countries and care systems, something which until now was not possible in the global severe asthma framework
- ISAR has the potential to **robustly interpret** and **generally apply** observations, but as it continues to grow, the aim is to no longer simply estimate, but rather to **describe the severe asthma population in its entirety**

ISAR's potential



ISAR: International Severe Asthma Registry; http://isaregistries.org/

ISAR in the future

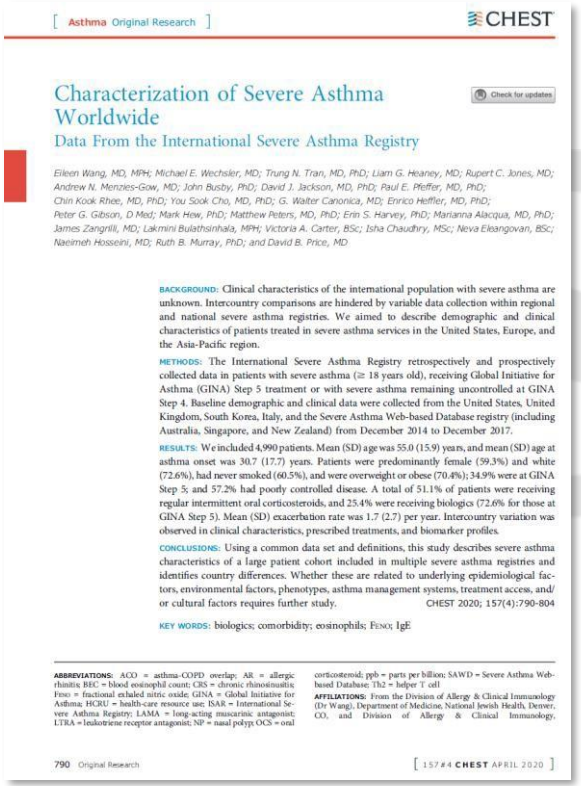
- Data provided by ISAR may be helpful in supporting, modifying and improving current severe **asthma guidelines**
- In the future ISAR may be more fully linked with EHRs to **streamline data collection** and with PROs to help patients and physicians make better personalized decisions
- Knowledge gathered by ISAR may be used to improve the management of those with moderate disease, to see whether **better care earlier may lead to better outcomes later**
- The ISAR database could be used to investigate the **effectiveness of novel approaches** to asthma treatment or the feasibility of new asthma treatment paradigms
- ISAR could be used, not only to examine asthma outcomes and identify patients likely to benefit, but also to assess **the cost-effectiveness** of the approach
- Potential benefits of ISAR are many and include **improved adherence and asthma control**, fewer ICS-related side effects and provision of a validated simplified asthma management programme offering greater convenience for patients

ISAR: International Severe Asthma Registry; http://isaregistries.org/

Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry

Eileen Wang et al, *CHEST* 2020;157(4):790-804.

Background and aims



[Asthma Original Research] CHEST

Characterization of Severe Asthma Worldwide

Data From the International Severe Asthma Registry

Check for updates

Eileen Wang, MD, MPH; Michael E. Wechsler, MD; Trung N. Tran, MD, PhD; Liam G. Heaney, MD; Rupert C. Jones, MD; Andrew N. Menzies-Gow, MD; John Busby, PhD; David J. Jackson, MD, PhD; Paul E. Pfeffer, MD, PhD; Chin Kook Rhee, MD, PhD; You Sook Cho, MD, PhD; G. Walter Canonica, MD; Enrico Heffler, MD, PhD; Peter G. Gibson, D Med; Mark Hew, PhD; Matthew Peters, MD, PhD; Erin S. Harvey, PhD; Marianna Alacqua, MD, PhD; James Zangrilli, MD; Lakmini Bulathsinhala, MPH; Victoria A. Carter, BSc; Isha Chaudhry, MSc; Neva Eleangovan, BSc; Naeimeh Hosseini, MD; Ruth B. Murray, PhD; and David B. Price, MD

BACKGROUND: Clinical characteristics of the international population with severe asthma are unknown. Intercountry comparisons are hindered by variable data collection within regional and national severe asthma registries. We aimed to describe demographic and clinical characteristics of patients treated in severe asthma services in the United States, Europe, and the Asia-Pacific region.

METHODS: The International Severe Asthma Registry retrospectively and prospectively collected data in patients with severe asthma (≥ 18 years old), receiving Global Initiative for Asthma (GINA) Step 5 treatment or with severe asthma remaining uncontrolled at GINA Step 4. Baseline demographic and clinical data were collected from the United States, United Kingdom, South Korea, Italy, and the Severe Asthma Web-based Database registry (including Australia, Singapore, and New Zealand) from December 2014 to December 2017.

RESULTS: We included 4,990 patients. Mean (SD) age was 55.0 (15.9) years, and mean (SD) age at asthma onset was 30.7 (17.7) years. Patients were predominantly female (59.3%) and white (72.6%), had never smoked (60.5%), and were overweight or obese (70.4%); 34.9% were at GINA Step 5; and 57.2% had poorly controlled disease. A total of 51.1% of patients were receiving regular intermittent oral corticosteroids, and 25.4% were receiving biologics (72.6% for those at GINA Step 5). Mean (SD) exacerbation rate was 1.7 (2.7) per year. Intercountry variation was observed in clinical characteristics, prescribed treatments, and biomarker profiles.

CONCLUSIONS: Using a common data set and definitions, this study describes severe asthma characteristics of a large patient cohort included in multiple severe asthma registries and identifies country differences. Whether these are related to underlying epidemiological factors, environmental factors, phenotypes, asthma management systems, treatment access, and/or cultural factors requires further study.

CHEST 2020; 157(4):790-804

KEY WORDS: biologics; comorbidity; eosinophils; FENO; IgE

ABBREVIATIONS: ACO = asthma-COPD overlap; AR = allergic rhinitis; BEC = blood eosinophil count; CRS = chronic rhinosinusitis; FENO = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; HCRU = health-care resource use; ISAR = International Severe Asthma Registry; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; NP = nasal polyp; OCS = oral corticosteroid; ppb = parts per billion; SAWD = Severe Asthma Web-based Database; Th2 = helper T cell

AFFILIATIONS: From the Division of Allergy & Clinical Immunology (Dr Wang), Department of Medicine, National Jewish Health, Denver, CO, and Division of Allergy & Clinical Immunology,

Background

- Clinical characteristics of the international population with severe asthma are unknown, and intercountry comparisons are hindered by variable data collection within regional and national severe asthma registries.

Aim

- To describe **baseline demographic and clinical characteristics** of patients treated in severe asthma services in the **United States**, **Europe**, and the **Asia-Pacific** region.

Full Text available here.

ISAR: International Severe Asthma Registry

Methods: A historical, registry study

- ISAR acts as a data custodian by including **patient-level data from other existing and newly-created registries** into the ISAR database at regular intervals.
  - Participating countries retain ownership of their own data but have agreed to provide access to anonymous patient-level data for approved research purposes.
- Before making the countrywide data available to ISAR, each country lead is responsible for overseeing **data collection and combining data** from any satellite sites.
  - This allows for the creation of a locally hosted central registry for the country's combined data, which can be used to **enhance local- and international-level research**.
- You may find ISAR's mission statement which fully describes how ISAR may improve our understanding of severe asthma here, and we described the protocol for registry development and management here.

Methods: Patient eligibility criteria

- Eligibility criteria were chosen to reflect patients with severe asthma in the **real-world setting** and to broaden the scope to include patients with **uncontrolled moderate to severe asthma**.
  - Additional information on definitions of severe asthma for registries participating in the ISAR Inclusion criteria can be found in the Online Supplement here.

- 18 years or older
- Received treatment at Global Initiative for Asthma (GINA) Step 5
- Had uncontrolled asthma at GINA Step 4 (at inclusion)
- Provided consent for their data to be included
  - Except in the United States, where consent was not required because data were deidentified
- Smokers and patients with asthma-COPD overlap (ACO) were NOT excluded

GINA: Global Initiative for Asthma; ACO: Asthma-COPD overlap

Methods: Data collection

- Data were collected from the following registries from **December 2014 to December 30, 2017**:

- National Jewish Health Electronic Medical Record (NJH EMR) Severe Asthma Cohort
  - United States, from all regions [predominantly Colorado and Wyoming] and a small proportion from other countries)

- UK Severe Asthma Registry (four sites)

- Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI; 15 sites)

- Severe Asthma Network Italy (SANI; 61 sites)

- Australasian Severe Asthma Registry (ASAR) hosted by the Thoracic Society of Australia and New Zealand (TSANZ)
  - i.e. Severe Asthma Web-based Database [SAWD], including patient data from Australia, Singapore, and New Zealand: 23 sites

Methods: Data collection

- ISAR captures **95 core variables** that were agreed through a modified Delphi process.
  - You may find our Delphi study which fully describes the process of reaching consensus on which core variables to collect in ISAR here.

Data collected	Definition
Number of exacerbations	• The number requiring rescue systemic corticosteroids in the past 12 months; • The United States used duration of OCS as a proxy for exacerbation (assuming one OCS course lasts ≥7 days), in line with GINA 2018 recommendations, previously published research, and based on discussion with the site investigator.
Prednisolone prescriptions	• Most were for at least 7 days for short-term use
Number of hospitalization and ED admissions for asthma	• The number in the past 12 months
Number of times invasive ventilation was used	• The number of episodes before data extraction
Comorbidity	• Based on a formal diagnosis or reliably inferred from relevant prescription data • For the United States, comorbidity data were captured using International Classification of Diseases, Tenth Revision codes for active diagnosis of comorbidity • Prescription data were used as a supplement to identify the comorbidity status of allergic rhinitis (AR) and eczema because their active diagnosis was underreported in the electronic medical records data.
Regular OCS use	• ≥90 days of OCS use in a year
Intermittent OCS use	• Prescription for repeated OCS use and/or ≥2 exacerbations in a 1-year period
Asthma control	• Categorized as controlled, partly controlled, or uncontrolled according to GINA criteria determined using the Asthma Control Test questionnaire or the Asthma Control Questionnaire

Methods: Statistical analysis

- Data were assessed using Stata version 14 (StataCorp) or SAS version 9.4 or 9.5 (SAS Institute) according to a predefined data analysis plan to minimize bias.
- Descriptive statistics were reported as categorical variables for all variables for the overall and country-specific patient populations.
- Health-care resource use (HCRU), IgE count, blood eosinophil count (BEC), and comorbidities also were stratified by severe asthma status and sex for the overall population.

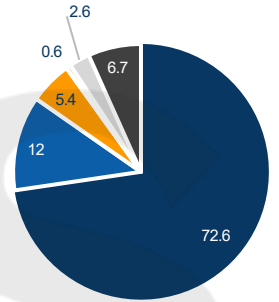
Results: Patient demographics

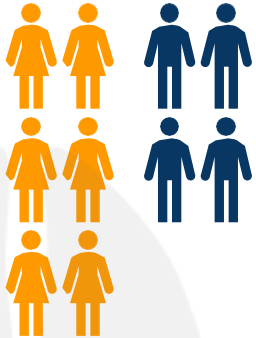
4,990
ELIGIBLE PATIENTS

MEAN AGE OF **55** YEARS

MEAN AGE OF **30.7** YEARS AT ASTHMA ONSET

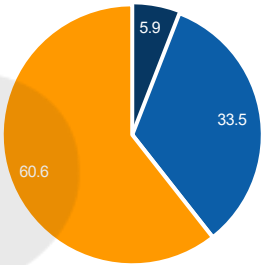
ETHNICITY





FEMALE (59.3%)
MALE (40.7%)

SMOKING STATUS



- Approximately 1/3 of individuals from the SAWD registry, SK, and the USA were ex-smokers.

70.4%
OVERWEIGHT/OBESE

51.1%
REGULAR INTERMITTENT ORAL CORTICOSTEROIDS

25.4%
RECEIVING BIOLOGICS (72.6% for those at GINA Step 5)

1.7
MEAN EXACERBATION RATE PER YEAR

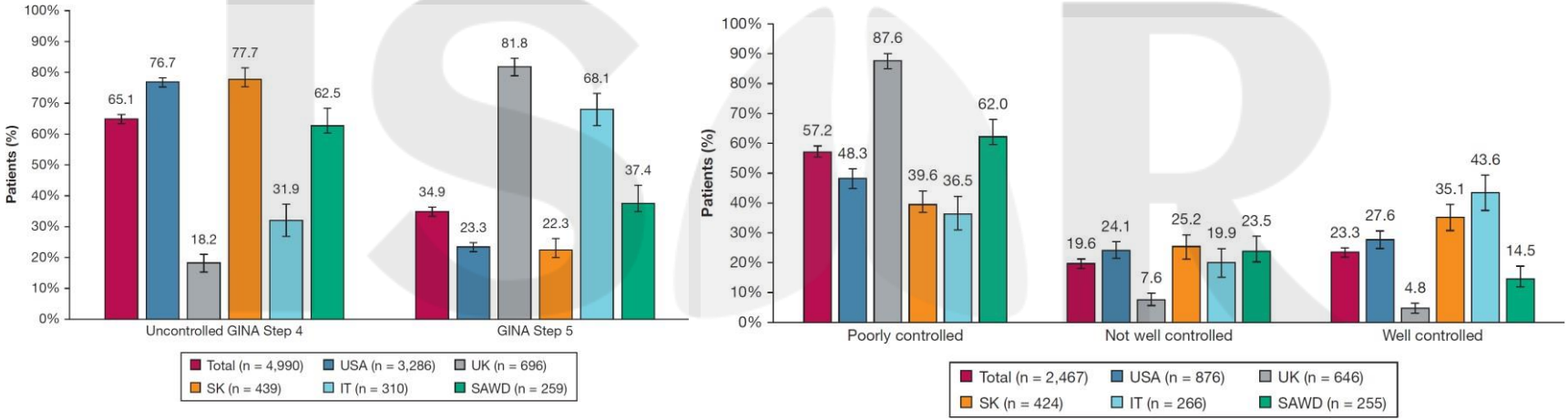
SK had the oldest patients, the lowest prevalence of patients who were overweight or obese, and the highest prevalence of current smokers.

USA: United States of America; SK: South Korea; SAWD: Severe Asthma Web-based Database

Results: Demographic characteristics

Asthma Control

- **34.9%** were at GINA Step 5 and **57.2%** had poorly controlled severe asthma,

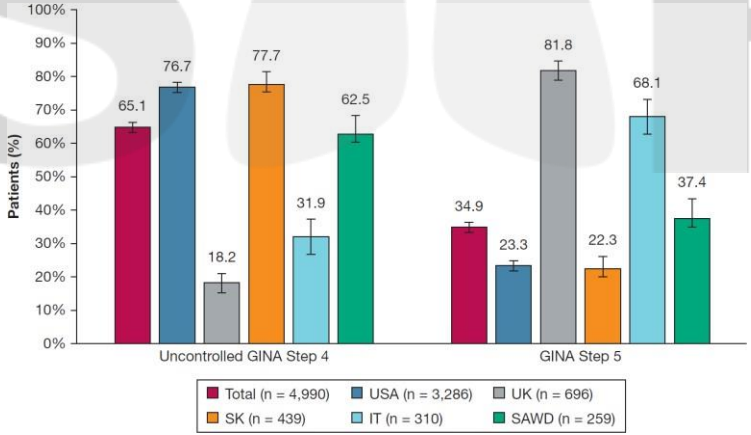


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Severity

- Most patients had **uncontrolled asthma at GINA Step 4**, and there was a **higher proportion of women** among patients with uncontrolled asthma at GINA Step 4 and among patients with asthma at GINA Step 5.
- Patients from the **UK and IT** tended to have **more severe** disease, and those from the **USA and SK** tended to have the **least severe** compared with patients in other countries.



USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Lung Function

- Percent predicted FEV_1 and FVC values appeared to be **independent of severity**, showed some **intercountry variability**, and showed **little postbronchodilator improvement**.
- Bronchoconstriction was considered **irreversible** for those in both severity groups and irrespective of smoking history. Some intercountry variability was also noted.
- These findings not only justify the ISAR inclusion criteria for severe asthma, but also ratify the definition of severe asthma as outlined by the European Respiratory Society (ERS) and American Thoracic Society (ATS).
  - Incidentally, those with low or limited reversibility are routinely excluded from asthma clinical trials.
- ISAR's inclusive nature and broad definition of severe asthma allowed for this population to be properly studied and characterised.

USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Age at Onset

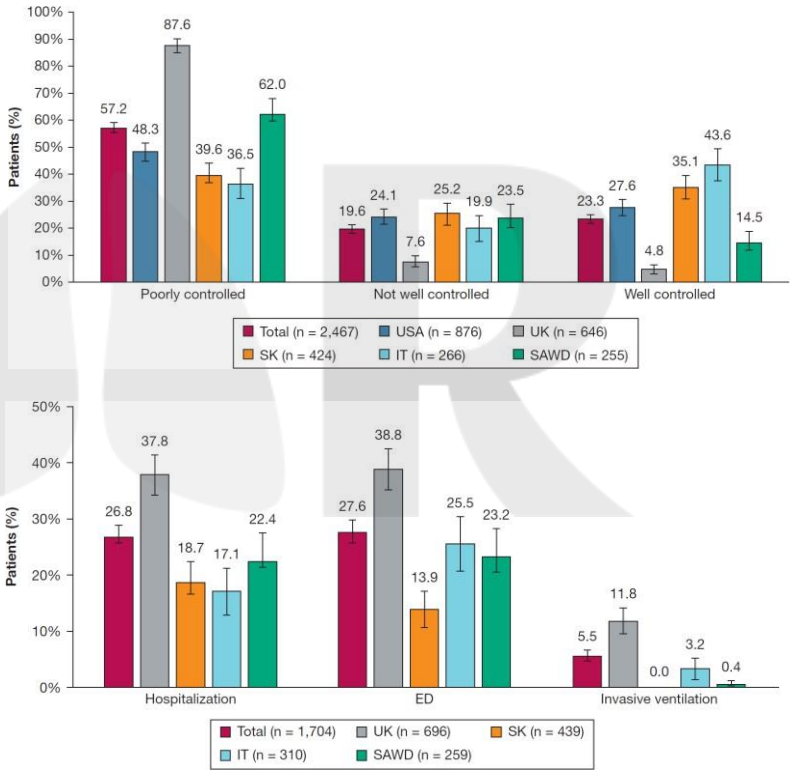
- The mean (SD) age at onset was **30.7** (17.7) **years**.
- 77.5% of patients developed asthma after the age of 12 years, and 34.4% developed it after the age of 40 years.
- Patients from the UK and the SAWD registry developed asthma slightly earlier than this, and those from South Korea and Italy slightly later.

USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Asthma Control and Health-Care Resource Use (HCRU)

- At entry to their national registry, 57.2% of patients had poorly controlled asthma.
  - This percentage was highest in the UK and the SAWD registry and lowest in IT and SK.
- The proportions of patients with well-controlled, partly controlled, and uncontrolled asthma were similar in the GINA Step 4 (uncontrolled asthma at entry) and GINA Step 5 groups.
- HCRU was high overall.
  - HCRU was highest in the UK, lowest in SK, and was slightly higher for patients at GINA Step 5.

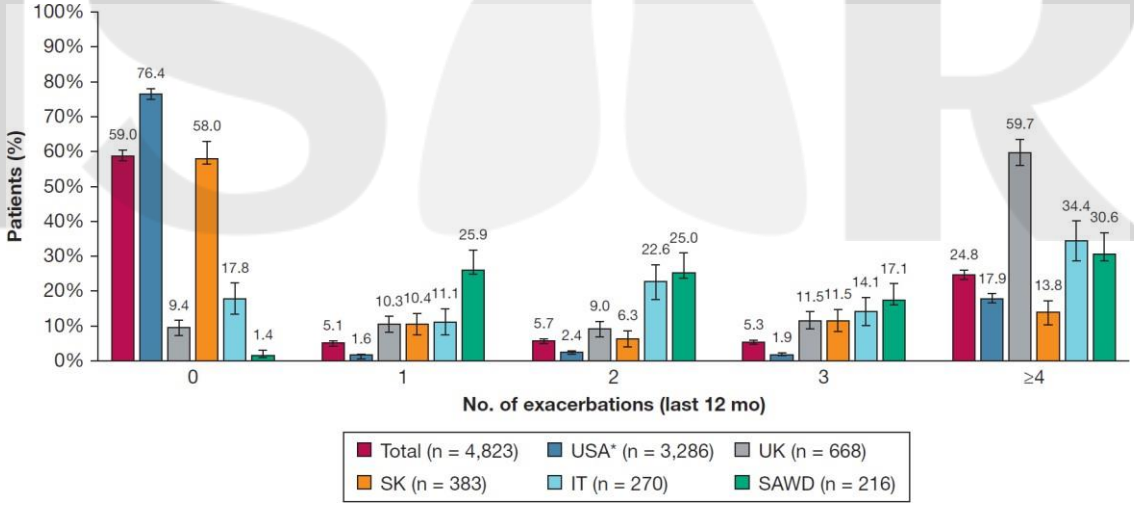


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Exacerbations

- The mean (SD) number of exacerbations (past 12 months) was 1.7 (2.7).
  - One quarter of patients reported ≥4 exacerbations.
  - The number of exacerbations was driven by severity, with most patients with uncontrolled asthma at GINA Step 4 (at inclusion) reporting 0 exacerbations (71.1%), whereas 42.5% of patients at GINA Step 5 reported ≥4 exacerbations.
  - The mean number of exacerbations was lowest in the United States and South Korea and highest in the United Kingdom.



USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Immunoglobulin E (IgE) Concentration

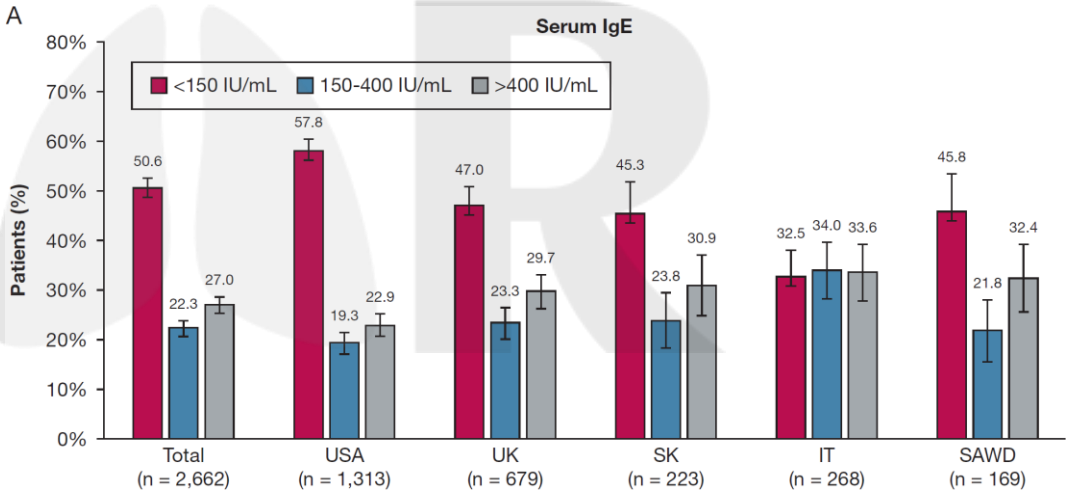
1. Overall, o**ne-half** of the patient population with severe asthma had **low IgE** concentrations, and IgE profile varied according to **severity**.

2. Gender:
   - More **women** had **low IgE** concentrations, and more **men** had **high IgE** concentrations, **irrespective of severity**.

3. Asthma Control:
   - More patients with uncontrolled asthma at **GINA Step 4** (vs GINA Step 5) had **low IgE** concentrations.

4. GINA:
   - More patients at GINA Step 5 (vs those with uncontrolled asthma at GINA Step 4) had **high IgE** concentrations.

5. Geographic location:
   - Most patients had **low IgE** serum concentrations.
   - An **even distribution** of patients across the IgE concentration categories was noted.
   - Patients showed a more **even split** between low vs. intermediate or high IgE concentrations.

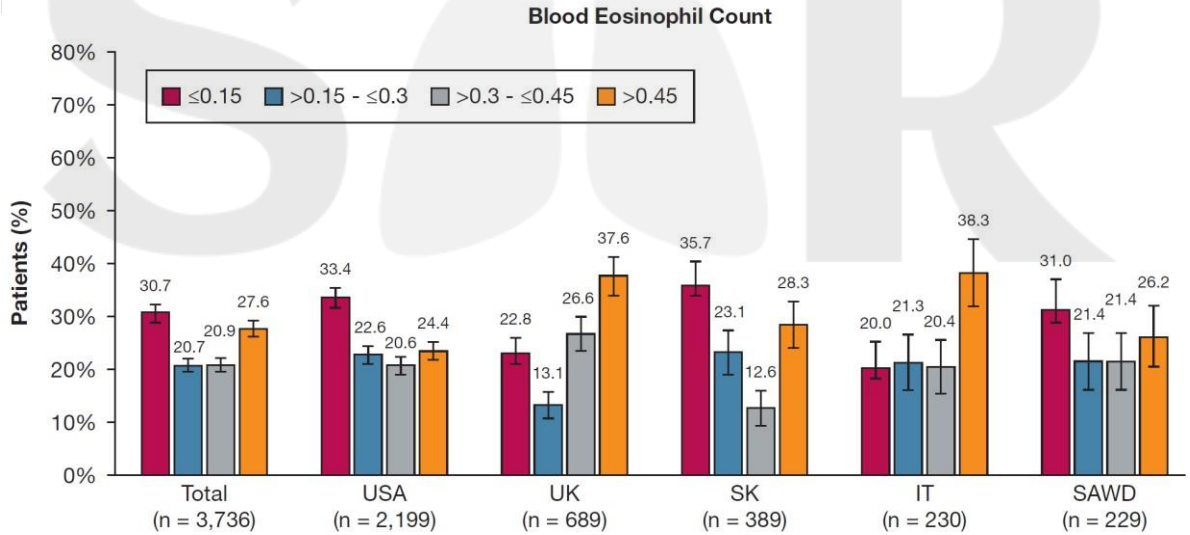


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Blood Eosinophil Count (BEC)

- 48.5% of patients had a BEC > 0.3x10⁹/L.
  - This comprises mostly patients from the UK and IT.
- Most patients had a BEC ≤ 0.3x10⁹/L.

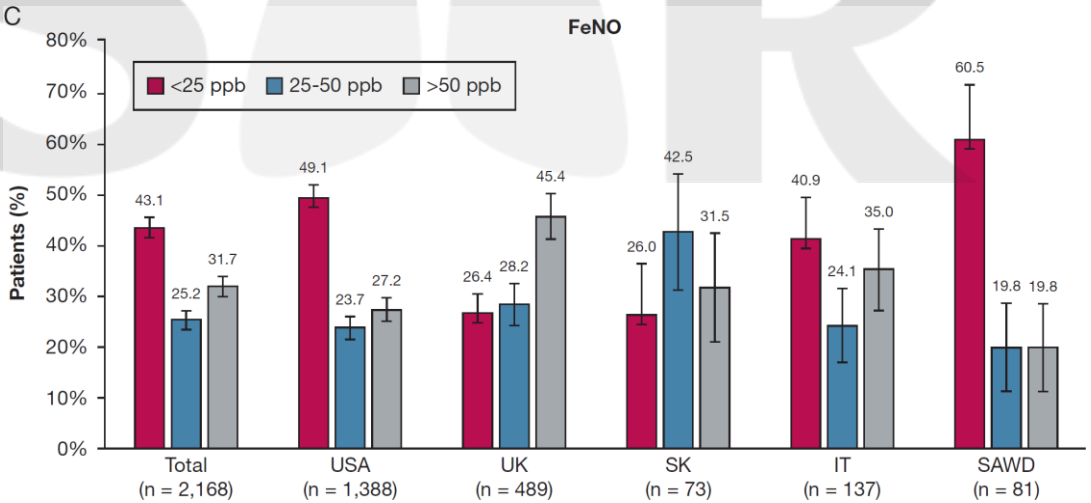


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Fractional Exhaled Nitric Oxide (FeNO)

- Overall, 43.1% of patients with severe asthma had fractional exhaled nitric oxide (FeNO) concentrations <25 parts per billion (ppb), and 56.9% had a concentration ≥25 ppb.
  - A similar proportion of patients had FeNO concentrations <25ppb and ≥25 ppb.
  - Most patients had FeNO concentrations ≥25ppb.
  - Most patients had FeNO concentrations <25 ppb.



USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Comorbidities

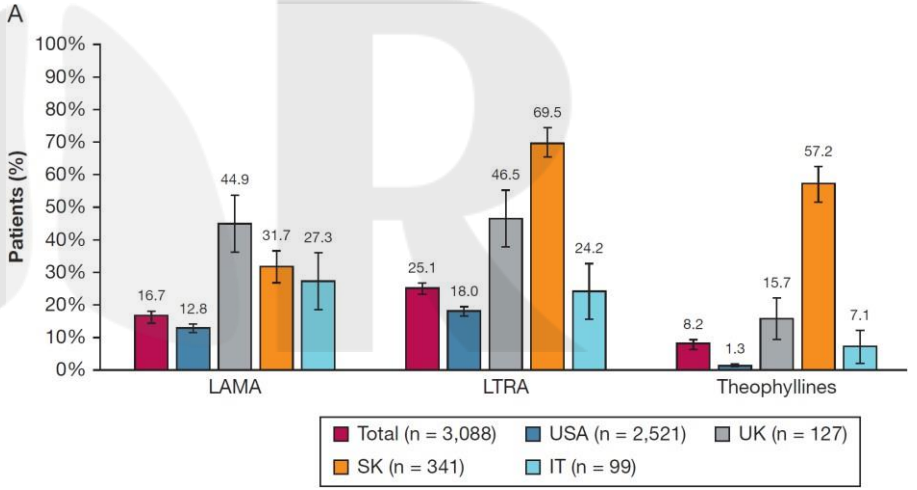
- Allergic rhinitis (AR) was the predominant comorbidity in the total population (49.4%), and in all countries.
  - This is followed by chronic rhinosinusitis (CRS; 21.4%), eczema (9.6%), and nasal polyps (NP; 7.3%).
- Highest prevalence of comorbid CRS (26.8%): 
- Highest eczema prevalence (20.5%): 
- Highest NP prevalence (22.3%): 

USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Treatment

- Half of all patients at GINA Step 4 or Step 5 were receiving repeated intermittent OCS.
  - Highest intermittent OCS use:
  - Lowest intermittent OCS use:
- All patients with uncontrolled asthma at GINA Step 4 were receiving inhaled corticosteroid and long-acting B_2-agonist therapy.
  - The most common add-on to inhaled corticosteroid and long-acting B_2-agonist was leukotriene receptor antagonist (LTRA), followed by long-acting muscarinic receptor antagonist (LAMA) and theophylline.
    - The same pattern was noted in the US and UK registries.
  - Theophylline was used more commonly than was LAMA:
  - LAMA was used more commonly than was LTRA:
  - Highest proportion of patients receiving add-on LAMA:
  - Add-on therapy was used sparingly for patients with uncontrolled asthma at GINA Step 4 (at baseline).

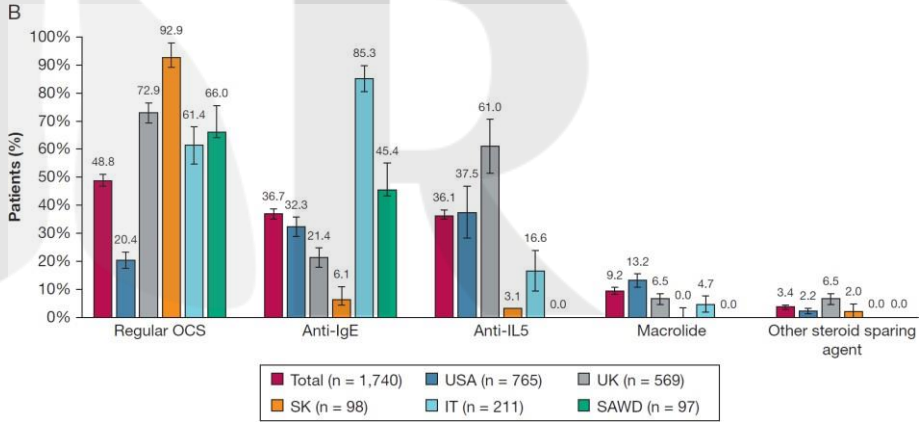


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

Treatment

- Add-on regular OCS was used by almost one-half of the patients at GINA Step 5.
  - A wide range of intercountry variability was noted for regular OCS use.
- Anti-IgE and anti-IL-5 were each used by approximately one-third of patients, and macrolides were prescribed for a minority.
- Overall, 72.6% of patients with severe asthma at GINA Step 5 were receiving therapeutic monoclonal antibody therapy (i.e. biologics).
  - Notably high rates in Italy and the United Kingdom, and a relatively low rate of use in South Korea.
- Predominant biologics:
  - Anti-IgE in IT and anti-IL-5 in the UK.
  - In the USA, there is a fairly even split between anti-IgE and anti-IL-5, with the highest proportion of patients receiving macrolides.



USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Conclusions

- This study provides the first description of an international population with managed severe asthma and identified **differences in demographic and clinical characteristics** both geographically and across health-care systems.

- Initial **country-specific biomarker profiles** have been identified, and further studies are required to determine whether inter-counter differences are related to:
  - Underlying epidemiological factors
  - Environmental factors
  - Phenotypes
  - Asthma management systems
  - Treatment access
  - Cultural factors

- Prospective data collection for the ISAR registry began in 2018 in Italy, the United States, South Korea, and the United Kingdom, and this ensures **better standardisation of data fields**, facilitating more **accurate cross-country comparisons** and **reducing any data incongruence** in upcoming ISAR data sets.

ISAR: International Severe Asthma Registry

International Severe Asthma Registry (ISAR): protocol for a global registry

J. Mark Fitzgerald et al, *BMC Medical Research Methodology* **20**, 212 (2020)

Background and aims

FitzGerald *et al. BMC Medical Research Methodology* (2020) 20:212
https://doi.org/10.1186/s12874-020-01065-0

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

International severe asthma registry (ISAR): protocol for a global registry

J. Mark FitzGerald[1], Trung N. Tran[2], Marianna Alacqua[2], Alan Altraja[3], Vibeke Backer[4], Leif Bjermer[5], Unnur Bjornsdottir[6], Arnaud Bourdin[7], Guy Brusselle[8,9], Lakmini Bulathsinhala[10], John Busby[11], Giorgio W. Canonica[12,13], Victoria Carter[10], Isha Chaudhry[10], You Sook Cho[14], George Christoff[15], Borja G. Cosio[16], Richard W. Costello[17], Neva Eleangovan[10], Peter G. Gibson[18,19], Liam G. Heaney[20], Enrico Heffler[12,13], Mark Hew[21], Naeimeh Hosseini[10], Takashi Iwanaga[22], David J. Jackson[23], Rupert Jones[24], Mariko S. Koh[25], Thao Le[10], Lauri Lehtimäki[26], Dora Ludviksdottir[27], Anke H. Maitland-van der Zee[28], Andrew Menzies-Gow[29], Ruth B. Murray[30], Nikolaos G. Papadopoulos[30,31], Luis Perez-de-Llano[32], Matthew Peters[33], Paul E. Pfeffer[34], Todor A. Popov[35], Celeste M. Porsbjerg[36], Chris A. Price[10], Chin K. Rhee[37], Mohsen Sadatsafavi[38], Yuji Tohda[22], Eileen Wang[39], Michael E. Wechsler[40], James Zangrilli[2] and David B. Price[10,41,42*]

Abstract

Background: Severe asthma exerts a disproportionately heavy burden on patients and health care. Due to the heterogeneity of the severe asthma population, many patients need to be evaluated to understand the clinical features and outcomes of severe asthma in order to facilitate personalised and targeted care. The International Severe Asthma Registry (ISAR) is a multi-country registry project initiated to aid in this endeavour.

Methods: ISAR is a multi-disciplinary initiative benefitting from the combined experience of the ISAR Steering Committee (ISC, comprising 47 clinicians and researchers across 29 countries, who have a special interest and/or experience in severe asthma management or establishment and maintenance of severe asthma registries) in collaboration with scientists and experts in database management and communication. Patients (≥18 years old) receiving treatment according to the 2018 definitions of the Global Initiative for Asthma (GINA) Step 5 or uncontrolled on GINA Step 4 treatment will be included. Data will be collected on a core set of 95 variables identified using the Delphi method. Participating registries will agree to provide access to and share standardised anonymous patient-level data with ISAR. ISAR is a registered data source on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ISAR's collaborators include Optimum Patient Care, the Respiratory Effectiveness Group (REG) and AstraZeneca. ISAR is overseen by the ISC, REG, the Anonymised Data Ethics & Protocol Transparency Committee and the ISAR operational committee, ensuring the conduct of ethical, clinically relevant research that brings value to all key stakeholders.

(Continued on next page)

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Background

- Severe asthma exerts a **disproportionately heavy burden** on patients and healthcare.
  - Due to the **heterogeneity** of the severe asthma population, many patients need to be evaluated to understand clinical features and disease outcomes in order to facilitate personalized and targeted care.
  - ISAR is a **multi-country registry project** initiated to aid in this endeavour.

Aims

- To describe the ISAR protocol for **registry development and management**, the **rationale behind each step** and the potential **benefits of ISAR** to the adult severe asthma population.

Full Text available here.

ISAR: International Severe Asthma Registry

Why is a global severe asthma registry needed?

1. **Connect** national/regional registries (retaining their values), enabling **inter-operability, data sharing and cross comparison**.
2. Have **sufficient statistical power** to answer pertinent clinical and research questions.
3. **Reduce the variability of data collected** by standardising variables across countries and regions.
4. Have pre-defined and extensive processes in place to ensure that **data capture and data harmonisation are of high quality**.
5. **Improve understanding** of the severe asthma population and **examine the response to therapies** according to nationality, phenotypes, biomarkers, treatment and socio-economic status.
6. Permit continued development with long-term patient follow-up to **enable a real-life understanding of severe asthma**.

ISAR design and governance

- ISAR is a **registered data source** on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), and is currently supported by **3 core collaborators**:

1. Optimum Patient Care (OPC),
   - A not-for-profit social enterprise providing medical research and services to improve the diagnosis, treatment and care of chronic diseases and is responsible for delivery of the ISAR database.
   - OPC is a co-funder of ISAR.

1. The Respiratory Effectiveness Group (REG), and
   - An investigator-led, not-for-profit research initiative promoting the value of real-life research.

2. AstraZeneca (AZ).
   - Together with OPC, AZ is a co-funder of ISAR.

- More details can be found on the ISAR website under the Collaboration Partners tab.

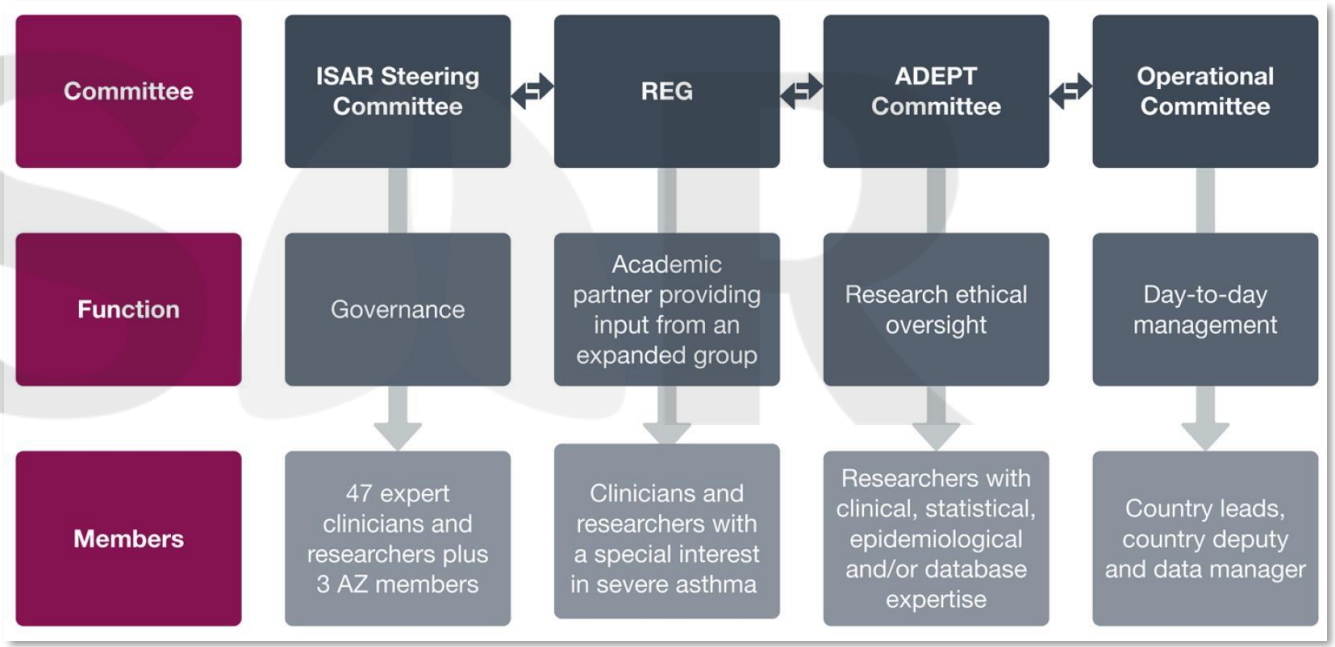
ISAR: International Severe Asthma Registry

Components of ISAR

ISAR: International Severe Asthma Registry

ISAR oversight: committees, functions and members

- ISAR is overseen by **4 governing bodies**:
  - The ISAR Steering Committee (ISC),
  - The Respiratory Effectiveness Group (REG),
  - The Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee, and
  - The ISAR Operational Committee.

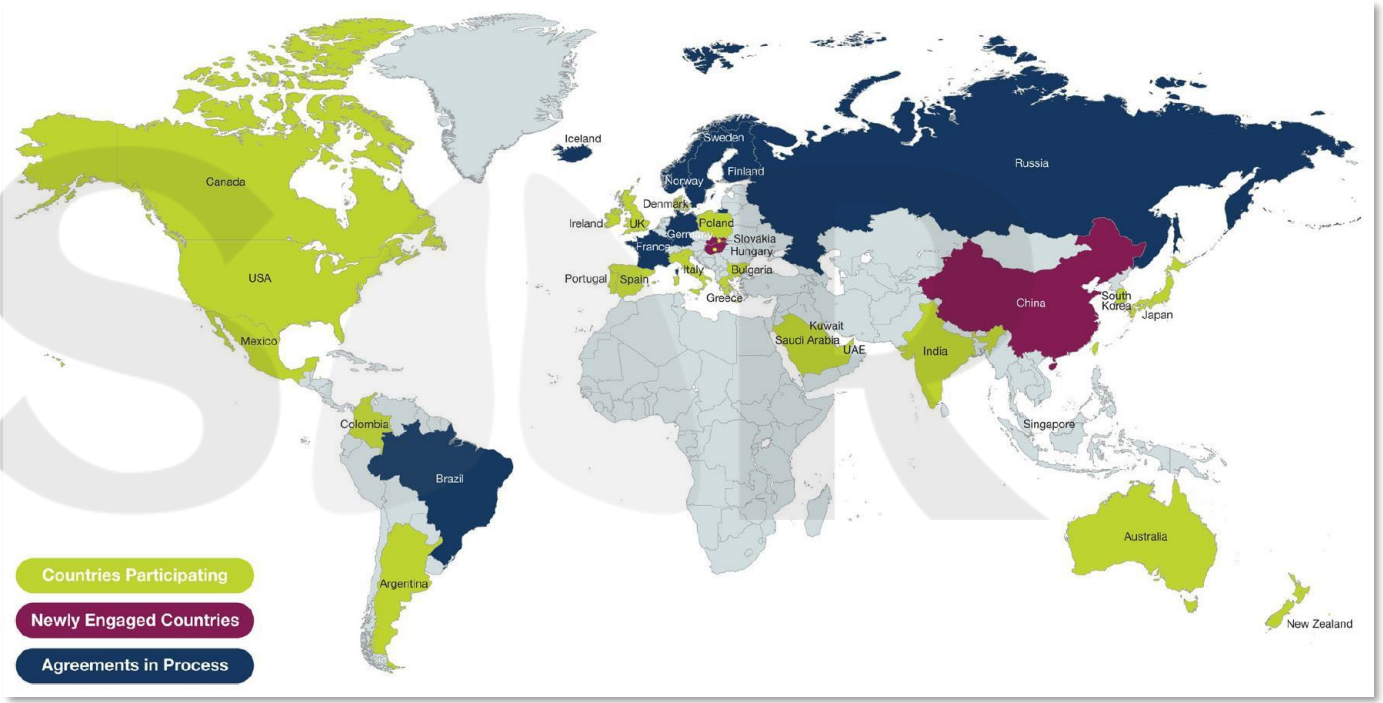


ISAR governance.

ISAR: International Severe Asthma Registry

ISAR registries, countries, and experts

- ISAR's membership currently includes registries from more than 30 participating countries, allowing for extensive collaboration and potentially new research ideas.



ISAR snapshot as at 21st July 2020.

ISAR: International Severe Asthma Registry

ISAR registries, countries, and experts

Registry Status	Collaborating Country	Registry Name	Start Year
Existing Registry	UK	UK Severe Asthma Registry	2006
	USA	National Jewish Health Electronic Medical Record (NJH EMR)	2010
	South Korea	Severe Asthma Work Group of Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI)	2010
	Germany	German Asthma Network (GAN)	2011
	Australia & New Zealand	Australasian Severe Asthma Registry (ASAR) hosted by TSANZ	2013
	Ireland	INhaler Compliance Assessment in Severe Unstable Asthma (INCA SUN)	2015
	Italy	Severe Asthma Network Italy (SANI)	2016
	Spain	Spanish Guideline on the Management of Asthma Database (GEMA-Data)	2017
New Registry	Denmark	Danish Severe Asthma Registry (DSAR)	2018
	Sweden	Swedish Severe Asthma Registry; *starting in 2020*	
	Finland	Currently collecting data independently from ISAR	2019
	Iceland	Currently collecting data independently from ISAR	2020
	Norway	*Starting in 2021*	
	Bulgaria	Bulgarian Severe Asthma Registry (BULSAR)	2018
	Portugal	Portugal Severe Asthma Registry (Registo de Asma Grave Portugal [RAG])	2018
	Russia	Russian Severe Asthma Registry (RSAR)	2018

Registry Status	Collaborating Country	Registry Name	Start Year
New Registry	Argentina	Argentinian Severe Asthma Registry	2019
	Belgium	Currently collecting data independently from ISAR	2018
	Brazil	Brazilian Severe Asthma Registry; *starting in 2020*	
	Canada	Canadian Severe Asthma Registry	2019
	China	*Starting in 2021*	
	Colombia	Colombian Severe Asthma Registry	2019
	France	French Severe Asthma Registry	2019
	Greece	Greek Severe Asthma Registry	2019
	India	Indian Severe Asthma Registry	2019
	Japan	Japanese Severe Asthma Registry	2019
	Kuwait	Kuwaitian Severe Asthma Registry	2018
	Mexico	Mexican Severe Asthma Registry	2019
	Poland	Polish Severe Asthma Registry	2020
	Saudi Arabia	Saudi Arabian Severe Asthma Registry	2019
	Singapore	Singapore Severe Asthma Registry (S-SAR)	2020
	Taiwan	Taiwanese Severe Asthma Registry	2019
	UAE	UAE Severe Asthma Registry	2019

ISAR patients

- On average, **2000 new patients** will be enrolled globally each year, for **at least 5 years** from the start of ISAR (May 2017).
- Eligibility criteria were chosen to **reflect severe asthma patients in the real-world setting** and to broaden the scope to **include patients with uncontrolled moderate-to-severe asthma**.
  - Patients with asthma-chronic obstructive pulmonary disease overlap (ACO) will also be included.

Inclusion	Exclusion
Adult (≥18 years old) patients with severe asthma	Lack of informed consent for participation
Undergoing GINA Step 5 treatment or Uncontrolled on GINA Step 4 treatment – defined as at least one of the following (per ATS/ERS guidelines): • Poor symptom control: ACQ consistently > 1.5, ACT < 20 (or 'not well controlled') or GINA not well controlled • Airflow limitation: Pre-bronchodilator FEV_1 < 80% predicted, with reduced FEV_1/FVC (defined as less than the lower limit of normal) • Serious exacerbations: ≥1 hospitalisation, ICU stay or mechanical ventilation in the previous year • Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids with each course > 3 days in the previous year	

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; ATS: American Thoracic Society; ERS: European Respiratory Society; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; ICU: intensive care unit; ISAR: International Severe Asthma Registry

ISAR core variables

- **95** standardised and mandatory core variables which include data on **patient demographics, medical history and diagnostics, clinical characteristics, patient-reported outcomes** and **treatment management plans** should be collected by any registry wishing to contribute data to ISAR.

I. Core variables[a]	II. Bolt-On variables	III. Optional research variables
• Inclusion criterion • Patient details • Occupation • Medical history • Comorbidity • Blood/Sputum • Diagnostics (biomarkers) • Lung function • Allergen testing • Asthma control (GINA) • Asthma medication • Adherence • Systematic assessment and management plan	***SAFETY*** • Severe infection • Malignancy • Anaphylactic reaction ***EFFECTIVENESS*** • Comorbidity • Dosage • Exacerbation • Medication switching	• Occupation history • Additional medical history • Additional comorbidities • Additional diagnostics • Additional spirometry variables • Severe asthma biomarkers • Additional asthma control • Quality of Life/Depression & Anxiety Questionnaire • Other asthma medication • Paediatric severe asthma

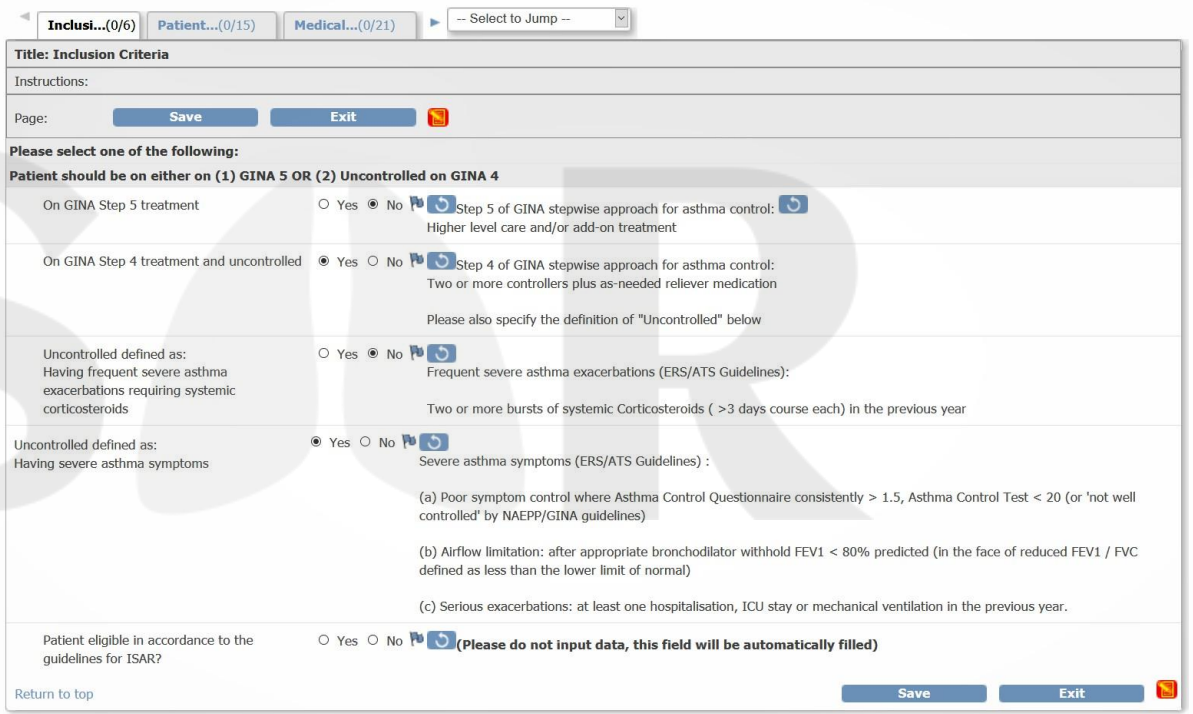
Newest developments:

- An **ISAR patient response questionnaire** to assist affected sites with collecting patient data **remotely** in the era of Covid-19.
  - **Optional Covid-19 variables included** for patients to complete, allowing ISAR to develop and evolve within the changing global respiratory environment.

GINA: Global Initiative for Asthma; ISAR: International Severe Asthma Registry

ISAR data collection

- Data will be collected using a comprehensive **electronic case report form** (eCRF).
- Registries can either enter data directly in the eCRFs or opt to collect the data on paper and enter it into the eCRF at a later date based on their clinical process.
- Data collection will comply with the standards established by the ISC and agreed by each participating registry.
  - This allows datasets across all registries to be **combined**, further **standardising ISAR data effectively**.



A screenshot of the ISAR eCRF.

ISAR: International Severe Asthma Registry

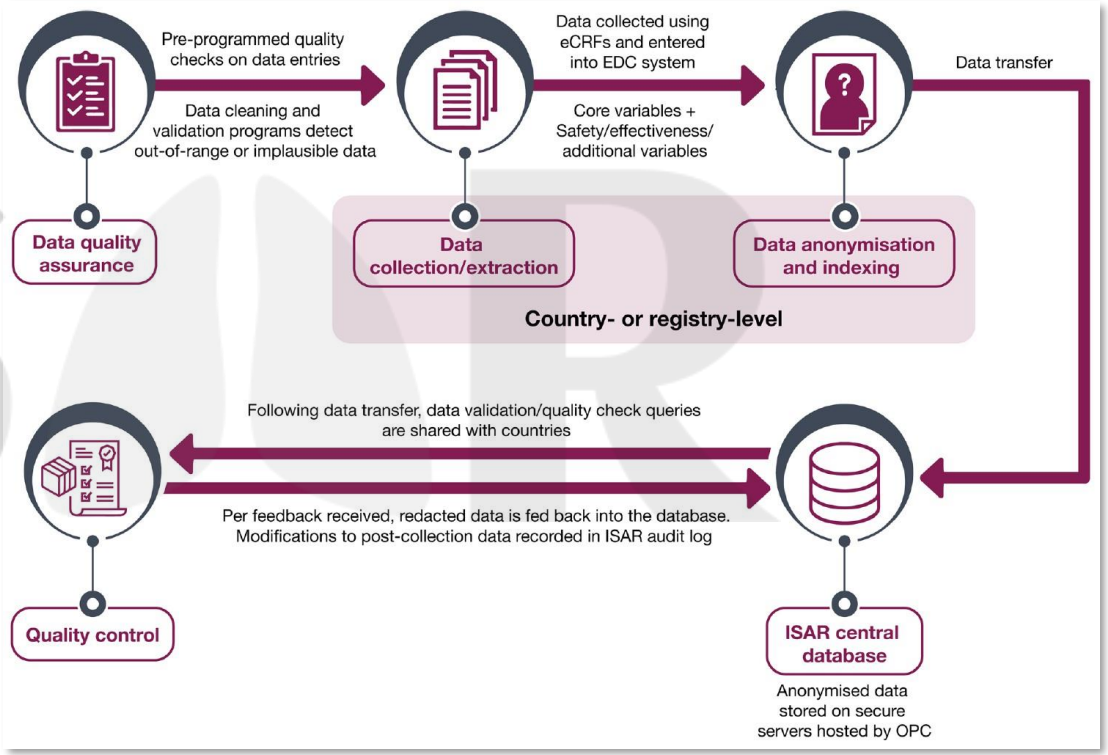
ISAR electronic data capture (EDC)

- All new data will be entered directly into the EDC system (REDCap or OpenClinica).
- EMR data will be integrated with eCRF data from the EDC systems and will be de-identified prior to importing it to the central data warehouse where the data will be stored with a unique patient identification number.
- All participating sites will
  - have **access and ownership** to their own data,
  - be **trained on** using the EDC systems, and
  - be responsible for extracting batches of patient data at a quarterly frequency for inclusion to ISAR.
- OPC will be responsible for
  - **monitoring and mapping the data** into the central ISAR data repository and safely transporting and importing each batch into the central ISAR data repository.
- For countries with data sharing regulations de-limiting data privacy, ISAR will accommodate anonymised data sharing on a project-by-project basis.

EMR: electronic medical records; ISAR: International Severe Asthma Registry; OPC: Optimum Patient Care; SNOMED CT: systematized nomenclature of medicine clinical terms

ISAR database

- Data will be collected from a combination of **existing and new registries** with systems that are largely aligned with the standard data collection fields of ISAR e.g.
  - Dendrite Clinical Systems (UK)
  - REDCap (Italy)
  - OpenClinica (e.g. Canada, Greece, and Japan)
  - Zitelab (Denmark)
- Data imported will be as per instructions listed in a separate **ISAR data management plan**, which will be provided to all registries.



Data acquisition, **quality control** and **management of ISAR** are illustrated above.

eCRF: electronic case report form; EDC: Electronic Data Capture; ISAR: International Severe Asthma Registry; OPC: Optimum Patient Care

ISAR data quality and management

- Data quality is ensured before and during the data collection process through a series of **pre-programmed data quality checks** that automatically detect out-of-range or anomalous entries on the eCRF.
  - To minimise data entry errors, most of the fields requested on the ISAR eCRF are **numeric or categorical**.

- After data extraction, further **data cleaning and validation processes** will also be performed on all data to **maximise data quality control**.
  - Ad hoc queries (done at the country level or OPC level) will be generated within the electronic data capture (EDC) system and followed up with country data managers and/or the country study coordinator (where applicable) for resolution.

- All data modifications will be recorded in an audit log and all data transfers and disputes will be shared and documented in the country and ISAR central data manager logs.

eCRF: electronic case report form; ISAR: International Severe Asthma Registry

ISAR data ownership

- Each country **retains ownership** of their data.
- All participating countries agree to allow output of data from their respective registries upon joining ISAR for collaborative independent research approved by the ISC and ADEPT.
- The extraction and integration of datasets for ethically approved research studies will be managed by OPC.
- The nature and frequency of data extraction and transfer (quarterly) from registries to OPC are detailed in the ISAR data sharing agreement.

ADEPT: Anonymised Data Ethics, Protocols & Transparency; ISAR: International Severe Asthma Registry; ISC: ISAR Steering Committee; OPC: Optimum Patient Care

ISAR research

- The research goal of ISAR is to complete **eight** global research projects and **eight** project-specific datasets for academic and commercial research by ISAR members **over a 5-year period.**
- New collaborators may also **join ISAR** by clicking the 'Join the registry' tab on the ISAR home page.
- ISC members, country leads, contributors and visitors to the ISAR website may **contribute research ideas** by clicking the 'Submit a proposal or request research' tab on the ISAR home page.
  - All research ideas will be reviewed, assessed and prioritised by the ISC.
- ISAR is also open to collaborating with and extracting data from other databases which consist of datasets that are not part of the core ISAR projects but have alignment of variables, enabling the combination of data for specific projects.

ISAR: International Severe Asthma Registry; ISC: ISAR Steering Committee

Key strengths of ISAR

- You may find the ISAR mission statement which fully describes how ISAR may improve our understanding of severe asthma here.

Global reach	High quality data	Organisational structure	Database experience	Inclusivity	Expertise
ISAR is the first global severe asthma registry large enough to ensure sufficient power to reduce variability, to increase external validity, to answer important clinical questions and to allow wide implementation	ISAR consistently facilitates the collection of standardised, individualised and comprehensive data	ISAR has in place scientific, academic and ethical oversight providing confidence in data collection, analysis and dissemination	ISAR has extensive experience in large data collection and management	ISAR operates on the principle of inclusivity and collaboration, continually seeking new partners, and prioritising relevant research pertinent to severe asthma	ISAR is a cross-disciplinary initiative, providing the experience of expert clinicians and researchers in severe asthma, basic scientists, data analysts and experts in database management and communication

ISAR: International Severe Asthma Registry

Future direction of ISAR

- ISAR plans to **include additional countries** covering Africa, Asia, South America, the Middle East, and Eastern Europe.
- Other prospects include **linkages with other databases** and **integration with electronic medical records**.
- Longitudinal research in patients with less severe asthma and the **development of a paediatric ISAR** in order to cover the entire severe asthma life cycle are also being considered.

ISAR: International Severe Asthma Registry

Conclusions and Summary

- By acting as a **data custodian** of international patient data, ISAR works as an **open border** initiative, providing a platform to **facilitate data sharing**.
- The registry provides **enough statistical power** to **address important research questions** in severe asthma aimed at a wide range of topics.
- Through ISAR, it is expected that the harmonised, standardised nature of data contained and the collaborative partnerships being made possible may **reveal previously unthought of or neglected research avenues**.
- In summary, ISAR aims to **offer a rich source of real-life data** for scientific research to understand and improve patient outcomes in severe asthma.
- Furthermore, the registry will provide an international platform for research collaboration in respiratory medicine, with the overarching aim of **improving primary and secondary care of adults with severe asthma globally**.

ISAR: International Severe Asthma Registry

Respiratory Effectiveness Group
Sociedad Española de Neumología y Cirugía Torácica SEPAR
Reunión Científica con el Reconocimiento SEPAR
Scientific Meeting with the Recognition of SEPAR
THE RESPIRATORY EFFECTIVENESS GROUP REG SUMMIT 2021 VIRTUAL
Capitalising on real-life research for best clinical guidance
18-20 March 2021

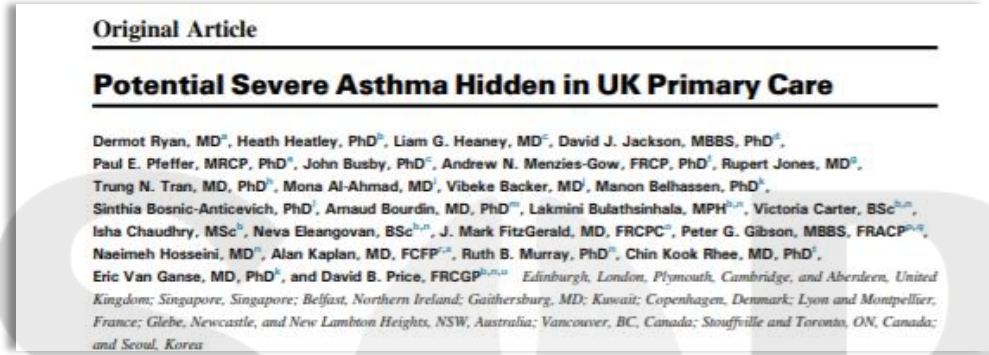
Potential Severe Asthma Hidden in UK Primary Care

Dermot Ryan, Heath Heatley, Liam G Heaney, David J Jackson, Paul E Pfeffer, John Busby, Andrew N Menzies-Gow, Rupert Jones, Trung N Tran, Mona Al-Ahmad, Vibeke Backer, Manon Belhassen, Sinthia Bosnic-Anticevich, Arnaud Bourdin, Lakmini Bulathsinhala, Victoria Carter, Isha Chaudhry, Neva Eleangovan, J Mark FitzGerald, Peter G Gibson, Naeimeh Hosseini, Alan Kaplan, Ruth B Murray, Chin Kook Rhee, Eric Van Ganse, David B Price

The Journal of Allergy and Clinical Immunology: In Practice 2021;9(4):1612-1623.e9

opc Global

Background

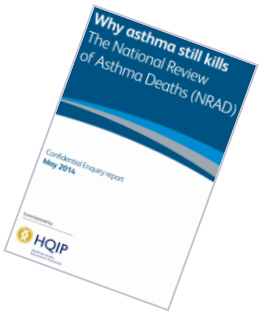


Original Article

Potential Severe Asthma Hidden in UK Primary Care

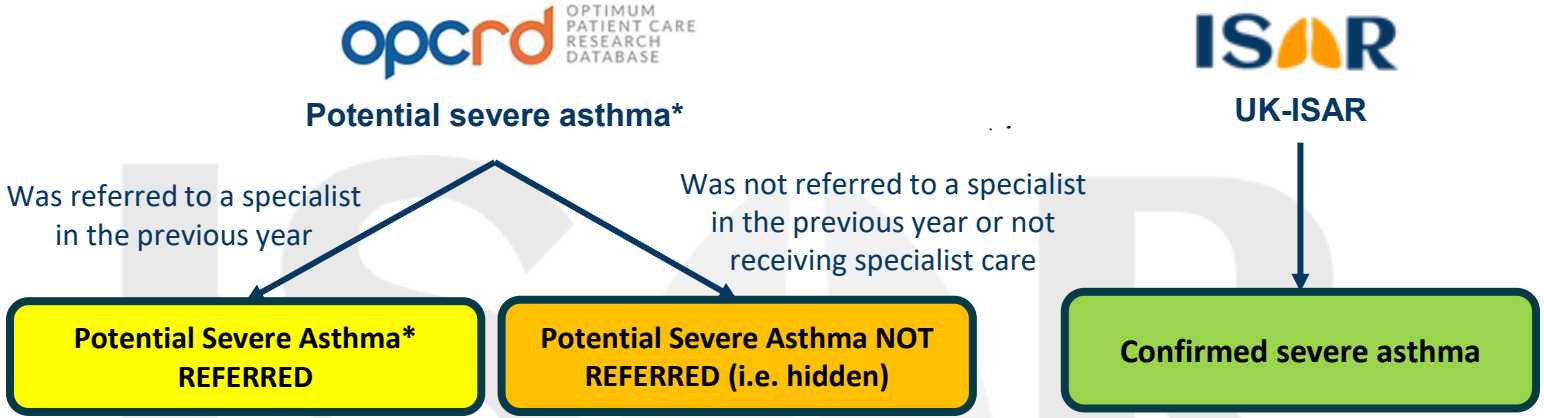
Dermot Ryan, MD[a], Heath Heatley, PhD[b], Liam G. Heaney, MD[c], David J. Jackson, MBBS, PhD[d], Paul E. Pfeffer, MRCP, PhD[e], John Busby, PhD[c], Andrew N. Menzies-Gow, FRCP, PhD[f], Rupert Jones, MD[g], Trung N. Tran, MD, PhD[h], Mona Al-Ahmad, MD[i], Vibeke Backer, MD[j], Manon Belhassen, PhD[k], Sinthia Bosnic-Anticevich, PhD[l], Arnaud Bourdin, MD, PhD[m], Lakmini Bulathsinhala, MPH[b,n], Victoria Carter, BSc[b,n], Isha Chaudhry, MSc[b], Neva Eleangovan, BSc[b,n], J. Mark FitzGerald, MD, FRCPC[o], Peter G. Gibson, MBBS, FRACP[p,q], Naeimeh Hosseini, MD[o], Alan Kaplan, MD, FCFP[r,s], Ruth B. Murray, PhD[o], Chin Kook Rhee, MD, PhD[t], Eric Van Ganse, MD, PhD[k], and David B. Price, FRCGP[b,n,u] *Edinburgh, London, Plymouth, Cambridge, and Aberdeen, United Kingdom; Singapore, Singapore; Belfast, Northern Ireland; Gaithersburg, MD; Kuwait; Copenhagen, Denmark; Lyon and Montpellier, France; Glebe, Newcastle, and New Lambton Heights, NSW, Australia; Vancouver, BC, Canada; Stouffville and Toronto, ON, Canada; and Seoul, Korea*

- Referral of difficult-to-treat asthma to specialist care is associated with **improved outcomes**[1].
- 19% of asthma deaths in the UK were associated with **potentially avoidable factors** related to access to specialist care[2].
- Identifying patients with potential severe asthma (PSA) who are hidden in primary care (i.e., not referred for specialist review) remains a challenge.



1. Erickson S et al. *Health Serv Res* 2005;40(5 Pt 1):1443-1465, 2. Royal College of Physicians. Accessed via: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills, 3. Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9

A Historical Cohort Study - Design



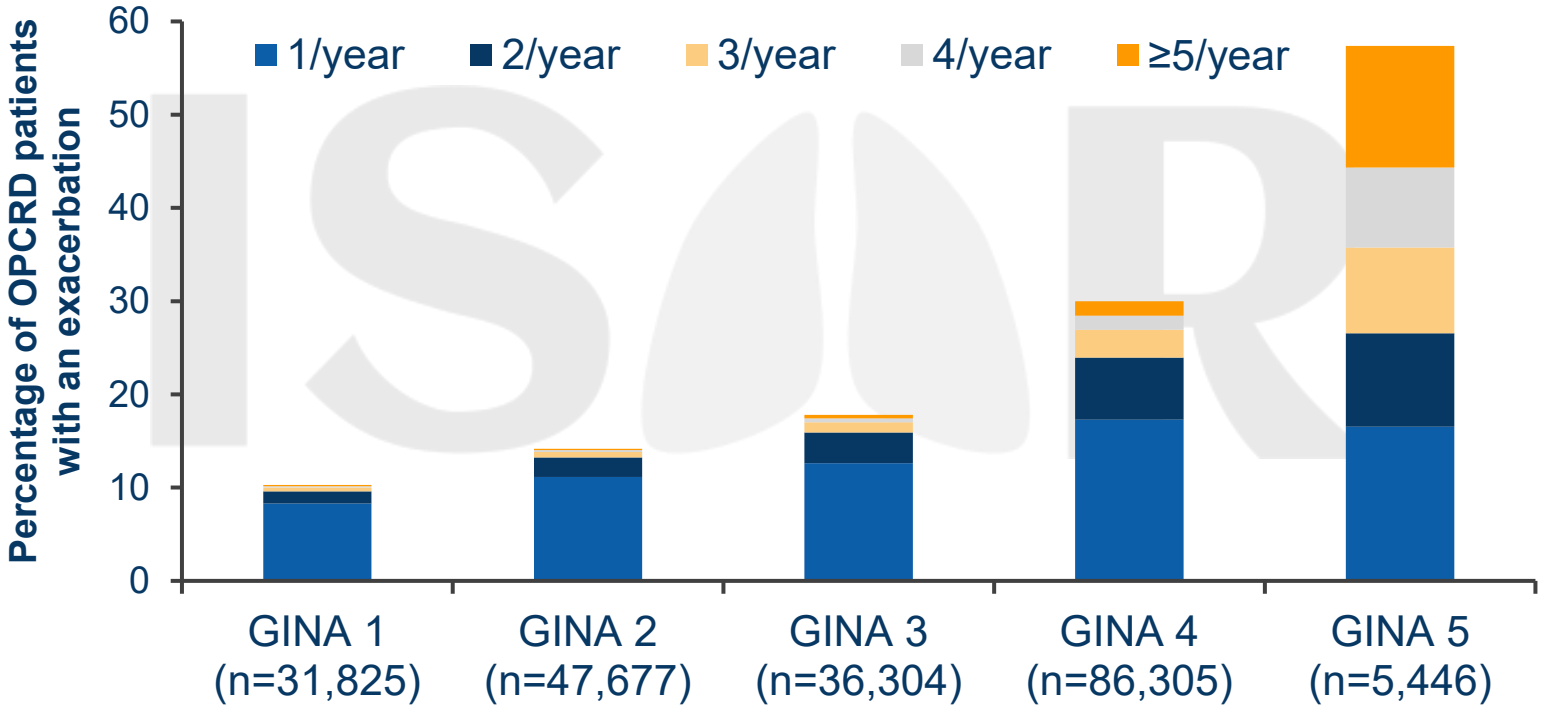
1. **Objective 1**: To identify patients with potential severe asthma (PSA)* managed in UK primary care
2. **Objective 2**: To estimate how many are hidden
3. **Objective 3:** To compare the demographics and clinical characteristics of patients with PSA with those of patients with a confirmed severe diagnosis

*Potential Severe Asthma Definition: Receiving treatment at GINA Step 4 & experiencing ≥2 exacerbations/year OR receiving treatment at GINA Step 5

Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9

Many Patients Managed in Primary Care Experience Frequent Exacerbations – Regardless of GINA Step

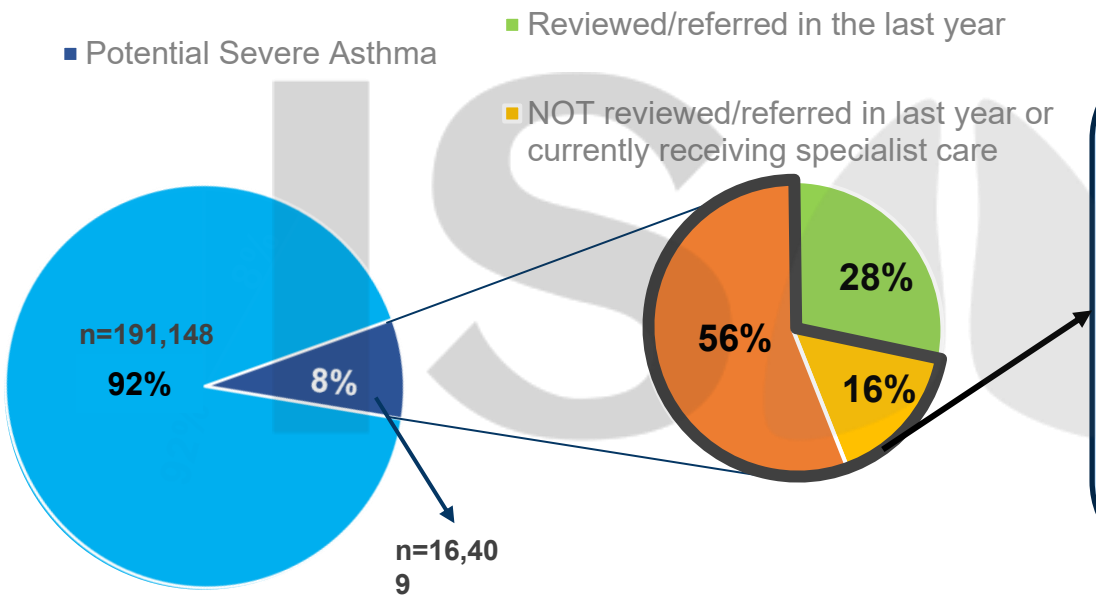
N=207,557



GINA, Global Initiative for Asthma; ISAR, International Severe Asthma Registry; OPCRD, Optimum Patient Care Research Database

Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9

An Estimated 8% of Asthma Patients In Primary Care Were Identified As Potential Severe Asthma Patients



- 72% were unreferred
- Common characteristics among these patients:
  - Poor lung function
  - Uncontrolled asthma
  - Comorbdities: allergic rhinitis & eczema
  - Ex-smoker
  - Female
  - In their 60s
  - Overweight/obese

Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9

Conclusion

- A significant proportion of severe asthma patients remain hidden in primary care
- The majority of these patients are never referred to a specialist and may be managed with long-term OCS
- Understanding the characteristics associated with potential severe asthma may help with earlier identification

Ryan D, Price D et al. J Allergy Clin Immunol Pract 2021;9(4):1612-1623.e9

Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry

Eve Denton, David B. Price, Trung N. Tran, G. Walter Canonica, Andrew Menzies-Gow, J. Mark FitzGerald, Mohsen Sadatsafavi, Luis Perez de Llano, George Christoff, Anna Quinton, Chin Kook Rhee, Guy Brusselle, Charlotte Ulrik, Njira Lugogo, Fiona Hore-Lacy, Isha Chaudhry, Lakmini Bulathsinhala, Ruth B. Murray, Victoria A. Carter, Mark Hew

Denton E., et al. *JACI In Pract* 2021:Article In press

The ISAR Initiative

- **A large observational registry with pooled data from multiple countries has the statistical power to better understand severe asthma epidemiology, clinical management and outcomes across international populations.**

The Broad Inclusion Criteria For Enrolment Captures a Diverse Patient Population Rarely Represented in RCTs

Inclusion

- Adult ≥18 years old with severe asthma
- Undergoing GINA Step 5 treatment OR uncontrolled on GINA Step 4 treatment
  - Uncontrolled as defined by ERS/ATS guidelines
- Poor symptom control where ACQ is consistently > 1.5, ACT <20
- Airflow limitation where pre-bronchodilator FEV_1 <80% predicted, with reduced FEV_1/FVC
- Serious exacerbations with ≥1 hospitalization, ICU stay or mechanical ventilation in the previous year
- Frequent severe exacerbations with ≥2 bursts of SCS with each course >3 days in the previous

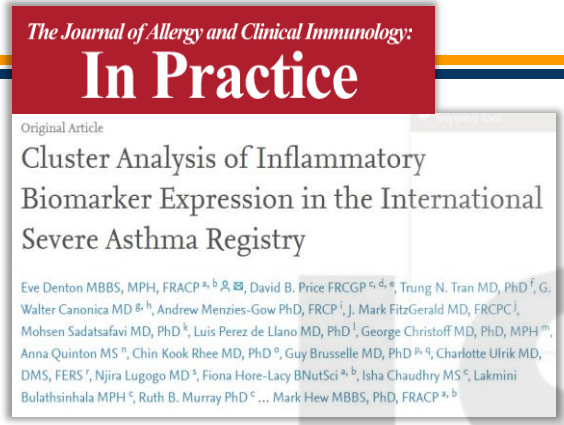
- ✓ Smokers
- ✓ ACO
- ✓ Moderate-to-severe asthma

Exclusion

- Lack of informed consent for participation

Fitzgerald JM, Price DB et al. BMC Med Res Methodol 2020;20:212

BRISAR: Background & Aim


The Journal of Allergy and Clinical Immunology: In Practice

Original Article

Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry

Eve Denton MBBS, MPH, FRACP [a, b], David B. Price FRCGP [c, d, e], Trung N. Tran MD, PhD [f], G. Walter Canonica MD [g, h], Andrew Menzies-Gow PhD, FRCP [i], J. Mark FitzGerald MD, FRCPC [j], Mohsen Sadatsafavi MD, PhD [k], Luis Perez de Llano MD, PhD [l], George Christoff MD, PhD, MPH [m], Anna Quinton MS [n], Chin Kook Rhee MD, PhD [o], Guy Brusselle MD, PhD [p, q], Charlotte Ulrik MD, DMS, FERS [r], Njira Lugogo MD [s], Fiona Hore-Lacy BNutSci [a, b], Isha Chaudhry MS [c], Lakmini Bulathsinhala MPH [c], Ruth B. Murray PhD [c] ... Mark Hew MBBS, PhD, FRACP [a, b]

Inflammatory pathway in severe asthma	Associated biomarker
Allergy	Serum IgE
Eosinophilic inflammation	Blood eosinophil count
Airway epithelial dysregulation	FeNO

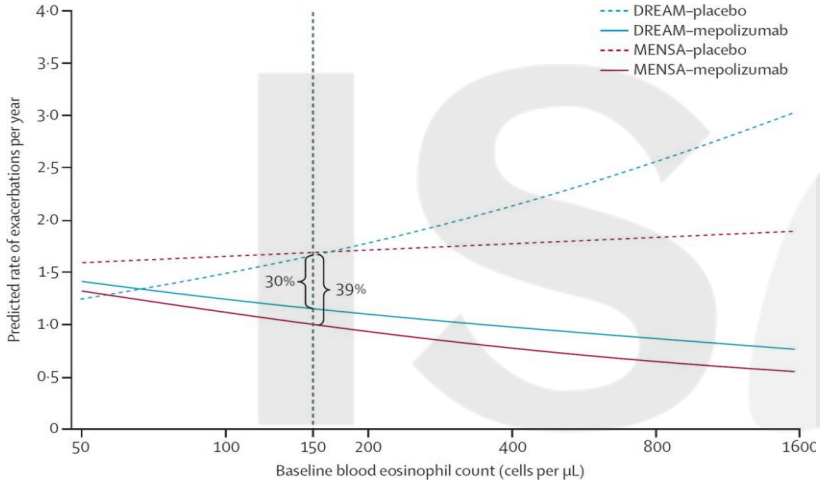
- Severe asthma is a heterogenous disease – a variety of cellular pathways are activated and differentially expressed
- Inflammatory biomarkers are used to characterize severe asthma phenotypes and guide the delivery of precision medicine; however, little is known about the overlap and relatability of these biomarkers in severe asthma

The aim of this study is to therefore describe the interrelation between inflammatory biomarker expression in severe asthma to characterize the activation of underlying inflammatory pathways using a large, international cohort

Denton E., et al. *JACI In Pract* 2021:Article In press

Differential Expression of Biomarkers Can Predict Treatment Response to Different Therapies

DREAM/MENSA: Increased blood eosinophil count associated with better response to Mepolizumab:



Patients with low eos and high FeNO respond to Dupilumab:

	AER relative risk in dupilumab vs placebo			
FeNO (ppb)		<25	25 to <50	≥50
Baseline Eos levels (cells/µL)	<150	1.154	0.643	0.551
	150 to <300	0.601	0.494	1.182
	≥300	0.564	0.347	0.194

Differential activation of inflammatory pathways → **Differential expression of biomarkers** → **Manifestation of associated clinical characteristics**

Ortega HG, et al. Lancet Respir Med 2016;4(7):549-556
Pavord ID et al. Presented at AACI 2020
Denton E., et al. *JACI In Pract* 2021:Article In press

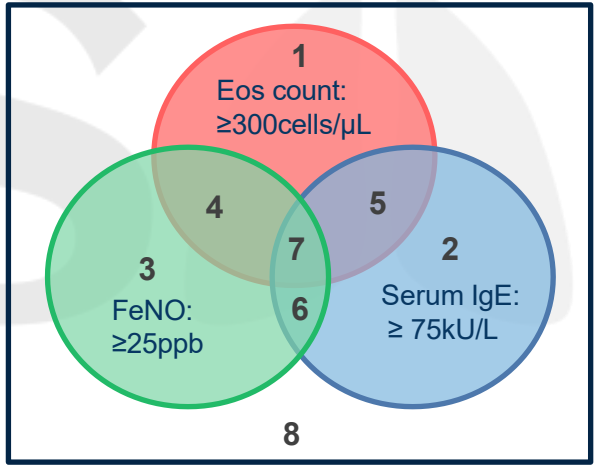
A Cross-Sectional Study: Design

Objective 1
To distinguish patient groups with different patterns of biomarker activation

Objective 2
To compare the clinical characteristics of the patient subgroups derived from these analyses

Inclusion:
- ISAR population
- At least one measurement of each biomarker

Categorized according to biomarker positivity*:



Outcomes:
- Demographics
- Lung function
- Asthma symptoms
- Exacerbations
- Allergic comorbidities
- Asthma medications

Index date: Date of enrolment in ISAR

Biomarker levels measured pre-biologic initiation

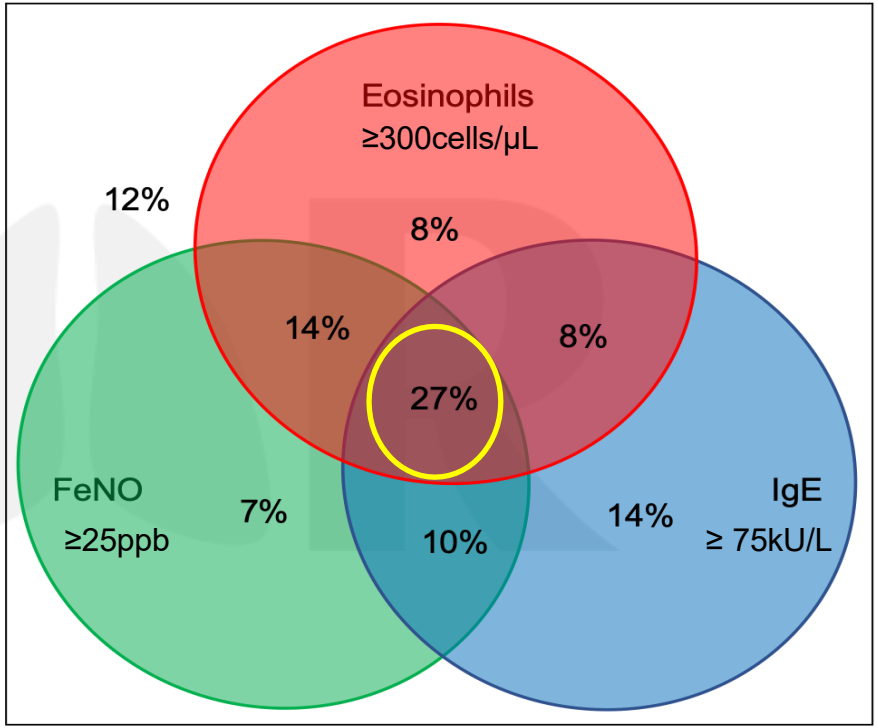
*Biomarkers were measured at baseline; the highest measurement was used in cases of multiple baseline measurements

Denton E., et al. *JACI In Pract* 2021:Article In press

Triple Positivity Was The Most Common Biomarker Overlap Group

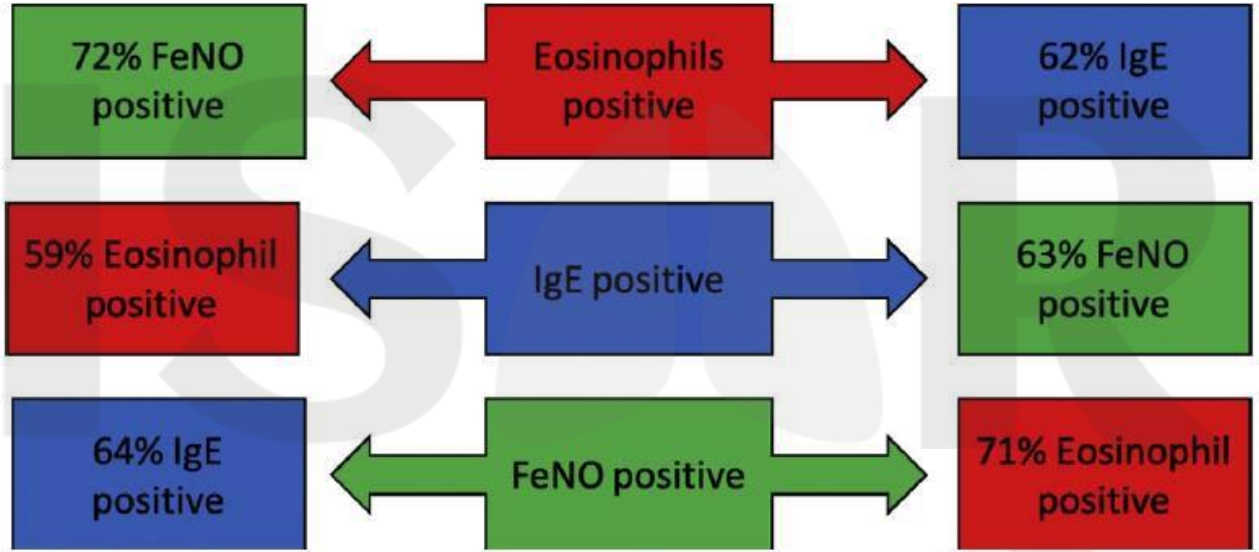
- There is substantial overlap between biomarker positivity groups
- A greater overlap was observed with eosinophils and FeNO than with IgE
- Overall:
  - 57% were positive for eosinophils
  - 58% were positive for FeNO
  - 59% were positive for IgE

n=1175



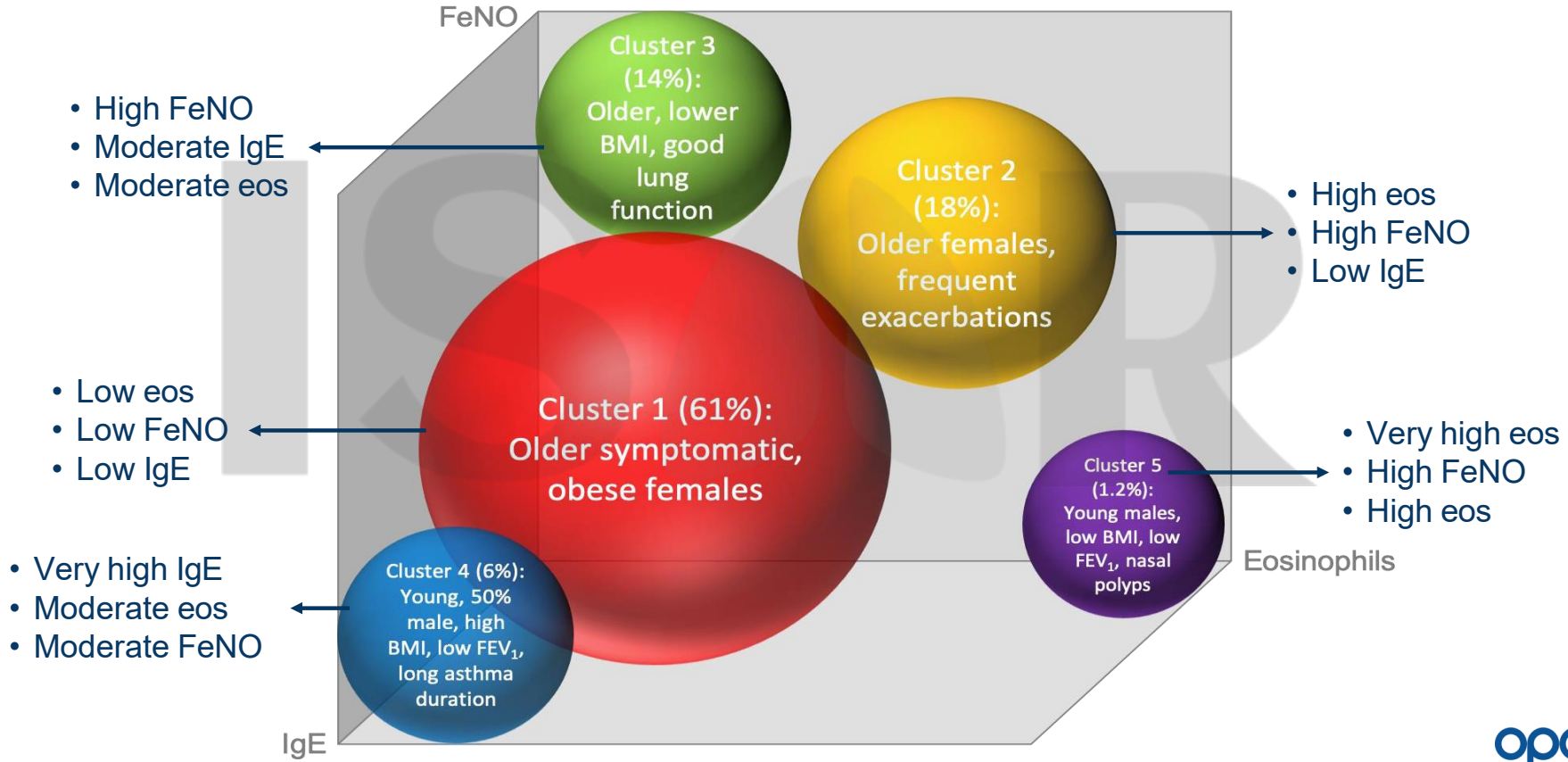
Denton E., et al. *JACI In Pract* 2021:Article In press

Likelihood of alternate biomarker positivity



Denton E., et al. *JACI In Pract* 2021:Article In press

Five Distinct Clusters Based on Biomarker Profiles



Denton E., et al. *JACI In Pract* 2021:Article In press

Clinical Characteristics Associated With Each Patient Subgroup

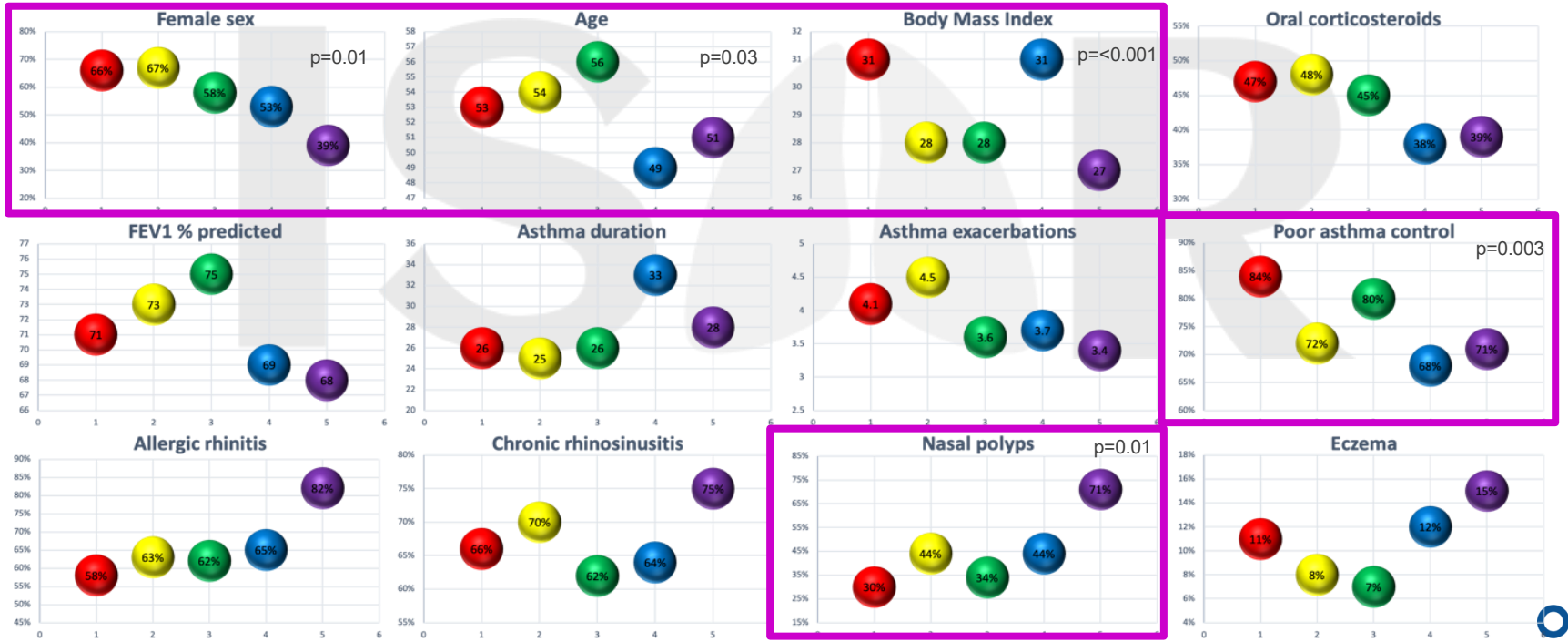
Cluster 1:
- Low eos
- Low FeNO
- Low IgE

Cluster 2:
- High eos
- High FeNO
- Low IgE

Cluster 3:
- High FeNO
- Moderate IgE
- Moderate eos

Cluster 4:
- Very high IgE
- Moderate eos
- Moderate FeNO

Cluster 5:
- Very high eos
- High FeNO
- High eos



Denton E., et al. *JACI In Pract* 2021:Article In press

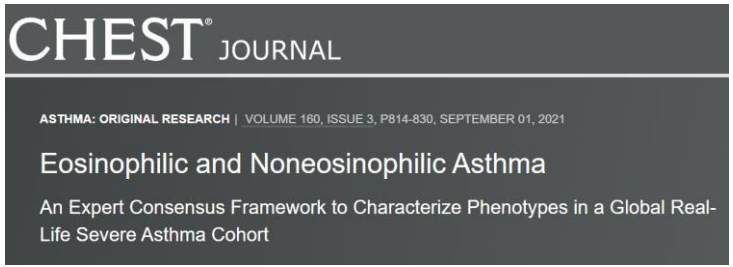
Implications for Clinical Practice

- New methods are required to determine the most appropriate choice of targeted therapy – simply relying on biomarker positivity is not appropriate due to the significant overlap groups
- There is an urgent unmet need in severe asthma, where patients negative for all three biomarkers cannot be appropriately treated by currently available biologics
- Discrete clusters of severe asthma phenotypes based on specific combinations of biomarker profiles can be identified – future research can use these patient sub-populations as a basis to better understand severe asthma disease mechanisms

Conclusion

- Many patients have an overlap in biomarker positivity, which may assist in delivering precision medicine
- Specific combinations of inflammatory pathway activation predominate in severe asthma
- Distinct inflammatory endotypes underpin clinically recognizable phenotypes

Characterization of the Eosinophilic Asthma Phenotype in a Global Real-Life Severe Asthma Cohort (International Severe Asthma Registry, ISAR) and Across All Asthma Severities in UK Primary Care



ISAR's overarching aim as a global adult severe asthma registry

ISAR provides statistical power to better understand severe asthma epidemiology, clinical management and outcomes internationally

ISAR = International Severe Asthma Registry
Canonica GW, Price DB et al. *CHEST* 2020;157(4):805-814

Why is characterization of the eosinophilic asthma phenotype important?

2020 Guidelines

Type 2 inflammation is found in ~50% of people with severe asthma

Type 2 inflammation is often characterized by eosinophils or increased FeNO, and may be accompanied by atopy

2021 Guidelines

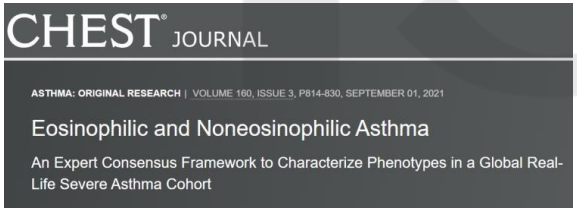
Type 2 inflammation is found in the majority of people with asthma

Type 2 targeted treatments are available, including non-biologics (ICS and add-on therapies like OCS) and biologics

FeNO = Fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; ICS = Inhaled corticosteroids; OCS = Oral corticosteroids

GINA. Diagnosis and management of difficult-to-treat and severe asthma. https://ginasthma.org/severeasthma/. Accessed 30 September 2021.

Eosinophilic and Noneosinophilic Asthma:
An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort



Liam G. Heaney, Luis Perez de Llano, Mona Al-Ahmad, Vibeke Backer, John Busby, Giorgio Walter Canonica, George C. Christoff, Borja G. Cosio, J. Mark FitzGerald, Enrico Heffler, Takashi Iwanaga, David J. Jackson, Andrew N. Menzies-Gow, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Paul E. Pfeffer, Todor A. Popov, Celeste M. Porsbjerg, Chin Kook Rhee, Mohsen Sadatsafavi, Yuji Tohda, Eileen Wang, Michael E. Wechsler, Marianna Alacqua, Alan Altraja, Leif Bjermer, Unnur S. Björnsdóttir, Arnaud Bourdin, Guy G. Brusselle, Roland Buhl, Richard W. Costello, Mark Hew, Mariko Siyue Koh, Sverre Lehmann, Lauri Lehtimäki, Matthew Peters, Camille Taillé, Christian Taube, Trung N. Tran, James Zangrilli, Lakmini Bulathsinhala, Victoria A. Carter, Isha Chaudhry, Neva Eleangovan, Naeimeh Hosseini, Marjan Kerkhof, Ruth B. Murray, Chris A. Price, David B. Price

Click here for the article

Background and Objectives[1]

Background

- **Severe asthma consists of different phenotypes and endotypes that differ in their clinical presentation, underlying pathways and response to treatment[2]**
- Various classifications for the eosinophilic and non-eosinophilic phenotypes of severe asthma have been suggested; however, their clinical applicability in the real world is limited

Objectives

1. Develop an **algorithm** to characterize severe eosinophilic and non-eosinophilic asthma using both phenotypic characteristics and biomarkers
2. Quantify the **proportions** of patients with these phenotypes in ISAR
3. Describe and compare their **demographics** and **clinical characteristics**

ISAR = International Severe Asthma Registry

[1]Heaney LG, Price D et al. *CHEST* 2021;3:814-830; [2]Bakakos A, et al. *J Clin Med* 2019;8:1375

Study design

Historical registry study

Inclusion criteria

- Aged ≥18 years old
- Severe asthma diagnosis
- ≥1 BEC recorded

ISAR gradient eosinophilic algorithm

- Phenotypes of patients were classified as:
  - **Grade 3**: most likely eosinophilic
  - **Grade 2**: likely eosinophilic
  - **Grade 1**: least likely eosinophilic
  - **Grade 0**: non-eosinophilic

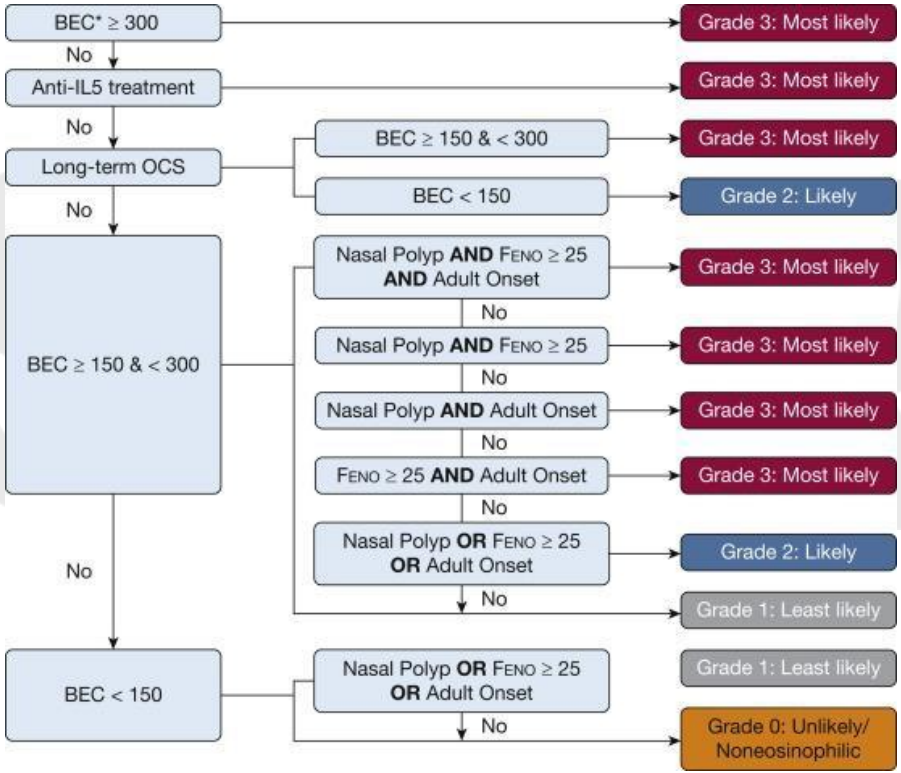
Analyses for each phenotype

- Demographic characteristics
- Clinical features
- Healthcare resource utilization

BEC = Blood eosinophil count; ISAR = International Severe Asthma Registry

Heaney LG, Price D et al. *CHEST* 2021;3:814-830

ISAR eosinophilic severe asthma phenotype algorithm



Anti-IL5 = Anti-interleukin 5; BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids

Heaney LG, Price D et al. *CHEST* 2021;3:814-830

Prevalence of eosinophilic severe asthma phenotypes in ISAR

Highest BEC Available (cells/µL)[a]	Treatment or Clinical Characteristic	Eosinophilic Phenotype	Prospective ISAR Population (N = 1,716) [Original Algorithm]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus Age of Onset]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus FENO]	
			No. (%)	(%)	No. (%)	%	No. (%)	%
≥ 300		Grade 3: most likely	1,196 (69.7)	83.8	1,196 (69.7)	82.6	1,196 (69.7)	82.7
Anti-IL5		Grade 3: most likely	178[b] (10.4)		178[b] (10.4)		178[b] (10.4)	
≥ 150-< 300	Long-term OCS	Grade 3: most likely	37 (2.2)		37 (2.2)		37 (2.2)	
	Presence of ≥ 2 of the following: NP, FENO ≥ 25 ppb, or adult onset[c] (no long-term OCS)	Grade 3: most likely	27 (1.6)		7 (0.4)		8 (0.5)	
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 2: likely	67 (3.9)	3.9	45 (2.6)	2.6	71 (4.1)	4.1
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 1: least likely	27 (1.6)	1.6	69 (4.0)	4.0	42 (2.4)	2.4
< 150	Long-term OCS	Grade 2: likely	75 (4.4)	4.4	75 (4.4)	4.4	75 (4.4)	4.4
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 1: least likely	81 (4.7)	4.7	40 (2.4)	2.4	64 (3.7)	3.7
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 0: unlikely (non-eosinophilic)	28 (1.6)	1.6	69 (4.0)	4.0	45 (2.6)	2.6

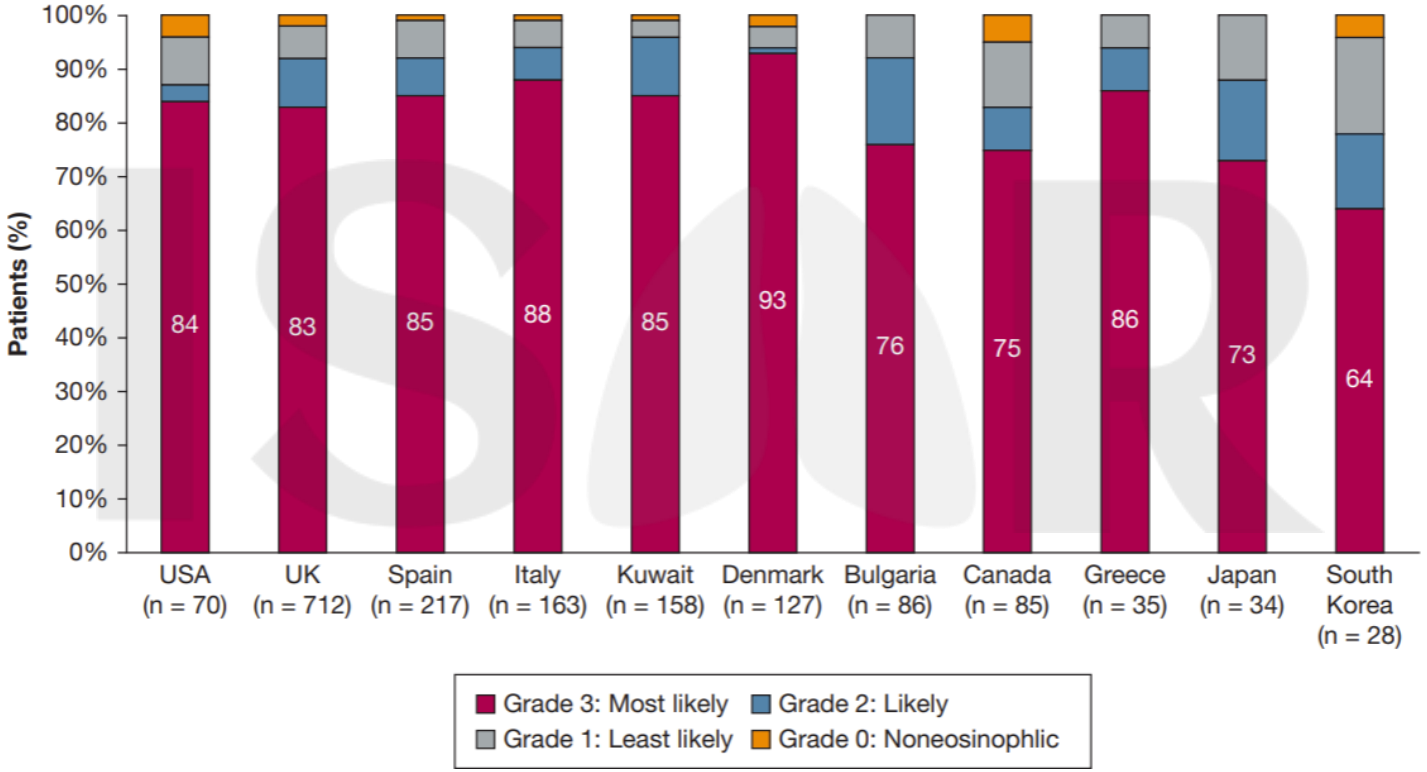
Most likely eosinophilic

Non-eosinophilic

Anti-IL5 = Anti-interleukin 5; BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; ISAR = International Severe Asthma Registry; NP = Nasal polyps; ppb = parts per billion; OCS = Oral corticosteroids

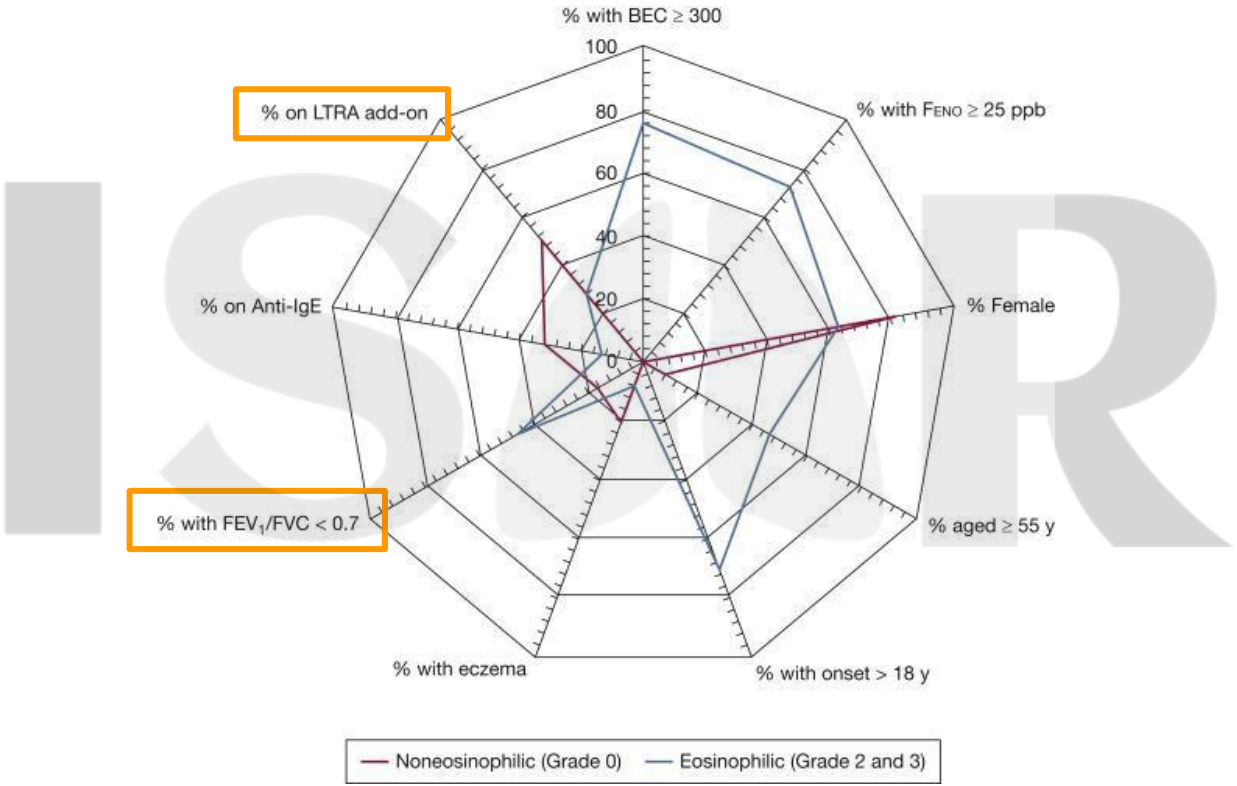
Heaney LG, Price D et al. *CHEST* 2021;3:814-830

Eosinophilic severe asthma was the most common phenotype globally



Heaney LG, Price D et al. *CHEST* 2021;3:814-830

Patients with eosinophilic severe asthma were more likely to have poorer lung function and adult-onset asthma



Anti-IgE = Anti-immunoglobulin E; BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; FEV1/FVC = ratio of forced expiratory volume in one second to forced vital capacity; LRTA = leukotriene receptor antagonist; ppb = parts per billion

Heaney LG, Price D et al. *CHEST* 2021;3:814-830

Conclusions

- **The ISAR eosinophil phenotype algorithm was developed by expert consensus to characterize and quantify the eosinophilic and non-eosinophilic phenotypes of severe asthma patients in ISAR**
- **The eosinophilic phenotype was predominant in severe asthma**
  - 83.8% of patients were most likely eosinophilic and 1.6% of patients were non-eosinophilic
  - Eosinophilic severe asthma was the most common phenotype globally
- **Patients with eosinophilic severe asthma were more likely to have poorer lung function and adult-onset asthma than those with non-eosinophilic severe asthma**
- **Asthma eosinophilic phenotyping can potentially lead to the identification of treatable traits and delivery of precision medicine in patients with severe asthma**

ISAR = International Severe Asthma Registry

Heaney LG, Price D et al. *CHEST* 2021;3:814-830

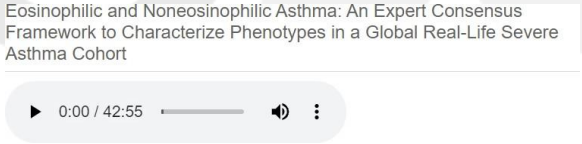
Editorial and Podcast in *CHEST*

Editorial

Click here for the editorial

Ramesh J. Kurukulaaratchy and Heena Mistry discussed the clinical importance of the ISAR eosinophilic gradient algorithm in characterizing severe asthma phenotypes in the real-world setting.[1]

Podcast



Click here for the podcast

David B. Price and Ramesh J. Kurukulaaratchy, together with the *CHEST* podcast moderator Dominique Pepper, discussed the prevalence and characterization of eosinophilic and non-eosinophilic severe asthma phenotypes.[2]

ISAR = International Severe Asthma Registry

[1]Kurukulaaratchy RJ and Mistry H. *CHEST* 2021;160:P789-790; [2]*CHEST*. Podcasts: September 2021. https://journal.chestnet.org/podcast-archive-2021. Accessed 30 September 2021.

Asthma Phenotyping in Primary Care:
Applying the International Severe Asthma Registry Eosinophil Phenotype Algorithm Across All Asthma Severities

Marjan Kerkhof, Trung N. Tran, Riyad Allehebi, G. Walter Canonica, Liam G. Heaney, Mark Hew, Luis Perez de Llano, Michael E. Wechsler, Lakmini Bulathsinhala, Victoria A. Carter, Isha Chaudhry, Neva Eleangovan, Ruth B. Murray, Chris A. Price, David B. Price

Click here for the article

Background and Objectives[1]

Background

- **Asthma types should be characterized using phenotypic characteristics and biomarkers, to potentially identify treatable traits and deliver precision treatment**
- Various classifications of asthma phenotypes in primary care have been proposed; however, they used variables that were not readily accessible in routine clinical practice or lacked characterization of underlying inflammatory disease pathways

Objectives

1. Apply the **ISAR eosinophil phenotype gradient algorithm**[2] across all asthma severities in a UK primary care cohort
2. **Quantify** and **characterize** the eosinophilic and non-eosinophilic phenotypes in this cohort
3. Study the association between the likelihood of eosinophilic asthma phenotype severity and **healthcare resource utilization**

ISAR = International Severe Asthma Registry

[1]Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056; [2]Heaney LG, Price D et al. *CHEST* 2021;3:814-830

Study design

OPTIMUM PATIENT CARE RESEARCH DATABASE

Clinical Practice Research Datalink

Historical cohort study

Inclusion criteria

- Aged ≥13 years old
- Active asthma diagnosis
- ≥1 BEC recorded

ISAR gradient eosinophilic algorithm

- Phenotypes of patients were classified as:
  - **Grade 3**: most likely eosinophilic
  - **Grade 2**: likely eosinophilic
  - **Grade 1**: least likely eosinophilic
  - **Grade 0**: non-eosinophilic

Analyses for each phenotype

- Demographic characteristics
- Clinical features
- Healthcare resource utilization

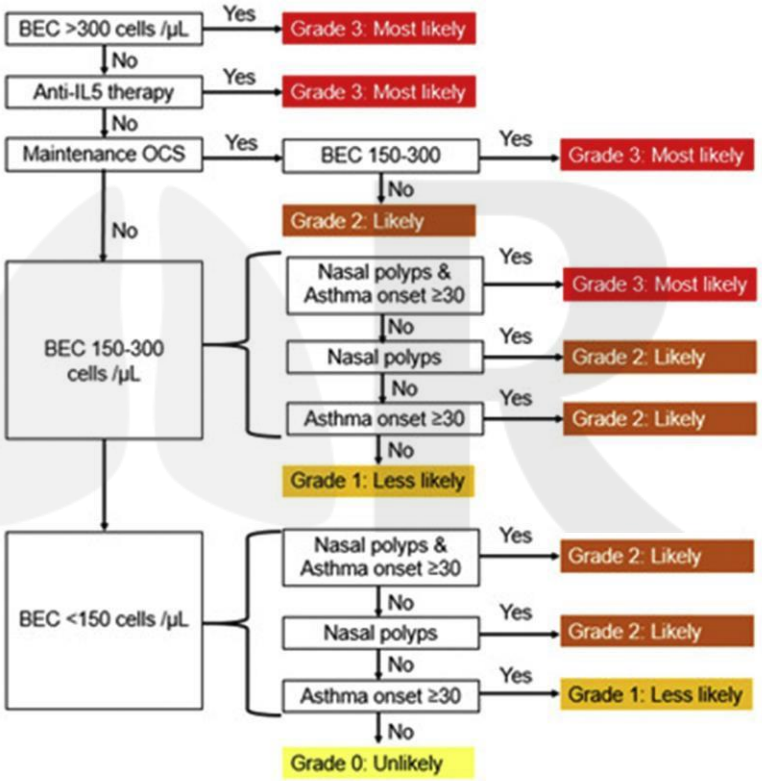
BEC = Blood eosinophil count; ISAR = International Severe Asthma Registry

Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056

ISAR eosinophil phenotype algorithm applied to a UK primary care asthma cohort

Overall distribution

Grade 3: Most likely	N=121,313 (50.3%)
Grade 2: Likely	N=53,431 (22.2%)
Grade 1: Less Likely	N=52,741 (21.9%)
Grade 0: Unlikely	N=13,521 (5.6%)

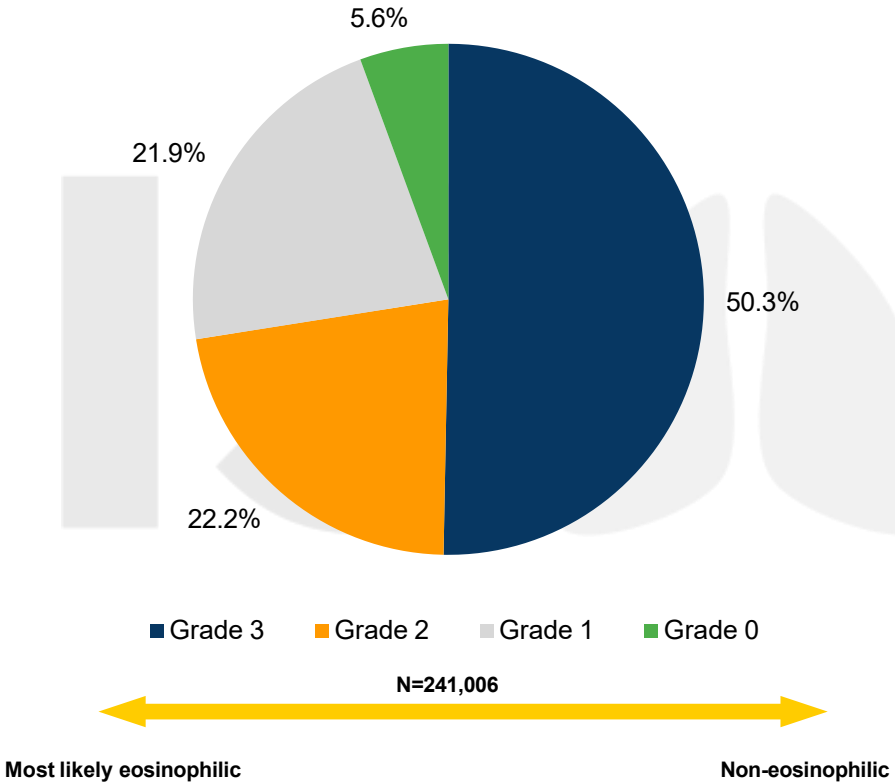


Number (%)
119,447 (49.6)
0 (0.0)
458 (0.2)
97 (0.0)
1,408 (0.6)
656 (0.3)
52,298 (21.7)
36,901 (15.3)
230 (0.1)
150 (0.1)
15,840 (6.6)
13,521 (5.6)

Anti-IL5 = Anti-interleukin 5; BEC = Blood eosinophil count; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids

Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056

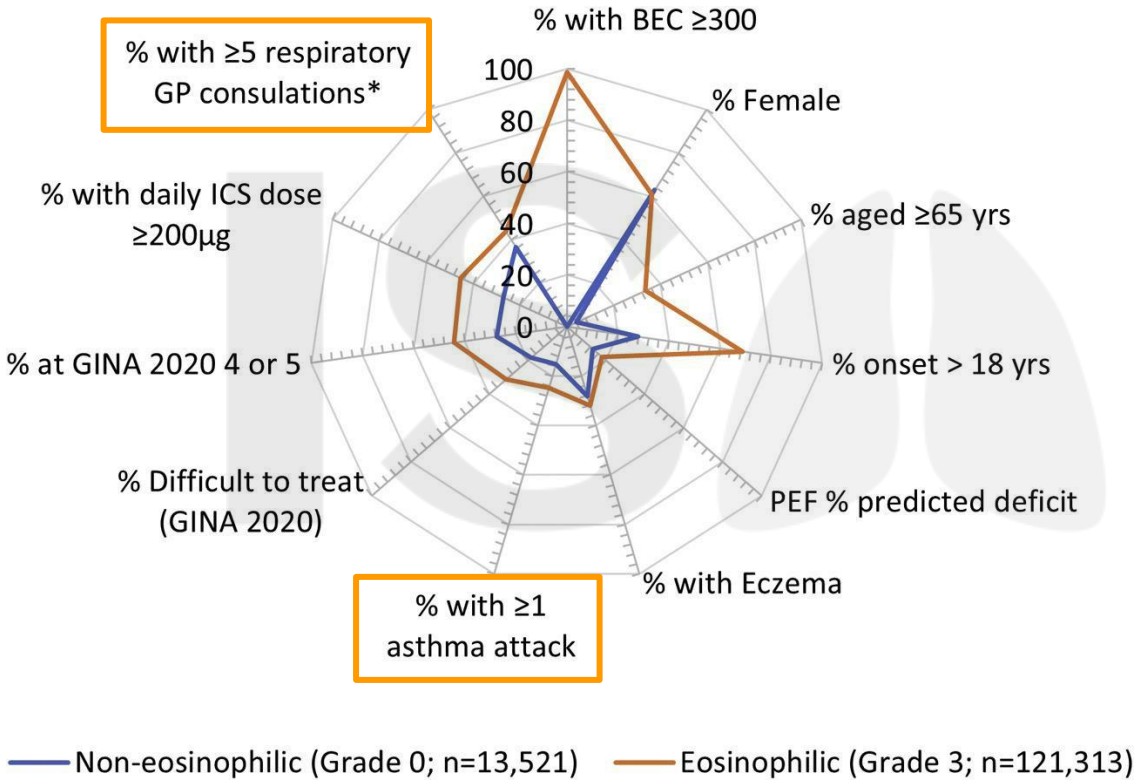
Prevalence of phenotypes across all asthma severities in UK primary care



Many patients in primary care had 'most likely eosinophilic' asthma, irrespective of disease severity

Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056

Characterization of phenotypes across all asthma severities in UK primary care



Eosinophilic patients were more likely to have poorer asthma control and greater healthcare utilization than non-eosinophilic patients

BEC = Blood eosinophil count; GINA = Global Initiative for Asthma; GP = General practice; ICS = Inhaled corticosteroid; PEF = Peak expiratory flow

Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056

Conclusions

- **The eosinophilic phenotype was predominant across all asthma severities in UK primary care**
  - 72.5% of patients had most likely or likely eosinophilic phenotypes
  - 5.6% of patients were non-eosinophilic
- **Patients with most likely eosinophilic asthma tended to have more comorbidities, poorer asthma control, and greater healthcare resource use than those with non-eosinophilic asthma**
  - **28.2%** of patients with most likely eosinophilic asthma versus **6.9%** of patients with non-eosinophilic asthma had a Charlson comorbidity index of ≥2
  - **24.8%** of patients with most likely eosinophilic asthma versus **15.3%** of patients with non-eosinophilic asthma experienced ≥1 asthma attacks
- **Asthma eosinophilic phenotyping should become part of routine clinical practice in primary care**
  - Patients with eosinophilic asthma phenotypes may benefit from earlier intervention with Type 2 targeted treatments, including ICS and steroid-sparing therapies such as biologics

ICS = Inhaled corticosteroids

Kerkhof M, Price D et al. *J Allergy Clin Immunol* 2021; doi: 10.1016/j.jaip.2021.07.056

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

John Busby, David Price, Riyad Al-Lehebi, Sinthia Bosnic-Anticevich, Job FM van Boven, Benjamin Emmanuel, J Mark FitzGerald, Mina Gaga, Susanne Hansen, Mark Hew, Takashi Iwanaga, Désirée Larenas Linnemann, Bassam Mahboub, Patrick Mitchell, Daniela Morrone, Jonathan Pham, Celeste Porsbjerg, Nicolas Roche, Eileen Wang, Neva Eleangovan, Liam G Heaney

Background and Objectives[1]

Background

- **Socioeconomic status (SES) is known to affect asthma outcomes such as morbidity, mortality and healthcare utilization**
- Suggested reasons for worse asthma outcomes in deprived populations include poorer living conditions and reduced access to specialist care
- UK guidelines: patients with asthma that remains uncontrolled despite standard therapies should be referred to specialists[2]

Objectives

1. Describe the **socioeconomic disparities** in a UK primary care asthma cohort
2. Identify the **factors** that influence the impact of SES on asthma outcomes
3. Study the impact of SES on **asthma presentations** (e.g., blood eosinophils), **treatment processes** (e.g., respiratory referrals) and **outcomes** (e.g., asthma control and exacerbations)

SES = Socioeconomic status

[1]Busby J, Price D et al. *J Asthma Allergy* 2021;in press; [2]BTS/SIGN. British guideline on the management of asthma: quick reference guide, 2019

Study design

OPTIMUM PATIENT CARE RESEARCH DATABASE

Historical cohort study

Inclusion criteria

- Aged ≥18 years old
- Asthma diagnosis
- ≥3 years of data available

Deprivation quintiles

- Socioeconomic status derived from UK 2011 Indices of Multiple Deprivation scores*:
  - **Quintile 5: least deprived**
  - **Quintile 1: most deprived**

1-year follow-up

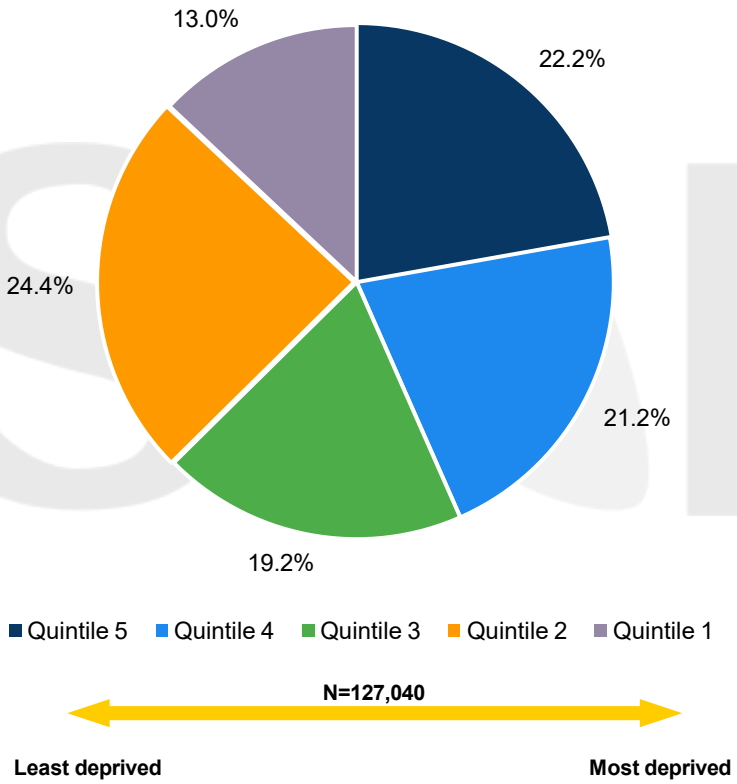
Analyses

- **Asthma presentations**
  - Blood eosinophils
  - Peak flow
- **Treatment processes**
  - Medication adherence
  - Asthma reviews
  - Respiratory referrals
- **Clinical outcomes**
  - Asthma control
  - Exacerbations
- **Sensitivity analyses:**
  - Impact of demographic factors and asthma severity (≥2 exacerbations) on clinical outcomes

*Indices of Multiple Deprivation scores reflect the relative deprivation of the areas where the general practices are located; they take a weighted average of income, employment, health, education, housing, crime and living environment

Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

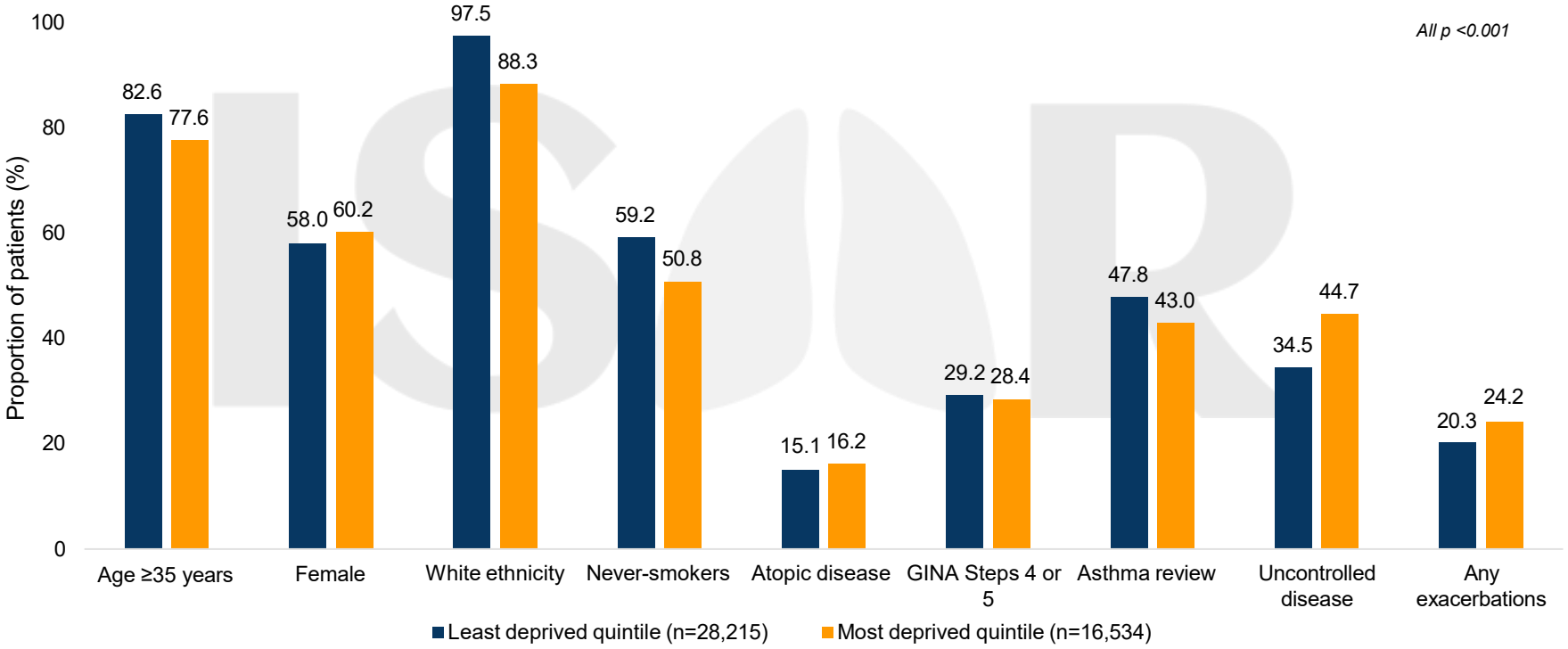
Socioeconomic disparities in a UK primary care asthma cohort



Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Demographic and clinical characteristics of asthma patients by SES

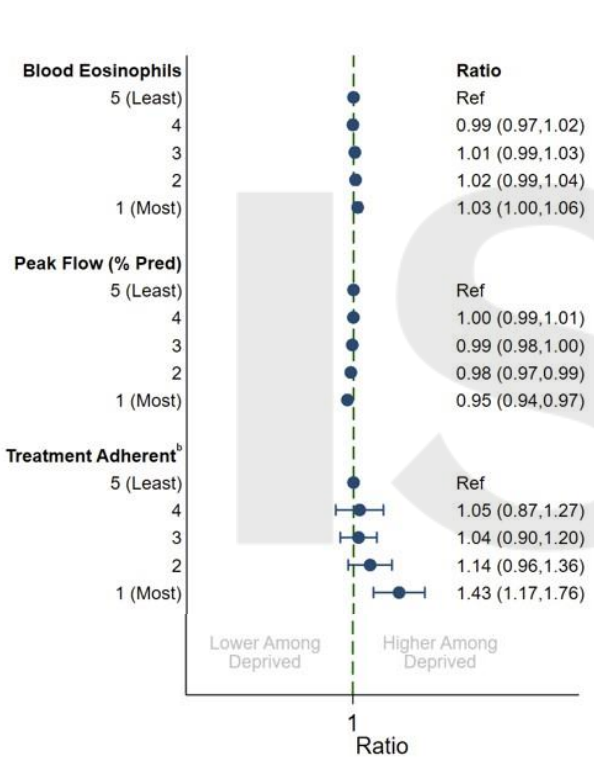
Most deprived patients were more likely to have atopic disease and uncontrolled asthma than least deprived patients

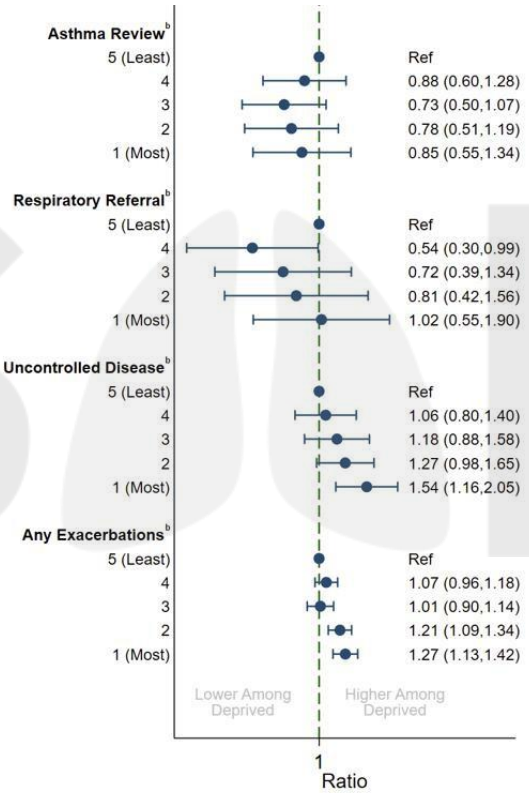


GINA = Global Initiative for Asthma; SES = Socioeconomic status

Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Impact of SES on asthma presentations, treatment processes and clinical outcomes in UK primary care[a]





Most deprived patients had more uncontrolled asthma and greater likelihood of exacerbations than least deprived patients, but rates of respiratory referrals remained comparable

↓

Sensitivity analysis: Similar rates of respiratory referrals between most and least deprived patients remained among those with ≥2 exacerbations

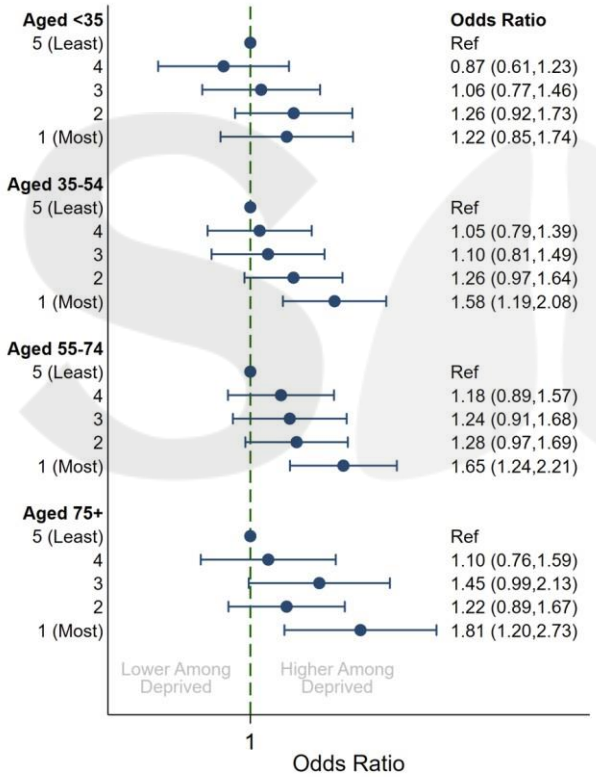
↓

Clinical implication: More deprived patients may have greater need for specialist reviews and phenotype-targeted treatments like biologics

[a]Adjusted for year, age (5-year groups) and sex; [b]Odds ratio. Patient numbers: n=45,761 for blood eosinophils; n=71,291 for peak flow; n=102,712 for treatment adherent; n=127,040 for asthma review; n=127,040 for respiratory referral; n=40,078 for uncontrolled disease; n=127,040 for any exacerbations
SES = Socioeconomic status
Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Age influences the magnitude of SES's impact on asthma outcomes

Uncontrolled asthma



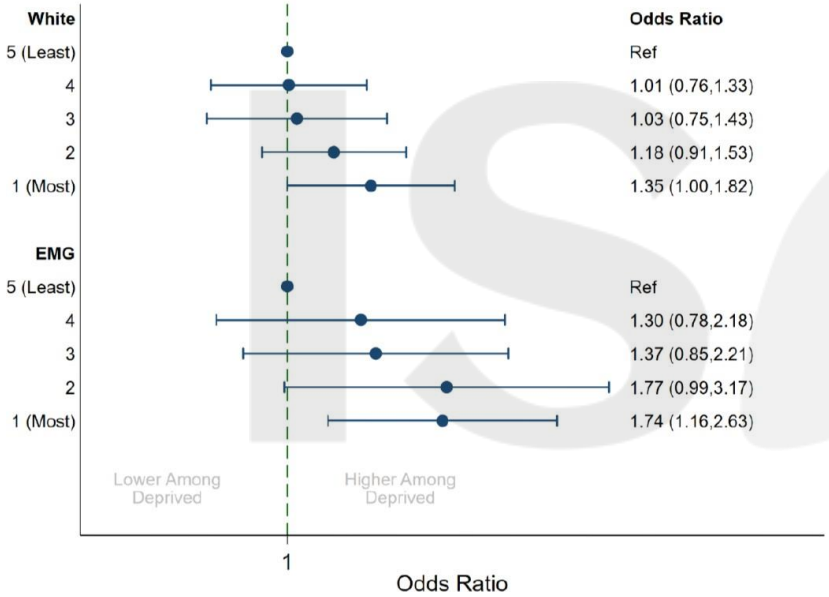
The impact of increased deprivation on asthma control was greater in patients aged ≥75 years than in those aged <35 years

SES = Socioeconomic status

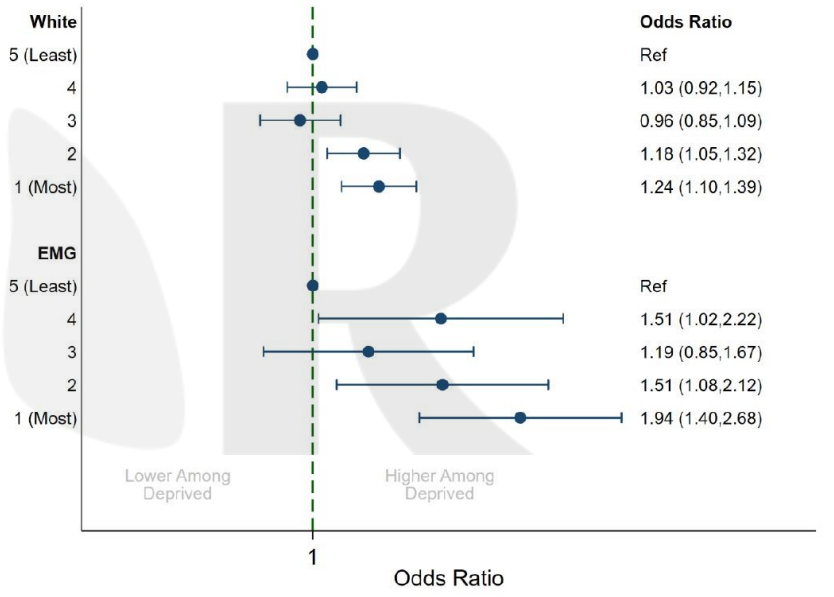
Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Ethnicity influences the magnitude of SES's impact on asthma outcomes

Uncontrolled asthma



Any exacerbations



The impact of increased deprivation on asthma control and exacerbations was greater in ethnic minority groups than in White patients

EMG = Ethnic minority groups; SES = Socioeconomic status

Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Conclusions

- **There was evidence of socioeconomic disparities in a UK primary care asthma cohort**
- **Socioeconomic deprivation has an adverse effect on asthma outcomes**
  - Most deprived patients were more likely to have worse peak flow, uncontrolled disease or an exacerbation during follow-up than least deprived patients
- **Although more deprived patients had more uncontrolled disease, rates of respiratory referrals were similar to those of less deprived patients**
  - More deprived patients may have greater need for specialist reviews and phenotype-targeted treatments like biologics
- **Age and ethnicity influence the magnitude of SES's impact on asthma outcomes**
  - The impact of increased deprivation on asthma control was more pronounced in older patients versus younger patients, and in ethnic minority groups versus White patients
- **Interventions to resolve socioeconomic disparities should be explored, both in the UK and globally, to improve overall asthma outcomes**

SES = Socioeconomic status

Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

Acknowledgements

- **We would like to thank all patients and collaborators who contributed to this academic research study, which was prioritized by ISAR.**
- **This research study was funded and delivered by the Observational and Pragmatic Research Institute Pte Ltd (OPRI). Optimum Patient Care Global received partial funding from AstraZeneca Ltd to support dataset creation.**
- OPCRD has been reviewed and ethically approved by the NHS Health Research Authority to hold and process anonymized data as part of service delivery (Research Ethics Committee reference: 15/EM/0150). Ethical approval for this research study was granted by the ADEPT committee (ADEPT0120). The study was designed, implemented and registered in accordance with the criteria of ENCePP (EUPAS32482).

ADEPT = Anonymised Data Ethics Protocols and Transparency; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ISAR = International Severe Asthma Registry; NHS = National Health Service

Busby J, Price D et al. *J Asthma Allergy* 2021;in press.

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

Celeste M. Porsbjerg, Andrew N. Menzies-Gow, Trung N. Tran, Ruth B. Murray, Bindhu Unni, Shi Ling Audrey Ang BSc, Marianna Alacqua, Mona Al-Ahmad, Riyad Al-Lehebi, Alan Altraja, Andrey S. Belevskiy, Unnur S. Björnsdóttir, Arnaud Bourdin, John Busby, G. Walter Canonica, George C. Christoff, Borja G. Cosio, Richard W. Costello, J. Mark FitzGerald, João A Fonseca, Susanne Hansen, Liam G. Heaney, Enrico Heffler, Mark Hew, Takashi Iwanaga, David J. Jackson, Janwillem W. H. Kocks, Maria Kallieri, Hsin-Kuo Bruce Ko, Mariko Siyue Koh, Désirée Larenas-Linnemann, Lauri A. Lehtimäki, Stelios Loukides, Njira Lugogo, Jorge Maspero, Andriana I. Papaioannou, Luis Perez-de-Llano, Paulo Márcio Pitrez, Todor A. Popov, Linda M. Rasmussen, Chin Kook Rhee, Mohsen Sadatsafavi, Johannes Schmid, Salman Siddiqui, Camille Taillé, Christian Taube, Carlos A. Torres-Duque, Charlotte Ulrik, John W. Upham, Eileen Wang, Michael E. Wechsler, Lakmini Bulathsinhala, Victoria Carter, Isha Chaudhry, Neva Eleangovan, Naeimeh Hosseini, Mari-Anne Rowlands, David Price, Job FM van Boven

Background and Objectives

Background

- **Five biologics are licensed by the FDA and EMA for severe asthma treatment**
  - Anti-IgE: Omalizumab
  - Anti-IL5/5R: Mepolizumab, benralizumab and reslizumab
  - Anti-IL4Rα: Dupilumab
- Accessibility to biologic therapy is restricted by clinical, administrative and reimbursement criteria that differ across countries
- No previous studies have compared biologic access globally

Objectives

1. Analyze national biologic access criteria in ISAR collaborating countries
2. Study global differences in ease-of-access to biologics
3. Compare national biologic access criteria in ISAR collaborating countries with established regulatory criteria

EMA = European Medicine Agency; FDA = Food and Drug Administration; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor; ISAR = International Severe Asthma Registry

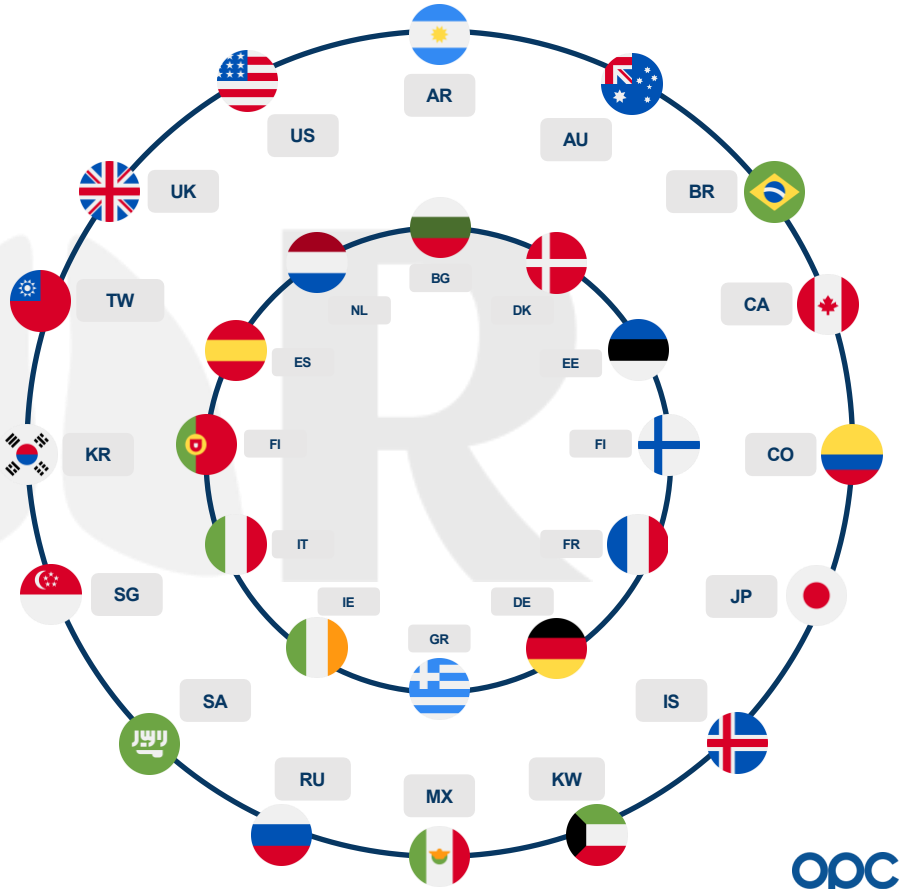
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Study design – Data collection

Biologic prescription criteria were obtained from publicly available drug regulation authority websites

A semi-structured survey was sent to severe asthma experts from 29 ISAR countries* to compare official criteria with real-life practice

Tabulated data were re-sent to the ISC members in ISAR countries to check the criteria for all biologics



*Responses were received from all countries except India, which was eventually removed from the data analysis.
ISAR = International Severe Asthma Registry; ISC = ISAR Steering Committee
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Study design – Development of the Biologic ACcessibility Score (BACS)

The composite BACS (ten criteria) compared biologic accessibility across countries. 0 = most difficult access and 10 = easiest access.

Criterion	Score
Age (years)	
Not required/undecided	10
≥6	8
≥12	4
≥18	0
Severity/Phenotype	
Not required/undecided	10
IgE mediated OR type II driven OR eosinophilic	8
Bronchial asthma refractory OR uncontrolled allergic	6
Moderate to severe (persistent, eosinophilic, OR OCS dependent)	4
Severe (persistent, eosinophilic, with type II inflammation OR allergic)	2
Severe (uncontrolled, uncontrolled + eosinophilic, uncontrolled allergic, refractory, refractory + eosinophilic)	0
Serum IgE (IU/ml)	
Not required/undecided	10
≥30, 35, or elevated	8
≥70, 75 or 76	4
≥150	2
≥400	0
BEC (cells/µL)	
Not required/undecided	10
≥150 or raised	8
≥150 in last 12 months	7
≥150 in last 1 month	6
≥300 or ≥150 on long-term OCS	5
≥300 in last 12 months or historical	4
≥300 x2 in last 12 months	3
≥400 or in last 12 months	2
≥500	0
FeNO (ppb)*	
Not required/undecided	10
≥20 or 25 or raised	5
≥50	0
Allergic Asthma	
Not required/undecided	10
SPT or RAST	5
SPT and RAST	0

Criterion	Score
Background Therapy	
Not required/undecided	10
ICS	8
High dose ICS (+/- LABA or long-term OCS or xanthine or LTRA)	6
Medium dose ICS/LABA (+/- LTRA)	5
High dose ICS/LABA (+/- LAMA or LTRA)	4
High dose ICS/LABA (+/- long-term OCS)	
High dose ICS/LABA + ≥ 1 other controller (not OCS)	2
High dose ICS/LABA + long term OCS	0
OCS†	
Not required/undecided	10
Long term OCS use	0
Exacerbations†	
Not required/undecided	10
≥1	8
≥1 requiring hospital admission, emergency room visit, or rescue OCS	6
≥2	4
≥2 requiring hospital admission, emergency room visit, or rescue OCS	3
≥3	2
≥4	0
Asthma Control	
Not required/undecided	10
Required	0
Lung Function	
Not required/undecided	10
FEV_1 ≤80%	8
≥12% reversibility +/- > 200 ml FEV_1	6
FEV_1 ≤80% & evidence of reversibility	4
FEV_1 ≤80% & 12% reversibility & AHR	2
FEV_1 ≤60%	0
Adherence	
Not required/undecided	10
Required	0

AHR: airway hyperresponsiveness; BACS = Biologic ACessibility Score; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; HCP: healthcare professional; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene antagonist; OCS: oral corticosteroids; RAST: radioallergosorbent test; SPT: skin prick test

Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Study design – Outcomes

Outcomes

Description of global access to biologics
- World maps were developed to summarize biologic accessibility
- Pearson's correlation testing was used to explore the relationship between BACS and GDP 2019

Individual access criteria
- Per country
- Per biologic

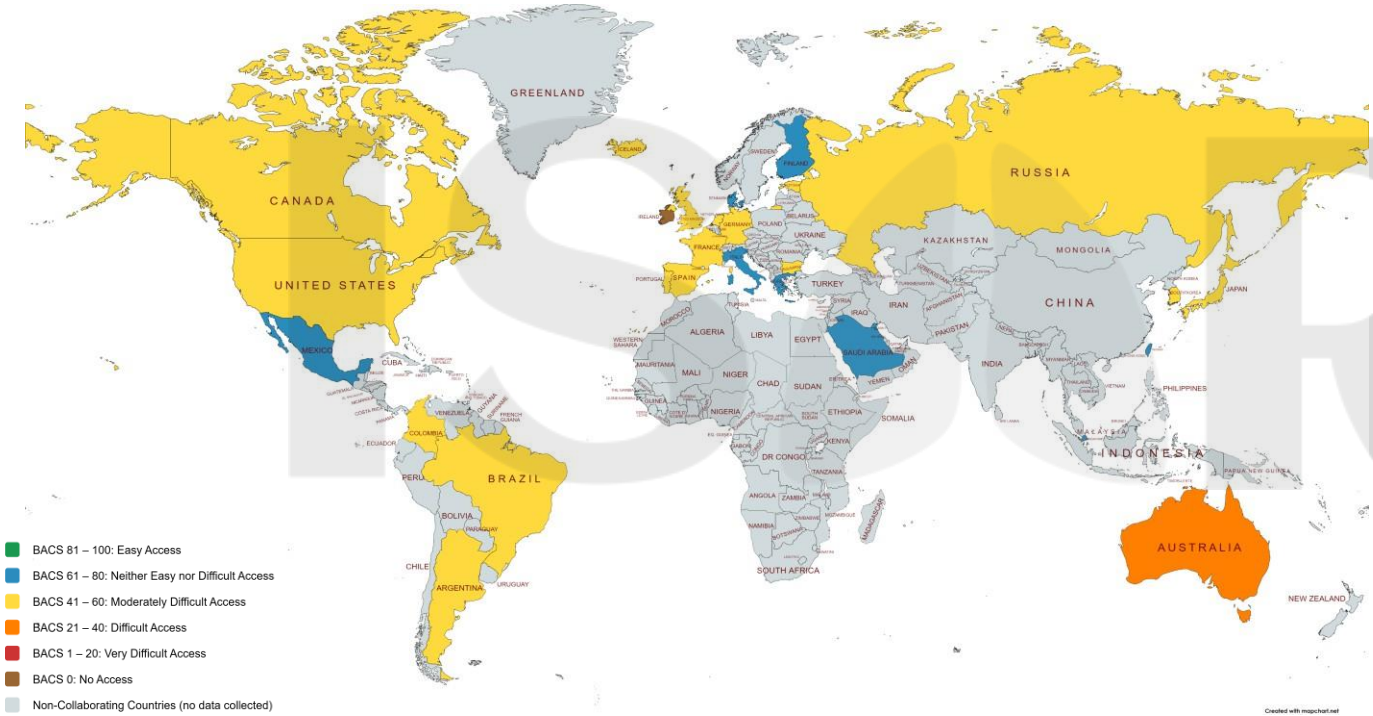
Overall ease-of-access to each biologic
- BACS scores were referenced to EMA regulatory criteria

Availability of the biologics
- Licensing and reimbursement status of omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab

BACS = Biologic ACessibility Score; EMA = European Medicines Agency; GDP = Gross Domestic Product

Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

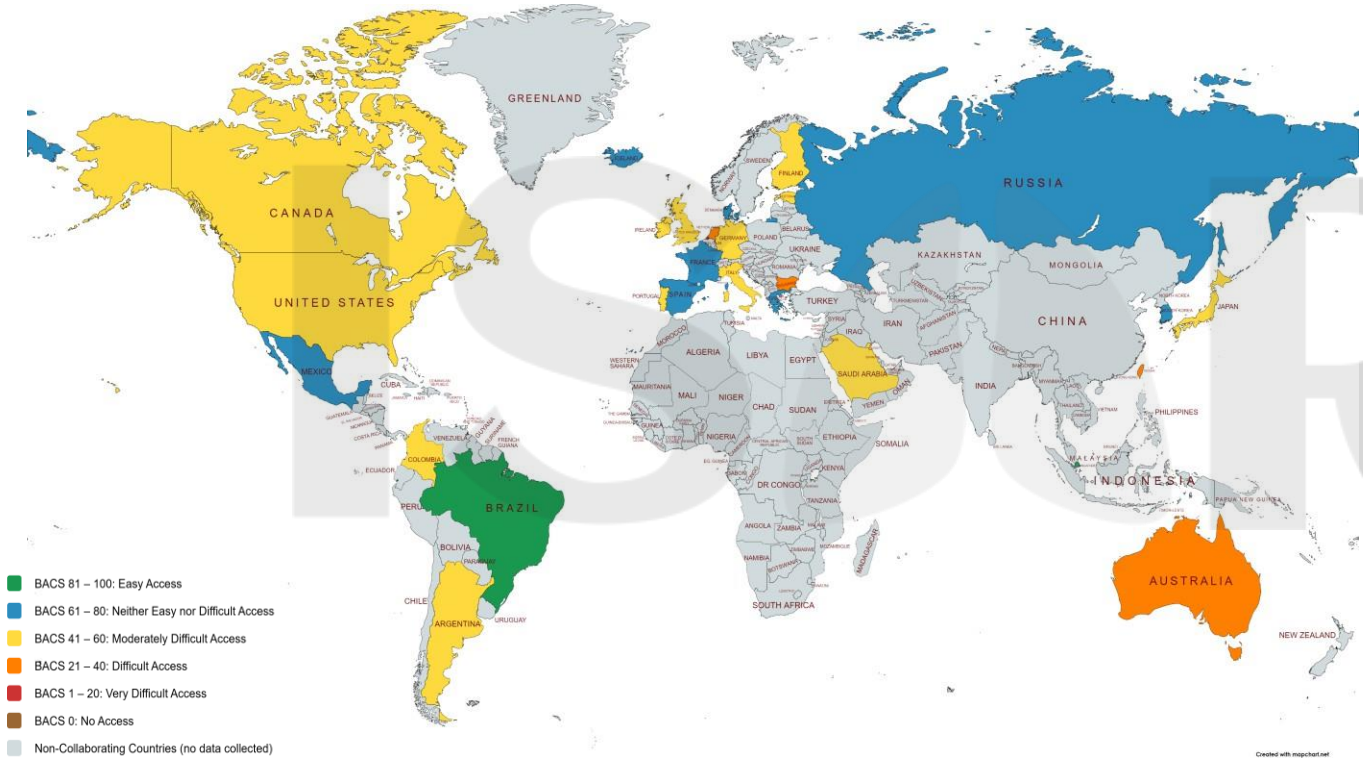
Results – Omalizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult to access** in 32% of countries
- ✓ **Moderately difficult to access** in 61% of countries
- ✓ **Difficult to access** in Australia
- ✓ **BACS range:** 39 (Australia) to 71 (Denmark)
- ✓ **Mean BACS:** 57, which is lower than EMA BACS of 69
- ✓ All countries (except Denmark and Finland) reported more stringent access to omalizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

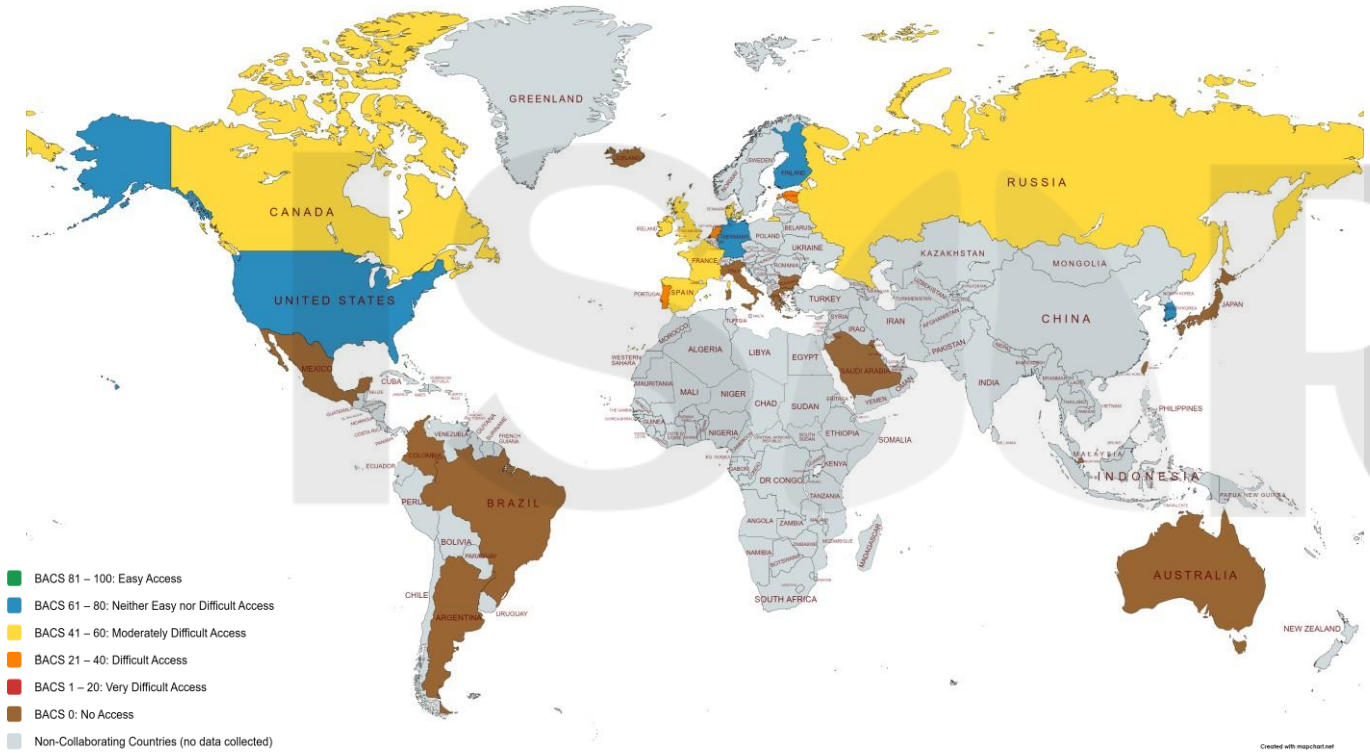
Results – Mepolizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult to access in** 29% of countries
- ✓ **Moderately difficult to access** in 50% of countries
- ✓ **Difficult to access** in Australia, Bulgaria, the Netherlands and Taiwan
- ✓ **BACS range:** 26 (Bulgaria) to 90 (Brazil)
- ✓ **Mean BACS:** 55, which is lower than EMA BACS of 87
- ✓ All countries (except Brazil and Singapore) reported more stringent access to mepolizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

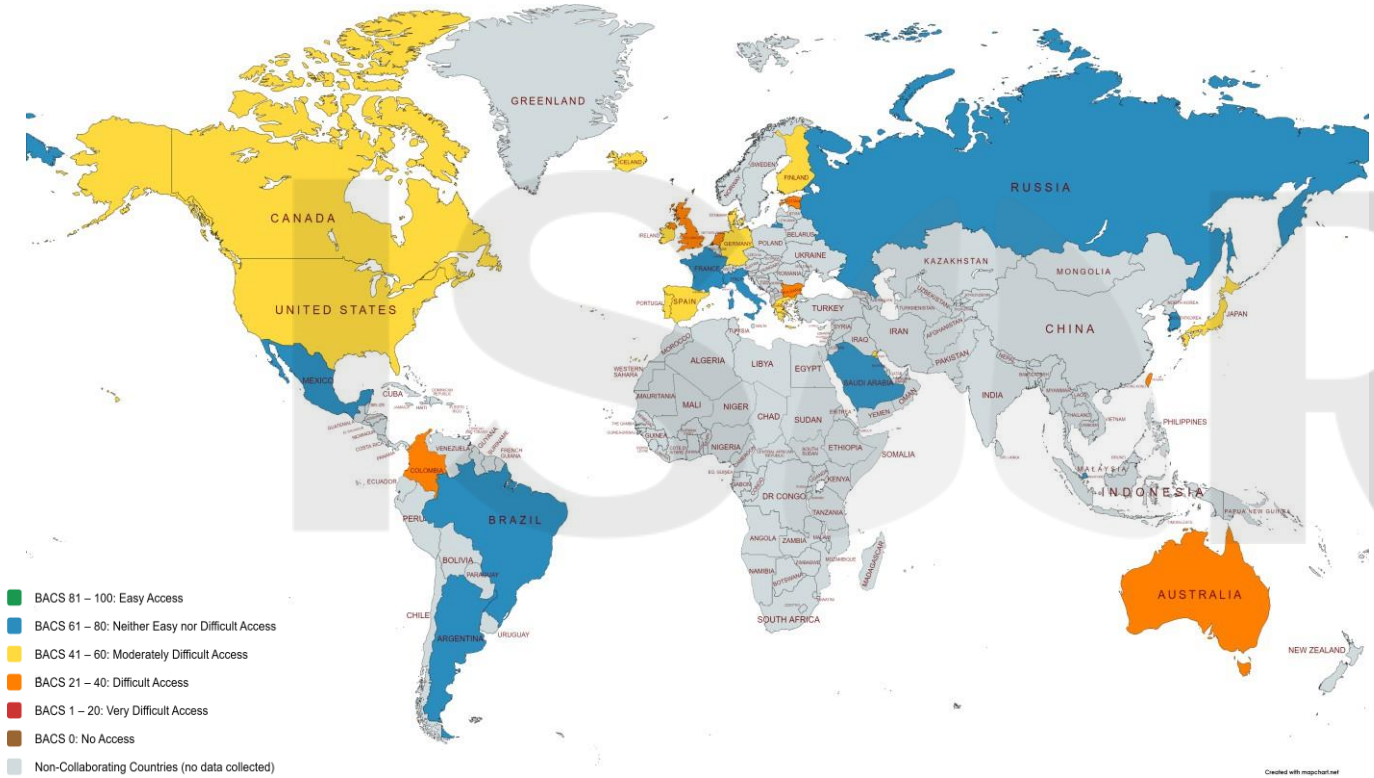
Results – Reslizumab BACS for ISAR countries



- ✓ Licensed in 15 countries
- ✓ **Neither easy nor difficult to access** in Finland, Germany, South Korea and the United States
- ✓ **Difficult or moderately difficult to access** in 67% of countries
- ✓ **BACS range:** 36 (the Netherlands) to 69 (South Korea)
- ✓ **Mean BACS:** 51, which is lower than EMA BACS of 76
- ✓ All countries reported more stringent access to reslizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

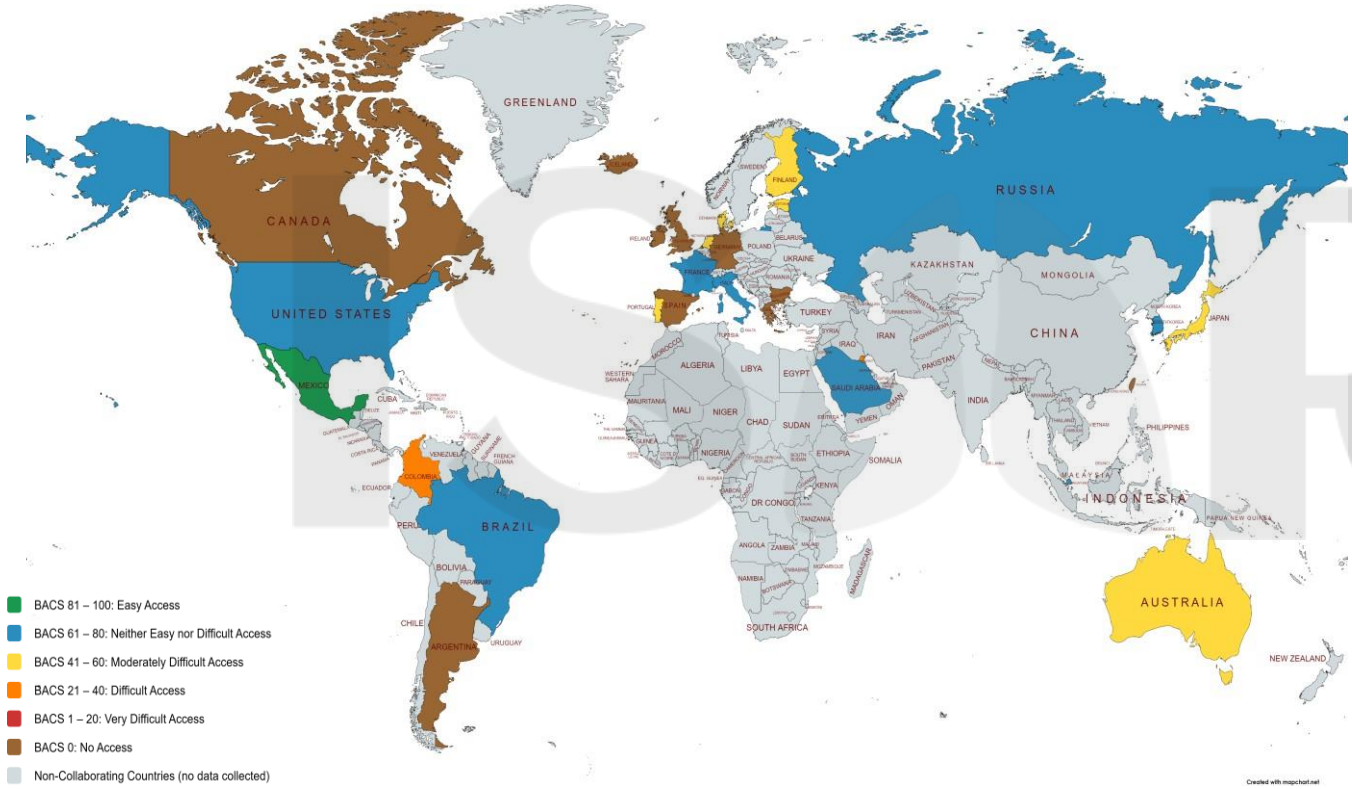
Results – Benralizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult, or moderately difficult to access** in 75% of countries
- ✓ **Difficult to access** in 25% of countries
- ✓ **BACS range:** 30 (Australia) to 80 (Mexico)
- ✓ **Mean BACS:** 54, which is lower than EMA BACS of 76
- ✓ All countries (except Brazil, Mexico, Singapore and South Korea) reported more stringent access to benralizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Results – Dupilumab BACS for ISAR countries



- ✓ Licensed in 20 countries
- ✓ **Neither easy nor difficult, or moderately difficult to access** in 80% of countries
- ✓ **Difficult to access** in Colombia and Kuwait
- ✓ **BACS range:** 33 (Colombia) to 88 (Mexico)
- ✓ **Mean BACS:** 59, which is lower than EMA BACS of 65
- ✓ 60% of countries reported more stringent access to dupilumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Results – Most common biologic prescription criteria globally

Age and phenotype

- **Age**
  - **Omalizumab and mepolizumab:** ≥6 years
  - **Reslizumab, benralizumab and dupilumab:** ≥12 years
- **Phenotype**
  - **Omalizumab:** Severe allergic asthma
  - **Mepolizumab, benralizumab, reslizumab and dupilumab:** Severe persistent or eosinophilic asthma with type 2 inflammation

Biomarkers

- **Serum IgE**
  - **Omalizumab:** ≥30 or ≥35 IU/mL, or elevated
- **Allergic diagnostics**
  - **Omalizumab:** Positive skin prick test or serum-specific IgE
- **Blood eosinophil counts***
  - **Mepolizumab and benralizumab:** ≥300 cells/μL
  - **Reslizumab**: ≥400 cells/μL
  - **Dupilumab**: ≥150 cells/μL
- **FeNO**
  - **Dupilumab:** ≥20 or ≥25 ppb, or raised (50% of countries)

Asthma control

- **Evidence of poor asthma control**
  - **All biologics**
- **Adherence to background therapy**
  - **All biologics except omalizumab**
- **Background therapy**
  - **All biologics:** high-dose ICS/LABA, ± LAMA, LTRA or theophylline
- **Lung function**
  - **Omalizumab:** FEV_1 ≤80% predicted
- **Exacerbations**
  - **All biologics:** ≥2 (range 0 to 4)*

(Up to 21% of countries require LTOCS use)

Biologic prescription criteria varied across the 28 countries

FeNO = Fractional exhaled nitric oxide; FEV_1 = Forced expiratory volume in 1 second; ICS = Inhaled corticosteroids; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor; LABA = Long-acting β-agonists; LAMA = Long-acting muscarinic receptor antagonists; LTOCS = Long-term oral corticosteroids; LTRA = Leukotriene receptor antagonists; ppb = parts per billion

Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

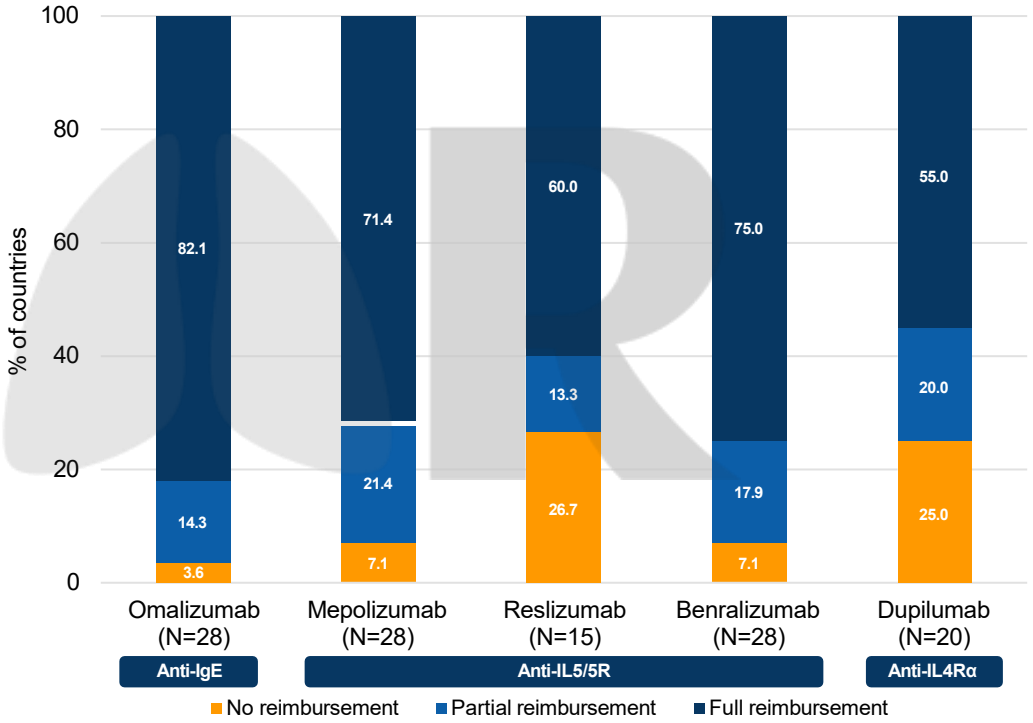
Results – Licensing and reimbursement status of biologics globally

Licensing status

- ✓ **Omalizumab:** 28 countries (100%)
- ✓ **Mepolizumab**: 28 countries (100%)
- ✓ **Benralizumab**: 28 countries (100%)
- ✓ **Reslizumab**: 15 countries (54%)
- ✓ **Dupilumab**: 20 countries (71%)

- Licensing is a central procedure by EMA or FDA, but reimbursement is a national or payer-specific procedure.
- Therefore, patients with similar clinical criteria may have varied access to biologics because of different national or payer reimbursement criteria.

Reimbursement status



Licensing and reimbursement status of the biologics were as of 2021.
EMA = European Medicines Agency; FDA = Food and Drug Administration; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor
Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Conclusions

- **There was wide variation in severe asthma biologic accessibility globally**
  - This could be attributed to global differences in clinical prescription criteria, licensing or reimbursement status of biologics
- **We developed BACS to quantify and compare the ease-of-access to biologics in ISAR countries**
  - The BACS highlighted marked between-country differences in accessibility to severe asthma biologics
  - For all biologics, most countries had lower BACS (more stringent access criteria in place) than the EMA
  - There were no significant correlations between BACS and GDP for all biologics, excluding the "overall wealth of a country" as an explanation for BACS variation
- **Biologic prescription criteria differed substantially across countries, though key criteria include:**
  - Blood eosinophil count thresholds (usually ≥300 cells/μL) for anti-IgE and anti-IL5/5R prescription, in ~80% of countries
  - Moderate or severe exacerbation rates of ≥2 (range: 0 to 4) per year for all biologics, in up to 54% of countries
- **The variation in biologic prescription criteria globally may adversely affect personalized medicine**
  - National regulators and payers should focus on minimizing this international variation
  - Standardization of biologic prescription and access criteria is recommended to ensure the availability of personalized treatment options for severe asthma patients globally

BACS = Biologic ACessibility Score; EMA = European Medicines Agency; GDP = Gross Domestic Product; IgE = Immunoglobulin E; IL5/5R = Interleukin 5/5 receptor; ISAR = International Severe Asthma Registry

Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Acknowledgements

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ADEPT = Anonymised Data Ethics Protocols and Transparency; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ISAR = International Severe Asthma Registry

Porsbjerg C, Price D et al. *J Allergy Clin Immunol Pract* 2022;doi:10.1016/j.jaip.2021.12.027.

Real World Biologic Use and Switch Patterns in Severe Asthma: Data from the International Severe Asthma Registry and the US CHRONICLE Study

Andrew N Menzies-Gow, Claire McBrien, Bindhu Unni, Celeste M Porsbjerg, Mona Al-Ahmad, Christopher S Ambrose, Karin Dahl Assing, Anna von Bülow, John Busby, Borja G Cosio, J Mark FitzGerald, Esther Garcia Gil, Susanne Hansen, Liam G Heaney, Mark Hew, David J Jackson, Maria Kallieri, Stelios Loukides, Njira L Lugogo, Andriana I Papaioannou, Désirée Larenas-Linnemann, Wendy C Moore, Luis A Perez-de-Llano, Linda M Rasmussen, Johannes M Schmid, Salman Siddiqui, Marianna Alacqua, Trung N Tran, Charlotte Suppli Ulrik, John W Upham, Eileen Wang, Lakmini Bulathsinhala, Victoria A Carter, Isha Chaudhry, Neva Eleangovan, Ruth B Murray, Chris A Price, David B Price

Real world biologic use and switch patterns in severe asthma

CHRONICLE Study (USA)

+

ISAR

Historical cohort study

Inclusion criteria

- ≥18 years old at biologic initiation
- Severe asthma (GINA Step 5 or uncontrolled asthma at GINA Step 4)
- Treated with a biologic
- ≥6 months of follow-up after biologic initiation

All subjects were treated in countries that had access to ≥2 biologics. Therefore continuation, stopping, or switching of biologics was feasible.

Analyses

Demographic and clinical characteristics pre-biologic initiation

Patterns of biologic use

- Patterns of biologic stopping, switching and continuations
- Time to cessation of first biologic
- Switch patterns by biologic class
- Reasons for stopping or switching biologics

Sensitivity analyses

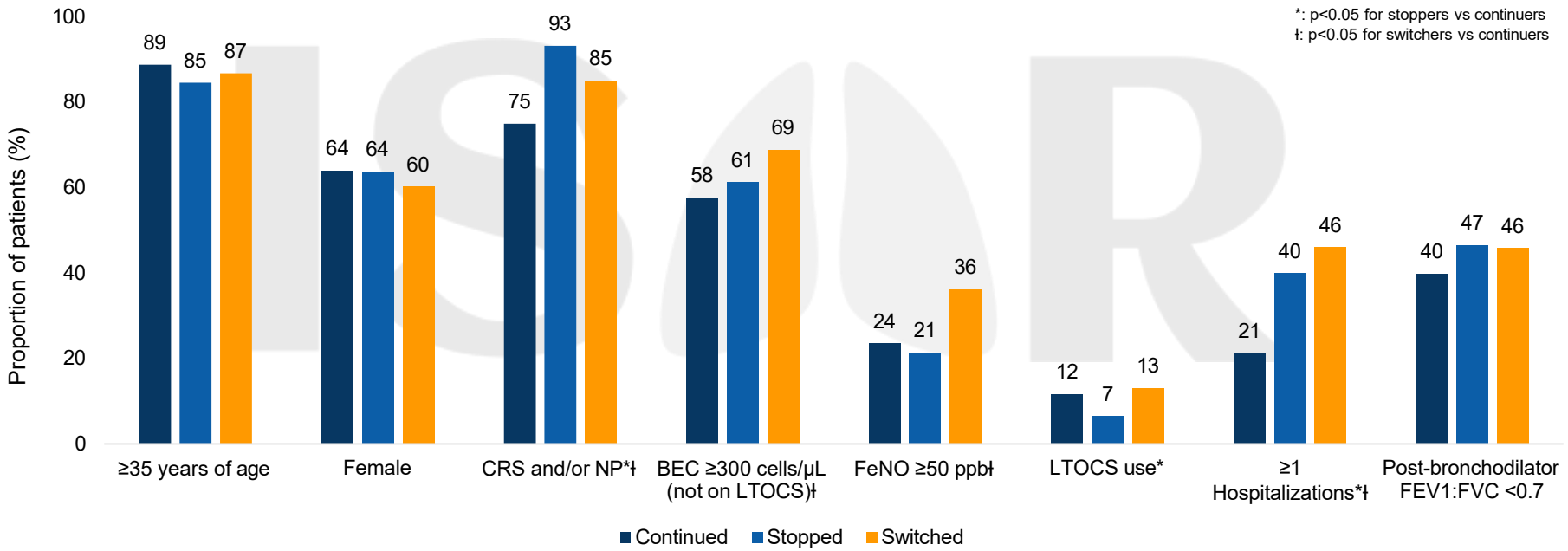
- Prospective patients (n=2656)
- Non-US (n=1404)

GINA = Global Initiative for Asthma; CHRONICLE = Observational Study of Characteristics, Treatment and Outcomes With Severe Asthma in the United States; USA = United States of America

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Demographic and clinical characteristics of severe asthma patients before initiation of the first biologic

Pre-biologic initiation, stoppers and switchers were more likely to have poorer lung function and greater healthcare resource utilization than continuers

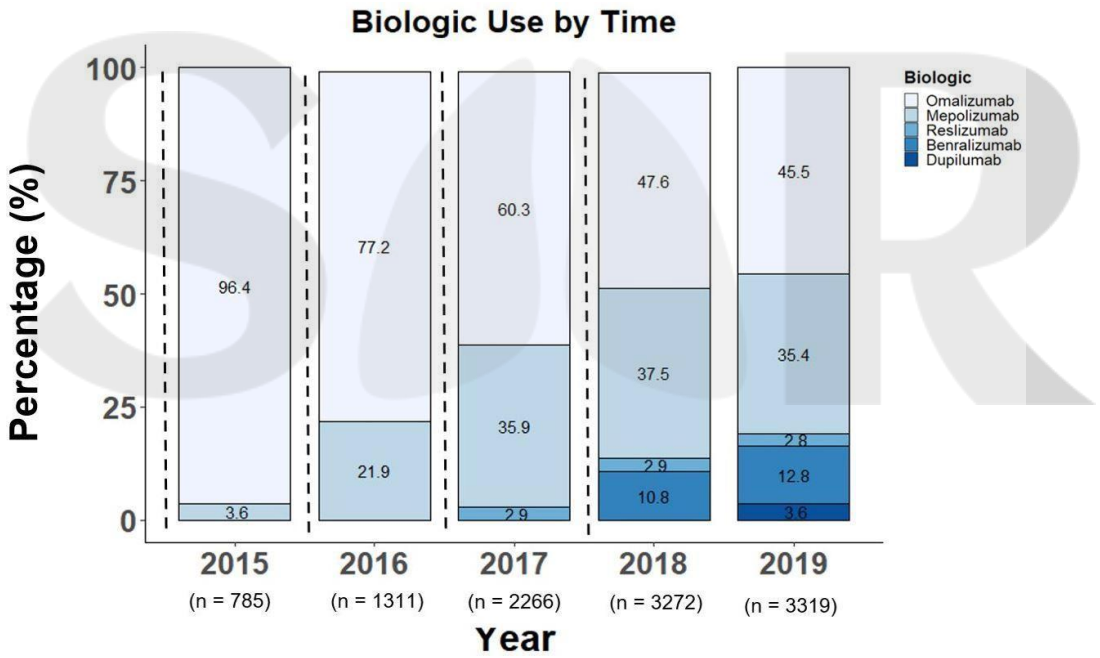


CRS and/or NP refers to CRS with NP, eosinophilic CRS or CRS without nasal polyps.
BEC = Blood eosinophil count; CRS = Chronic rhinosinusitis; FeNO = Fractional exhaled nitric oxide; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; LTOCS = Long-term oral corticosteroids; NP = Nasal polyps

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Patterns of biologic use over time by biologic class

Over time, the proportional use of Anti-IgE therapy ↓ while that of Anti-IL5/5R therapies ↑.

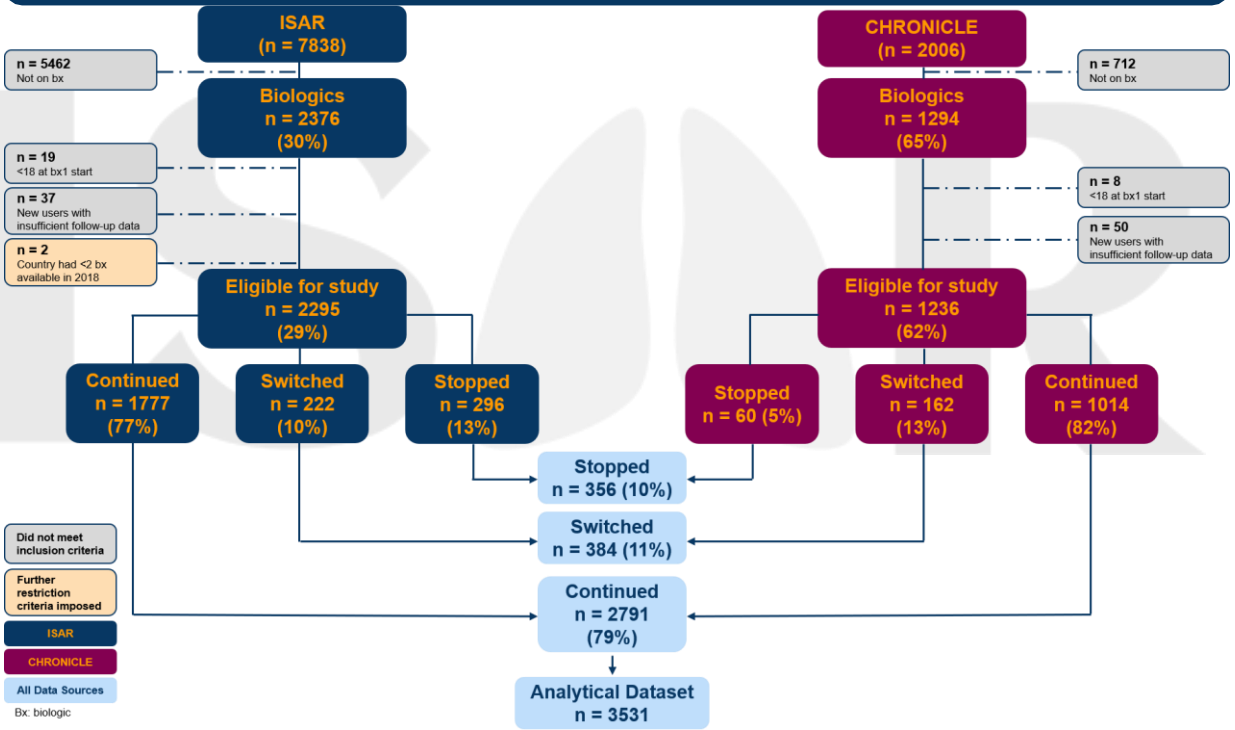


IgE = Immunoglobulin E; IL5/5R = Interleukin 5/5 receptor

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Patterns of biologic use in patients with severe asthma

79% of patients continued their first biologic for at least 6 months while 10.2% stopped and 10.8% switched during follow ups.

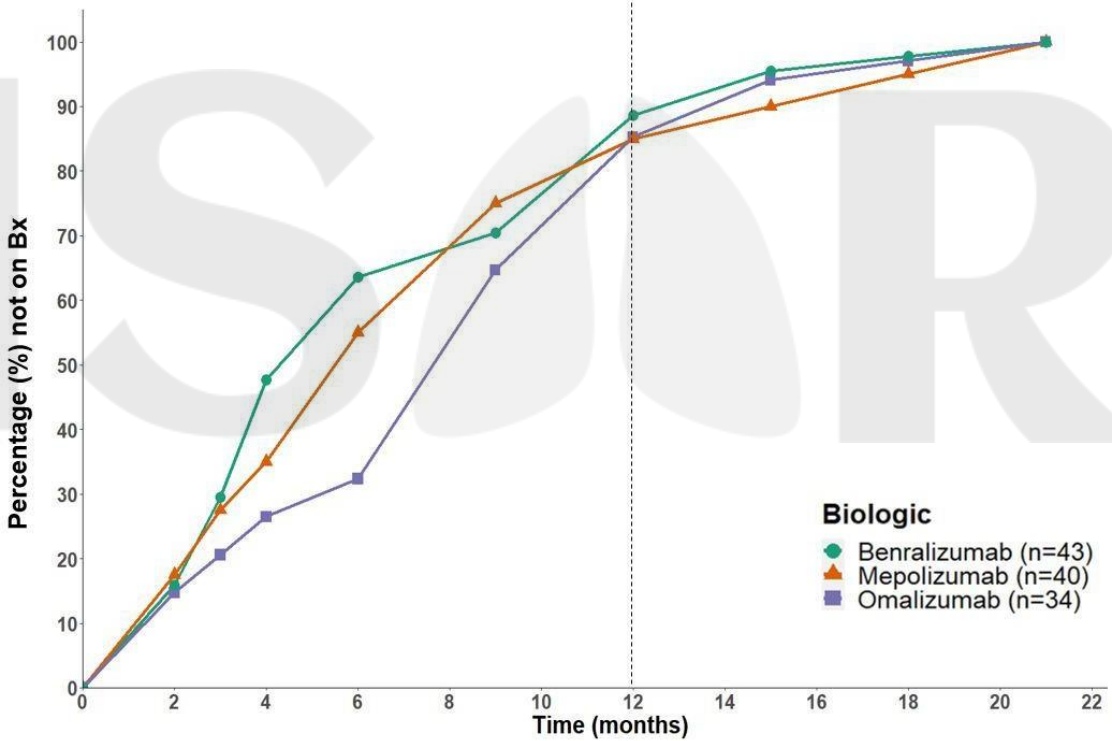


ISAR = International Severe Asthma Registry; CHRONICLE = Observational Study of Characteristics, Treatment and Outcomes With Severe Asthma in the United States

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Time to biologic cessation in patients with severe asthma

Most patients stopped their first biologic within 12 months. The time patients received their initial biologic varied for those who switched.

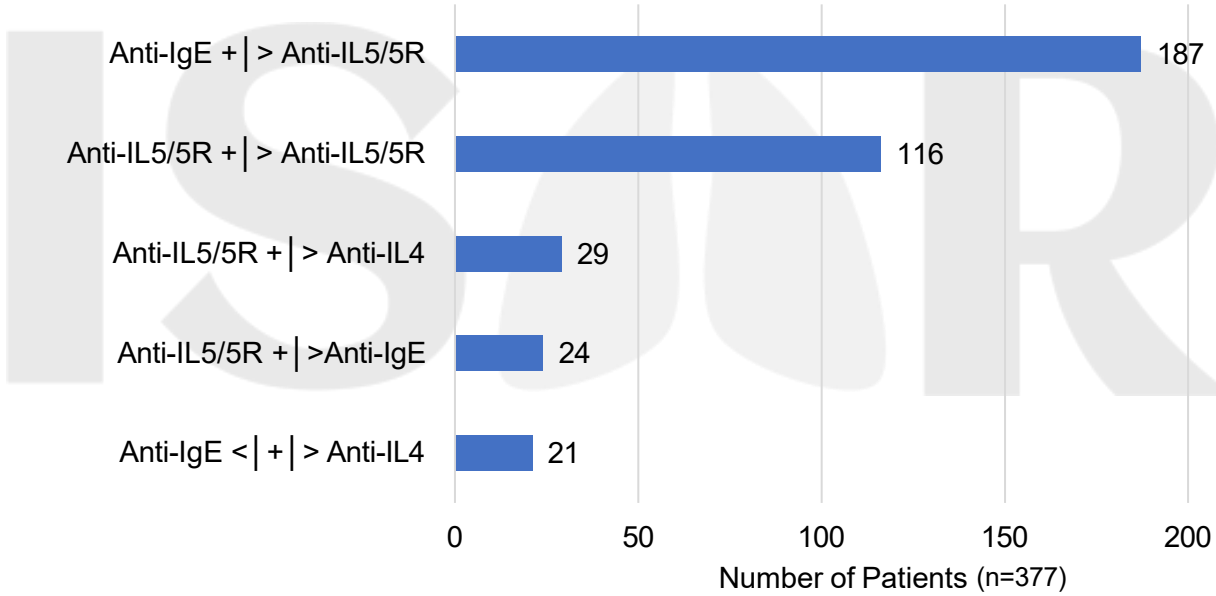


Bx = Biologic

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Patterns of biologic switches for patients with severe asthma

Of patients who stopped or switched their first biologic, the most common first switch was from omalizumab to (or, rarely, combined with) an anti–IL-5/5R.

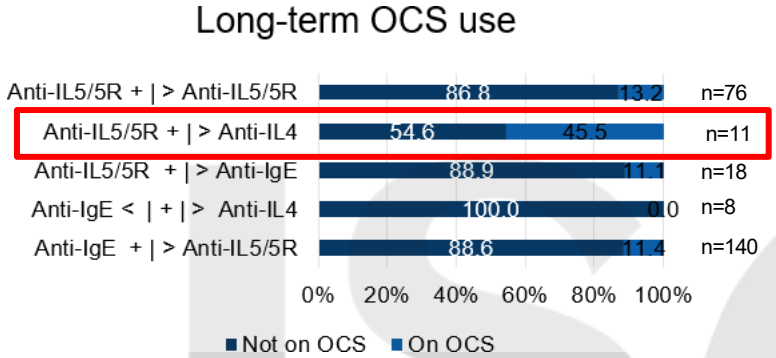


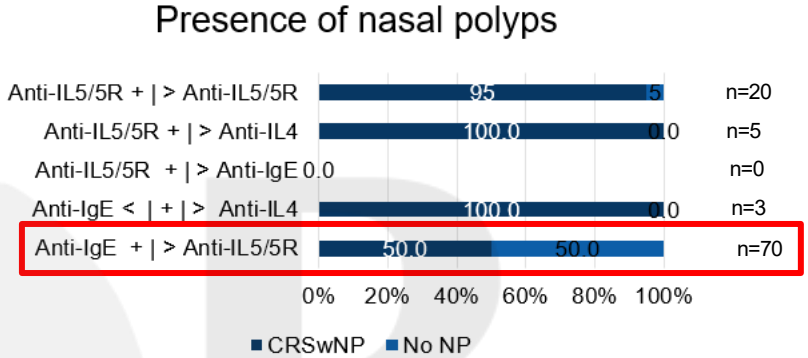
Patterns are mutually exclusive; | : or, < , >: sequence of switch; +: add-on use

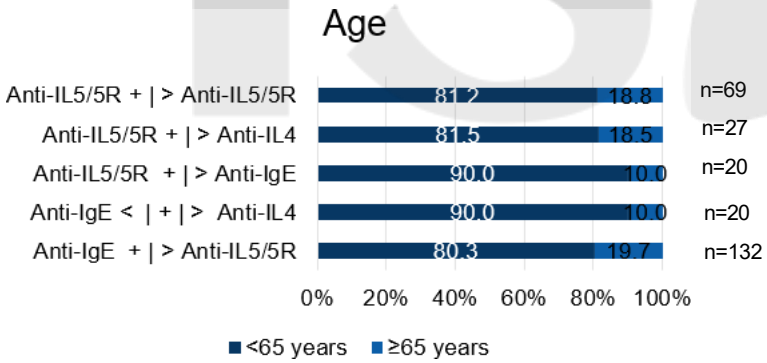
IgE = Immunoglobulin E; IL4/13 = Interleukin 4/13; IL5/5R = Interleukin 5/5 receptor

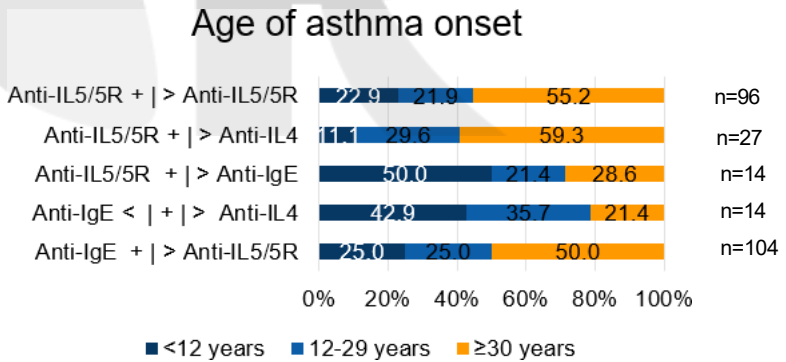
Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Patterns of biologic switches by age, LTOCS use, age of asthma onset and presence of nasal polyps









CRSwNP = Chronic rhinosinusitis with nasal polyps; IgE = Immunoglobulin E; IL4 = Interleukin 4; IL5/5R = Interleukin 5/5 receptor; LTOCS = Long-term oral corticosteroid; NP = Nasal polyps; OCS = Oral corticosteroids

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

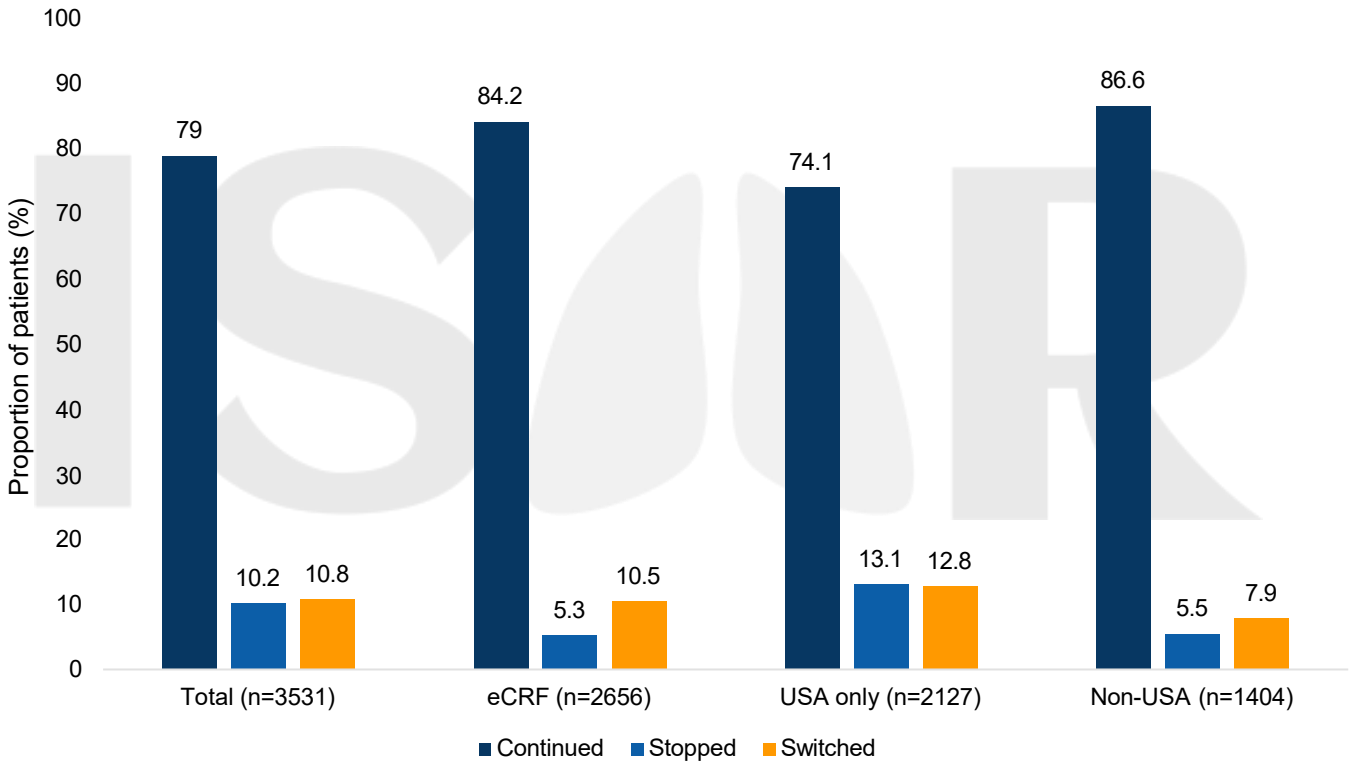
Reasons a patient stopped or switched their first-prescribed biologic

The most commonly cited reasons for stopping or switching a biologic were insufficient clinical efficacy and adverse outcomes.

Reason	Stopped (n=139)	Switched (n=280)
Reason available n (%)	113	183
Insufficient Clinical Efficacy	72 (63.7%)	158 (86.3%)
Potential Adverse Outcomes	18 (15.9%)	14 (7.7%)
Biologic Access Restriction	8 (7.1%)	5 (2.7%)
Patient Preference	4 (3.5%)	3 (1.6%)
Other	12 (10.6%)	11 (6.0%)

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Sensitivity analyses of prospective and non-US patients: Patterns of biologic use



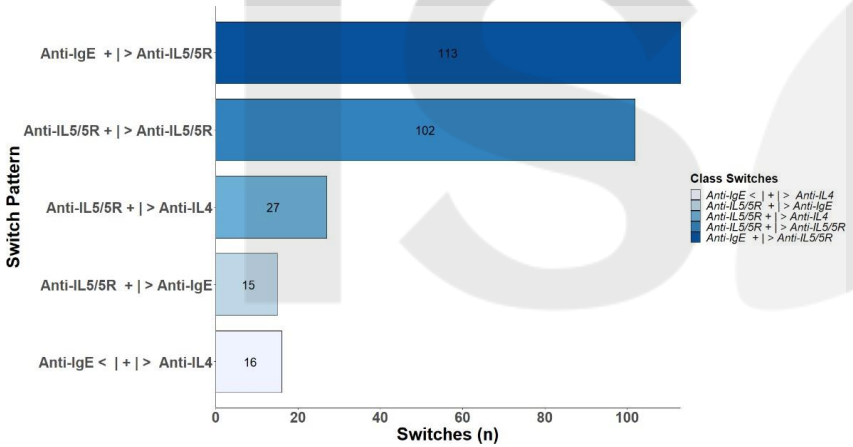
eCRF = Electronic case report form; US = United States

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

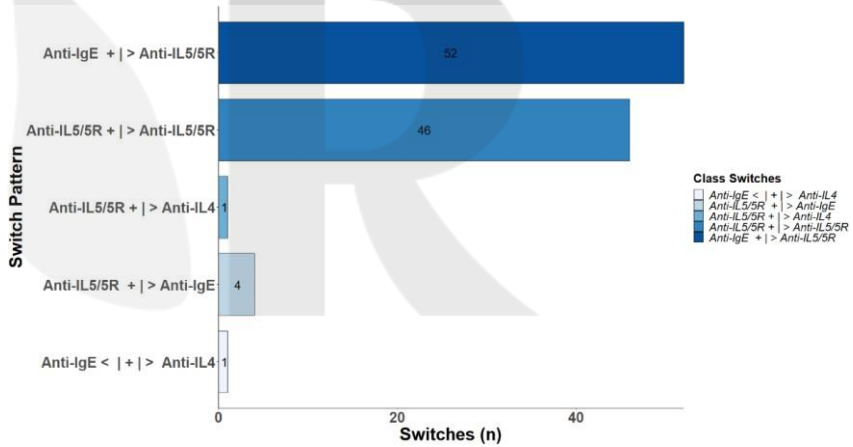
Sensitivity analyses of prospective and non-US patients: Patterns of first biologic switch

Like in the overall population, the most common first switch in prospective and non-US patients was from omalizumab to an anti-IL5/5R therapy.

eCRF data only (n=273)



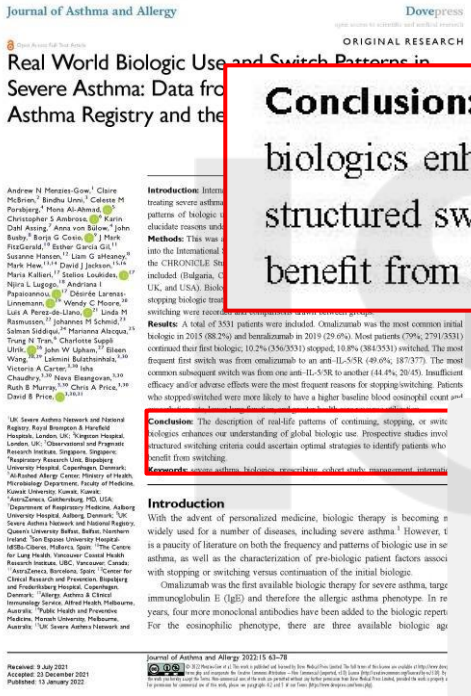
Non-US data only (n=104)



eCRF = Electronic case report form; IgE = Immunoglobulin E; IL4 = Interleukin 4; IL5/5R = Interleukin 5/5 receptor; US = United States

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Conclusions



Journal of Asthma and Allergy

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ORIGINAL RESEARCH

Real World Biologic Use and Switch Patterns in Severe Asthma: Data fro… Asthma Registry and the…

Conclusion: The description of real-life patterns of continuing, stopping, or switching biologics enhances our understanding of global biologic use. Prospective studies involving structured switching criteria could ascertain optimal strategies to identify patients who may benefit from switching.

Introduction

Journal of Asthma and Allergy 2022:15 63–78

Received: 9 July 2021
Accepted: 23 December 2021
Published: 13 January 2022

“

Our findings naturally trigger the question: Is the first biologic prescribed to a patient usually the best one for that individual, or are we under-switching?

ISAR = International Severe Asthma Registry

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Acknowledgements

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ADEPT = Anonymised Data Ethics Protocols and Transparency; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ISAR = International Severe Asthma Registry

Menzies-Gow AN, Price D et al. *J Asthma Allergy* 2022;15:63-78.

Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study

Seyi Soremekun, Liam G Heaney, Derek Skinner , Lakmini Bulathsinhala, Victoria Carter, Isha Chaudhry, Naeimeh Hosseini, Neva Eleangovan, Ruth Murray, Trung N Tran, Benjamin Emmanuel, Esther Garcia Gil, Andrew Menzies-Gow, Matthew Peters, Njira Lugogo, Rupert Jones, David B Price

The role of exacerbations on lung function trajectory in a broad asthma population

Historical cohort study

n=,

Inclusion criteria

- Aged ≥ years old
- Asthma diagnosis
- Active asthma during the baseline year
- years of lung function data
- valid lung function measurements of the same type

Exclusion criteria

- Diagnosis of COPD or other chronic respiratory conditions

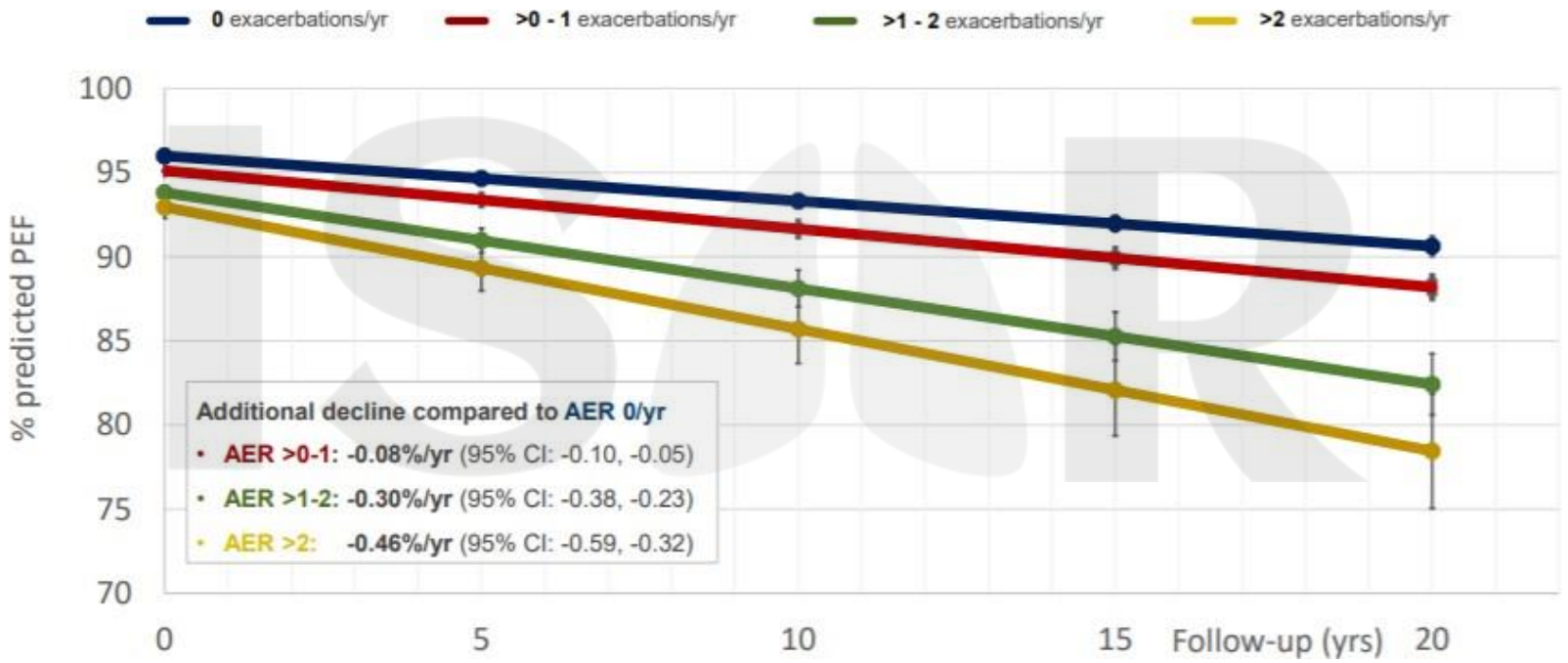
Primary outcome

Peak Expiratory Flow (PEF) rate – used to track lung function trajectories according to annual exacerbation rate

COPD = Chronic obstructive pulmonary disease

Soremekun S et al. Thorax 2022; 10.1136/thorax-2021-217032

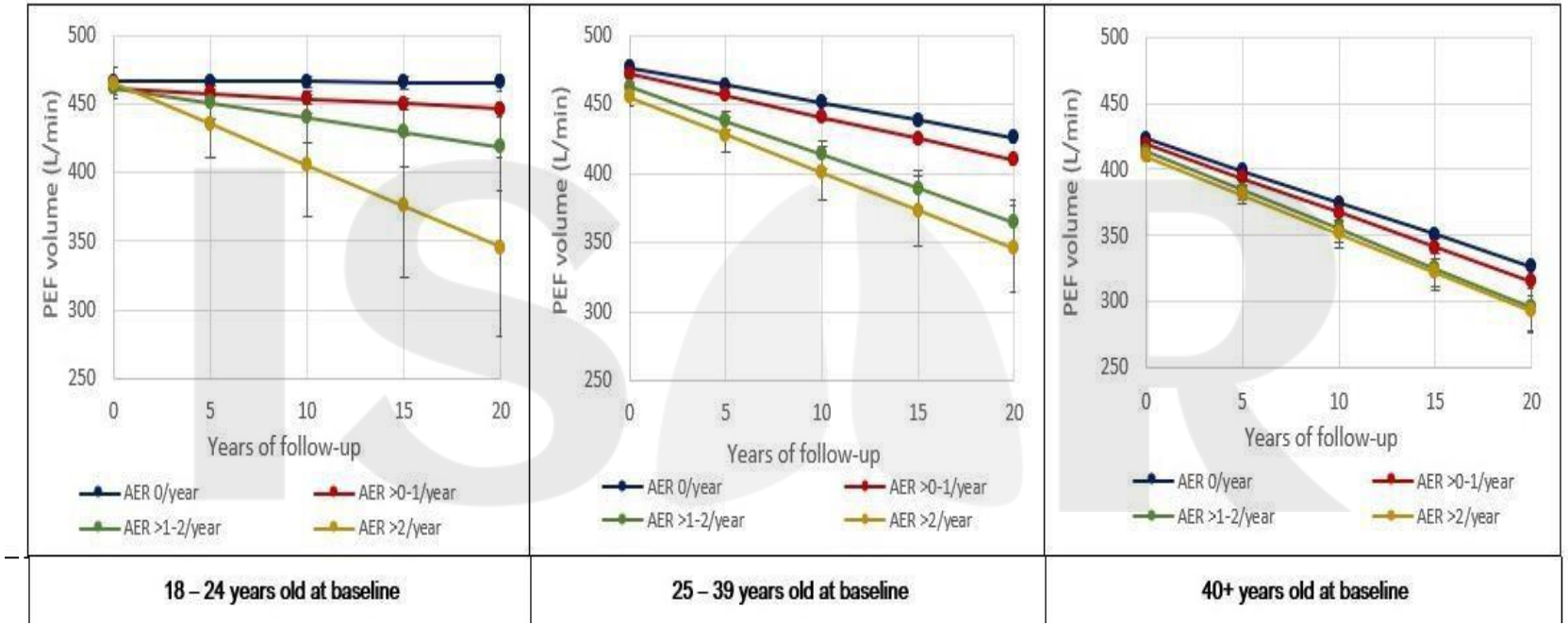
Exacerbations and lung function decline in asthma



AER = Annual exacerbation rate; PEF = Peak expiratory flow

Soremekun S et al. Thorax 2022; 10.1136/thorax-2021-217032

Age and lung function decline



Treating exacerbations may benefit lung function in the long term

AER = Annual exacerbation rate; PEF = Peak expiratory flow

Soremekun S et al. Thorax 2022; 10.1136/thorax-2021-217032

Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy

GLITTER I

Wenjia Chen, Mohsen Sadatsafavi , Trung N Tran, Ruth B Murray, Chong Boon Nigel Wong, Nasloon Ali, Cono Ariti , Esther Garcia Gil, Anthony Newell, Marianna Alacqua, Mona Al-Ahmad, Alan Altraja, Riyad Al-Lehebi, Mohit Bhutani, Leif Bjermer, Anne Sofie Bjerrum, Arnaud Bourdin, Lakmini Bulathsinhala, Anna von Bülow, John Busby, Giorgio Walter Canonica, Victoria Carter, George C Christoff, Borja G Cosio, Richard W Costello, J Mark FitzGerald, João A Fonseca, Kwang Ha Yoo, Liam G Heaney, Enrico Heffler, Mark Hew, Ole Hilberg, Flavia Hoyte, Takashi Iwanaga, David J Jackson, Rupert C Jones, Mariko Siyue Koh, Piotr Kuna, Désirée Larenas-Linnemann, Sverre Lehmann, Lauri A Lehtimäki, Juntao Lyu, Bassam Mahboub, Jorge Maspero, Andrew N Menzies-Gow, Concetta Sirena, Nikolaos Papadopoulos, Andriana I Papaioannou, Luis Pérez de Llano, Diahn-Warng Perng, Matthew Peters, Paul E Pfeffer, Celeste M Porsbjerg, Todor A Popov, Chin Kook Rhee, Sundeep Salvi, Camille Taillé, Christian Taube, Carlos A Torres-Duque, Charlotte S Ulrik, Seung Won Ra, Eileen Wang, Michael E Wechsler, David B Price

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Aim and Methods

Background

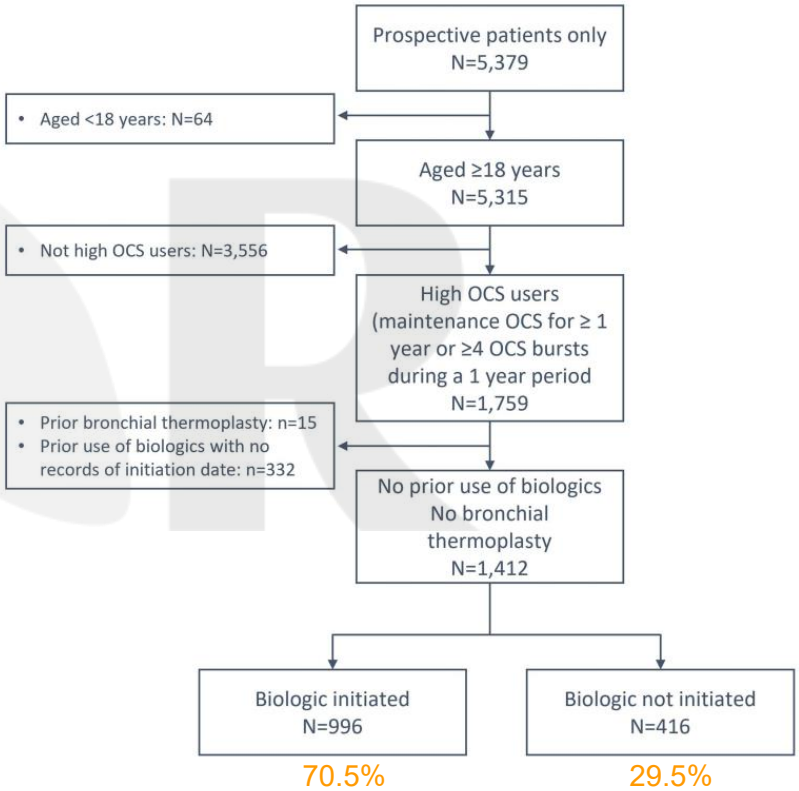
Many severe asthma patients with high oral corticosteroid exposure (HOCS) often do not initiate biologics despite being eligible

Aim

Compare the characteristics of severe asthma patients with HOCS who did and did not initiate biologics

Methods

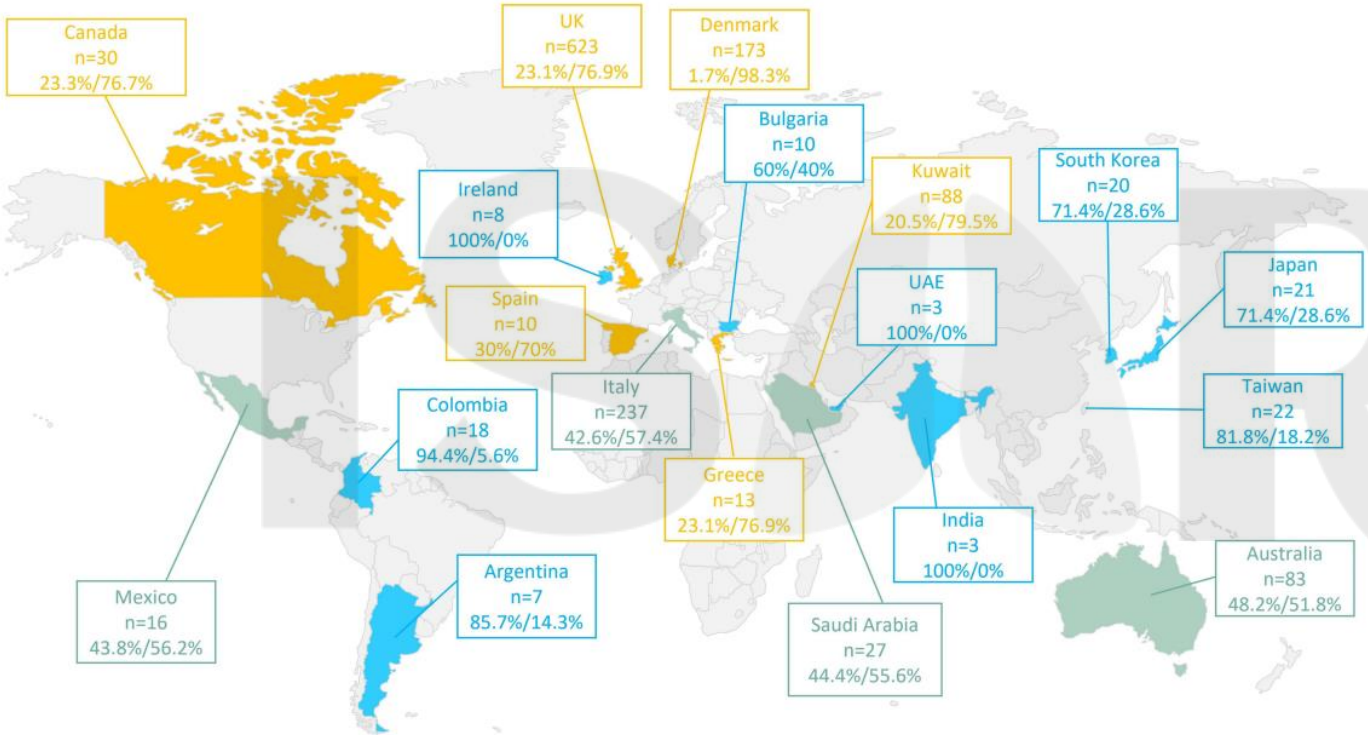
- Baseline characteristics of patients with HOCS (long-term maintenance OCS therapy for at least 1 year, or ≥4 courses of steroid bursts in a year) from ISAR who initiated or did not initiate biologics (anti-IgE, anti-IL5/5R or anti-IL4R), were described at the time of biologic initiation or registry enrolment
- Statistical relationships were tested using Pearson's chi-squared tests for categorical variables, and t-tests for continuous variables, adjusting for potential errors in multiple comparisons



International Severe Asthma Registry data : ISAR, OCS: Oral corticosteroids, anti-IgE: Anti-immunoglobulin E, anti-IL5: anti-immunoglobulin 5, anti-IL4: Anti-immunoglobulin 4

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Disparity in biologic accessibility worldwide evident:
29% of SA patients with high oral corticosteroid exposure did not receive biologics



- **Pattern of biologic initiation related to country-income level**
- **Inconsistency between the initiation of biologics and country-specific biologic accessibility-** suggesting that prescription criteria, and by extension, biologic accessibility, not the sole determinants for biologic initiation in certain countries

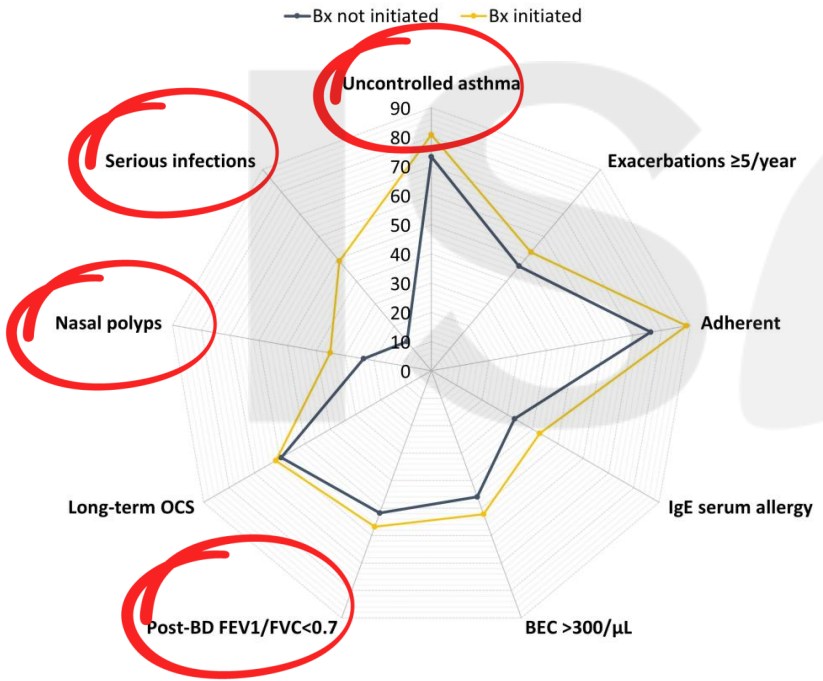
Figure 2 Geographic distribution of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR according to biologic initiation status. ISAR: International Severe Asthma Registry. Data are presented as % not initiated/% initiated. Green: approximately equal proportion of biologic non-initiators to initiators; Blue: More likely not to initiate biologics; Yellow: more likely to initiate biologics.

International Severe Asthma Registry data : ISAR, HOCS: High Oral Corticosteroid exposure, SA: Severe Asthma

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Serious infectious events, nasal polyps and inadequate asthma control appear to encourage biologic prescribing for SA patients with high oral corticosteroid exposure

Clinical characteristics of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR who did and did not initiate biologic therapy



Compared to non-initiators, patients who **initiated biologics** were/had:

- More likely to have **uncontrolled asthma** (80.8% vs 73.2%, p=0.004)
- More likely to have a **serious infection**, defined as an infection that required hospitalization, invasive or non-invasive ventilation, IV antibiotics, or that resulted in a fatal outcome (49.0% vs 13.3%, p<0.001)
- More likely to have **nasal polyps** (35.2% vs 23.6%, p<0.001)
- Modestly **greater degree of airflow limitation** according to the proportion with a FEV1/FVC ratio of less than 0.7 (56.8% vs 51.8%, p=0.013)

BEC, blood eosinophil count; BD, bronchodilator; Bx, biologic; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; OCS, oral corticosteroid, HOCS: High Oral Corticosteroid exposure, SA: Severe Asthma, IV:Intravenous

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Initiation of biologic therapy more likely in those with greater degree of eosinophilic asthma

Clinical characteristics of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR who did and did not initiate biologic therapy

Patients who **initiated biologics** had/were:

- **Higher mean BEC** (483/µL vs 399/µL, p=0.003)
- **Higher FeNO concentrations** (25–50 ppb, 31.4% vs 24.3%; >50 ppb, 39.4% vs 35.8%, p=0.010)
- **More likely to be of ISAR Grade 3 eosinophilic phenotype** (90.8% vs 68.0%, p<0.001)

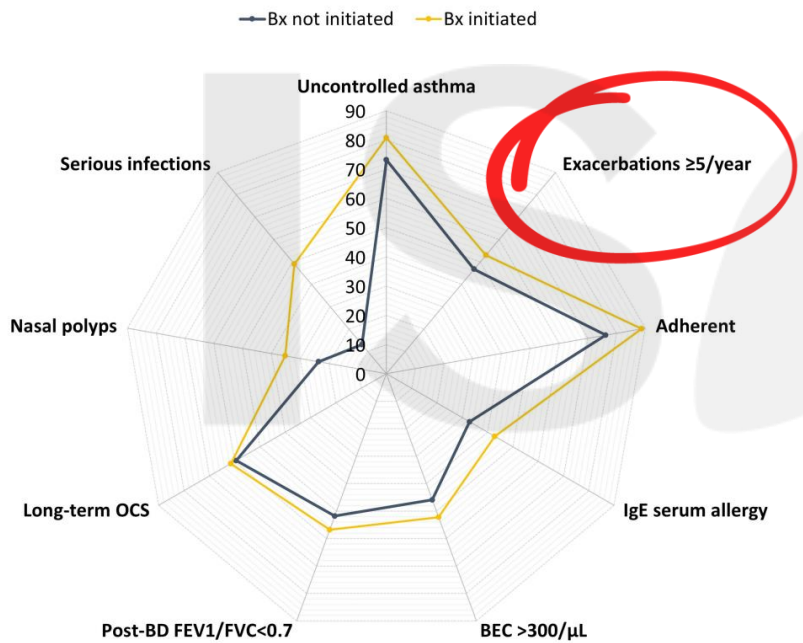
Fewer biologic initiators had low T2 biomarkers compared to non-initiators (8.7% vs 16.4%, p=0.003), defined as BEC <150/µL and FeNO<25ppb)

BEC, blood eosinophil count; BD, bronchodilator; Bx, biologic; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; OCS, oral corticosteroid, HOCS: High Oral Corticosteroid exposure, FeNO: Fractional Exhaled Nitric Oxide, T2: Type 2

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

One third of severe asthma patients with high oral corticosteroid exposure did not receive biologics despite similar exacerbation frequency and HCRU as those who initiated a biologic

Clinical characteristics of adult severe asthma patients with high oral corticosteroid exposure enrolled in ISAR who did and did not initiate biologic therapy



Compared to non-initiators, patients who **initiated biologics** were/had:

- **Similar number of asthma exacerbations** over the past year (5.7 vs 5.3, p=0.15)
- **Similar post-bronchodilator FEV1** as a percentage of predicted FEV1 (73.1% vs 72.7%, p=0.85)
- **Similar proportions of patients with hospital admissions** (28.7% vs 31.5%, p=0.30) **and ICU admissions involving use of invasive ventilations** (6.9% vs 6.5%, p=0.77)

BEC, blood eosinophil count; BD, bronchodilator; Bx, biologic; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; OCS, oral corticosteroid, HOCS: High Oral Corticosteroid exposure, HCRU: healthcare resource utilisation, ICU: Intensive Care Unit

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Summary: One third of severe asthma patients with high oral corticosteroid exposure did not receive biologics despite similarities in disease burden

Key findings:

- **Eosinophilic phenotype, serious infectious events, nasal polyps, airflow limitation and inadequate asthma control** appear to encourage physicians to **prescribe biologic** therapy
- However, **one third of severe HOCS** (high oral corticosteroid exposure) **asthma patients did not receive biologics despite similar exacerbation frequency and HCRU** as those who initiated a biologic therapy

Practice change needed:

- **Multiple characteristics need to be considered to guide the initiation of biologics in SA patients**
- **Individualized treatment algorithms are needed to guide the initiation of biologics**

HOCS: High Oral Corticosteroid exposure, HCRU: healthcare resource utilisation, SA: Severe Asthma

Chen W. et al., Characterization of Patients in the International Severe Asthma Registry with High Steroid Exposure Who Did or Did Not Initiate Biologic Therapy. J Asthma Allergy. 2022;15:1491-1510 https://doi.org/10.2147/JAA.S377174

Impact of Initiating Biologics in Patients With Severe Asthma on Long-term Oral Corticosteroids or Frequent Rescue Steroids (GLITTER II): Data From the International Severe Asthma Registry

Wenjia Chen, Trung N Tran, Mohsen Sadatsafavi, Ruth Murray, Nigel Chong Boon Wong, Nasloon Ali, Con Ariti, Lakmini Bulathsinhala, Esther Garcia Gil, J Mark FitzGerald, Marianna Alacqua, Mona Al-Ahmad, Alan Altraja, Riyad Al-Lehebi, Mohit Bhutani, Leif Bjermer, Anne-Sofie Bjerrum, Arnaud Bourdin, Anna von Bülow, John Busby, Giorgio Walter Canonica, Victoria Carter, George C Christoff, Borja G Cosio, Richard W Costello, João A Fonseca, Peter G Gibson, Kwang-Ha Yoo, Liam G Heaney, Enrico Heffler, Mark Hew, Ole Hilberg, Flavia Hoyte, Takashi Iwanaga, David J Jackson, Rupert C Jones, Mariko Siyue Koh, Piotr Kuna, Désirée Larenas-Linnemann, Sverre Lehmann, Lauri Lehtimäki, Juntao Lyu, Bassam Mahboub, Jorge Maspero, Andrew N Menzies-Gow, Anthony Newell, Concetta Sirena, Nikolaos G Papadopoulos, Andriana I Papaioannou, Luis Perez-de-Llano, Diahn-Warng Perng Steve, Matthew Peters, Paul E Pfeffer, Celeste M Porsbjerg, Todor A Popov, Chin Kook Rhee, Sundeep Salvi, Camille Taillé, Christian Taube, Carlos A Torres-Duque, Charlotte Ulrik, Seung-Won Ra, Eileen Wang, Michael E Wechsler, David B Price

Aim and Methods

Aim

To examine the effectiveness of initiating biologics in a large, real-world cohort of adult patients with severe asthma and high oral corticosteroid exposure (HOCS)*.

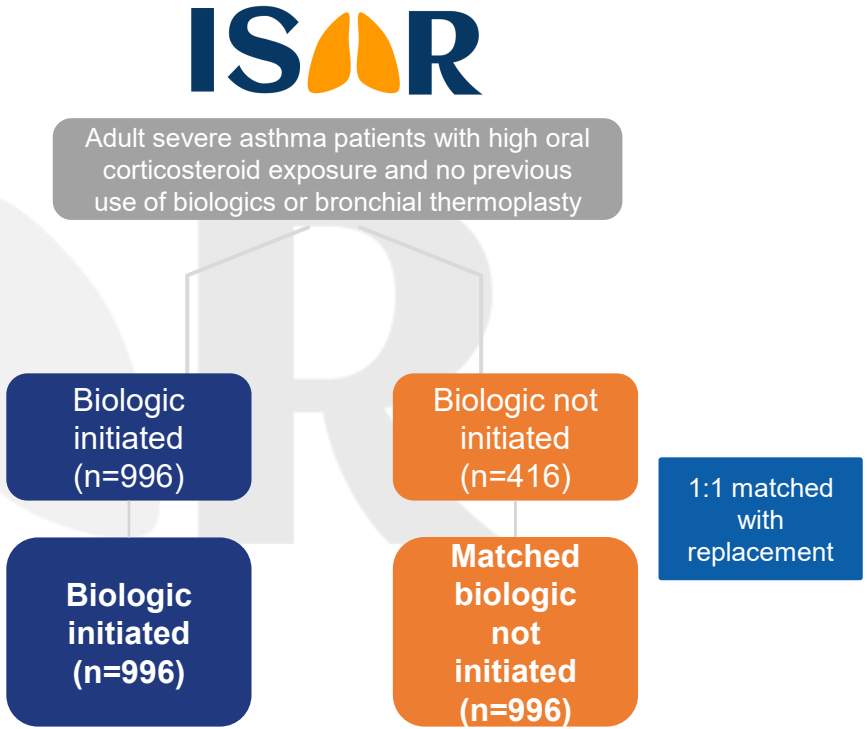
Outcomes

Primary outcome: reduced rate of asthma exacerbations

Secondary outcomes

- improvement in asthma control
- reduction in OCS dose
- reduced number of asthma-related emergency department visits and asthma-related hospital admissions

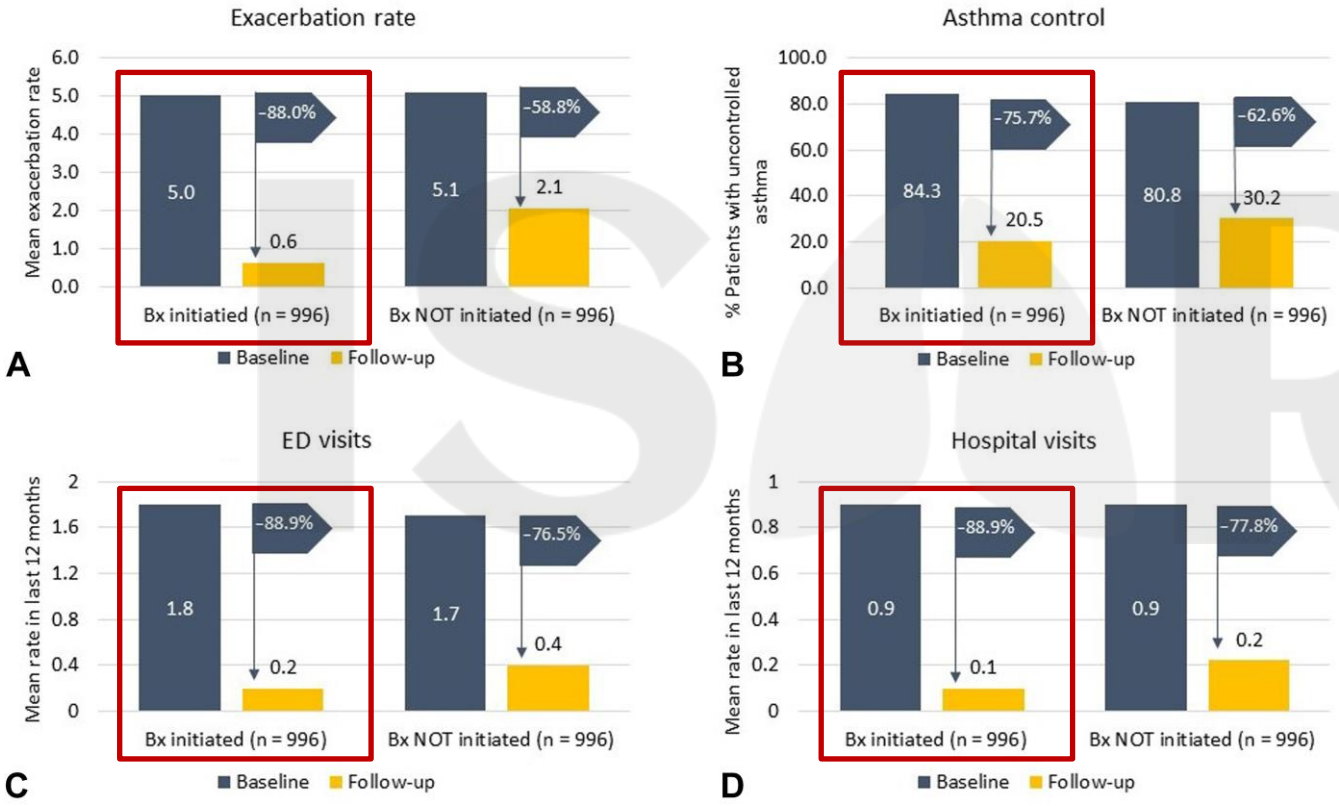
Outcomes were estimated over a 12-month follow-up period.



*HOCS was defined as long-term OCS ≥1 year or ≥4 courses of rescue OCS within a 12-month period in the current study.

Chen, W, Tran, TN, et al. *J Allergy Clin Immunol Pract.* 2023. doi: 10.1016/j.jaip.2023.05.044.

Change from baseline in exacerbation rates, asthma control, emergency department visits, and hospital visits



Patients who initiated a biologic experienced an **88.0% reduction** in exacerbation rates, an **89% reduction** in emergency department visits and hospital visits, and a **76% reduction** in asthma control in the 12-month follow-up period.

Chen, W, Tran, TN, et al. *J Allergy Clin Immunol Pract.* 2023. doi: 10.1016/j.jaip.2023.05.044.

Effectiveness of biologic initiation vs non-initiation on OCS reduction

Outcome	Biologic not initiated	Biologic initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
Total OCSs				
Increased dose (%)	27.6	16.0	−11.6 (−29.8 to 6.7)	0.51 (0.17 to 1.51)
Low reduction (%)	63.6	54.4	−9.2 (−24.8 to 6.4)	0.87 (0.61 to 1.24)
Moderate reduction (%)	5.5	16.2	10.7 (4.2 to 17.3)	3.82 (1.58 to 9.25)
Optimal reduction (%)	3.3	13.4	10.0 (−0.6 to 20.7)	7.73 (0.71 to 84.27)
Long-term OCSs				
Increased dose (%)	14.3	8.6	−5.7 (−18.0 to 6.5)	0.51 (0.12 to 2.17)
Low reduction (%)	73.6	68.5	−5.1 (−22.5 to 12.3)	0.94 (0.69 to 1.28)
Moderate reduction (%)	4.2	8.9	4.8 (−1.7 to 11.2)	2.55 (0.78 to 8.37)
Optimal reduction (%)	7.9	14.0	6.1 (−7.7 to 19.9)	4.16 (0.21 to 82.18)

Patients who initiated a biologic were **2.48 times more likely** to achieve a daily total OCS dose of <5 mg compared with those who did not (estimated risk probability of 38.0% vs 15.3%; P = .011) and **2.20 times more likely** to achieve a daily long-term OCS dose (i.e., maintenance dose only) of <5 mg (risk probability, 49.6% vs 22.5%; P = .002).

Compared with those who did not initiate a biologic, those who initiated a biologic were **7.73 times more likely** to have an optimal (>75%) total OCS reduction.

OCS = oral corticosteroids

Chen, W, Tran, TN, et al. *J Allergy Clin Immunol Pract.* 2023. doi: 10.1016/j.jaip.2023.05.044.

Effectiveness of biologic initiation vs non-initiation on healthcare resource utilisation

Outcome	Biologic not initiated	Biologic initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
ED Visits				
Risk of ED visit (%)	14	6	−9 (−14, −3)	0.35 (0.21, 0.58)
Hospitalisation				
Risk of hospitalization (%)	12	5	−7 (−10, −3)	0.31 (0.18, 0.52)

Compared with patients who did not, patients who initiated a biologic had approximately **one-third the risk and frequency** of asthma-related emergency department visits and hospitalizations (i.e., serious exacerbations).

ED = emergency department

Chen, W, Tran, TN, et al. *J Allergy Clin Immunol Pract.* 2023. doi: 10.1016/j.jaip.2023.05.044.

Conclusions

In a real-world setting, keeping severe asthma patients on HOCS or initiating biologics can both result in improvements in severe asthma.

However, HOCS **patients who received biologics experienced the combined benefit of improvements in health outcomes** (including exacerbation rates, and healthcare resource utilization) whilst being able **to reduce high levels of both short- and long-term oral steroid exposure.**

HOCS = high oral corticosteroid exposure

Chen, W, Tran, TN, et al. *J Allergy Clin Immunol Pract.* 2023. doi: 10.1016/j.jaip.2023.05.044.

Comparative effectiveness of Anti-IL5 and Anti-IgE biologic classes in patients with severe asthma eligible for both

Paul E. Pfeffer, Nasloon Ali, Ruth Murray, Charlotte Ulrik, Trung N. Tran, Jorge Maspero, Matthew Peters
... See all authors

First published: 17 March 2023 | https://doi.org/10.1111/all.15711

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

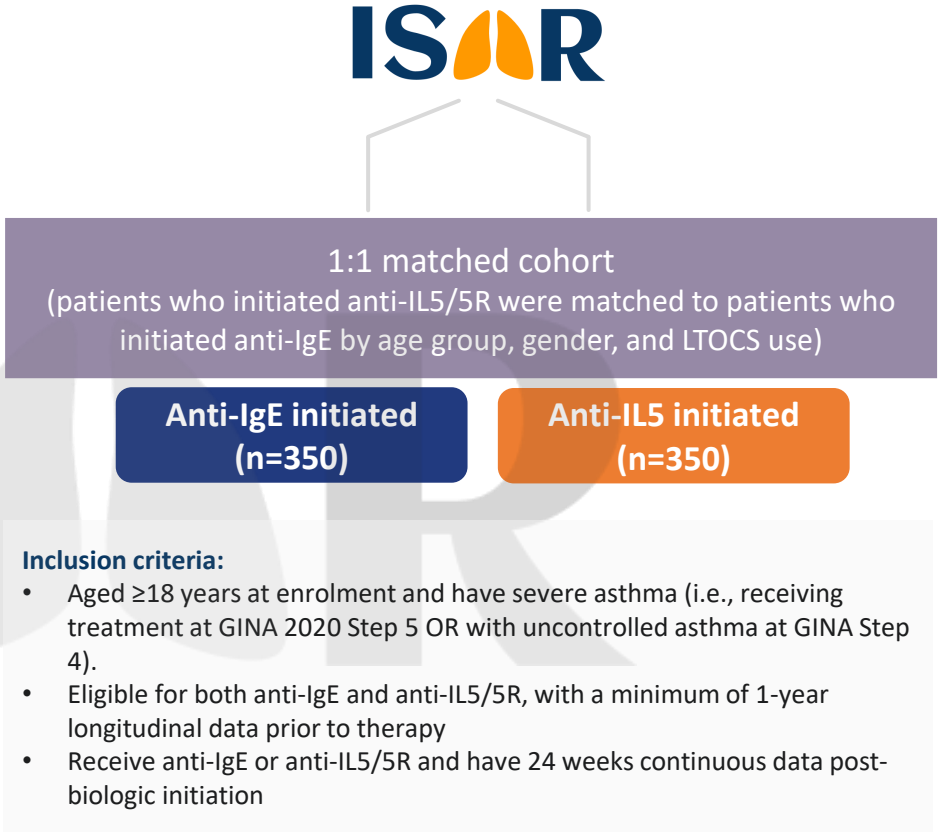
Aim and Methods

Aims

Compare the effectiveness of anti-IgE and anti-IL5/5R among patients eligible for both classes of treatment in real life.

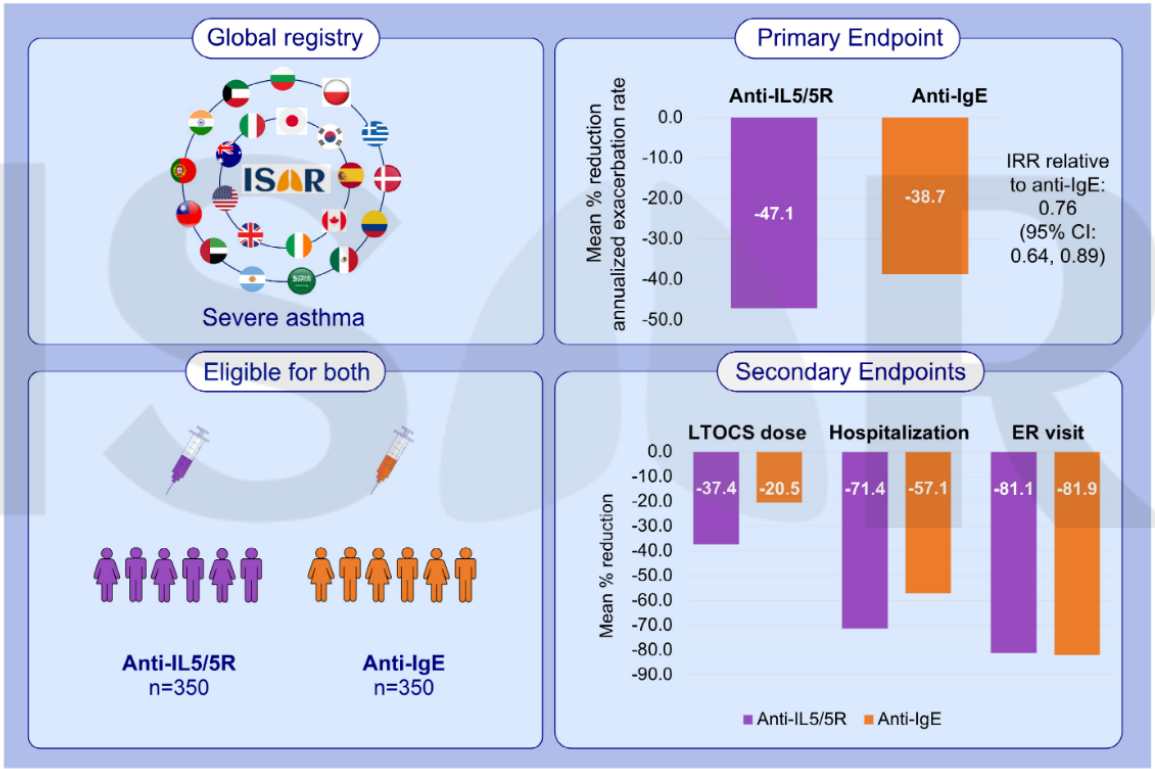
Outcomes

- **Primary outcome:** Exacerbation rate
- **Secondary outcomes:**
  - Long-term oral corticosteroid use
  - Emergency room visits
  - Hospitalizations



*OCS dependence is defined as being on long-term OCS upon initiation of biologic therapy.
IgE = Immunoglobulin E; IL5 = IL5/5R = Interleukin 5/5-receptor; ISAR = International Severe Asthma Registry; GINA = Global Initiative for Asthma; LTOCS = Long-term oral corticosteroids;

Comparative effectiveness of Anti-IgE and Anti-IL5/5R



IgE = Immunoglobulin E; IL5 = IL5/5R = Interleukin 5/5-receptor; ISAR = International Severe Asthma Registry; LTOCS = Long-term oral corticosteroids; ER = emergency room; IRR = Incidence Rate Ratio

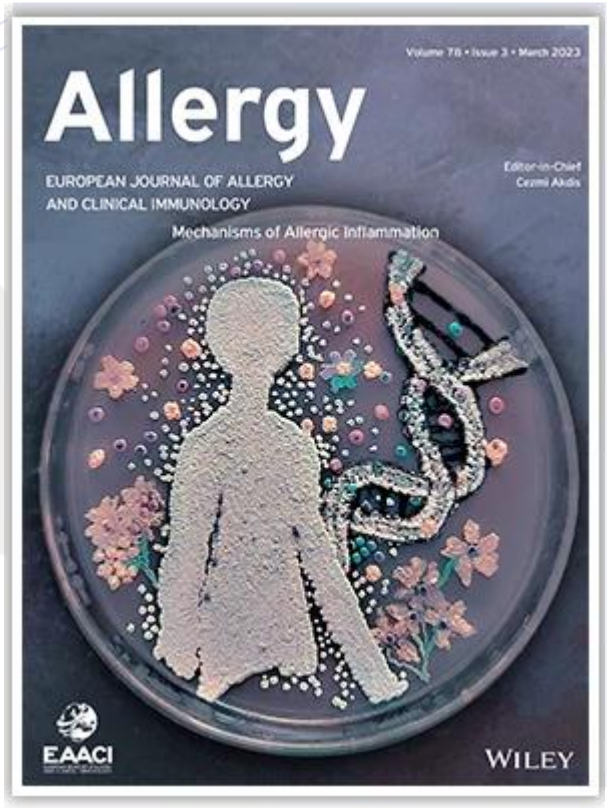
Conclusions

In real-life, both anti-IgE and anti-IL5/5R improve asthma outcomes in patients eligible for both biologic classes.

Anti-IL5/5R was superior in reducing asthma exacerbations and LTOCS use.

These findings can **assist treatment decisions** and add to the growing body of robust real-life data on biologics.

IgE = Immunoglobulin E; IL5/5R = Interleukin 5/5-receptor; LTOCS = Long-term oral corticosteroids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Editor-in-Chief
Cezmi Akdis
Mechanisms of Allergic Inflammation
EAACI
WILEY

Thank you!

Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry: PRISM I

Ghislaine Scelo, PhD, Carlos A. Torres-Duque, Jorge Maspero, Trung N. Tran, MD, Ruth Murray, PhD, Neil Martin, MD, PhD,· Andrew N. Menzies-Gow, PhD, Mark Hew, PhD, Matthew J. Peters, PhD, Peter G. Gibson, MBBS, George C. Christoff, MD, MPH, PhD,· Todor A. Popov, MD, PhD, Andréanne Côté, MD, MSc, Celine Bergeron, MD, MSc, Delbert Dorscheid, MD, PhD, J. Mark FitzGerald, MD, · Kenneth R. Chapman, MD, Louis Philippe Boulet, MD, · Mohit Bhutani, MD,· Mohsen Sadatsafavi, MD, PhD, · Libardo Jiménez-Maldonado, MD, · Mauricio Duran-Silva, MD, Bellanid Rodriguez, BSc, Carlos Andres Celis-Preciado, MD, MSc,· Diana Jimena Cano-Rosales, MD, · Ivan Solarte, MD, MHPE,· Maria Jose Fernandez-Sanchez, MD, MSc, Patricia Parada-Tovar, BSc, · Anna von Bülow, MD, PhD,· Anne Sofie Bjerrum, MD, PhD,· Charlotte S. Ulrik, MD, DMSc,· Karin Dahl Assing, MD, · Linda Makowska Rasmussen, MD, PhD, Susanne Hansen, PhD,· Alan Altraja, MD, PhD, Arnaud Bourdin, MD, PhD, Camille Taille, MD, PhD, Jeremy Charriot, MD, PhD, Nicolas Roche, MD, PhD, Andriana I. Papaioannou, MD, PhD, Konstantinos Kostikas, MD, PhD,· Nikolaos G. Papadopoulos, MD, PhD, Sundeep Salvi, MD, PhD,· Deirdre Long, RGN, RANP, MSc, · Patrick D. Mitchell, MD,· Richard Costello, MB, MD, · Concetta Sirena, PhD, · Cristina Cardini, MD, · Enrico Heffler, MD, PhD,· Francesca Puggioni, MD, Giorgio Walter Canonica, MD, · Giuseppe Guida, MD, PhD, · Takashi Iwanaga, MD, PhD, · Mona Al-Ahmad, MBBCh, · Désirée Larenas Linnemann, MD, · Ulises Garcia, MD, · Piotr Kuna, MD, PhD,· João A. Fonseca, MD, PhD,· Riyad Al-Lehebi, MD, · Mariko Siyue Koh, MBBS,· Chin Kook Rhee, MD, PhD, · Borja G. Cosio, MD, PhD, Luis Perez de Llano, MD, PhD, · Diahn-Warng Perng (Steve), MD, PhD,· Erick Wan-Chun Huang, MD, PhD, · Hao-Chien Wang, MD, PhD,· Ming-Ju Tsai, MD, PhD, Bassam Mahboub, MD,· Laila Ibraheem Jaber Salameh, PhD, David Jackson, PhD, John Busby, PhD, · Liam G. Heaney, MD,· Paul Pfeffer, PhD,· Amanda Grippen Goddard, DO, · Eileen Wang, MD, MPH, · Flavia Hoyte, MD, · Michael E. Wechsler, MD,· Nicholas Chapman, DO,· Rohit Katial, MD, · Victoria Carter, BSc, Lakmini Bulathsinhala, MPH, Neva Eleangovan, · Con Ariti, MSc,· Juntao Lyu, PhD, David B. Price, MB Bchir,· Celeste Porsbjerg, MD, PhD

Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Aim and Methods

Rationale

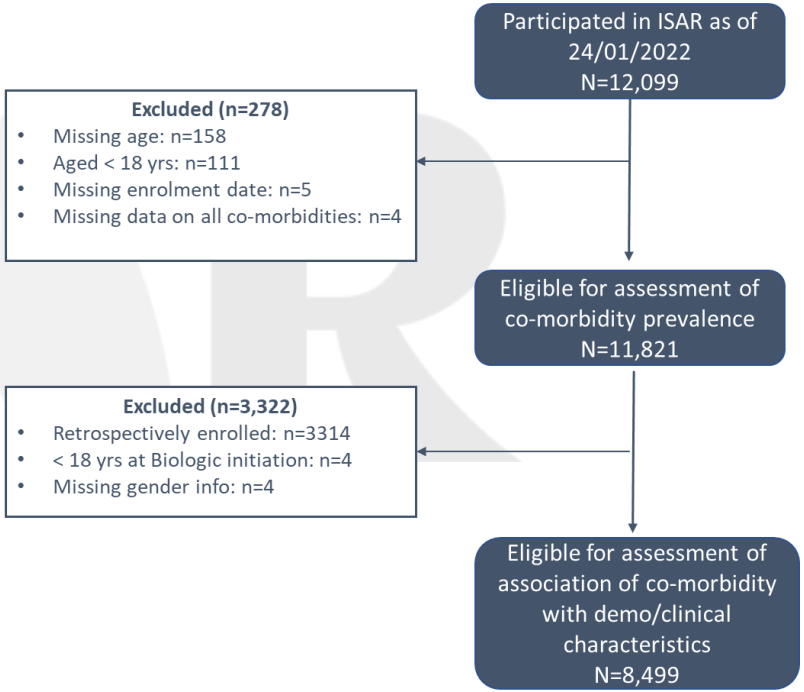
Investigation for the presence of asthma comorbidities is recommended by the Global Initiative for Asthma because their presence can complicate asthma management

Aim

To understand the prevalence and pattern of comorbidities and multimorbidity in adults with severe asthma and their association with asthma-related outcomes

Methods

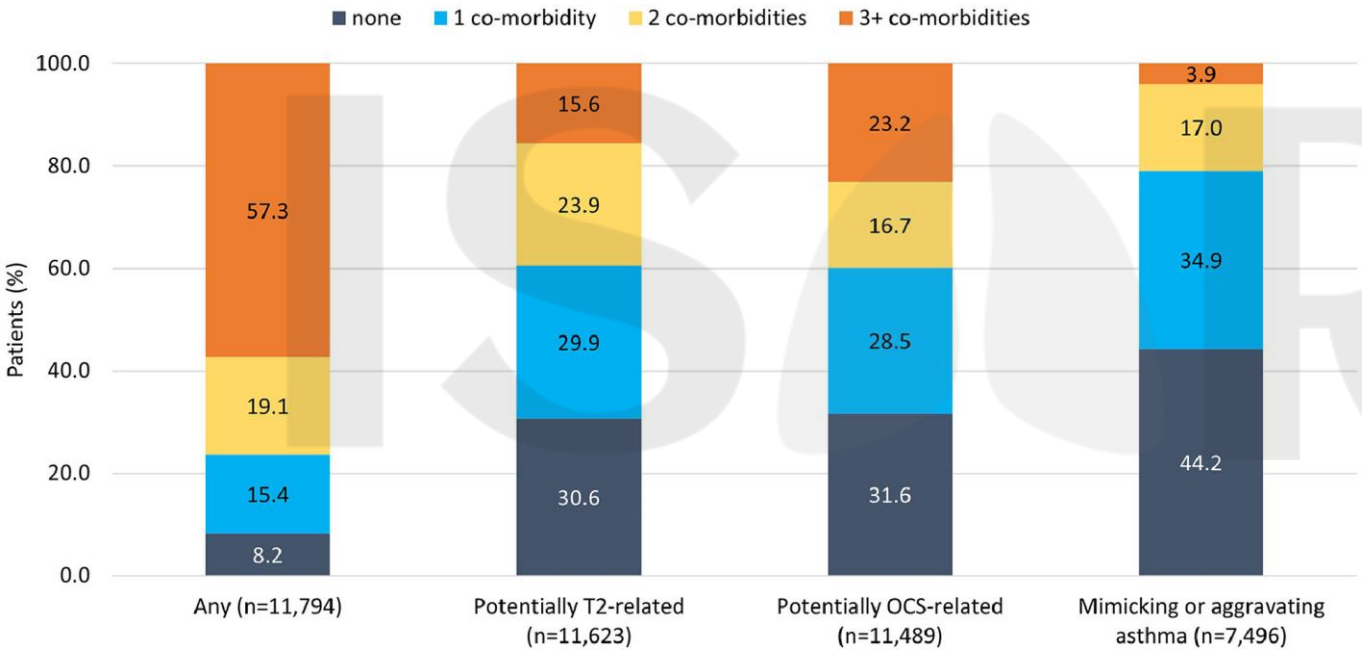
- Cross-sectional study using ISAR data from 22 countries
- 30 comorbidities were identified and categorized a priori as any of the following: (1) potentially type 2–related comorbidities, (2) potentially OCS-related comorbidities, or (3) comorbidities mimicking or aggravating asthma.
- The association between comorbidities and asthma-related outcomes was investigated using multivariable models adjusted for country, age at enrollment, and sex (ie male or female).



International Severe Asthma Registry data : ISAR, OCS: oral corticosteroid

Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Most patients had at least 3 comorbidities of any type



- 39.5% had 2 or more potentially T2-related comorbidities
- 39.9% had 2 or more potentially OCS-related comorbidities
- 20.9% had 2 or more comorbidities mimicking or aggravating asthma

T2: Type 2, OCS: Oral Corticosteroid

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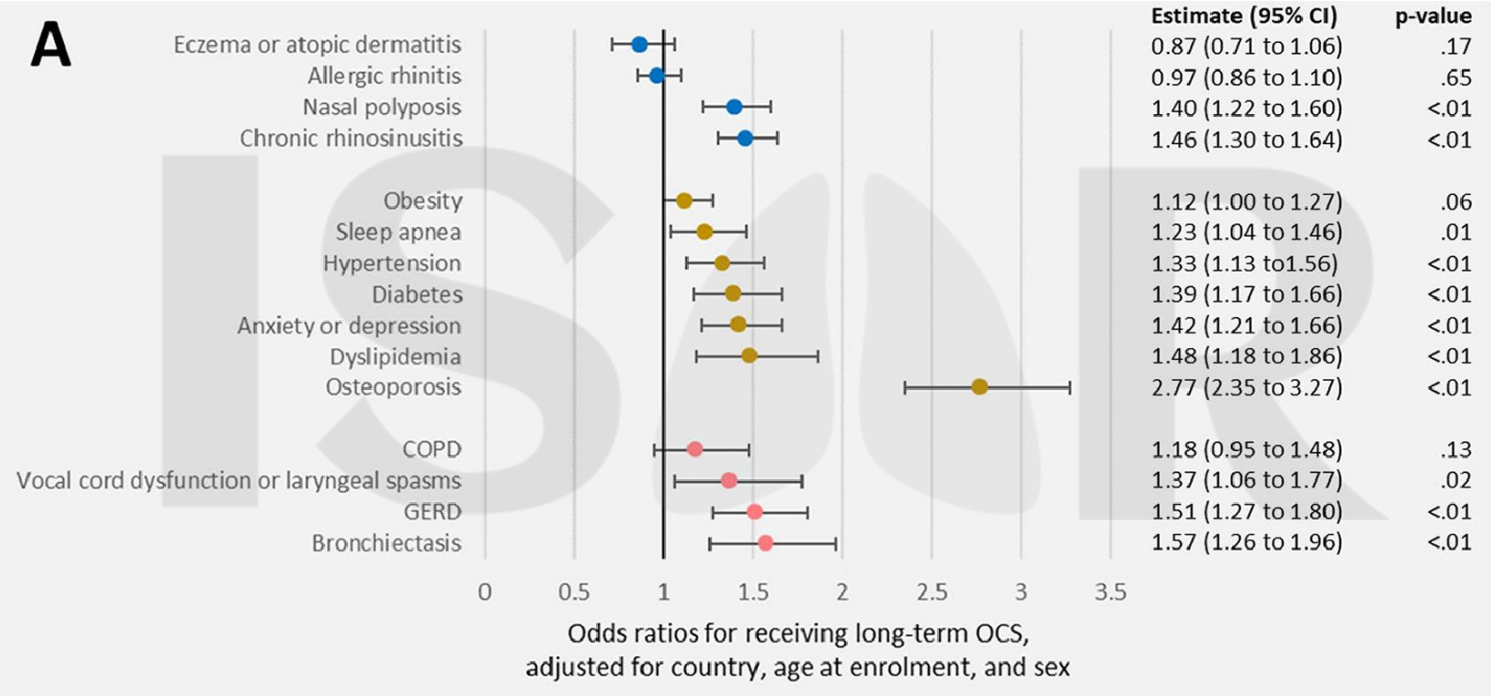
Many individual comorbidities were associated with receiving LTOCS*



*The reference category for each analysis was absence of the comorbidity of interest

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; OCS, oral corticosteroid; OR, odds ratio, LTOCS: Long-term Oral Corticosteroids.

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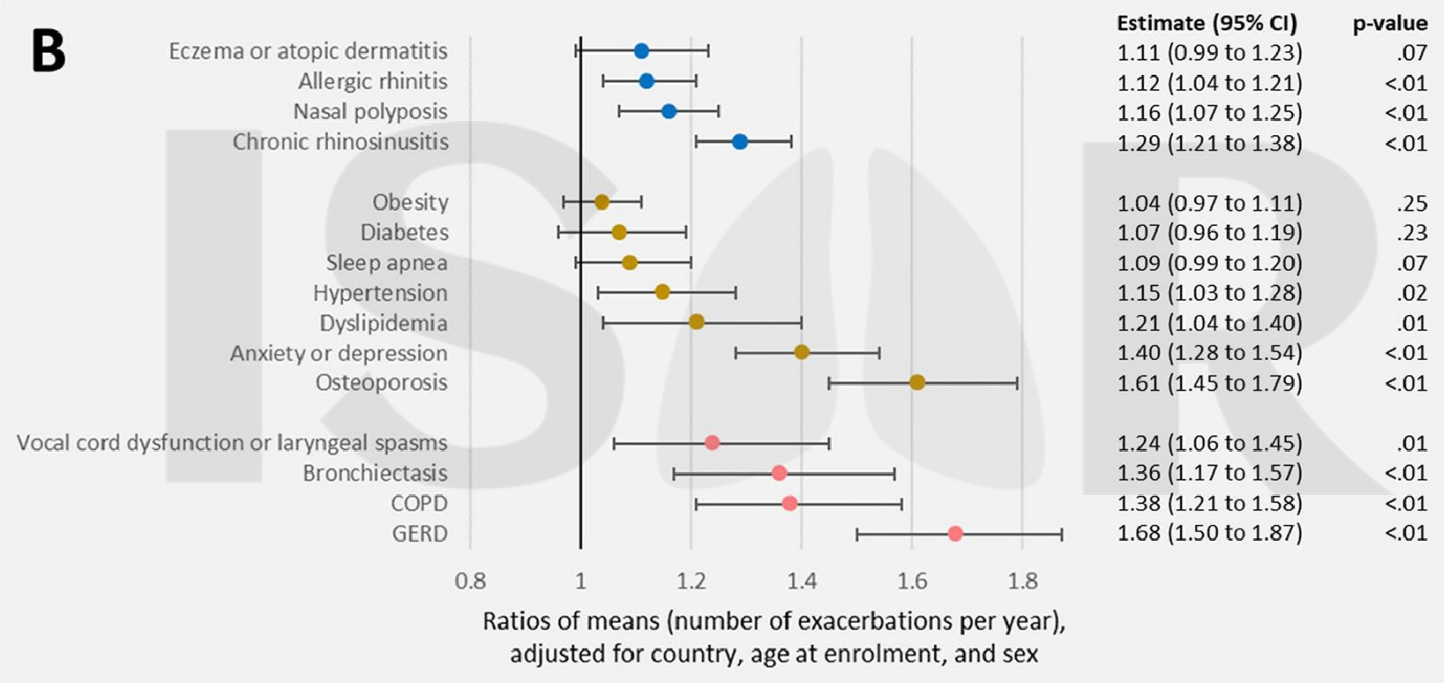
Many individual comorbidities were associated with higher exacerbation rates*



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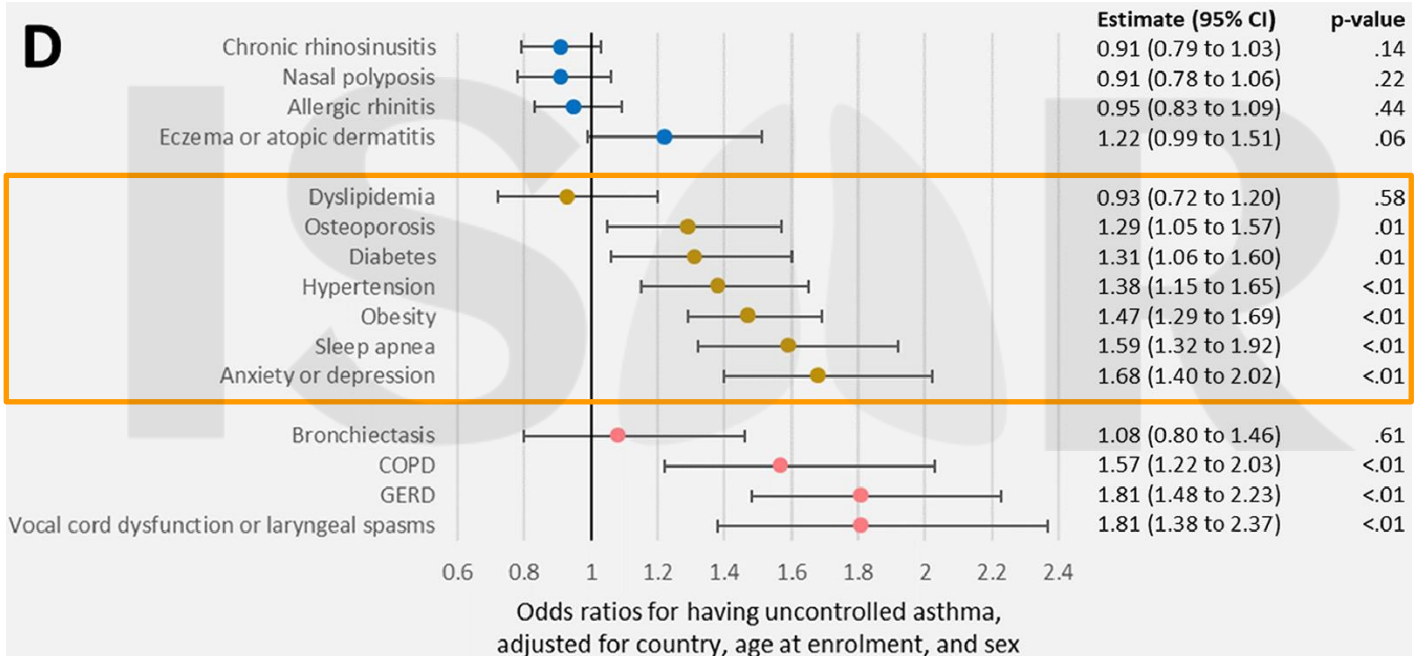
Poor asthma control associated with almost all potentially OCS-related comorbidities*



*The reference category for each analysis was absence of the comorbidity of interest

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; OCS, oral corticosteroid; OR, odds ratio, LTOCS: Long-term Oral Corticosteroids.

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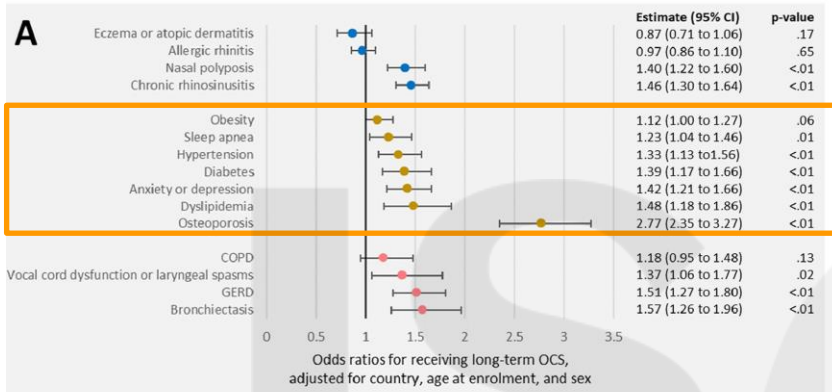
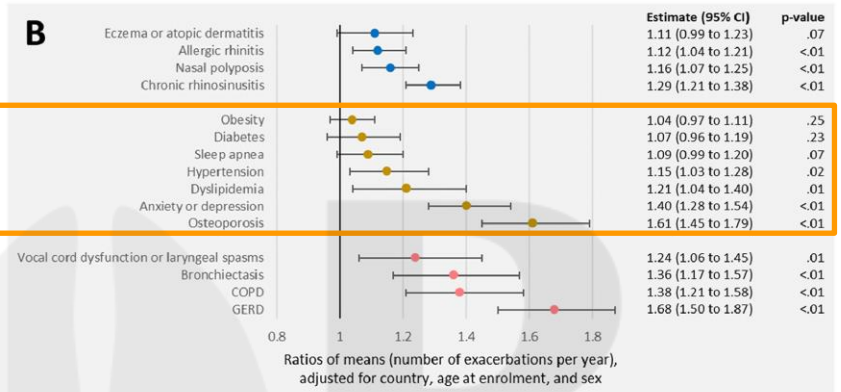
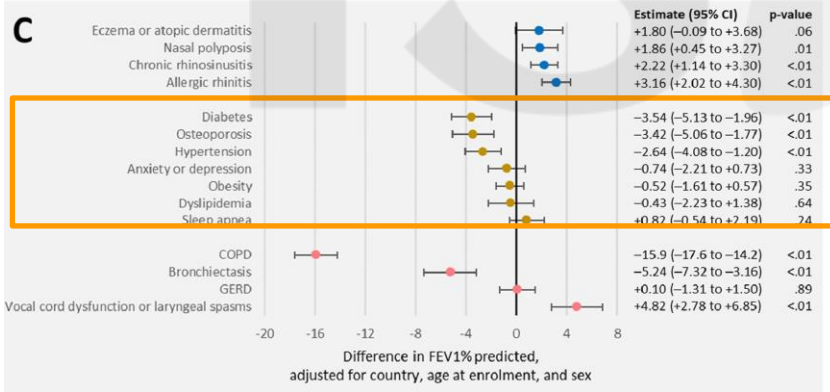
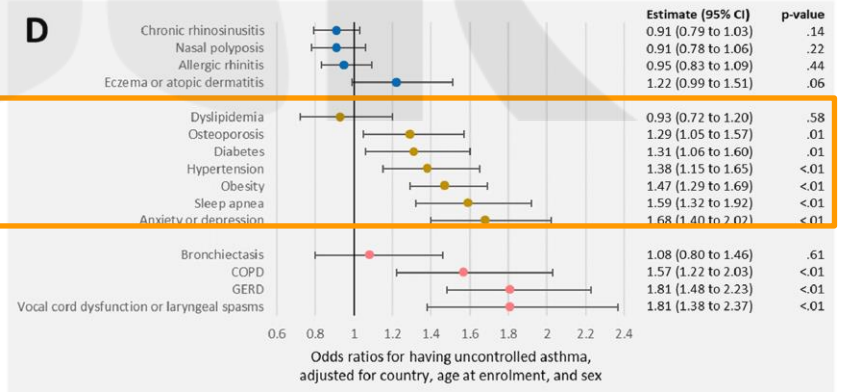
Having hypertension or osteoporosis was associated with a worse outcome in each of the 4 asthma outcomes assessed*









*The reference category for each analysis was absence of the comorbidity of interest

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; OCS, oral corticosteroid; OR, odds ratio, LTOCS: Long-term Oral Corticosteroids.

Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Chronic Rhinosinusitis and Nasal Polyps associated with greater number of exacerbations and use of LTOCS*

Odds Ratios and 95% CIs of Receiving **Long-Term OCS** Associated With the Presence of Comorbidities

Comorbidities	Sample size	OR (95% CI)	P value
Potentially T2-related categories			
Allergic rhinitis	7976	0.97 (0.86-1.10)	.65
Chronic rhinosinusitis	8020	1.46 (1.30-1.64)	<.001
Nasal polyposis	8271	1.40 (1.22-1.60)	<.001
Eczema/atopic dermatitis	8255	0.87 (0.71-1.06)	.17

Ratios of Means and 95% CIs of Number of **Exacerbations** in the Year Preceding Enrolment Associated With the Presence of Comorbidities

Comorbidities	Sample size	Ratio of means (95% CI)	P value
Potentially T2-related categories			
Allergic rhinitis	7060	1.12 (1.04-1.21)	.003
Chronic rhinosinusitis	7036	1.29 (1.21-1.38)	<.001
Nasal polyposis	7283	1.16 (1.07-1.25)	<.001
Eczema/atopic dermatitis	7265	1.11 (0.99-1.23)	.07

- Compared with those without CRS, patients with comorbid **CRS had 29% more exacerbations and were 46% more likely to receive LTOCS**
- **Nasal polyposis was also associated with a poorer outcome** for these 2 variables
- Allergic rhinitis was associated with higher exacerbation rates only
- **AD was not associated with a significantly poorer asthma outcome for any variable** assessed

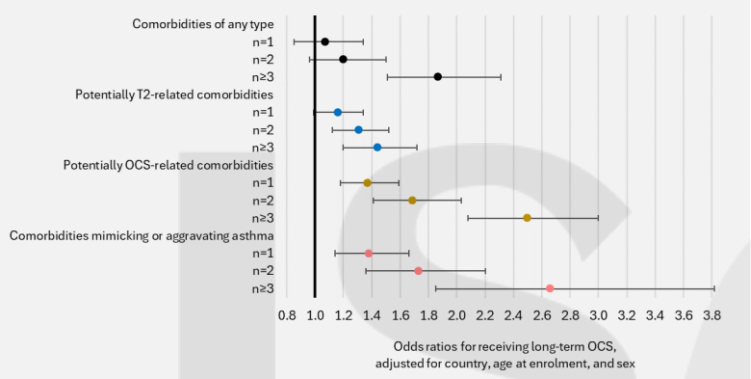
*The reference category for each analysis was absence of the comorbidity of interest

OCS, oral corticosteroid; OR, odds ratio; T2, type 2, CRS: Chronic Rhinosinusitis, AD: Atopic Dermatitis, LTOCS: Long-term Oral Corticosteroids, CI: Confidence Intervals

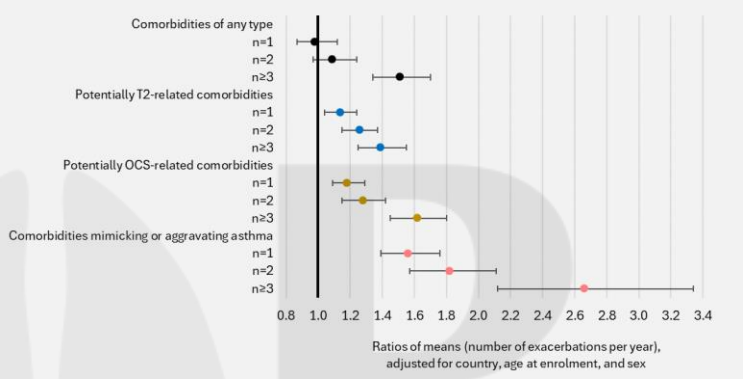
Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Patients with a greater number of comorbidities, both overall and for each comorbidity category, had worse asthma outcomes

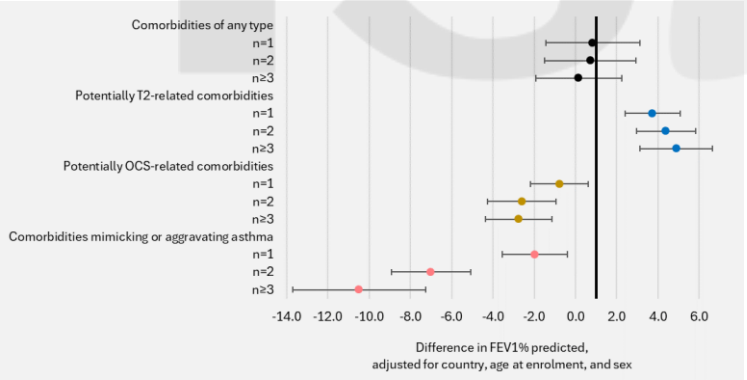
Long-term OCS use



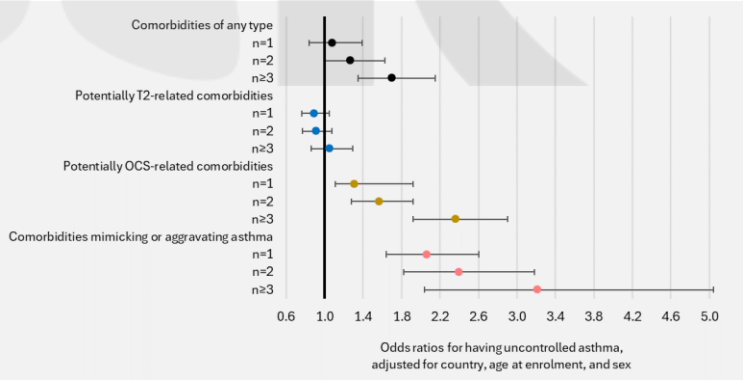
Exacerbation rates



FEV_1 percent predicted



Uncontrolled asthma



FEV1, forced expiratory volume in 1 second; OCS, oral corticosteroids; T2, type 2. The reference category for each analysis was to have no comorbidity of the type of interest.

Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Summary: Comorbidity or multimorbidity is reported in most adults with severe asthma and is associated with poorer asthma-related outcomes

Key findings:

- **Over 50%** of patients had **3 or more comorbidities**
- **Exacerbation rates and odds of LTOCS use higher** for those with comorbid **AR, CRS, or NP**
- **Marked cumulative negative effect of multiple T2-related comorbidities on exacerbation rate and LTOCS**: particularly important since 40% had at least 2 T2-related comorbidities
- **Poor asthma control** associated with **all potentially OCS-related comorbidities** (with the exception of dyslipidemia)
- **LTOCS associated with the largest number of comorbidities** across the spectrum

Practice change needed:

- **Systematic evaluation for comorbidities** during routine asthma review
- **Standardized comorbidity data collection**
- **Multidisciplinary and holistic approach** to asthma management, to **improve outcomes for severe asthma** patients

The reference category for each analysis in the study was absence of the comorbidity of interest
OCS, oral corticosteroid; T2, type 2, CRS: Chronic Rhinosinusitis, AR: Allergic Rhinitis, LTOCS: Long-term Oral Corticosteroids, NP: Nasal Polyps
Scelo, G., et al. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, Annals of Allergy, Asthma & Immunology, Volume 132, Issue 1, 42 – 53, DOI: 10.1016/j.anai.2023.08.021

Association between T2-related co-morbidities and effectiveness of biologics in severe asthma

Michael E Wechsler, Ghislaine Scelo, PhD, Désirée E.S. Larenas-Linnemann, Carlos A Torres-Duque, Jorge Maspero, Trung N Tran, Ruth B Murray, Neil Martin, Andrew N Menzies-Gow, Mark Hew, Matthew J Peters, Peter G Gibson, George C Christoff, Todor A Popov, Andréanne Côté, Celine Bergeron, Delbert Dorscheid, J Mark FitzGerald, Kenneth R. Chapman, Louis Philippe Boulet, Mohit Bhutani, Mohsen Sadatsafavi, Libardo Jiménez-Maldonado, Mauricio Duran-Silva, Bellanid Rodriguez, Carlos Andres Celis-Preciado, Diana Jimena Cano-Rosales, Ivan Solarte, Maria Jose Fernandez- Sanchez, Patricia Parada-Tovar, Anna von Bülow, Anne Sofie Bjerrum, Charlotte S Ulrik, Karin Dahl Assing, Linda Makowska Rasmussen, Susanne Hansen, Alan Altraja, Arnaud Bourdin, Camille Taille, Jeremy Charriot, Nicolas Roche, Andriana I Papaioannou, Konstantinos Kostikas, Nikolaos G Papadopoulos, Sundeep Salvi, Deirdre Long, Patrick D Mitchell, Richard Costello, Concetta Sirena, Cristina Cardini, Enrico Heffler, Francesca Puggioni, Giorgio Walter Canonica, Giuseppe Guida, Takashi Iwanaga, Mona Al-Ahmad, Ulises García, Piotr Kuna, João A Fonseca, Riyad Al-Lehebi, Mariko S Koh, Chin Kook Rhee, Borja G Cosio, Luis Perez de Llano, Diahn-Warng Perng, Erick Wan-Chun Huang, Hao-Chien Wang, Ming-Ju Tsai, Bassam Mahboub, Laila Ibraheem Jaber Salameh, David J. Jackson, John Busby, Liam G Heaney, Paul E. Pfeffer, Amanda Grippen Goddard, Eileen Wang, Flavia C.L. Hoyte, Nicholas M Chapman, Rohit Katial, Victoria Carter, Lakmini Bulathsinhala, Neva Eleangovan, Con Ariti, Juntao Lyu, Celeste Porsbjerg, and David B. Price

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.

Aim and Methods

Rationale

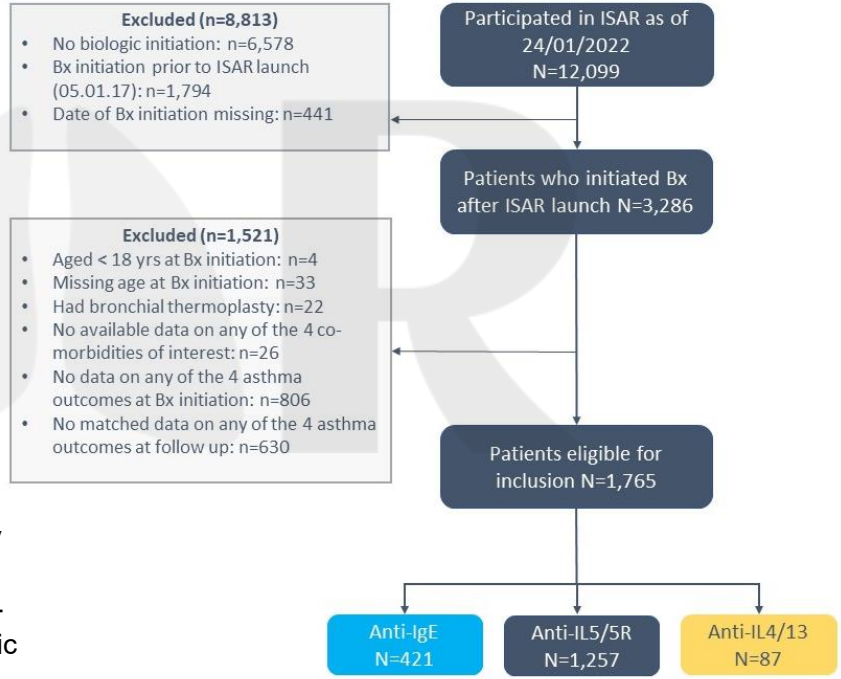
Previous studies investigating comorbidity impact on biologic effectiveness have been relatively small, of short duration, and have not compared biologic classes

Aim

To determine the association between T2-related comorbidities and biologic effectiveness in adults with severe asthma (SA)

Methods

This cohort study used ISAR data (n=21 countries, 2017-2022) to quantify pre- to post-biologic change for four outcomes (annual asthma exacerbation rate, % predicted FEV1 (ppFEV1), asthma control, and long-term oral corticosteroid daily dose [LTOCS]) in patients with/without allergic rhinitis (AR), chronic rhinosinusitis +/- nasal polyps (CRS+/-NP), NP, or eczema/atopic dermatitis (AD).



International Severe Asthma Registry data : ISAR
American Journal of Respiratory and Critical Care Medicine (AJRCCM)

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.

Irrespective of T2 comorbidities all groups showed improvement but greater in those with CRS+/- NP

Asthma-related outcome	Allergic rhinitis		Chronic rhinosinusitis		Nasal polyposis		Eczema/atopic dermatitis	
	Ever N=761	Never N=493	Ever N=968	Never N=748	Ever N=636	Never N=1120	Ever N=243	Never N=1510
Exacerbation rates: mean (SD)	N=559	N=363	N=719	N=541	N=463	N=818	N=189	N=1092
Pre-biologics	2.24 (2.34)	2.16 (2.23)	2.65 (2.77)	3.37 (3.74)	2.88 (3.02)	3.05 (3.40)	1.97 (2.00)	3.15 (3.39)
Post-biologics	0.65 (1.21)	0.65 (1.04)	0.75 (1.25)	1.13 (1.62)	0.77 (1.21)	1.01 (1.55)	0.72 (1.35)	0.96 (0.46)
Change	**-1.59 (2.54)**	**-1.51 (2.33)**	**-1.89 (2.74)**	**-2.24 (3.51)**	**-2.11 (2.82)**	**-2.04 (3.30)**	**-1.25 (2.30)**	**-2.19 (3.22)**
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
$ppFEV_1$: mean (SD)	N=313	N=267	N=493	N=386	N=306	N=573	N=101	N=776
Pre-biologics	76.4 (21.7)	72.2 (23.3)	75.8 (22.5)	71.0 (22.6)	76.4 (22.1)	72.2 (22.9)	73.9 (22.5)	73.6 (22.7)
Post-biologics	80.1 (22.6)	76.6 (23.2)	79.5 (23.3)	73.0 (22.1)	79.7 (23.0)	75.1 (22.8)	75.6 (21.7)	76.8 (23.1)
Change	**+3.7 (17.9)**	**+4.4 (16.0)**	**+3.8 (17.1)**	**+2.0 (17.1)**	**+3.3 (17.1)**	**+2.9 (17.1)**	**+1.7 (13.7)**	**+3.1 (17.5)**
p-value*	<0.001	<0.001	<0.001	0.023	0.001	<0.001	0.210	<0.001
Asthma control: % of uncontrolled/ partly controlled/well controlled	N=430	N=237	N=570	N=450	N=414	N=629	N=118	N=923
Pre-biologics	**65.6**/22.6/11.9	**57.8**/23.2/19.0	**65.8**/21.2/13.0	**69.6**/18.9/11.6	**65.2**/21.3/13.5	**70.3**/18.6/11.1	**71.2**/19.5/9.3	**67.8**/19.7/12.5
Post-biologics	**25.6**/31.9/42.6	**27.0**/29.1/43.9	**30.2**/26.5/43.3	**42.4**/25.3/32.2	**29.5**/24.9/45.7	**39.6**/27.2/33.2	**39.0**/33.1/28.0	**35.2**/25.4/39.4
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LTOCS								
Users, n (%)	283 (37.2)	202 (41.0)	445 (46.0)	383 (51.2)	312 (49.1)	543 (48.5)	243 (33.3)	772 (51.1)
LTOCS: mean daily dose in users pre-biologics (SD)	N=128	N=74	N=243	N=262	N=196	N=332	N=42	N=485
Pre-biologics	13.2 (10.9)	15.5 (15.4)	12.2 (10.0)	13.2 (10.6)	12.0 (9.3)	13.1 (10.7)	10.5 (10.1)	12.8 (10.2)
Post-biologics	11.7 (9.9)	13.9 (14.7)	10.5 (9.5)	11.0 (10.1)	9.8 (8.3)	11.4 (10.4)	8.8 (9.0)	10.9 (9.8)
Change	**-1.4 (7.6)**	**-1.6 (11.7)**	**-1.7 (6.9)**	**-2.2 (7.6)**	**-2.2 (7.2)**	**-1.7 (7.1)**	**-1.7 (8.9)**	**-1.9 (7.0)**
p-value*	0.020	0.204	<0.001	<0.001	<0.001	<0.001	0.116	<0.001

*Comparing pre- to post-biologics, using paired Wilcoxon test for exacerbations and LTOCS dose, paired t-test for $ppFEV_1$, and McNemar test (nominal symmetry test) for asthma control.

Exacerbation rates reduce (reduction shown in red) with biologics for all, regardless of presence of T2 comorbidity

ppFEV1 increases (increase shown in red) for all following biologic initiation, irrespective of comorbidity status

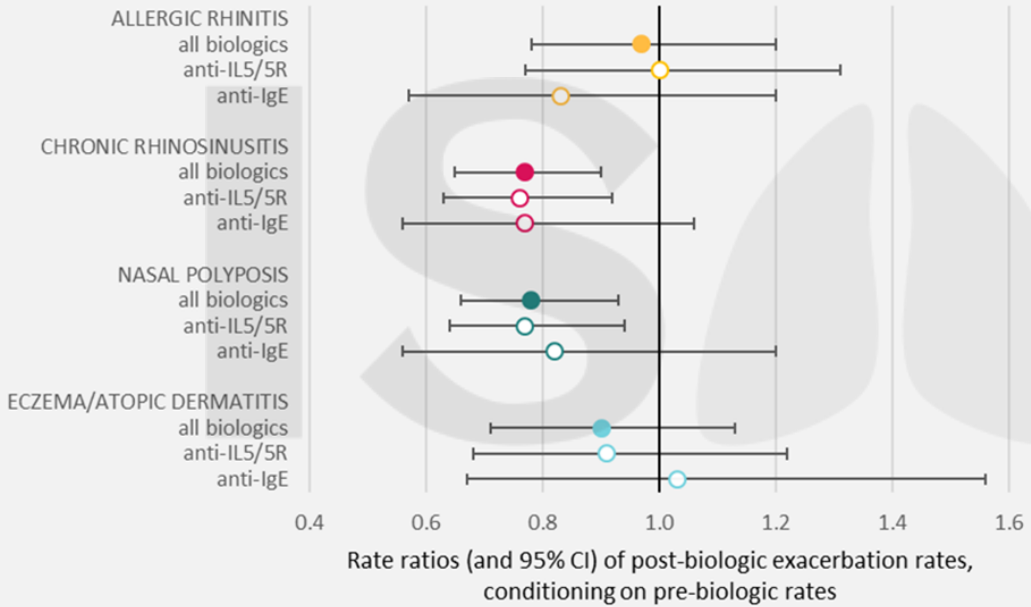
%of patients with uncontrolled asthma decreases significantly (shown in red) across all groups irrespective of comorbidity status, following biologic initiation

Figures in red show the **drop in mean LTOCS dose following biologic initiation, with reduction in dose achieved for all** groups irrespective of presence of T2 comorbidities

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.

ppFEV1: Forced expiratory volume in one second, expressed in percentage of predicted value in healthy individuals of same age, gender, and height; LTOCS: long-term oral corticosteroids.

Severe asthma patients with CRS / NP benefit from biologics to a greater extent than patients without: exacerbations



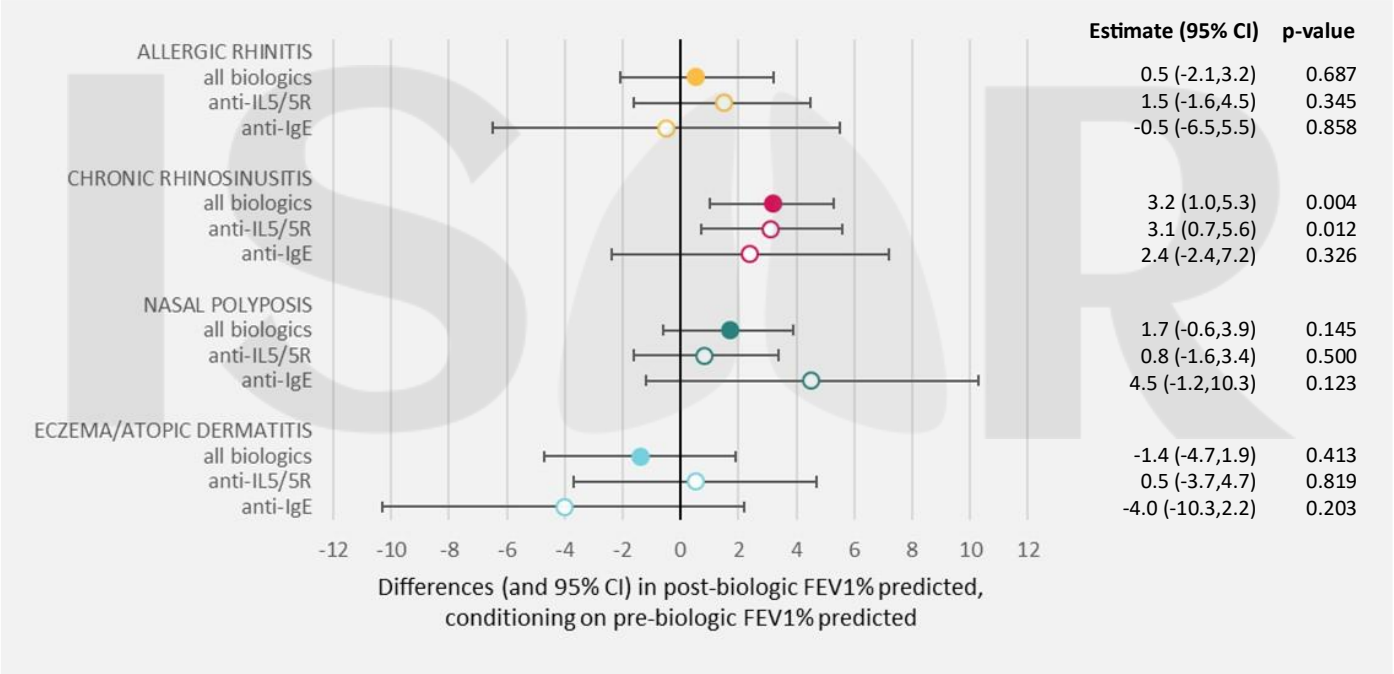
	Estimate (95% CI)	p-value
ALLERGIC RHINITIS		
all biologics	0.97 (0.78,1.20)	0.770
anti-IL5/5R	1.00 (0.77,1.31)	0.995
anti-IgE	0.83 (0.57,1.20)	0.330
CHRONIC RHINOSINUSITIS		
all biologics	0.77 (0.65,0.90)	<0.001
anti-IL5/5R	0.76 (0.63,0.92)	0.004
anti-IgE	0.77 (0.56,1.06)	0.113
NASAL POLYPOSIS		
all biologics	0.78 (0.66,0.93)	0.004
anti-IL5/5R	0.77 (0.64,0.94)	0.009
anti-IgE	0.82 (0.56,1.20)	0.297
ECZEMA/ATOPIC DERMATITIS		
all biologics	0.90 (0.71,1.13)	0.357
anti-IL5/5R	0.91 (0.68,1.22)	0.535
anti-IgE	1.03 (0.67,1.56)	0.906

Biomarker independent

Adjusting for **BEC had no impact on the estimate** for exacerbations for patients with CRS +/- NP (rate ratio = 0.77, 95% CI: 0.65, 0.91, p=0.002)

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.
BEC: Blood Eosinophil Count, CRS: Chronic rhinosinusitis; NP: Nasal polyposis; 95% CI: 95% confidence interval.

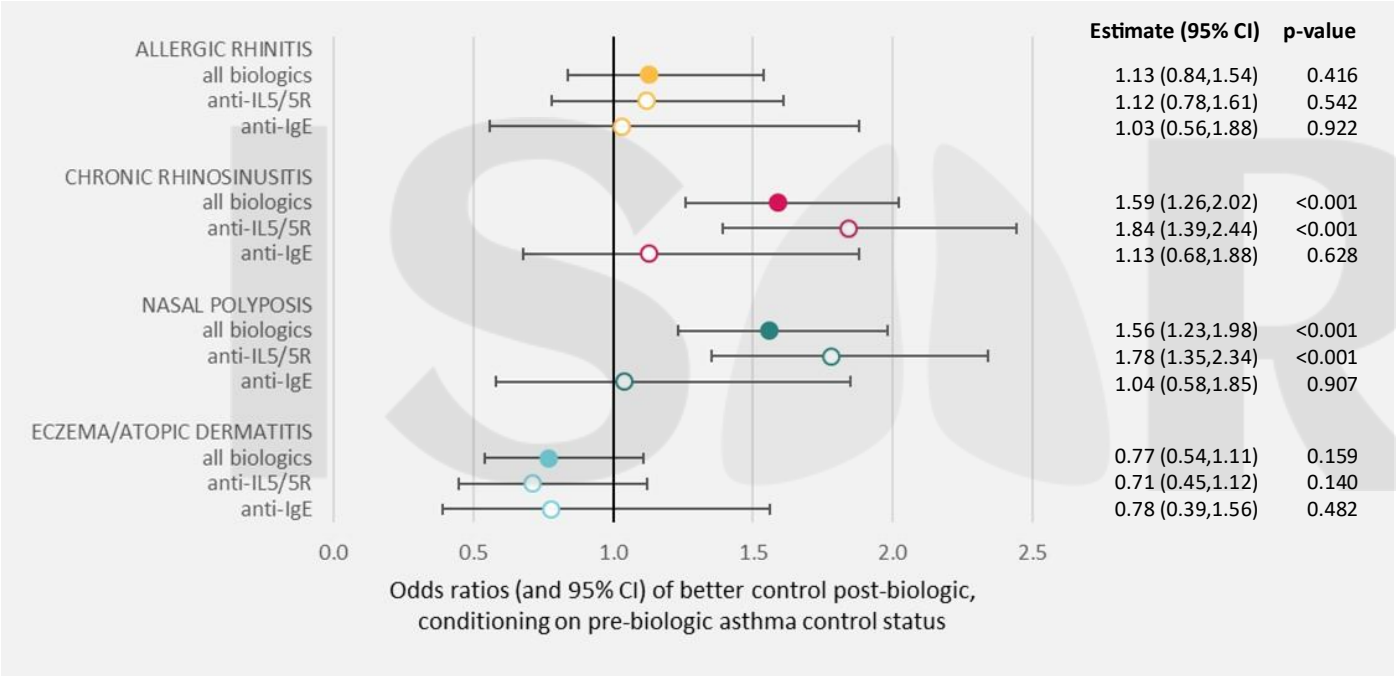
Severe asthma patients with CRS / NP benefit from biologics to a greater extent than patients without: lung function



Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.

CRS: Chronic rhinosinusitis; FEV1% predicted: : Forced expiratory volume in one second, expressed in percentage of predicted value in healthy individuals of same age, gender, and height; NP: Nasal polyposis; 95% CI: 95% confidence interval.

Severe asthma patients with CRS / NP benefit from biologics to a greater extent than patients without: asthma control

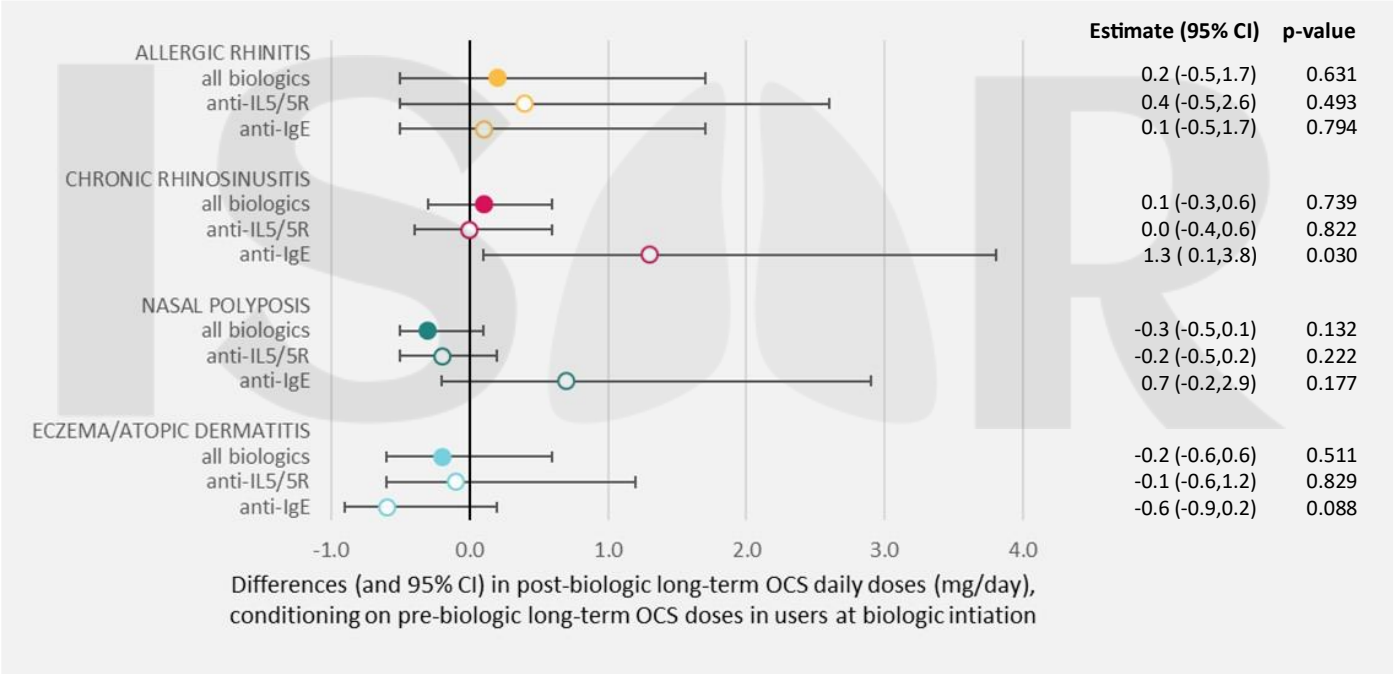


Biomarker independent

Although attenuated, **association for asthma control trends in patients with NP remain when adjusting for BEC** (odds ratio=1.37, 95% CI: 1.06-1.77), p=0.015)

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.
BEC: Blood Eosinophil Count, CRS: Chronic rhinosinusitis; NP: Nasal polyposis; 95% CI: 95% confidence interval.

No additional benefit observed in terms of LTOCS dose reduction



Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.
95% CI: 95% confidence interval.

PRISM II Summary

The power of biologics to improve severe asthma outcomes in patients with T2 comorbidities

Association between T2-related co-morbidities and effectiveness of biologics in severe asthma

Where

ISAR Global Study

21 countries + 1765 severe asthma patients

Who

With/without AR, CRS+/-NP NP, or AD

Initiated on anti–IL-5/5R, anti-IgE,or anti–IL-4/13

What

Pre and post biologic change in:

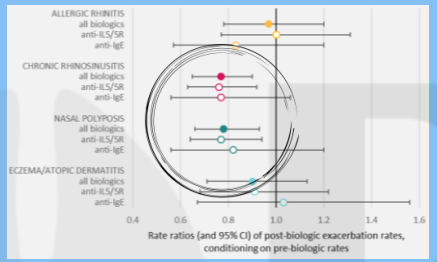
Annual exacerbation rate,

% predicted FEV1

asthma control

LTOCS daily dose

Results



- Biologics led to **improvements in all four asthma outcomes irrespective of comorbidity status**
- **Comorbid CRS+/-NP : 23% fewer exacerbations, 59% higher odds of better post-biologic control**
- Similar estimates for those with comorbid NP
- **Independent of biomarker** profile
- **AR and AD conversely were not predictive** of treatment effect

Practice change

- ✓ **CRS +/- NP key components in predicting successful treatment with biologics**
- ✓ **Systematic evaluation for comorbidities + multidisciplinary collaboration vital** in achieving optimal outcomes in severe asthma care

Wechsler, Michael E., et al. "Association between T2-related comorbidities and effectiveness of biologics in severe asthma." American journal of respiratory and critical care medicine 209.3 (2024): 262-272.

AR: allergic rhinitis, CRS+/-NP: chronic rhinosinusitis +/- nasal polyps , AD: eczema/atopic dermatitis, LTOCS: Long term Oral Corticosteroids

Adult severe asthma registries: a global and growing inventory

Breda Cushen, Mariko Siyue Koh, Trung N Tran, Neil Martin, Ruth Murray, Thendral Uthaman, Celine Yun Yi Goh, Rebecca Vella, Neva Eleangovan, Lakmini Bulathsinhala, Jorge F Maspero, Matthew J Peters, Florence Schleich, Paulo Pitrez, George Christoff, Mohsen Sadsatsafavi, Carlos A. Torres-Duque, Celeste Porsbjerg, Alan Altraja, Lauri Lehtimäki, Arnaud Bourdin, Christian Taube, Nikolaos G. Papadopoulos, Csoma Zsuzsanna, Unnur Björnsdóttir, Sundeep Salvi, Enrico Heffler, Takashi Iwanaga, Mona Al-Ahmad, Désirée Larenas-Linnemann, Job FM van Boven, Bernt Bøgvald Aarli, Piotr Kuna, Cláudia Chaves Loureiro, Riyad Al-Lehebi, Jae Ha Lee, Nuria Marina, Leif Bjermer, Chau-Chyun Sheu, Bassam Mahboub, John Busby, Andrew Menzies-Gow, Eileen Wang, David B. Price

Aim and Methods

Rationale

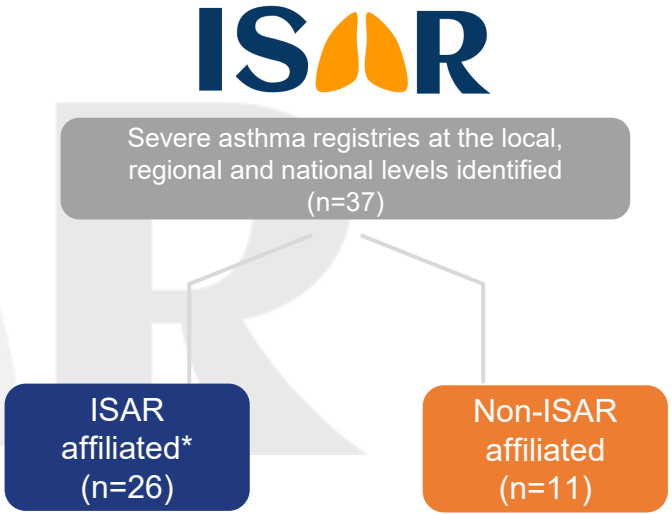
Currently, severe asthma inter-registry variability in data being collected is unknown

Aim

To examine data that ISAR and non-ISAR countries report collecting that enable global research and support individual country interests

Methods

Registries were identified by **online searches** (up to August 2022) and approaching **36 severe asthma experts globally**
Participating registries provided data collection specifications or confirmed variables collected



Variables summarized:

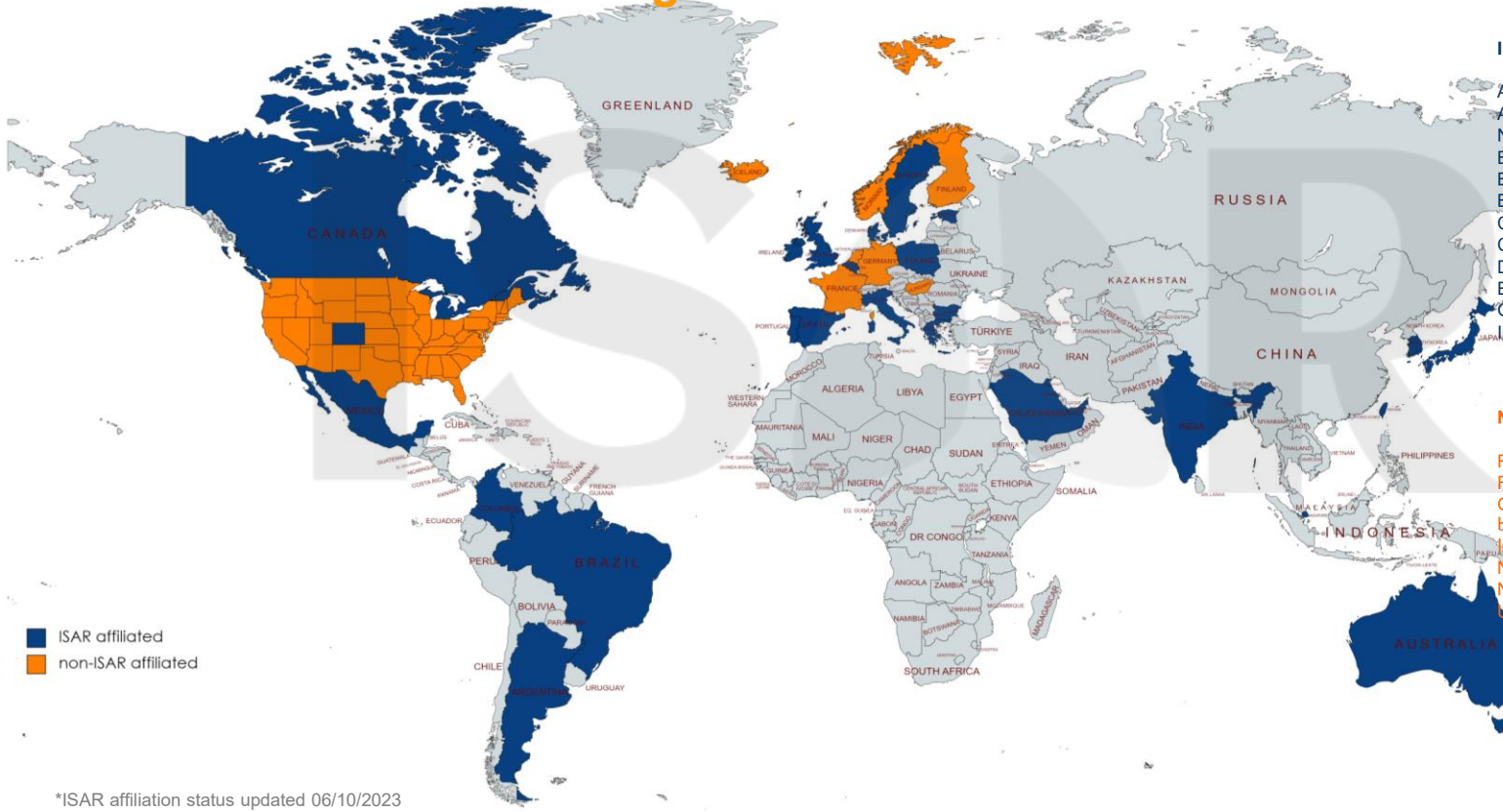
- Core variables (results from ISAR's Delphi study)
- Steroid-related comorbidity variables
- Biologic safety variables (serious infection, anaphylaxis, and cancer)
- COVID-19 variables
- Additional variables (not belonging to the aforementioned categories)

*contributing data to ISAR

Cushen, B. et al., Adult Severe Asthma Registries: A Global and Growing Inventory. Pragmat Obs Res. 2023;14:127-147 https://doi.org/10.2147/POR.S399879

Severe asthma registries from across the globe

37 Registries across 35 countries



ISAR-affiliated registries*:

Argentina
Australia & New Zealand
Belgium
Brazil
Bulgaria
Canada
Colombia
Denmark
Estonia
Greece
India
Ireland
Italy
Japan
Kuwait
Mexico
Poland
Portugal
Saudi Arabia
Singapore
South Korea
Spain
Sweden
Taiwan
United Arab Emirates
United Kingdom
United States (National Jewish Health,and Michigan state)

Non–ISAR-affiliated registries:

Finland
France
Germany (2 registries)
Hungary
Iceland
Netherlands
Norway
United States (CHRONICLE)

*ISAR affiliation status updated 06/10/2023

Cushen, B. et al., Adult Severe Asthma Registries: A Global and Growing Inventory. Pragmat Obs Res. 2023;14:127-147 https://doi.org/10.2147/POR.S399879

Majority of severe asthma registries collect >90% of ISAR's core variables and most registries collect safety variables

25 ISAR-registries and 4 non-ISAR registries reported **collecting >90% of the 65 core variables**

24 registries reported collecting **additional variables** including data from asthma questionnaires

8 registries are **linked to databases** such as electronic medical records and national claims or disease databases

Cushen, B. et al., Adult Severe Asthma Registries: A Global and Growing Inventory. Pragmat Obs Res. 2023;14:127-147 https://doi.org/10.2147/POR.S399879

Conclusions

The **majority of severe asthma registries** reported collection of **>90% of ISAR's core variables**

Most registries reported collecting safety variables and OCS comorbidity data, reflecting a **common goal of documenting OCS burden and safety events in patients**

The ISAR initiative has fostered data standardisation across countries.
This enables collection of unified data and **increases statistical power for severe asthma research**

Maintaining **individuality** alongside standardized variables supports registries to develop **locally relevant research priorities and clinical interests**

Severe asthma registries can **inform local health policy**, be **incorporated into clinical guidelines**, and be translated into **quality improvement** programs that **enhance the care of asthma** patients globally

Cushen, B. et al., Adult Severe Asthma Registries: A Global and Growing Inventory. Pragmat Obs Res. 2023;14:127-147 https://doi.org/10.2147/POR.S399879

Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma (BEAM)

Luis Perez-de-Llano, Ghislaine Scelo, G. Walter Canonica, Wenjia Chen, William Henley, Désirée Larenas-Linnemann, Matthew J Peters, Paul E. Pfeffer, Trung N. Tran, Charlotte Suppli Ulrik, Todor A. Popov, Mohsen Sadatsafavi, Mark Hew, Jorge Maspero, Peter G. Gibson, George C. Christoff, J. Mark Fitzgerald, Carlos A. Torres-Duque, Celeste M. Porsbjerg, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Enrico Heffler, Takashi Iwanaga, Mona Al-Ahmad, Piotr Kuna, João A Fonseca, Riyad Al-Lehebi, Chin Kook Rhee, Mariko Siyue Koh, Borja G. Cosio, Diahn-Warng Perng (Steve), Bassam Mahboub, Andrew N. Menzies-Gow, David J. Jackson, John Busby, Liam G. Heaney, Pujan H Patel, Eileen Wang, Michael E. Wechsler, Alan Altraja, Lauri Lehtimäki, Arnaud Bourdin, Leif Bjermer, Lakmini Bulathsinhala, Victoria Carter, Ruth Murray, Aaron Beastall, Eve Denton, David B. Price

Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.023

Aim and Methods

Rationale

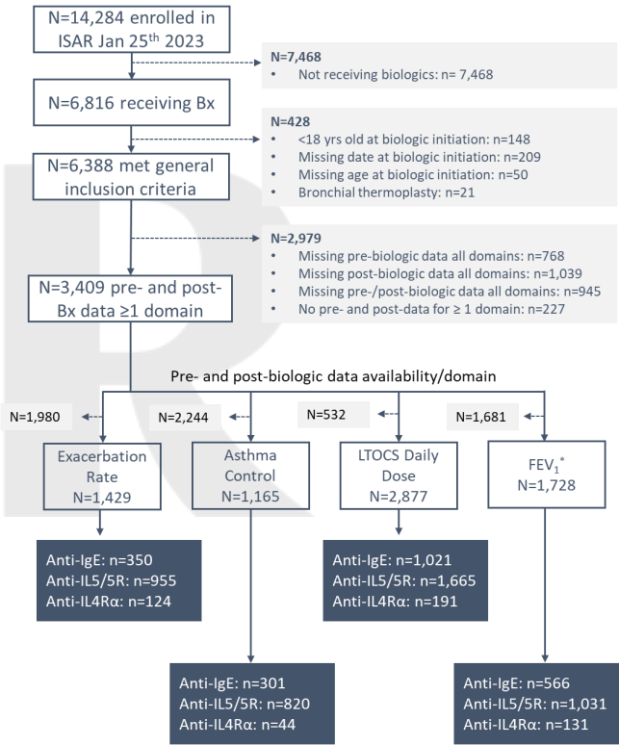
There is little agreement on clinically useful criteria for identifying real-world responders to biologic treatments for asthma.

Objective

To investigate the impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in adults with severe asthma.

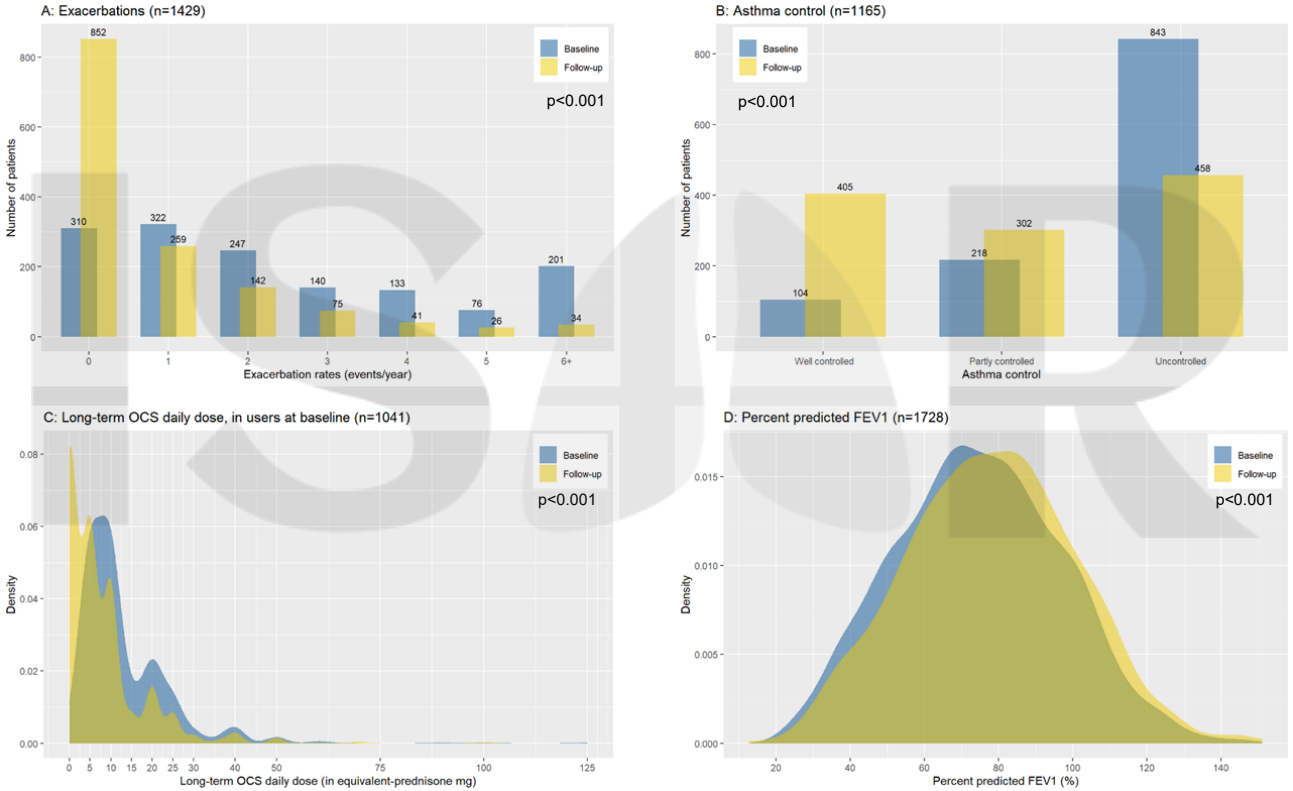
Methods

- Longitudinal cohort study across 22 countries participating in ISAR from May 2017 to January 2023.
- Change in four asthma domains (exacerbation rate, asthma control, long-term oral corticosteroid [LTOCS] dose, and lung function) was assessed from biologic initiation to one year post-treatment (minimum 24 weeks)
- Pre- to post-biologic changes for responders and non-responders were described along a categorical gradient for each domain derived from pre-biologic distributions (exacerbation rate: 0 to 6+/year; asthma control: well-controlled to uncontrolled; LTOCS: 0 to >30 mg/day; ppFEV1: <50 to ≥80%)



Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.025
ISAR: International Severe Asthma Registry, Bx: biologic, Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, Anti-IL4: Anti-Interleukin 4, FEV1: Forced Expiratory Volume 1 second, *both percent predicted and absolute.

Statistically significant improvements were observed from pre- to post-biologic initiation for all asthma outcome domains assessed



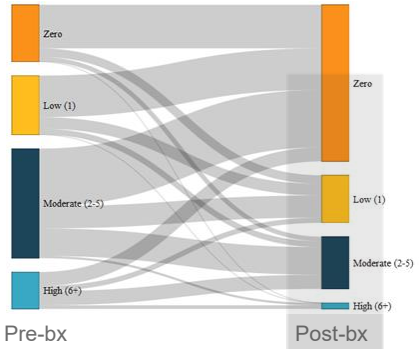
FEV1: forced expiratory volume in one second; OCS: oral corticosteroid

Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI:https://doi.org/10.1016/j.anai.2023.12.023

Responders to biologics increased with greater pre-biologic impairment:

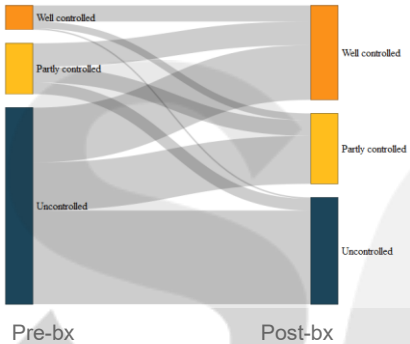
Increasing from 70.2 to 90.0% for exacerbation rate, 46.3 to 52.3% for asthma control, 31.1 to 58.5% for LTOCS daily dose, and 35.8 to 50.6% for ppFEV1

Exacerbations



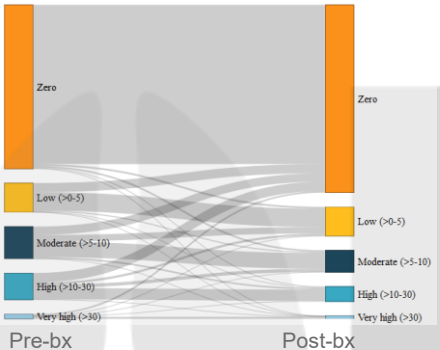
Pre-biologic exacerbation number/yr	Post-biologic status: Worsened	Unchanged	Improved
	N (% of patients)		
Zero: 0/yr (n=310)	73 (23.5)	237 (76.5)	NA
Low: 1/yr (n=322)	33 (10.2)	63 (19.6)	226 (70.2)
Moderate: 2-5/yr (n=596)	12 (2.0)	150 (25.2)	434 (72.8)
High: 6+/yr (n=201)	NA	20 (10.0)	181 (90.0)

Asthma Control



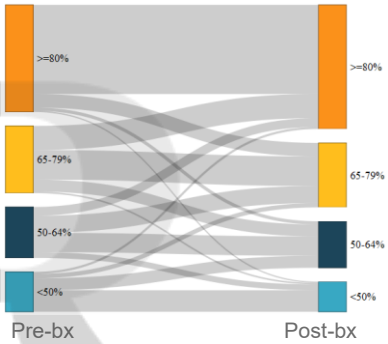
Pre-biologic control status	Post-biologic status: Worsened	Unchanged	Improved
	N (% of patients)		
Well controlled (n=104)	35 (33.7)	69 (66.3)	NA
Partly controlled (n=218)	50 (22.9)	67 (30.7)	101 (46.3)
Uncontrolled (n=843)	NA	402 (47.7)	441 (52.3)

LTOCS daily dose



Pre-biologic daily LTOCS dose, mg	Post-biologic status: Worsened	Unchanged	Improved
	N (% of patients)		
Zero: 0mg (n=1,836)	53 (2.9)	1,783 (97.1)	NA
Low: >0-5mg (n=328)	20 (6.1)	206 (62.8)	102 (31.1)
Moderate: >5-10mg (n=360)	19 (5.3)	175 (48.6)	166 (46.1)
High: >10-30mg (n=300)	5 (1.7)	127 (42.3)	168 (56.0)
Very high: >30mg (n=53)	NA	22 (41.5)	31 (58.5)

% predicted FEV1



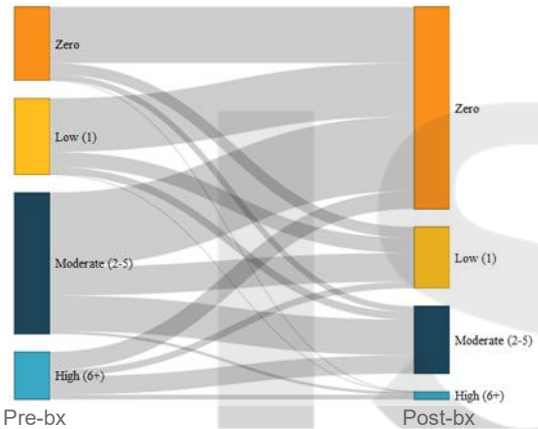
Pre-biologic ppFEV1	Post-biologic status: Worsened	Unchanged	Improved
	N (% of patients)		
≥80% (n=698)	117 (16.8)	581 (83.2)	NA
65-79% (n=438)	88 (20.1)	193 (44.1)	157 (35.8)
50-64% (n=332)	38 (11.4)	126 (38.0)	168 (50.6)
<50% (n=260)	NA	140 (53.8)	120 (46.2)

Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.023

Bx: biologic, ppFEV1: percent predicted Forced Expiratory Volume 1 second, LTOCS: Long-term Oral Corticosteroid, NA: Not Applicable

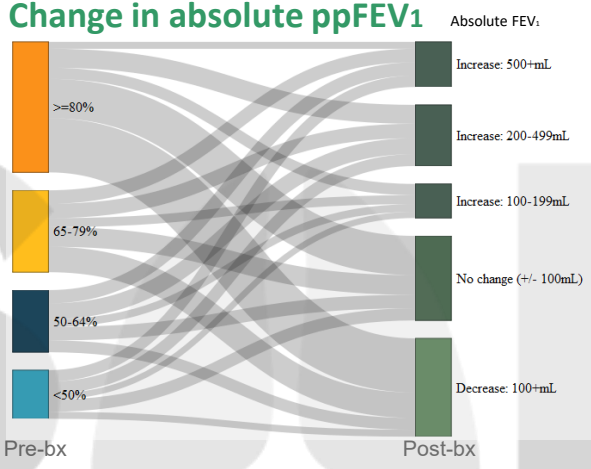
Even those with low pre-biologic impairment, who would be actively excluded from RCTs investigating biologic efficacy, exhibited clinically meaningful post-biologic improvement

Exacerbations



Pre-biologic exacerbation number/yr	Post-biologic status: Worsened	Unchanged	Improved
	N (% of patients)		
Zero: 0/yr (n=310)	73 (23.5)	237 (76.5)	NA
Low: 1/yr (n=322)	33 (10.2)	63 (19.6)	226 (70.2)
Moderate: 2-5/yr (n=596)	12 (2.0)	150 (25.2)	434 (72.8)
High: 6+/yr (n=201)	NA	20 (10.0)	181 (90.0)

Change in absolute ppFEV1



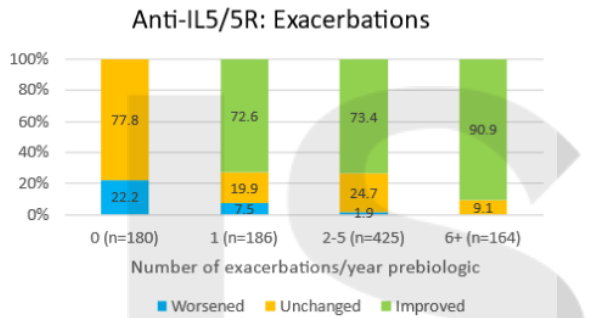
ppFEV1 at baseline	Post-biologic status: dec. 100+mL	No change	inc. 100-199mL	inc. 200-499mL	inc. 500+mL
	N (% of patients)				
≥80% (n=698)	290 (41.5)	210 (30.1)	60 (8.6)	101 (14.5)	37 (5.3)
65-79% (n=438)	138 (31.1)	105 (24.0)	48 (11.0)	77 (17.6)	72 (16.4)
50-64% (n=332)	63 (18.9)	72 (21.7)	41 (12.3)	85 (25.6)	71 (21.4)
<50% (n=260)	37 (14.2)	65 (25.0)	33 (12.7)	64 (24.6)	61 (23.5)

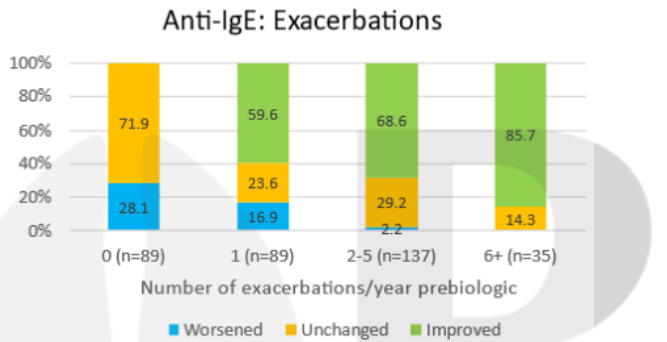
- 70% of patients with only 1 exacerbation per year improved to zero exacerbations
- 28% of patients with ppFEV1≥80% improved by ≥100mL FEV1

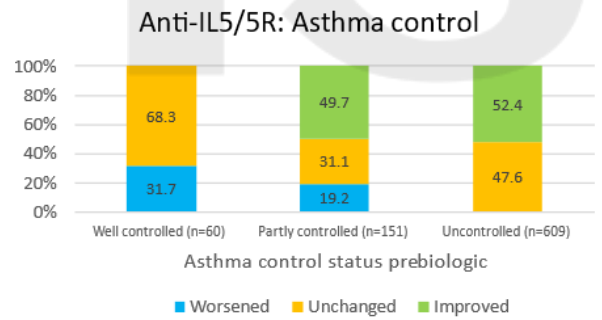
Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.023 Bx: biologic, ppFEV1: percent predicted Forced Expiratory Volume 1 second, RCT: Randomised Controlled Trial

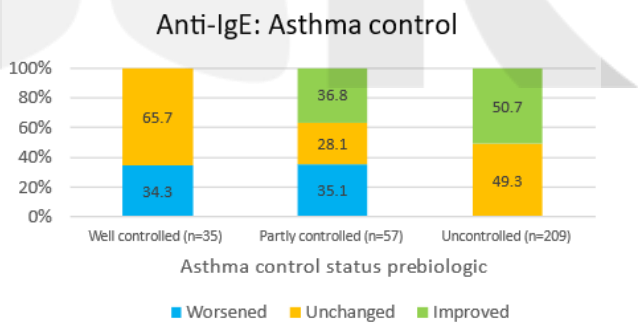
Proportion of patients showing improvement post-biologic tended to be greater for anti–IL-5/5R compared to anti-IgE, irrespective of the degree of pre-biologic impairment

Post-biologic status (worsened, unchanged, improved) according to pre-biologic impairment and biologic class for the asthma outcome domains exacerbation rate and asthma control









Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.023

Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R

Summary

BEAM: Improvement across all domains, with greater pre-biologic disease, but meaningful change even with pre-biologic impairment

Statistically significant improvements were observed from pre- to post-biologic treatment **for all asthma outcome domains** assessed

The proportion of patients showing **improvement post-biologic tended to be greater for anti–IL-5/5R** compared to anti-IgE for exacerbation, asthma control, and ppFEV1 domains irrespective of pre-biologic impairment

Those with **greater disease burden pre-biologic therapy tended to have a greater magnitude of effect** for each domain assessed

Even those with low pre-biologic impairment, who would be actively excluded from RCTs investigating the efficacy of biologics, exhibited **clinically meaningful post-biologic improvement**

A **multi-dimensional approach** to define and assess biologic responders and response needed

Perez-de-Llano et al., Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma, Ann Allergy Asthma Immunol, published Dec 2023, in press, DOI :https://doi.org/10.1016/j.anai.2023.12.023

Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, RCT: Randomized Controlled Trial, ppFEV1: percent predicted Forced Expiratory Volume 1 second,

International Variation in Severe Exacerbation Rates in Patients with Severe Asthma

Tae Yoon Lee, MSc, David Price, FRCGP, Chandra Prakash Yadav, PhD, Rupsa Roy, MSc, Laura Lim Huey Mien, MSc, Eileen Wang, MD, PhD, Michael E. Wechsler, MD, David J. Jackson, MBBS, MRCP (UK), PhD, John Busby, PhD, Liam G. Heaney, MD, Paul E. Pfeffer, MRCP(UK), PhD, Bassam Mahboub, MD, Diahn- Warng Perng (Steve), MD, PhD, Borja G. Cosio, MD, PhD, Luis Perez-de-Llano,MD, PhD, Riyad Al-Lehebi, MD, FRCPC, Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI, Mona Al-Ahmad, MD, FRCPC, Chin Kook Rhee, MD, PhD, Takashi Iwanaga, MD, PhD, Enrico Heffler, MD, PhD, Giorgio Walter Canonica, MD, Richard Costello, MB, MD, FRCPI, Nikolaos G. Papadopoulos, MD, PhD, FRCP, Andriana I. Papaioannou, MD, PhD, Celeste M. Porsbjerg, MD, PhD, Carlos A. Torres-Duque, MD, George C. Christoff, MD, PhD, MPH, Todor A. Popov, MD, PhD, Mark Hew, MBBS, PhD, FRACP, Matthew Peters, MD, PhD, Peter G. Gibson, MBBS, FRACP, Jorge Maspero, PhD, Celine Bergeron, MD, FRCPC, MSc, Saraid Cerda, MD, Elvia Angelica Contreras Contreras, MD, Wenjia Chen, PhD, Mohsen Sadatsafavi, MD, PhD

Aim and Methods

Rationale

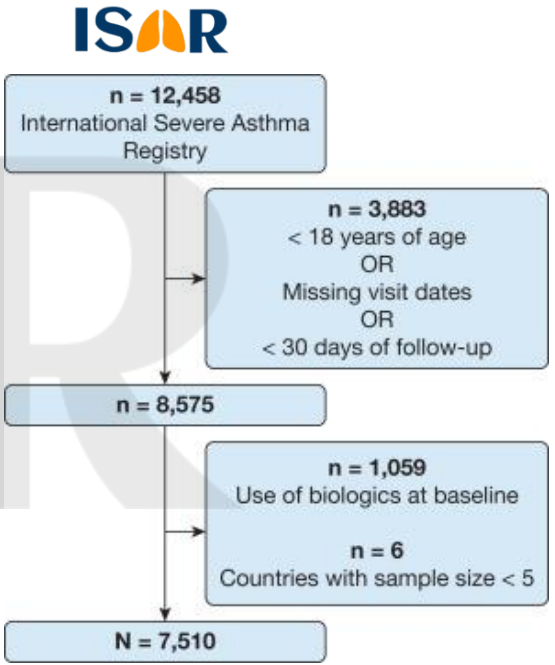
Exacerbation frequency strongly influences treatment choices in patients with severe asthma, but the rate of exacerbations varies across countries.

Aim

To examine the extent of the variability of exacerbations rate across countries and its implications in disease management.

Methods

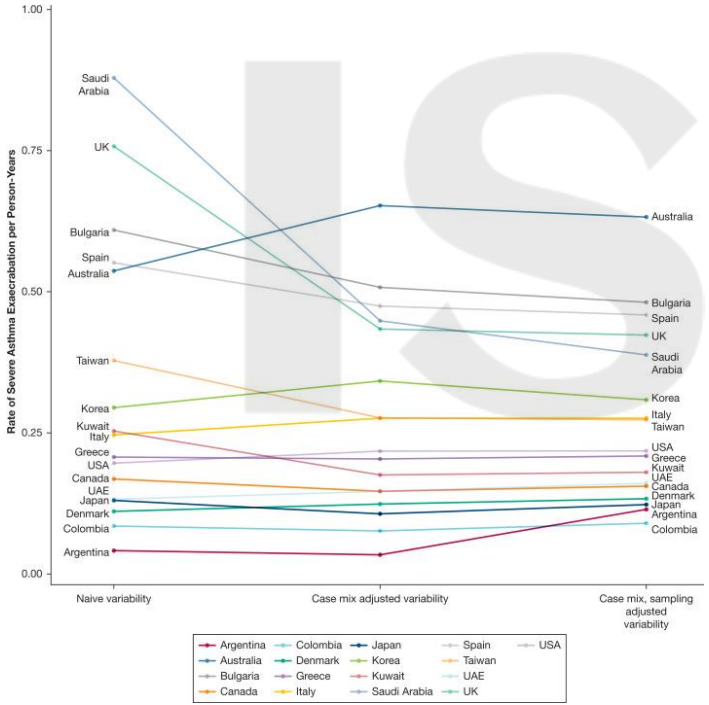
- **Data source:** The International Severe Asthma Registry (ISAR).
- **Study population:** Patients ≥ 18 years of age who did not initiate any biologics before baseline visit.
- **Statistical analyses:** Negative binomial models to estimate country-specific severe exacerbation rates during 365 days of follow-up in naïve and adjusted models.



Flow diagram of the International Severe Asthma Registry cohort

Large between-country variations of severe asthma exacerbation rates

Estimates of country-specific severe asthma exacerbation rates (per person-years) using the average marginal effect framework for naïve, case mix adjusted (fixed-effect), and case mix and sampling adjusted (random-effects) models.



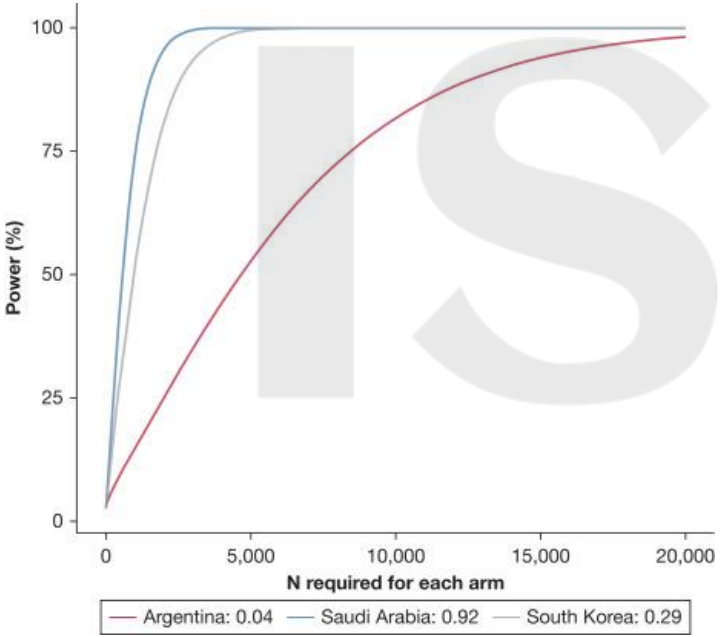
Findings

- **Large between-country variation** in observed severe exacerbation rate (minimum, 0.04 [Argentina]; maximum, 0.88 [Saudi Arabia]; interquartile range, 0.13-0.54).
- Remained substantial after adjusting for patient characteristics and sampling variability (interquartile range, 0.16-0.39).

UAE = United Arab Emirates; UK = United Kingdom; USA = United States.

Design of future severe asthma trials (desired sample sizes)

Power analysis for the lowest, median, and highest severe exacerbation rates (per person-years) observed in the International Severe Asthma Registry to detect a reduction of 20% in severe exacerbation rates from the comparator.



Findings

- To detect a **20% reduction in severe exacerbation rate** with 90% power
  - 12,699 patients per arm required in Argentina;
  - 2,503 patients in South Korea;
  - 1,432 patients in Saudi Arabia
- International clinical studies recruiting patients from specialty care should balance trial design's efficiency and representativeness of countries and regions.

Conclusions

- **Considerable heterogeneity** in severe exacerbation rates in patients with severe asthma across countries.

- Unidentified patient-specific factors and/or systemic intricacies contributing to the observed variations.

- Each country or jurisdiction should **adapt clinical recommendations for severe asthma to their setting** for optimal treatment escalation strategies.

- Risk prediction models **calibrated for each jurisdiction** will be needed to optimize treatment strategies.

Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma (IGNITE)

Celeste M. Porsbjerg, John Townend, Celine Bergeron, George C. Christoff, Gregory P. Katsoulotos, Désirée Larenas Linnemann, Trung N. Tran,, Riyad Al-Lehebi, Sinthia Z. Bosnic-Anticevich, John Busby, Mark Hew, Konstantinos Kostikas, Nikolaos G. Papadopoulos, Paul E. Pfeffer, Todor A. Popov, Chin Kook Rhee, Mohsen Sadatsafavi, Ming-Ju Tsai, Charlotte Suppli Ulrik, Mona AlAhmad, Alan Altraja, Aaron Beastall,, Lakmini Bulathsinhala, Victoria Carter, Borja G. Cosio, Kirsty Fletton, Susanne Hansen, Liam G. Heaney, Richard B. Hubbard, Piotr Kuna, Ruth Murray, Tatsuya Nagano, Laura Pini, Diana Jimena Cano Rosales, Florence Schleich, Michael E. Wechsler, Rita Amaral, Arnaud Bourdin, Guy G. Brusselle, Wenjia Chen, Li Ping Chung, Eve Denton, João A. Fonseca, Flavia Hoyte, David J. Jackson, Rohit Katial, Bruce J. Kirenga,, Mariko Siyue Koh, Agnieszka Ławkiedraj, Lauri Lehtimäki, Mei Fong Liew, Bassam Mahboub, Neil Martin, Andrew N. Menzies-Gow, Pee Hwee Pang, Andriana I. Papaioannou, Pujan H. Patel, Luis Perez-de-Llano, Matthew J. Peters,, Luisa Ricciardi, Bellanid Rodríguez-Cáceres, Ivan Solarte, Tunn Ren Tay, Carlos A. Torres-Duque, Eileen Wang, Martina Zappa, John Abisheganaden,, Karin Dahl Assing, Richard W. Costello, Peter G. Gibson, Enrico Heffler, Jorge Máspero, Stefania Nicola, Diahn-Warng Perng (Steve), Francesca Puggioni, Sundeep Salvi, Chau- Chyun Sheu,, Concetta Sirena, Camille Taillé, Tze Lee Tan, Leif Bjermer, Giorgio Walter Canonica, Takashi Iwanaga, Libardo Jiménez-Maldonado, Christian Taube, Luisa Brussino, and David B. Price

Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

Aim and Methods

Rationale

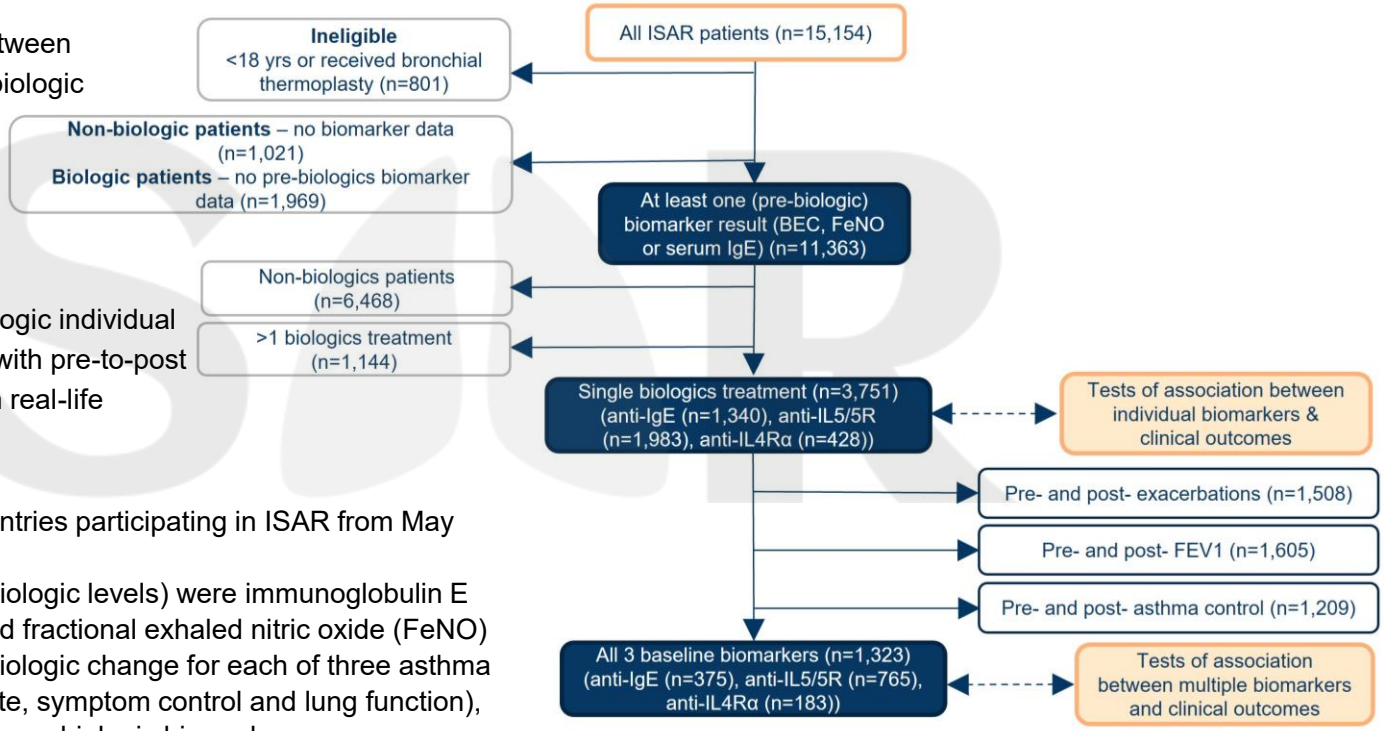
Studies investigating the association between pre-biologic biomarker levels and post-biologic outcomes have been limited to single biomarkers and assessment of biologic efficacy from structured clinical trials

Objective

To elucidate the associations of pre-biologic individual biomarker levels or their combinations with pre-to-post biologic changes in asthma outcomes in real-life

Methods

- Cohort study using data across 23 countries participating in ISAR from May 2017 to February 2023.
- Investigated biomarkers (highest pre-biologic levels) were immunoglobulin E (IgE), blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO)
- Pre- to approximately 12-month post-biologic change for each of three asthma outcome domains (i.e. exacerbation rate, symptom control and lung function), and the association of this change with pre-biologic biomarkers was investigated for individual and combined biomarkers



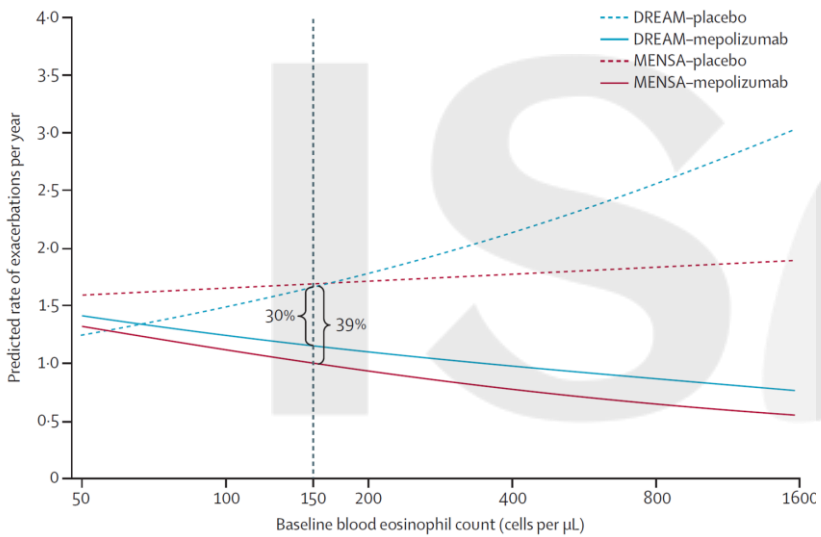
Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

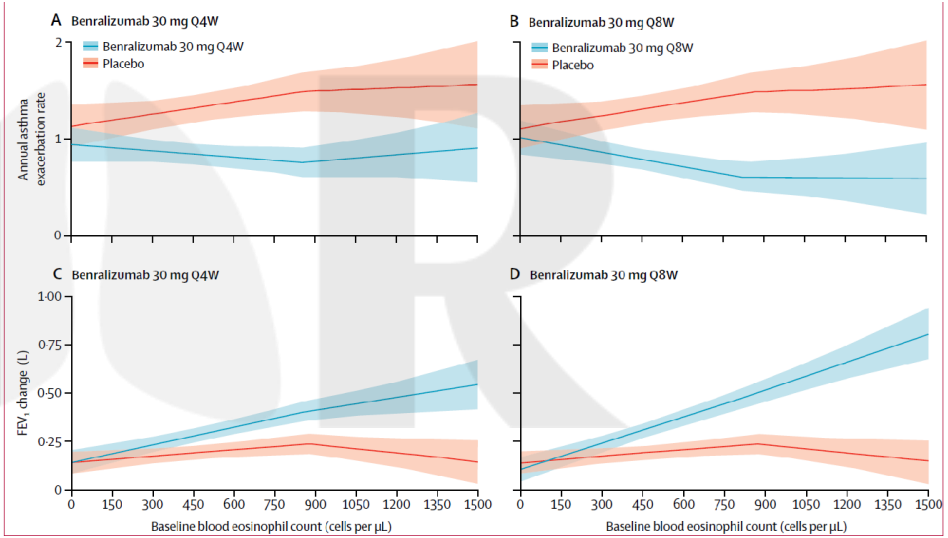
ISAR: International Severe Asthma Registry, Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, Anti-IL4: Anti-Interleukin 4, FEV1: Forced Expiratory Volume 1 second, FeNO: Fractional exhaled Nitric Oxide, BEC: Blood Eosinophil Count

What is already known? Background and rationale:

BEC predicts less exacerbations with biologics than placebo but little dose response within the active arm

Response to Anti-IL5 Treatment According to Blood Eosinophil Count (evidence from clinical trials)





SIROCCO/CALIMA: Response to Benralizumab Treatment According to Blood Eosinophil Count[2]

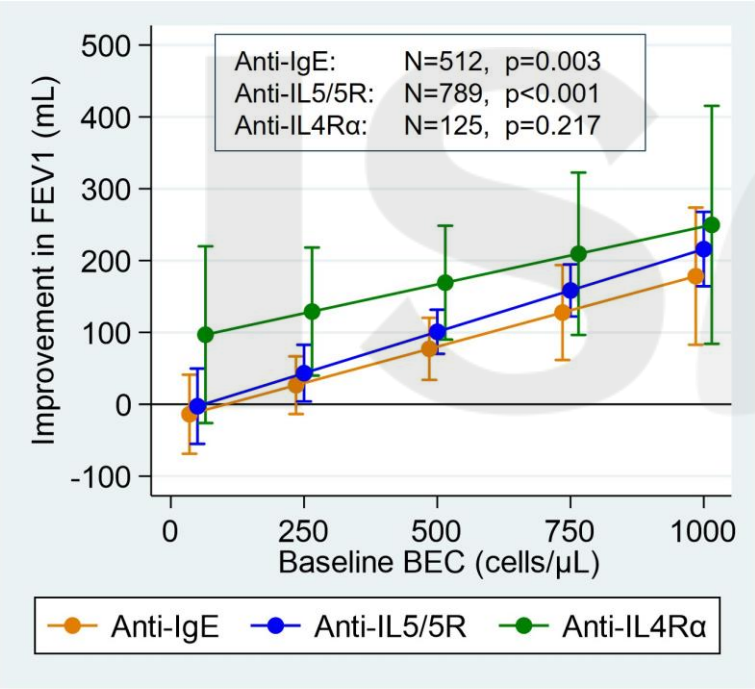
Low association between BEC and exacerbations has been seen in clinical trials of anti-IL5 treatments

Ortega HG, et al. Lancet Respir Med 2016;4(7):549-556
FitzGerald JM, Goldman M, et al. Lancet Respir Med 2018;6(1):51-64

Anti-IL5/5R: Anti-Interleukin 5/5R, BEC: Blood Eosinophil Count

BEC and FeNO significantly associated with degree of lung function improvement following treatment with anti-IL5/5R or anti-IgE biologics

Association between improvement in FEV_1 and highest pre-biologic blood eosinophil count



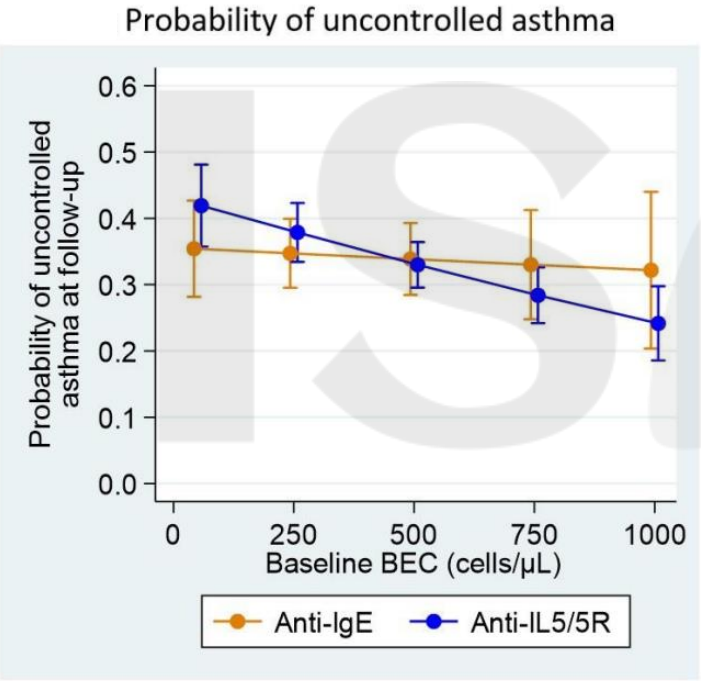
- **Patients with the highest pre-biologic levels (1000 cells/µL BEC and 100 ppb FeNO) achieved mean improvements of approximately 200 mL in FEV_1**
- **Patients with the lowest levels (<250 cells/µL BEC and <25 ppb FeNO) achieved less than a third of the mean improvement in FEV_1**

Using a combination of pre-biologic BEC + FeNO combined gave a marginal improvement in prediction of FEV1 reduction but probably not of clinical significance.

Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, Anti-IL4: Anti-Interleukin 4, FEV1: Forced Expiratory Volume 1 second, BEC: Blood Eosinophil Count,, FeNO: Fractional exhaled Nitric Oxide

BEC associated with greater asthma control for patients receiving anti-IL5/5R



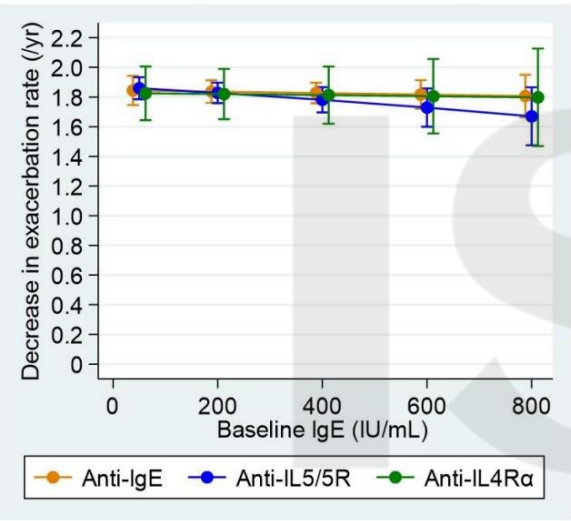
- Patients with pre-biologic BEC of 1000 cells/µL had a 24% probability of uncontrolled asthma after one year (reduced from 68% before treatment) with anti-IL5/5R treatment
- For patients with a pre-biologic BEC level of 50 cells/µL this was only reduced to 42%
- The improvement in control was consistent across different pre-biologic BEC levels with anti-IgE

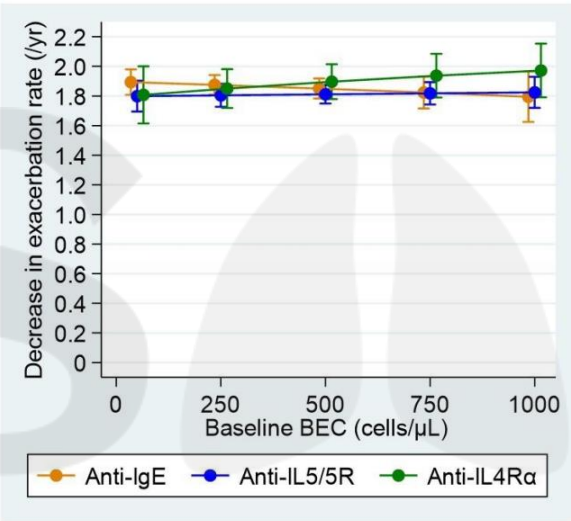
Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

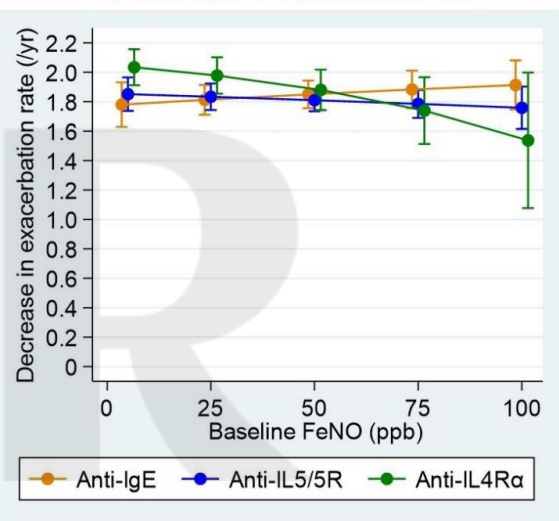
Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, BEC: Blood Eosinophil Count

Pre-biologic biomarkers not strongly associated with the extent of pre- to post-therapy reduction in exacerbations

Decrease in exacerbation rates:







Most patients in the study achieved a marked decrease one year after initiating any of the biologic treatments studied (anti-IgE, anti-IL5/5R or anti-IL4Rα) irrespective of pre-biologic biomarker levels

Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, Anti-IL4: Anti-Interleukin 4 FEV1: Forced Expiratory Volume 1 second, FeNO: Fractional exhaled Nitric Oxide, BEC: Blood Eosinophil Count

Summary
IGNITE: BEC and FeNO predict effectiveness of biologic therapies in Severe Asthma

BEC and FeNO significantly associated with degree of lung function improvement following treatment with anti-IL5/5R or anti-IgE biologics

BEC associated with greater asthma control for patients receiving anti-IL5/5R

Pre-biologic biomarkers not strongly associated with the extent of pre- to post-therapy reduction in **exacerbations**

Using **BEC and FeNO as biomarkers can give insight** into **which severe asthma patients will benefit most** from treatment with biologics

The ability of higher baseline BEC, FeNO and their combination to predict biologic associated lung function improvement highlights **opportunity for earlier intervention in patients with impaired lung function or at risk of accelerated lung function decline**

Porsbjerg CM, Townend J, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. Frontiers in Immunology. 2024 Apr 19;15. Epub 2024 Apr 19. doi: 10.3389/fimmu.2024.1361891, 10.3389/fimmu.2024.1361891/full#supplementary-material

Anti-IgE: Anti-Immunoglobulin E, Anti-IL5/5R: Anti-Interleukin 5/5R, FEV1: Forced Expiratory Volume 1 second, FeNO: Fractional exhaled Nitric Oxide, BEC: Blood Eosinophil Count

Exploring different composite definitions of responders and non-responders to biologic treatment for severe asthma (FULL BEAM response)
Exploring Definitions and Predictors of Severe Asthma Clinical Remission Post-Biologic in Adults (FULL BEAM remission)

ISAR FULL BEAM

Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

Aims and Methods

Rationale

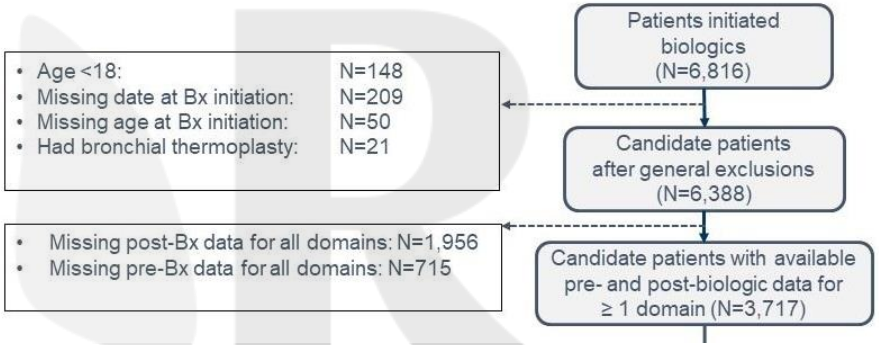
There is little agreement on definitions of real-world responders to biologic treatments for asthma and the concept of remission in severe asthma remains to be explored.

Objective

To explore composite definitions of response and remission in adults with severe asthma.

Methods

- Longitudinal cohort study across 22 countries participating in ISAR from May 2017 to January 2023
- Quantification of individual and composite definitions of response and remission at one year post-treatment using four asthma domains: exacerbation rate, asthma control, long-term oral corticosteroid (LTOCS) dose, and lung function
- Comparison of patient characteristics between response and non-response groups, and between remission and non-remission group



bx: biologics

Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

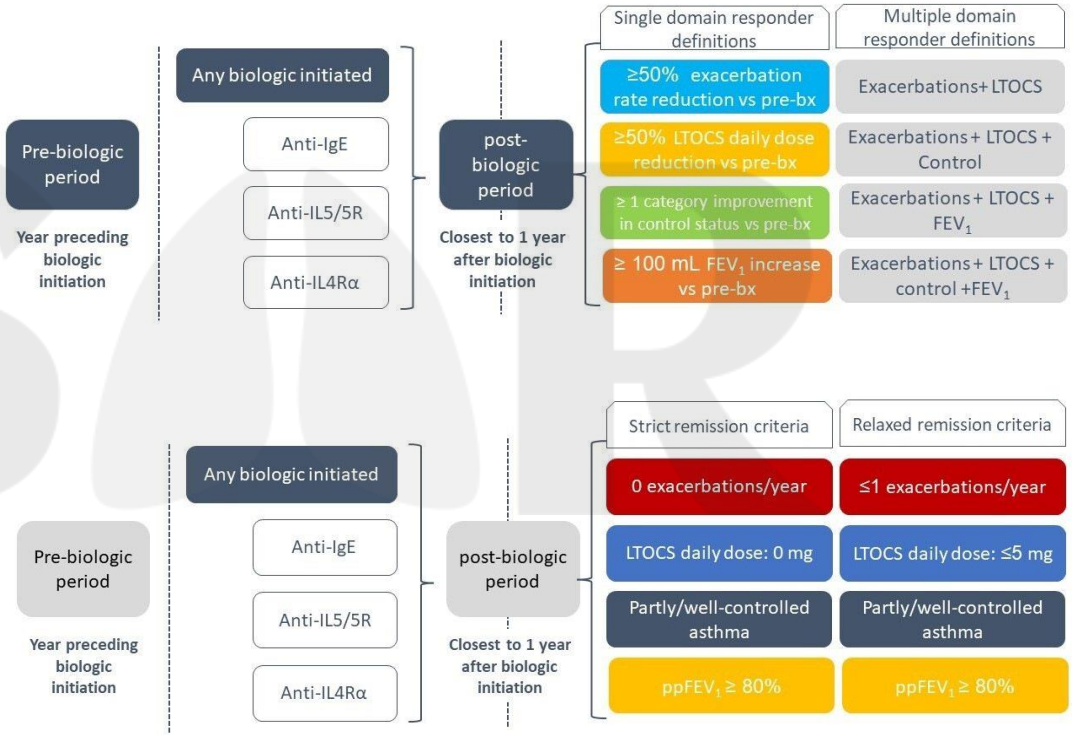
Response and remission definitions

• Response

Minimum impairment pre-biologic:
- Exacerbations: ≥2/year, and/or
- LTOCS: use in past year, and/or
- Asthma control: uncontrolled or partly controlled, and/or
- Lung function: <80% predicted FEV1

• Remission

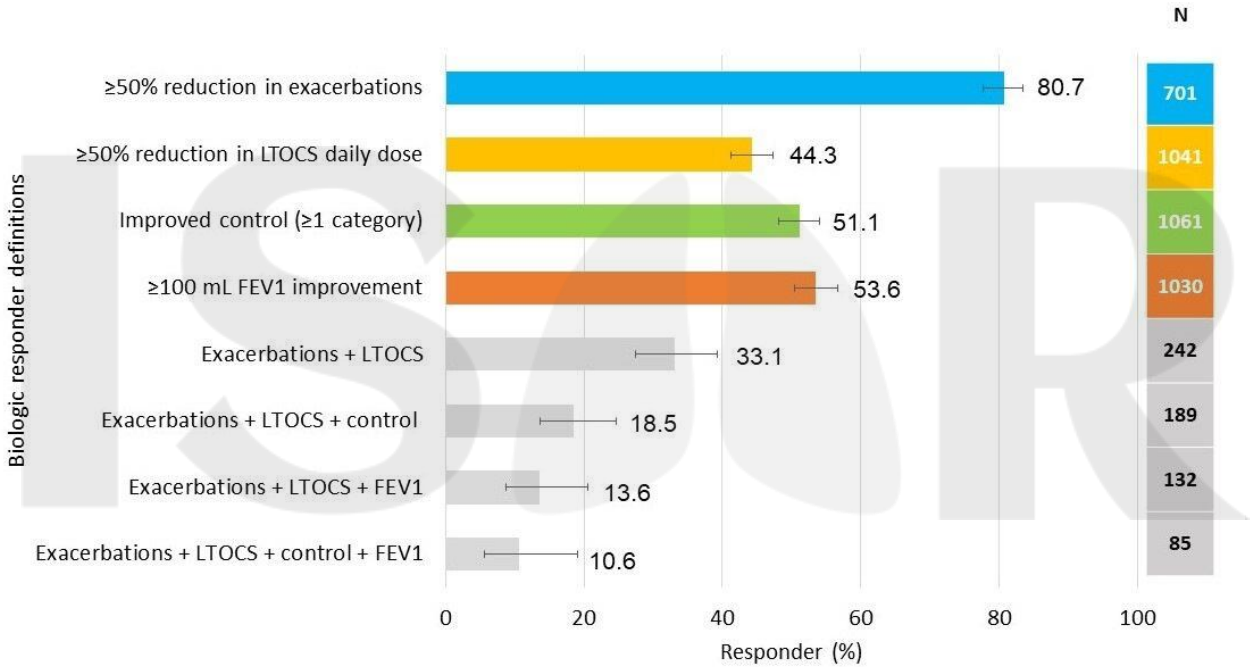
(No minimum impairment)



LTOCS: Long-term Oral Corticosteroids, ppFEV1: percent predicted forced expiratory volume in 1 second, anti-IgE: Anti-Immunoglobulin E, Anti-IL5: Anti-Interleukin 5, Anti-IL4Rα: Anti-Interleukin4Rα

Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

Spectrum of biologic responders, ranging from 11-80% depending upon type and number of domains used to define response



LTOCS: Long-term Oral Corticosteroids, FEV1: forced expiratory volume in 1 second.

Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

Patient and clinical characteristics associated with response

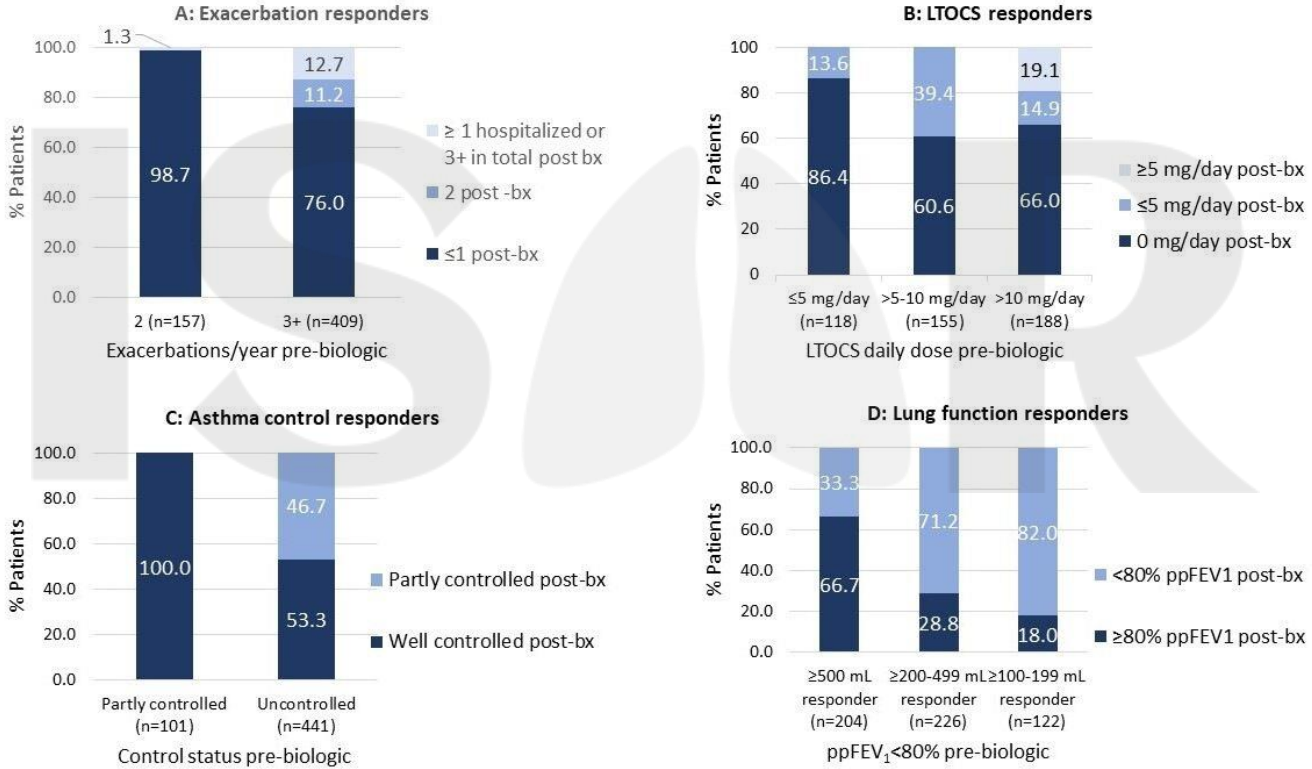
Pre-biologic characteristics	Trend or significant positive association with Exacerbation responders	Trend or significant positive association with LTOCS responder	Trend or significant positive association with Asthma control responder	Trend or significant positive association with Lung function responder
Responder domains	Higher exacerbation rate*	Lower exacerbation rate*	Lower exacerbation rate*	
	Lower LTOCS daily dose*	Higher LTOCS daily dose*	Lower LTOCS daily dose*	Lower LTOCS daily dose*
			Worse asthma control	
			Better lung function*	Worse lung function*
Biomarkers		Higher BEC*	Higher BEC*	Higher BEC*
				Higher FeNO*
Asthma metrics				Older asthma onset*
				Shorter asthma duration*
BMI		Lower BMI*	Lower BMI*	Lower BMI
Treatment	No theophylline	No theophylline*	No theophylline*	No theophylline*
		Sleep apnea*	No sleep apnea*	
	No osteoporosis			No osteoporosis*
Comorbidity profile		CRS*	CRS*	CRS*
		AR*	AR	AR
			NP*	NP*
	AD	AD*		

* p<0.05

LTOCS: Long-term Oral Corticosteroids, BMI: Body Mass Index, AD: Atopic Dermatitis, AR: Allergic Rhinitis, CRS: Chronic Rhinosinusitis, BEC: Blood Eosinophil Count, NP: Nasal Polyps, FeNO: Fractional Exhaled Nitric Oxide

Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

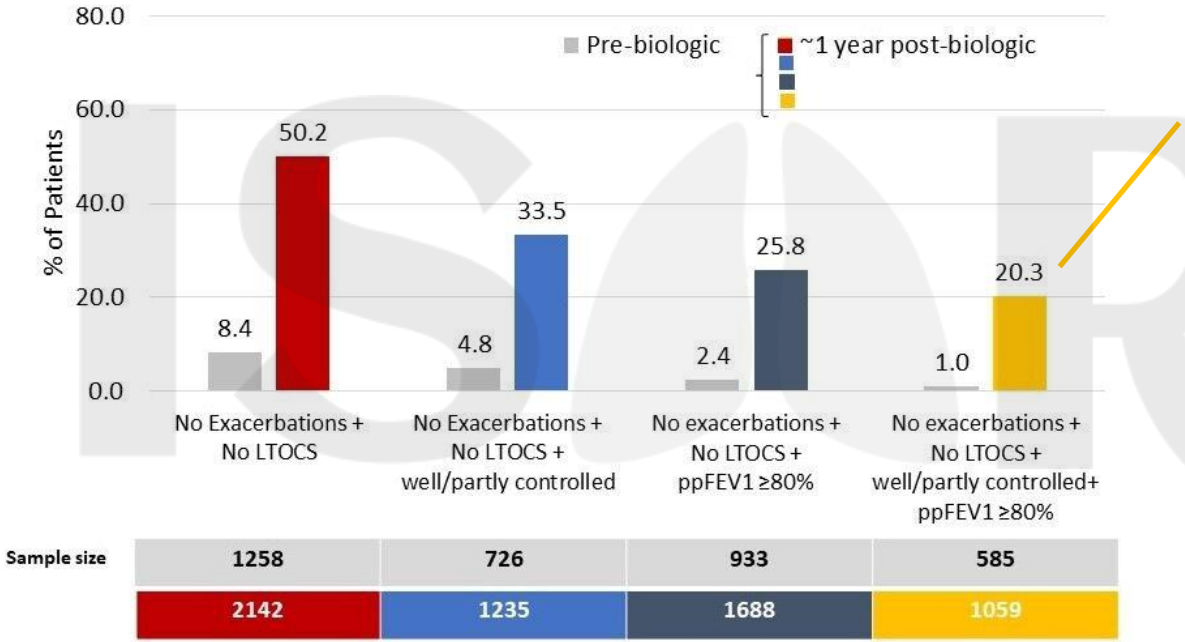
Residual impairments in responders by pre-biologic levels of impairment



LTOCS: Long-term Oral Corticosteroids, ppFEV1: percent predicted forced expiratory volume in 1 second, bx: biologics

Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

Proportion of patients in remission by different definitions



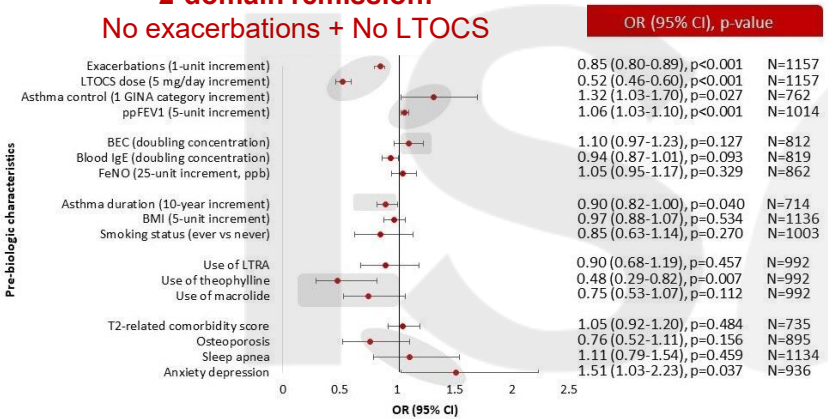
1 in 5 patients meet remission criteria in all 4 domains

LTOCS: Long-term Oral Corticosteroids, ppFEV1: percent predicted forced expiratory volume in 1 second

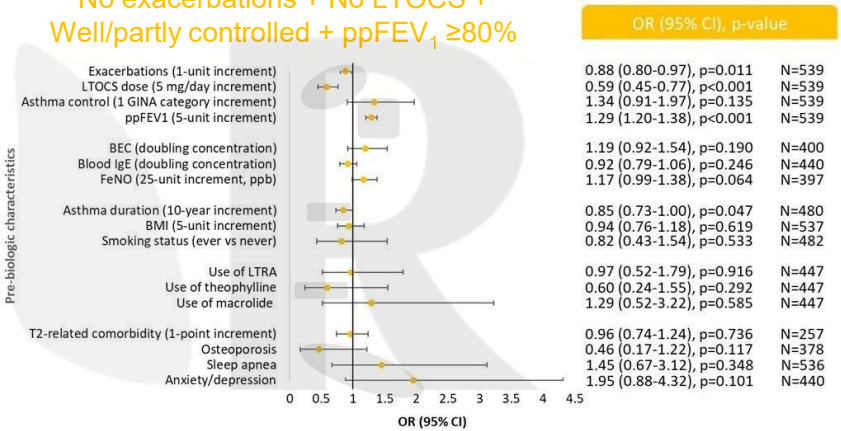
Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC

Patients with less severe disease and shorter duration of asthma pre-biologic have a better chance of achieving clinical remission post-biologic

2-domain remission:
No exacerbations + No LTOCS



4-domain remission:
No exacerbations + No LTOCS + Well/partly controlled + ppFEV$_1$ ≥80%



LTOCS: Long-term Oral Corticosteroids, ppFEV1: percent predicted forced expiratory volume in 1 second, GINA: Global Initiave for Asthma, BMI: Body Mass Index, T2: Type 2, BEC: Blood Eosinophil Count, NP: Nasal Polyps, FeNO: Fractional Exhaled Nitric Oxide, IgE: Immunoglobulin E, LTRA: Leukotriene Receptor Antagonist

Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC

FULL BEAM Response summary:
High response does not mean remission
Need for flexible interpretation of response to biologics

- Large proportion of responders (80% of patients reduced exacerbations by at least 50%), however residual impairment observed in responders
- Responses and their predictors vary according to the outcome assessed
- Greater pre-biologic impairment is associated with a better response for all outcomes assessed. However, a shorter asthma duration is associated only with a better lung function response
- Flexible interpretation to biologic response is needed, considering the degree of pre-biologic impairment and identification of characteristics (such as asthma duration) that can affect the response, to formulate a personalized likelihood of response

LTOCS: Long-Term Oral Cortocosteroids, ppFEV1: percent predicted Forced Expiratory Volume in 1 second

Scelo, G. et al., J Allergy Clin Immunol Pract. 2024 May 19:S2213-2198(24)00530-0. doi: 10.1016/j.jaip.2024.05.016.

FULL BEAM Remission summary:

Greater chance of remission if less severe impairment and shorter asthma duration at initiation of biologics

Only 20% of patients reached the strictest remission definition (no exacerbation, no LTOCS, well/partly controlled, and ppFEV1 >=80%)

Patients with less severe disease and shorter duration of asthma pre-biologic-initiation had a better chance of achieving remission post-biologic
The odds of achieving 4-domain remission decreased by 15% for every additional 10-years asthma duration

These results highlight the need to consider earlier intervention with biologics for patients with severe asthma prior to significant and irreversible lung function impairment

Since remission is more likely to occur if targeted earlier in the asthma life cycle, a paradigm shift away from targeting response in those with more severe asthma, towards the promotion of remission in those with less severe disease but at risk of developing severe asthma is needed

LTOCS: Long-Term Oral Corticosteroids, ppFEV1: percent predicted Forced Expiratory Volume in 1 second

Perez-de-Llano, L. et al., Am J Respir Crit Care Med 2024, https://doi.org/10.1164/rccm.202311-2192OC

Real-World Biologics Response and Super-Response in the International Severe Asthma Registry cohort (LUMINANT)

Observational & Pragmatic Research Institute

Real-World Biologics Response and Super-Response in the International Severe Asthma Registry cohort (LUMINANT)

Eve Denton, Mark Hew, Matthew J. Peters, John W. Upham, Lakmini Bulathsinhala, Trung N. Tran, Neil Martin, Celine Bergeron, Mona Al-Ahmad, Alan Altraja, Désirée Larenas-Linnemann, Ruth Murray, Carlos Andrés Celis-Preciado, Riyad Al-Lehebi, Manon Belhassen, Mohit Bhutani, Sinthia Z. Bosnic-Anticevich, Arnaud Bourdin, Guy G. Brusselle, John Busby, Giorgio Walter Canonica, Enrico Heffler, Kenneth R. Chapman, Jérémy Charriot, George C. Christoff, Chung, Li Ping, Borja G. Cosio, Andréanne Côté, Richard W. Costello, Breda Cushen, James Fingleton, João A. Fonseca, Peter G. Gibson, Liam G. Heaney, Erick Wan-Chun Huang, Takashi Iwanaga, David J. Jackson, Mariko Siyue Koh, Lauri Lehtimäki, MD, Jorge Máspero, Bassam Mahboub, Andrew N. Menzies-Gow, Patrick D. Mitchell, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Luis Perez-de-Llano, Diahn-Warng Perng (Steve), Paul E. Pfeffer, Todor A. Popov, Celeste M. Porsbjerg, Chin Kook Rhee, Nicolas Roche, Mohsen Sadatsafavi, Sundeep Salvi, Johannes Martin Schmid, Chau-Chyun Sheu, Concetta Sirena, Carlos A. Torres-Duque, Laila Salameh, Pujan H. Patel, Charlotte Suppli Ulrik, Eileen Wang, Michael E. Wechsler, and David B. Price, on behalf of the ISAR LUMINANT Working Group.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Methods

- **Objective**
  - Describe responsiveness to biologic asthma therapies in real-world patients with severe asthma
- **Study population**
  - Data from the International Severe Asthma Registry (www.isar.opcglobal.org)
  - Includes electronic medical records from 20,000 patients in 28 countries
- **Inclusion criteria**
  - Uncontrolled asthma on GINA Step 4 treatment or on GINA Step 5 treatment (ISAR inclusion criteria)
  - Age ≥18 years
  - ≥24 weeks of follow-up
- **Study groups**
  - Patients prescribed biologic medication after their baseline visit
  - Patients with baseline impairment in predefined outcome domains but who did not initiate biologics
- **Outcome domains**
  - Forced expiratory volume in 1 second (FEV_1)
  - Improved asthma control (controlled, partial, uncontrolled)
  - Annualized exacerbation rate reduction
  - Long-term OCS dose reduction.

ISAR, International Severe Asthma Regstry; GINA, Global Initiative for Asthma; OCS oral corticosteroids.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Sub-analyses

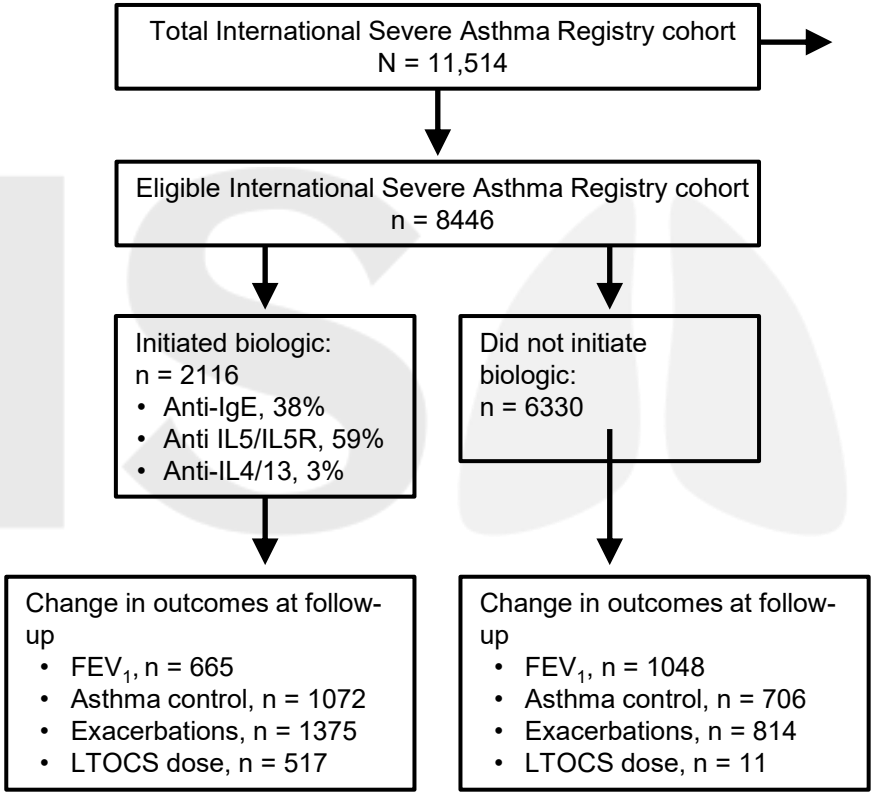
- **Bronchodilator reversibility in biologics initiators**
  - Defined as ≥12% and ≥200 mL FEV_1 improvement following short-acting bronchodilator administration
- **Type 2 inflammation gradient in the total cohort**
  - Defined by criteria modified by *Heaney et al:*[1] Type 2 phenotypes classified as Grade 3 (most likely eosinophilic), Grade 2 (likely eosinophilic), Grade 1 (least likely eosinophilic), and Grade 0 (non-eosinophilic)
- **Eligibility for randomized controlled trials**
  - Defined as severe asthma and all three of: bronchodilator reversibility on high dose ICS and a second controller; FEV_1 <80% predicted; and smoking history of <10 pack years

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids.

1. Heaney L, et al. *Chest*. 2021;160:814-830. doi: 10.1016/j.chest.2021.04.013

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

LUMINANT study population flow



Excluded:
- Ceased biologic <24 weeks, n = 118
- On biologic at baseline visit, n = 2767
- Inadequate follow-up data, n = 183

IgE, immunoglobulin E; IL5, interleukin 5; IL5R, IL5 receptor; IL 4/13 interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Response domains and criteria

Single-domain definitions of response and super-response in patients with severe asthma between baseline and 12-month visit

Outcome domain	Definition of responders	Definition of super-responders	Excluded from analysis if[a]:
Asthma exacerbations	≥50% reduction in annualized exacerbation rate	Exacerbation elimination	No 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, uncontrolled)	New achievement of well-controlled asthma	Well-controlled asthma at baseline
LTOCS burden	Any reduction in LTOCS dose (mg)	Cessation of LTOCS or tapering to ≤5 mg/day	Not on LTOCS at baseline

FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

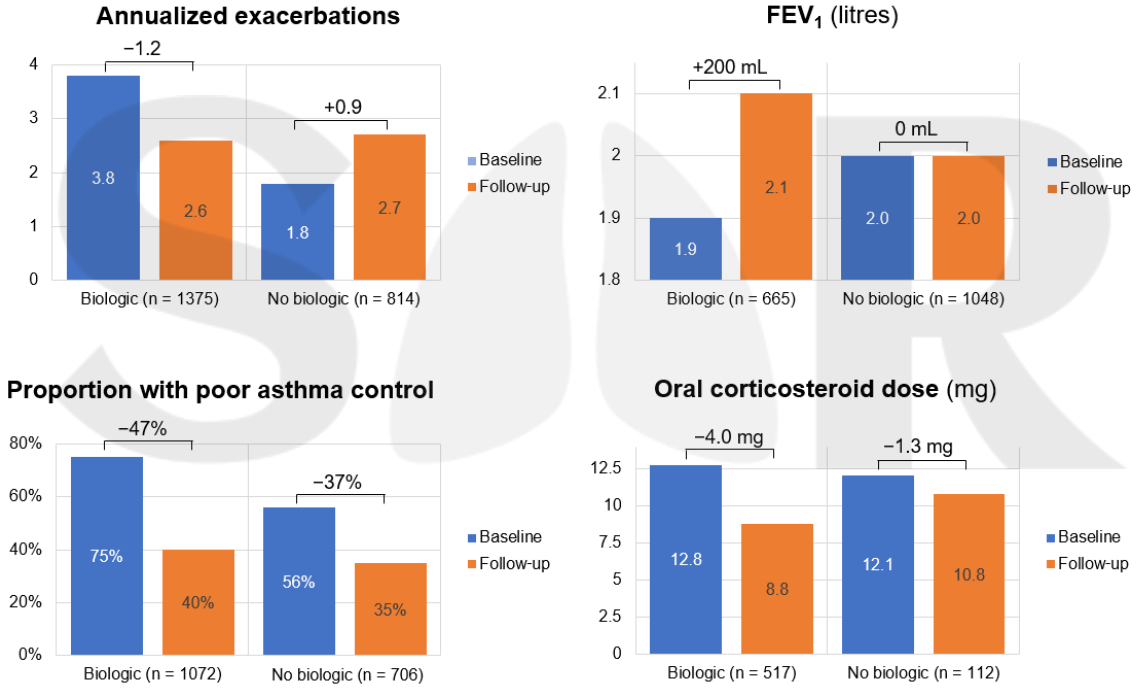
[a]Patients who had incomplete data (ie, no follow-up data related to the outcome domain of interest) or no capacity to respond in a particular domain, eg, who had no exacerbations at baseline, had well-controlled asthma, or were not on LTOCS, were excluded from the analysis relating to that particular domain; however, they remained in analyses related to other domains.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Changes from baseline in single outcome domains

- Biologic initiators had greater improvements from baseline than non-initiators[a,b]

[a]The increase in annual exacerbations among non-biologic users was largely seen in EMR data, where there the 'baseline' may potentially be misclassified, as a patient's first visits in EMR may not fully capture exacerbations; this would lead to an apparent increase in the first year of follow-up.



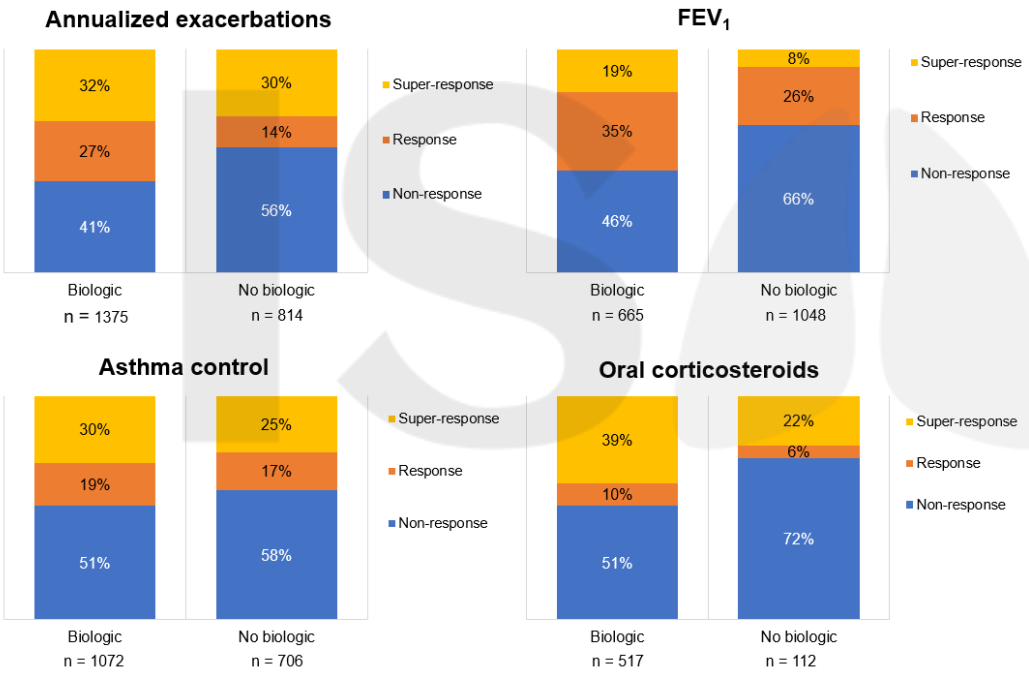
FEV_1, forced expiratory volume in 1 second.

[b]Baseline differences between biologic initators and non-initiators were not adjusted for by matching or multivariable adjustment methods.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Responses to biologic or non-biologic asthma treatments

- More frequent responses/super-responses in biologic initiators than in non-initiators[a]



- Biologic initiators had more frequent super-responses than responses (except FEV_1)
- **However, 40-50% of biologic initiators did not meet response criteria**

FEV_1, forced expiratory volume in 1 second.

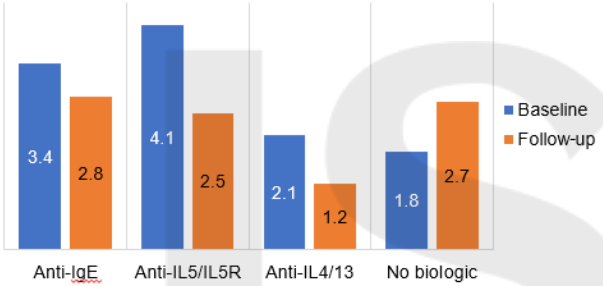
[b]Baseline differences between biologic initators and non-initiators were not adjusted for by matching or multivariable adjustment methods.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

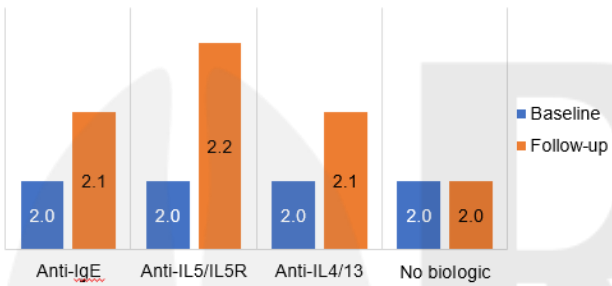
Changes from baseline (unadjusted) by biologic class

- Biologic treatments were associated with asthma improvement in all domains assessed

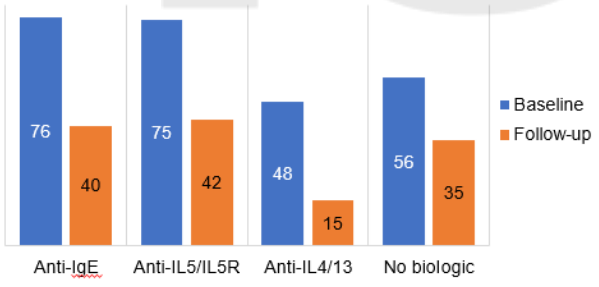
Annualized exacerbations



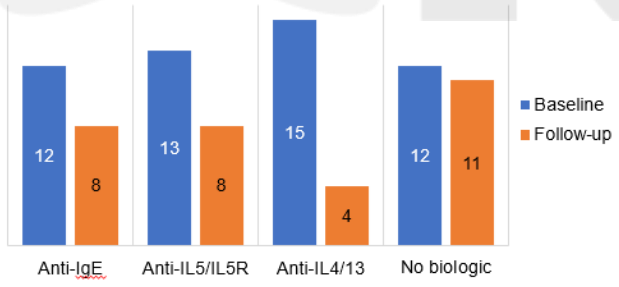
FEV_1 (litres)



Poor asthma control (%)



Long-term OCS dose (mg)



FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; IL-5R, IL5 receptor; OCS, oral corticosteroids.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Treatment responsiveness by biologic class

- Anti-IL5/IL5R initiators had greater improvement in AER than anti-IgE initiators despite worse baseline impairment

Proportions of responders and super-responders in single outcome domains, by biologic class

	Anti-IgE n = 809	Anti-IL5/IL5R n = 1244	Anti-IL4/13[a] n = 63	P-value
Response				
AER reduced ≥50%, % (number)	52% (253/489)†	62% (542/874)†	69% (18/26)	<0.001
FEV_1 pre improved ≥100 mL, % (number)	49% (144/292)	58% (212/369)	67% (10/15)	<0.001
Asthma control improved, % (number)	49% (215/437)	48% (293/616)	75% (18/24)	0.001
LTOCS dose reduced, % (number)	40% (37/92)	52% (125/240)	50% (2/4)	<0.001
Super-response				
Exacerbation elimination, % (number)	22% (134/618)†	31% (303/987)†	32% (10/31)	<0.001
FEV_1 pre improved ≥500 mL, % (number)	15% (44/292)	22% (80/369)	27% (4/15)	<0.001
New well-controlled asthma, % (number)	27% (116/437)†	31% (188/616)‡	58% (14/24)†‡	<0.001
LTOCS ceased or tapered to <5 mg/day, % (number)	34% (31/92)	43% (103/240)	25% (1/4)	<0.001

AER, annualized exacerbation rate; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor; IL 4/13, interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

†, ‡ denote columns with significant difference on post-hoc testing (p <0.05).

[a]Note small numbers of patients on anti-IL4/13 therapy limit interpretation of data from this group.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Treatment responsiveness by biologic class

- Anti-IL4/13 initiators had the highest proportions of responders in all outcome domains
  - 75% achieved improved asthma control and 58% new well-controlled asthma

Proportions of responders and super-responders in single outcome domains, by biologic class

	Anti-IgE n = 809	Anti-IL5/IL5R n = 1244	Anti-IL4/13[a] n = 63	P-value
Response				
AER reduced ≥50%, % (number)	52% (253/489)†	62% (542/874)†	69% (18/26)	<0.001
FEV_1 pre improved ≥100 mL, % (number)	49% (144/292)	58% (212/369)	67% (10/15)	<0.001
Asthma control improved, % (number)	49% (215/437)	48% (293/616)	75% (18/24)	0.001
LTOCS dose reduced, % (number)	40% (37/92)	52% (125/240)	50% (2/4)	<0.001
Super-response				
Exacerbation elimination, % (number)	22% (134/618)†	31% (303/987)†	32% (10/31)	<0.001
FEV_1 pre improved ≥500 mL, % (number)	15% (44/292)	22% (80/369)	27% (4/15)	<0.001
New well-controlled asthma, % (number)	27% (116/437)†	31% (188/616)‡	58% (14/24)†‡	<0.001
LTOCS ceased or tapered to <5 mg/day, % (number)	34% (31/92)	43% (103/240)	25% (1/4)	<0.001

AER, annualized exacerbation rate; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor; IL 4/13, interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

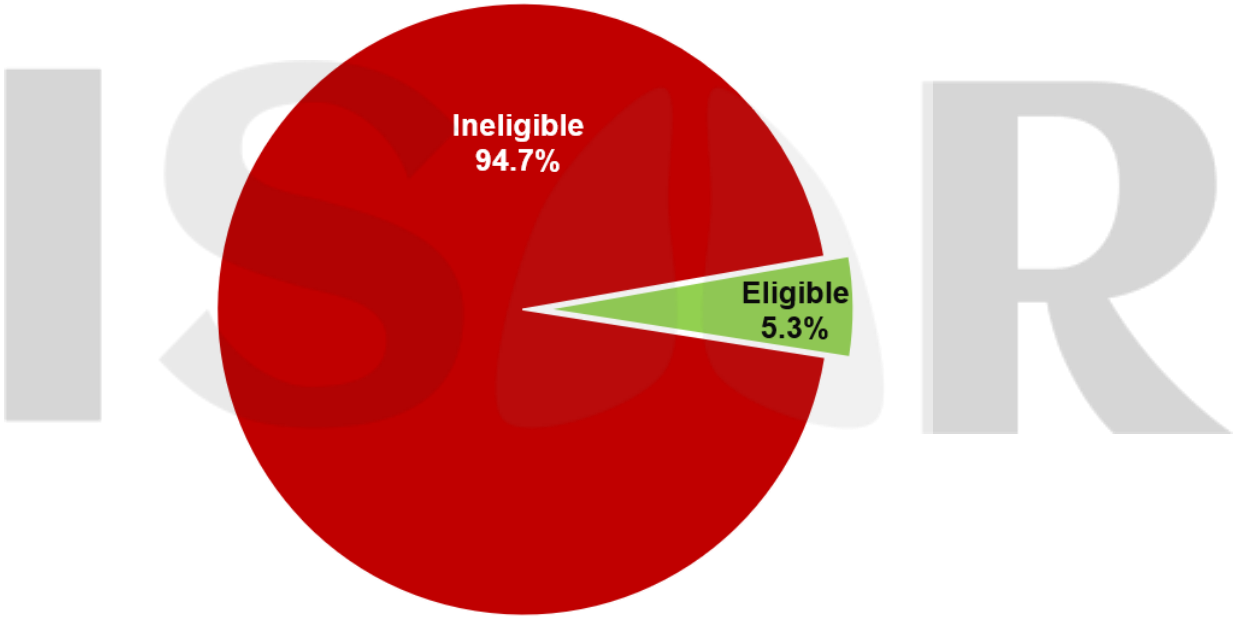
†, ‡ denote columns with significant difference on post-hoc testing ($p < 0.05$).

[a]Note small numbers of patients on anti-IL4/13 therapy limit interpretation of data from this group.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Eligibility for randomized controlled trials

- 5.3% (211) among 4001 subjects with enough data to determine potential RCT eligibility, fulfilled all criteria[a] at baseline



RCT, randomized controlled trial; FEV_1, forced expiratory volume in 1 second.

[a]FEV_1 reversibility on high-dose inhaled corticosteroid; FEV1 <80%; smoking history of <10 pack years).

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Bronchodilator FEV_1 reversibility

- FEV_1 response was more likely in biologics initiators with FEV_1 reversibility at baseline than in those without reversibility

Table S3. Responses in single outcome domains in patients who initiated a biologic, by FEV_1 reversibility

Response domain	FEV_1 reversibility		P-value
	Present	Absent	
Annualized exacerbations reduced by ≥50%, % (number)	57 (69/138)	61 (366/599)	0.36
FEV_1 improved ≥100 mL, % (number)	72 (68/94)	52 (223/427)	<0.001
Asthma control improved, % number)	48 (47/99)	45 (208/463)	0.66
LTOCS dose reduced, % (number)	14 (2/14)	43 (46/107)	0.08

Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Type 2 inflammation gradient

- Most patients (85%) were T2 gradient Grade 3
  - Patients with T2 grade 3 more frequently had a longitudinal exacerbation improvement

Table S4. Responses in single outcome domains in the LUMINANT cohort, by T2 inflammation gradient grade

	T2 inflammation gradient grade[a]				
Response domain	**0** (n = 84)	**1** (n = 195)	**2** (n = 76)	**3** (n = 2050)	**P-value**
AER reduced by ≥50%	26%	33%	44%	58%	<0.001
Exacerbation elimination	10%	12%	15%	25%	<0.001
FEV_1 improved by ≥100 mL	43%	44%	37%	53%	NS
LTOCS dose reduced	33%	33%	29%	49%	NS

Abbreviations: AER, annualized exacerbation rate; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids; NS, not significant.

[a]Phenotypes classified as grade 3 (most likely eosinophilic), grade 2 (likely eosinophilic), grade 1 (least likely eosinophilic), and grade 0 (non-eosinophilic), according to Heaney, et al. Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. Chest. 2021;160:814-830. doi: 10.1016/j.chest.2021.04.013

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Key insights from LUMINANT

- Only 5.3% of ISAR patients met usual RCT inclusion criteria[a]
- Biologic initiators had worse baseline impairment than non-initiators, despite similar biomarker levels
- Responses/super-responses were more frequent in biologic initiators than in non-initiators
- 40–50% of biologic initiators did not meet response criteria
- Patients initiating anti-IL5/IL5R agents had significantly greater improvement in AER than those initiating an anti-IgE agent despite worse baseline impairment

ISAR, International Severe Asthma Registry; RCT, randomized controlled trial; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor, AER, annualized exacerbation rate.
[a]Severe asthma and all 3 of: bronchodilator reversibility on high-dose ICS and a second controller, FEV_1 <80% predicted, and smoking history of <10 pack years.

Denton E, et al. *Allergy*. 2024. doi: 10.1111/all.16178

Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry (EVEREST)

Tham T Le, David B Price, Clement Erhard, Bill Cook, Anna Quinton, Rohit Katial, George C Christoff, Luis Perez-de-Llano, Alan Altraja, Celine Bergeron, Arnaud Bourdin, Mariko Siyue Koh, Lauri Lehtimäki, Bassam Mahboub, Nikolaos G Papadopoulos, Paul Pfeffer, Chin Kook Rhee, Victoria Carter, Neil Martin, Trung N Tran, on behalf of the EVEREST Study Working Group

Tham T. et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry. *J Asthma Allergy*. In press

Aim and Methods[1]

Background

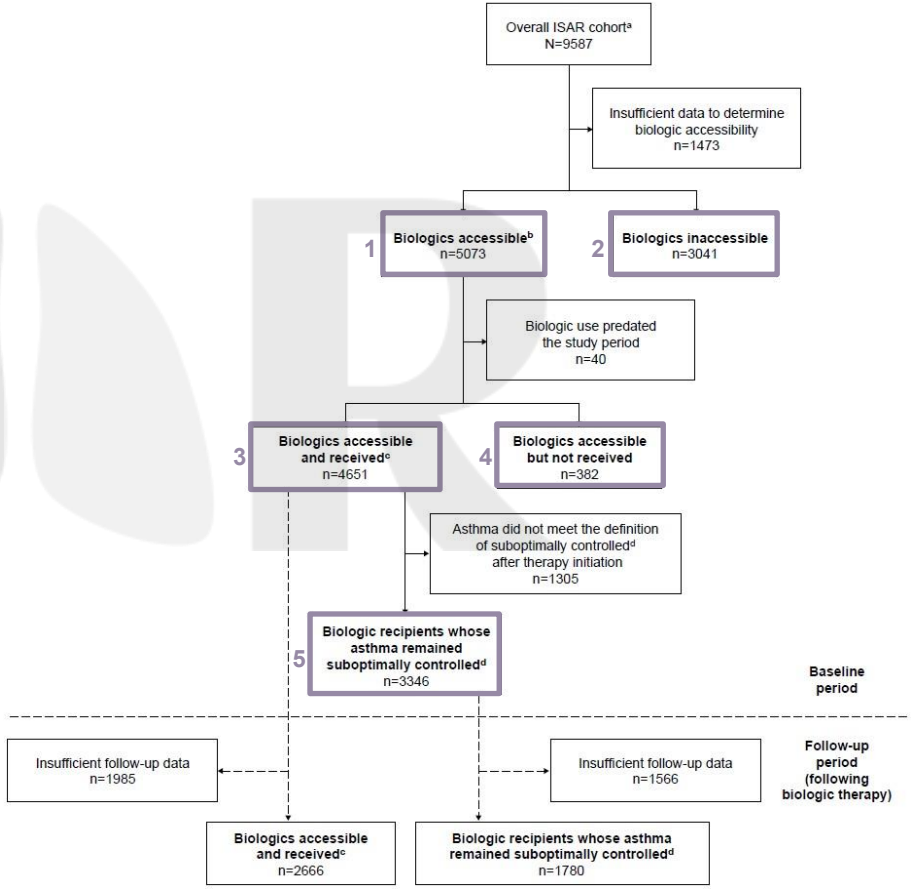
Patients with severe asthma may be prescribed biologics to improve disease control. There are variations in access to biologics globally.[2]

Aim

Characterize the global disease burden of patients with severe asthma **without access to biologics** and those who **have access but do not receive biologics**, as well as the remaining **unmet need** despite use of these therapies.

Methods

- Historical cohort study of patients with severe asthma (aged ≥18 years) in ISAR receiving GINA 2018 step 5 treatment, or with uncontrolled disease at GINA step 4
- Prospective data on patient clinical characteristics, healthcare resource utilization, and medication use over a 12-month period between December 2017 and May 2022 were assessed for five groups

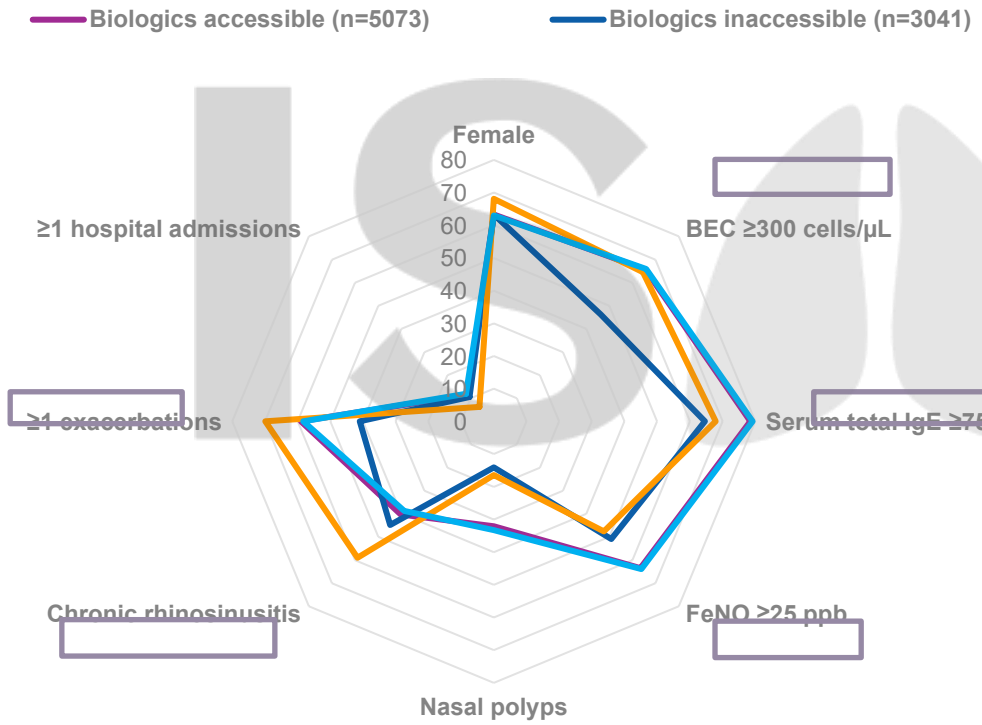


GINA = Global Initiative for Asthma; ISAR = International Severe Asthma Registry

[1]Tham T. et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry. *J Asthma Allergy*. In press; [2]Porsbjerg CM et al., Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract.* 2022;10(5):1202-1216.e1223.

High biomarkers, comorbidity prevalence and disease burden across all groups, including T2-targeted biologic recipients and those who did not receive biologics

Baseline clinical characteristics and asthma-related HCRU (% of patients)



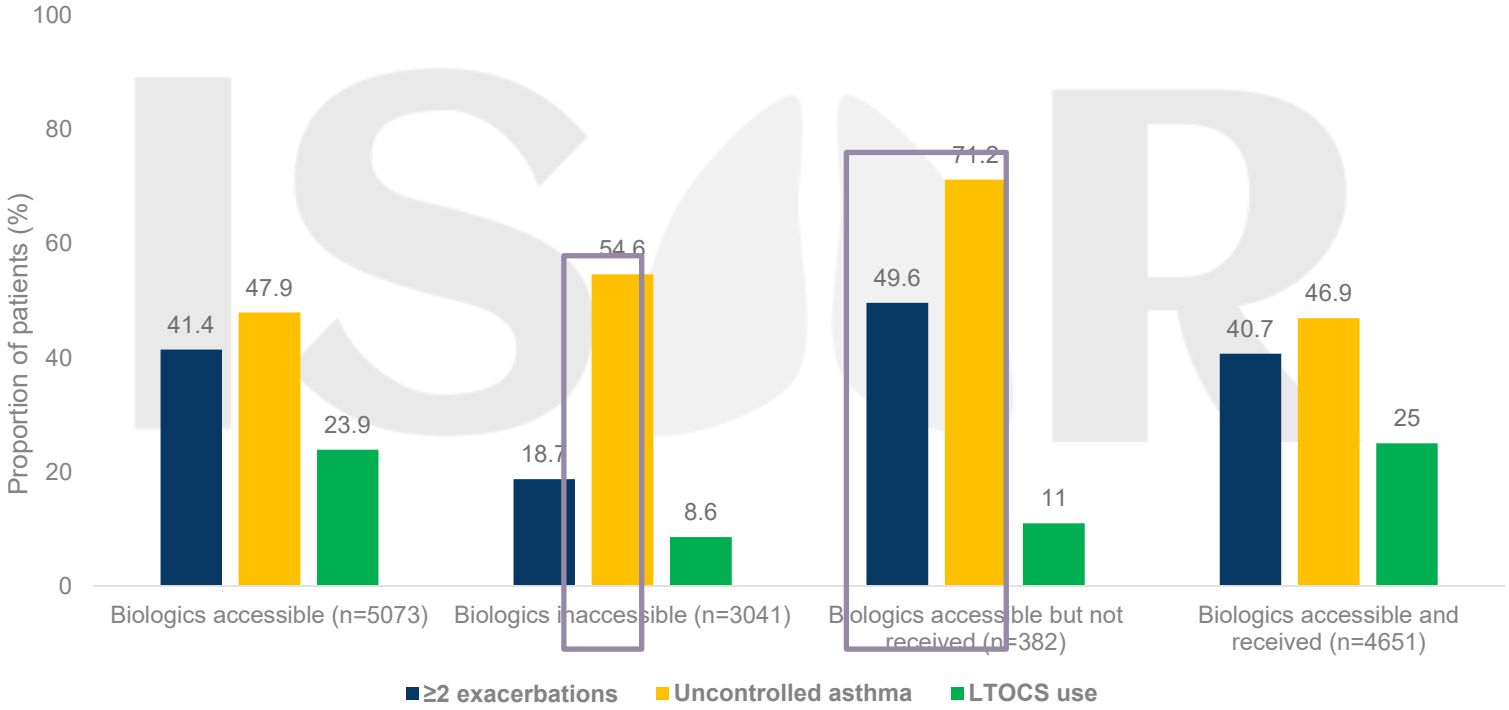
- Approximately two-thirds of patients across groups had **BEC ≥300 cells/µL**, except for the biologics inaccessible group (46.3%).
- Approximately half of patients in the biologics inaccessible and biologics accessible but not received groups, and two-thirds of patients in the other groups, had **FeNO ≥25 ppb**.
- **Chronic rhinosinusitis** was present in ~40% of patients across groups, but was more common in the biologics accessible but not received group (59.0%).
- Among the patients who lacked access to biologics, ~40% experienced **≥1 exacerbations**.

BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; HCRU = Healthcare resource utilization; IgE = Immunoglobulin E; T2 = Type 2

Tham T, et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry, *J Asthma Allergy*. In press

Substantial burden of exacerbations and uncontrolled asthma across all groups, particularly in patients without access to biologics and those who have access but did not receive biologics

Proportions of patients with severe asthma who experienced ≥2 exacerbations, had uncontrolled asthma and received LTOCS during the 12 months before the first ISAR visit*



LTOCS = Long-term oral corticosteroids

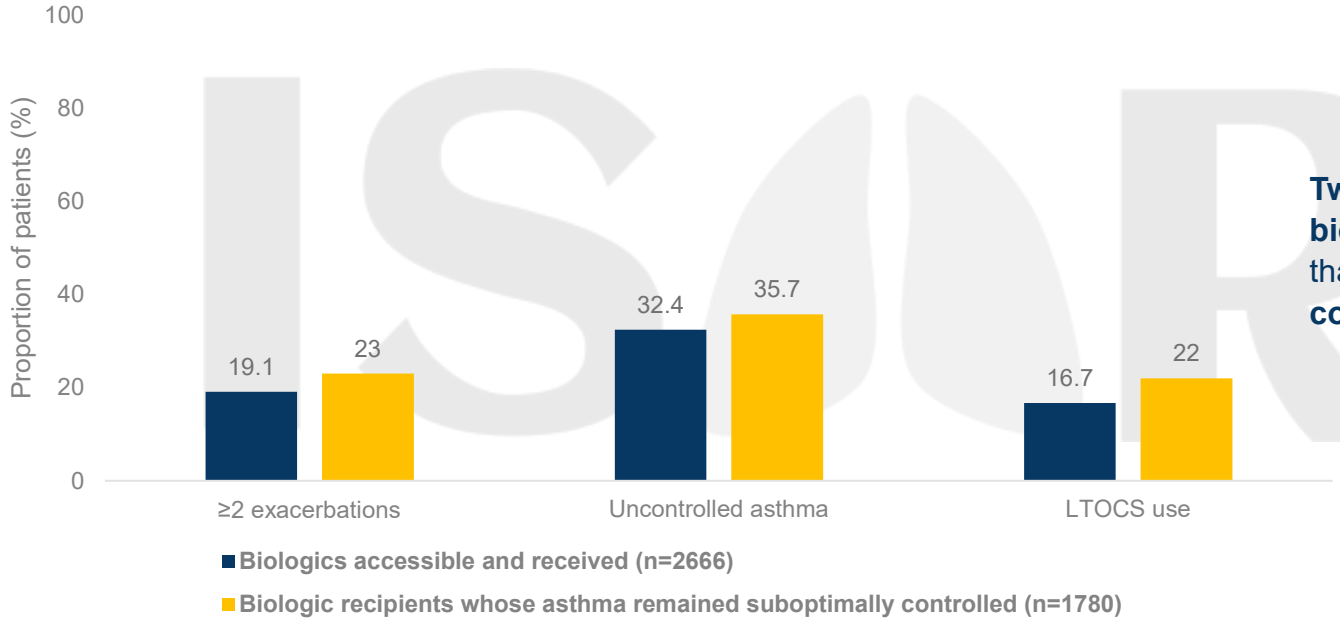
*The index date was the first visit recorded in ISAR with measurements meeting the group eligibility criteria; for biologic users, the index date was the ISAR visit that is closest to the date on first biologic.

Percentages exclude patients with missing values. Asthma control as an outcome was assessed using the Global Initiative for Asthma (GINA) 2019 criteria.

Tham T. et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry. *J Asthma Allergy*. In press

Considerable burden of exacerbations, asthma control and LTOCS use among T2-targeted biologic recipients despite treatment

Proportions of patients with severe asthma who experienced ≥2 exacerbations, had uncontrolled asthma and received LTOCS during the 12 months post-biologic initiation*



Two-thirds of T2-targeted biologic recipients had asthma that remained **suboptimally controlled**† despite treatment.

LTOCS = Long-term oral corticosteroids; T2 = Type 2

*The index date was the first visit recorded in ISAR with measurements meeting the group eligibility criteria; for biologic users, the index date was the ISAR visit that is closest to the date on first biologic. For the subgroup of biologic recipients whose asthma remained suboptimally controlled, the index date was the date of the third dose of biologic treatment; among those that switched or stopped biologics, the index date was the ISAR visit closest to the date on first biologic.

†The biologic recipients whose asthma remained suboptimally controlled group was defined as patients within the biologics accessible and received group who were prescribed at least three doses of a biologic and either had uncontrolled asthma following biologic initiation, had a severe exacerbation following biologic initiation, or received LTOCS treatment. Patients who had switched or stopped their biologic treatment owing to a reported lack of clinical efficacy were also included in this group.

Tham T. et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry. *J Asthma Allergy*. In press

Summary: Substantial disease burden was observed in patients without access to biologics, those who have access but did not receive biologics, and T2-targeted biologic recipients

Key findings

- ~55% of patients who lacked access to biologics and ~71% of patients who had access but did not receive biologics had uncontrolled asthma during the 12 months before the first ISAR visit*.
- Among T2-targeted biologic recipients, a sizable proportion still experienced considerable burden in terms of exacerbations, HCRU, asthma control, and LTOCS use.

Practice change needed

- There is a need for regulators to increase and standardize access to biologics, and for healthcare systems to better allocate resources and enhance treatment pathways.
- There remains a high unmet need among T2-targeted biologic recipients, highlighting the importance of ongoing research and the development of more effective therapy options.

HCRU = Healthcare resource utilization; LTOCS = Long-term oral corticosteroids; T2 = Type 2
*The index date was the first visit recorded in ISAR with measurements meeting the group eligibility criteria.
Tham T. et al., Disease Burden and Access to Biologic Therapy in Patients with Severe Asthma, 2017–2022: An Analysis of the International Severe Asthma Registry. *J Asthma Allergy*. In press

Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study

Trung N. Tran, Stephanie Chen, Benjamin Emmanuel, Alan Altraja, Arnaud Bourdin, Chau-Chyun Sheu, Ming-Ju Tsai, Flavia C. L. Hoyte, Anna Quinton, Bill Cook, Lakmini Bulathsinhala, William Henley, Celine Y. Y. Goh, Yang Liu, Cono Ariti, Victoria Carter, and David B. Price, on behalf of the CLEAR Study Working Group

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

Aim and Methods

Background

Biologics are effective in severe asthma, however individual patients' responses may be suboptimal, leading to therapy switching or stopping

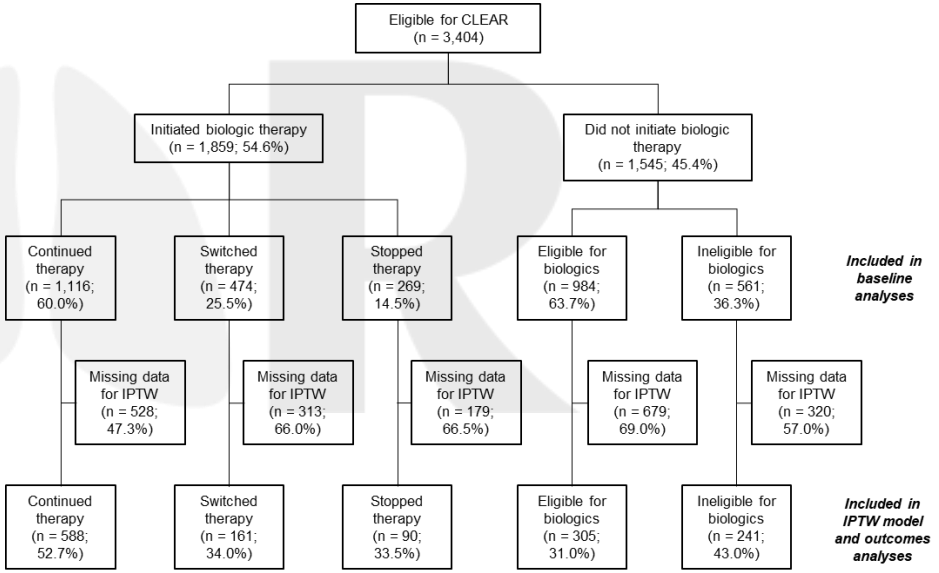
Aim

Assess real-world biologic use patterns and associated clinical outcomes in patients receiving care for severe asthma

Methods

- Multicenter, observational study that included adults (≥18 years old) from 23 ISAR countries between December 2015 and August 2021
- Biologic initiators were categorized as:
  - **Continuing** the initial biologic for 6 months
  - **Switching** to another biologic within 6 months
  - **Stopping** biologic treatment within 6 months
- Outcomes were assessed using the closest available data to 12 months after biologic initiation, using propensity score-weighted multivariable regression models

Patients and patterns of biologic use

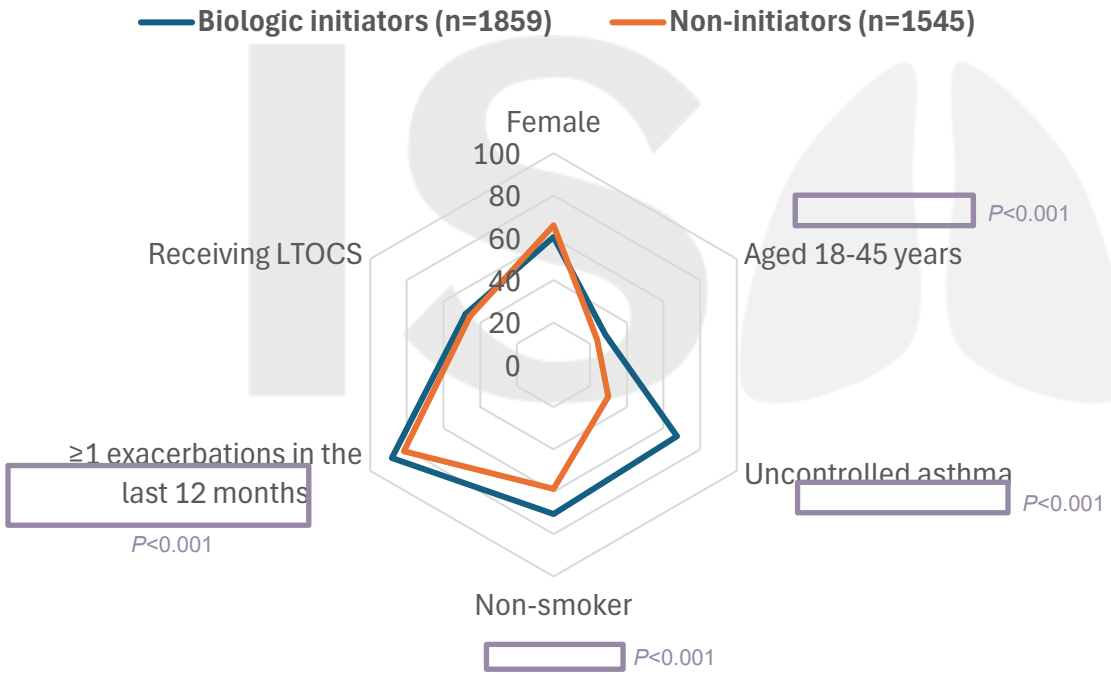


IPTW = Inverse probability of treatment weighting; ISAR = International Severe Asthma Registry

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

Biologic initiators (pre-biologic initiation) were more likely to have uncontrolled asthma, and had more exacerbations and higher biomarker levels than non-initiators (within 12 months before the index date)

Characteristics of initiators (before biologic initiation) and non-initiators (within 12 months before the index date), % of patients



Biomarkers of initiators (before biologic initiation) and non-initiators (within 12 months before the index date)

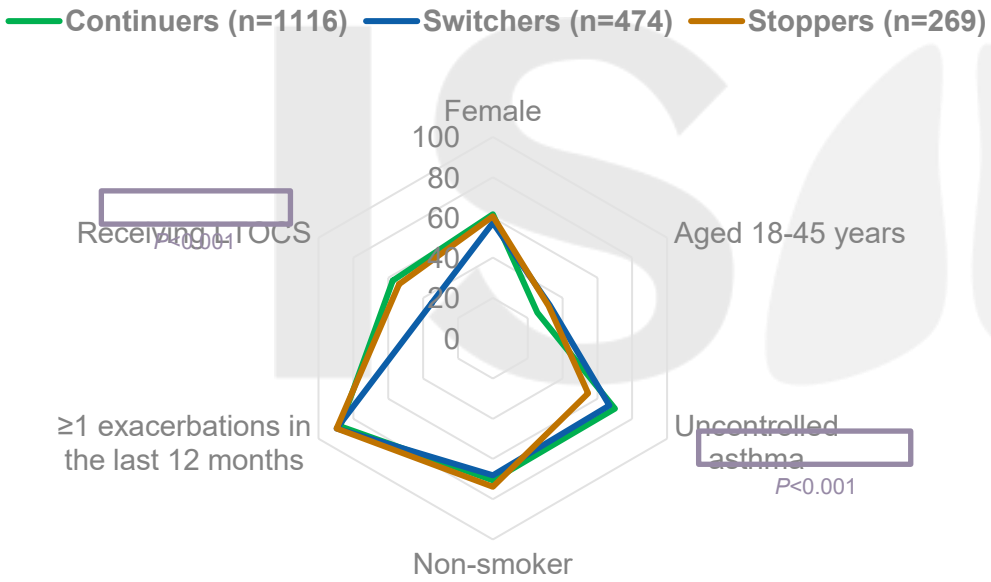
Biomarker	Initiators	Non-initiators	*P* value
BEC, median (IQR), cells/μL	N=1671 300 (480)	N=1216 200 (260)	<0.001
FeNO, median (IQR), ppb	N=1159 35 (49)	N=544 22 (32)	<0.001
Serum total IgE, median (IQR), IU/mL	N=1476 191 (428)	N=893 63 (229)	<0.001

BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; IgE = Immunoglobulin E; IQR = Interquartile range; LTOCS = Long-term oral corticosteroids

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

Pre-biologic initiation, continuers were more likely than switchers or stoppers to have uncontrolled asthma; switchers had higher FeNO levels and were less likely to be receiving LTOCS than continuers or stoppers

Characteristics of continuers, switchers and stoppers before biologic initiation, % of patients



Biomarkers of continuers, switchers and stoppers before biologic initiation

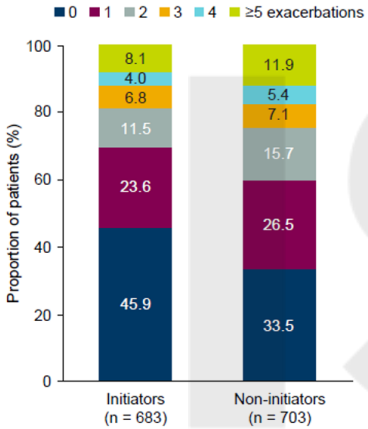
Biomarker	Continuers	Switchers	Stoppers	*P* value
BEC, median (IQR), cells/μL	N=1005 340 (480)	N=433 300 (510)	N=233 300 (400)	0.007
FeNO, median (IQR), ppb	N=691 33 (44)	N=313 42 (53)	N=155 30 (53)	0.001
Serum total IgE, median (IQR), IU/mL	N=904 185 (411)	N=367 197 (519)	N=205 238 (390)	0.105

BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; IgE = Immunoglobulin E; IQR = Interquartile range; LTOCS = Long-term oral corticosteroids

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

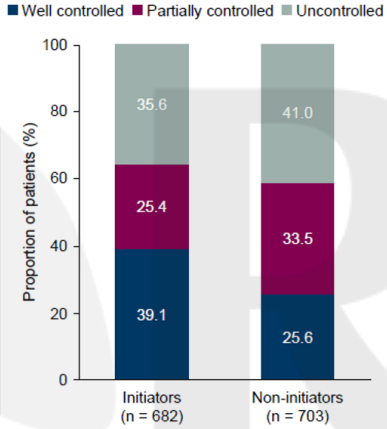
Biologic initiators had fewer exacerbations, were less likely to have uncontrolled asthma and had a greater reduction in daily LTOCS dose than non-initiators during the follow-up period*

Exacerbations at follow-up*



- Initiators had a **lower AAER** than non-initiators (adjusted IRR: 0.76 [95% CI: 0.65, 0.88]), with a mean (SD) AAER of 1.6 (2.9) for initiators and 2.1 (3.5) for non-initiators.
- Initiators had a **longer time to first exacerbation** than non-initiators (HR: 0.39 [95% CI: 0.33, 0.47]).

Asthma control at follow-up*



- Initiators were **less likely to have uncontrolled asthma** than non-initiators (adjusted odds ratio: 0.76 [95% CI: 0.55, 1.06]).

LTOCS dose at follow-up*

- The mean (SD) daily LTOCS dose was 7.8 (10.0) mg for initiators and 9.5 (8.8) mg for non-initiators.
- Initiators had a **greater reduction in daily LTOCS dose** than non-initiators (adjusted β: −2.73 mg [95% CI: −4.77, −0.68]).

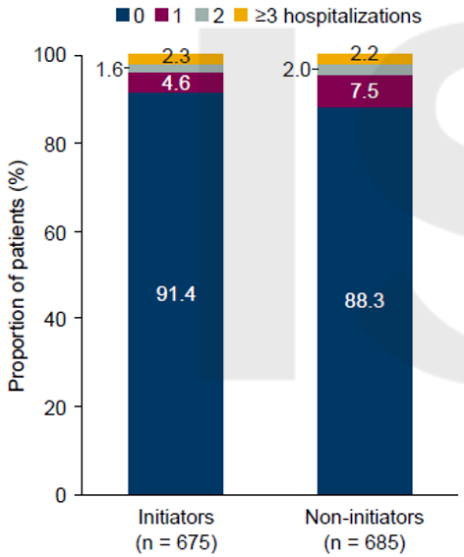
*After inverse probability of treatment weighting. Exacerbations are annualized numbers. Asthma control is the last available assessment. Outcomes were assessed at follow-up (after biologic initiation for initiators) using the closest available data to 12 months after the index date. The index date was the date of biologic initiation for initiators and ISAR enrolment for non-initiators.

AAER: Annualized asthma exacerbation rate; CI: Confidence interval; HR: Hazard ratio; IRR: Incidence rate ratio; LTOCS: Long-term oral corticosteroids; SD: Standard deviation

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

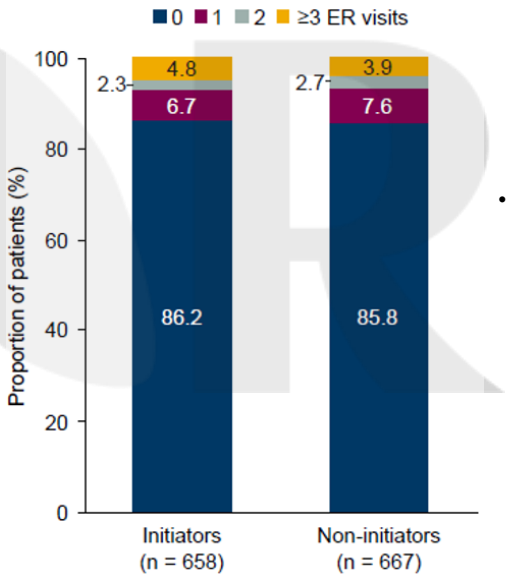
There were no substantive differences between biologic initiators and non-initiators in rates of healthcare resource utilization during the follow-up period*

Hospitalizations at follow-up*



- The annualized mean (SD) number of hospitalizations was 0.2 (0.9) for initiators and 0.2 (0.6) for non-initiators.

ER visits at follow-up*

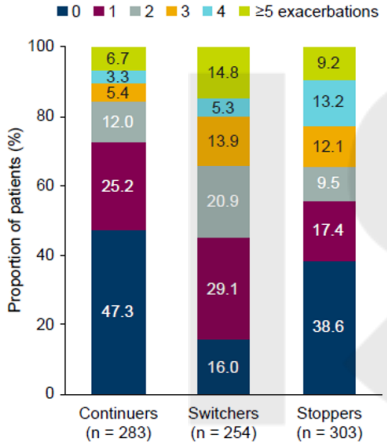


- The annualized mean (SD) number of ER visits was 0.4 (2.1) for initiators and 0.3 (1.2) for non-initiators.

*After inverse probability of treatment weighting. Hospitalizations and emergency room visits are annualized numbers. Outcomes were assessed at follow-up (after biologic initiation for initiators) using the closest available data to 12 months after the index date. The index date was the date of biologic initiation for initiators and ISAR enrolment for non-initiators.
ER: Emergency room; SD: Standard deviation
Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

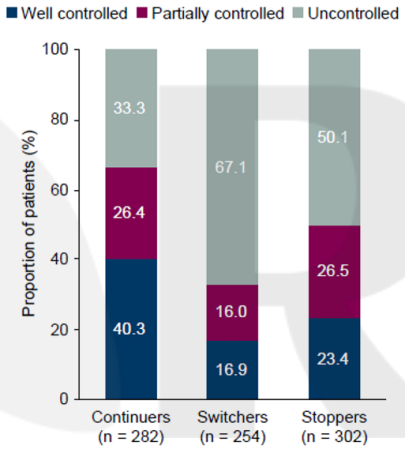
After biologic initiation, continuers had fewer exacerbations, lower LTOCS use and were less likely to have uncontrolled asthma than switchers or stoppers at follow-up*

Exacerbations at follow-up*



- The mean (SD) AAER was 1.4 (2.7) for continuers, 2.5 (2.9) for switchers and 2.0 (2.4) for stoppers.
- **Compared with continuers**, both **switchers** (HR: 2.59 [95% CI: 1.57, 4.27]) and **stoppers** (HR: 2.12 [95% CI: 1.11, 4.04]) had a **shorter time to first exacerbation**.
- >50% of continuers still had ≥1 exacerbation.

Asthma control at follow-up*



- **Switchers and stoppers were more likely to have uncontrolled asthma than continuers** (switchers versus continuers adjusted OR: 5.40 [95% CI: 3.12, 9.33]; stoppers versus continuers adjusted OR: 4.02 [95% CI: 2.32, 6.98]).
- One-third of continuers still had uncontrolled asthma.

LTOCS dose at follow-up*

- The mean (SD) daily LTOCS dose during the follow-up period was 6.2 (8.7) mg for continuers, 11.1 (11.4) mg for switchers and 10.8 (12.5) mg for stoppers.
- The **reduction in daily LTOCS dose was smaller for switchers and stoppers than for continuers** (adjusted β: 3.77 mg [95% CI: 1.71, 4.37] and 3.09 mg [95% CI: −0.27, 6.45] for switchers and stoppers, respectively, versus continuers).

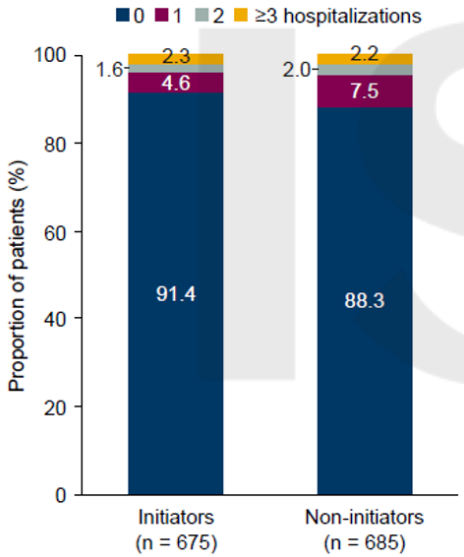
*After inverse probability of treatment weighting. Exacerbations are annualized numbers. Asthma control is the last available assessment. Outcomes were assessed at follow-up (after biologic initiation for initiators) using the closest available data to 12 months after the index date. The index date was the date of biologic initiation for initiators and ISAR enrolment for non-initiators.

AAER: Annualized asthma exacerbation rate; CI: Confidence interval; HR: Hazard ratio; OR: Odds ratio; LTOCS: Long-term oral corticosteroids; SD: Standard deviation

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

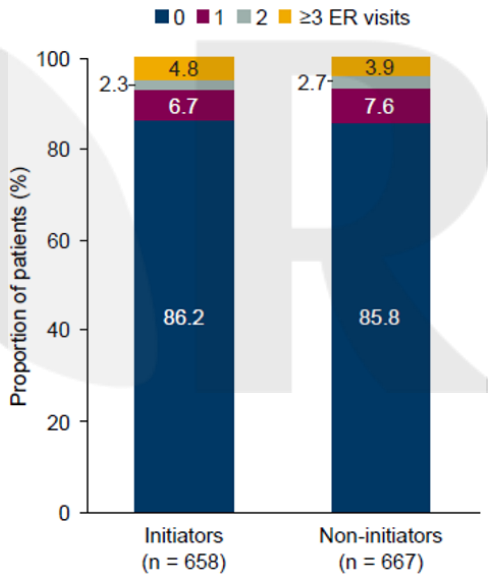
After biologic initiation, continuers had lower rates of healthcare resource utilization than switchers at follow-up*

Hospitalizations at follow-up*



- **Switchers had a higher rate of hospitalizations than continuers** (adjusted IRR [95% CI]: 2.58 [1.52, 4.37]; there was **no substantive difference between stoppers and continuers** (adjusted IRR [95% CI]: 1.20 [0.59, 2.42]).
- The annualized mean (SD) number of hospitalizations was 0.1 (0.5) for continuers, 0.5 (1.6) for switchers and 0.3 (1.1) for stoppers.

ER visits at follow-up*



- **Switchers had a higher rate of ER visits than continuers** (adjusted IRR [95% CI]: 2.12 [1.39, 3.24]; there was **no substantive difference between stoppers and continuers** (adjusted IRR [95% CI]: 1.10 [0.60, 2.01]).
- The annualized mean (SD) number of ER visits was 0.3 (1.1) for continuers, 1.3 (3.9) for switchers and 0.4 (1.7) for stoppers.

*After inverse probability of treatment weighting. Hospitalizations and emergency room visits are annualized numbers. Outcomes were assessed at follow-up (after biologic initiation for initiators) using the closest available data to 12 months after the index date. The index date was the date of biologic initiation for initiators and ISAR enrolment for non-initiators.
ER: Emergency room; SD: Standard deviation
Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res*. In press

Summary: Among biologic initiators, switching or stopping biologic therapy was associated with worse clinical outcomes than continuing the initial therapy

Key findings

- Biologic initiators had fewer exacerbations, lower LTOCS use and were less likely to have uncontrolled asthma than non-initiators during the follow-up period.
- After biologic initiation, continuers had fewer exacerbations, lower LTOCS use and were less likely to have uncontrolled asthma than switchers or stoppers.
- There remained a high unmet need among biologic continuers: >50% had ≥1 exacerbation and one-third had uncontrolled asthma during the follow-up period.

Practice change needed

- There is a need for regulators to increase and standardize access to biologics (e.g., reimbursement and availability of biomarker tests for phenotyping).
- Selecting the right initial biologic for continual therapy, accurate phenotyping and the optimal management of comorbidities are essential. Further research on how to predict patient response to biologic treatment is needed.
- Earlier initiation of biologic therapy or switching to alternatives may benefit patients who experience lack of clinical effectiveness with their initial biologic.

LTOCS = Long-term oral corticosteroids

Tran TN. et al., Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: the CLEAR Study. *Pragmat Obs Res.* In press

Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data

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Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Summary of the SOLAR I study

Objective

To estimate the **efficacy of biologic initiation on total OCS exposure** in patients with severe asthma

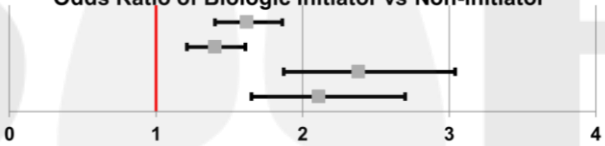
Methods

1,356 biologic initiators were propensity score-matched with 1,356 non-initiators from **ISAR (22 countries)**; 984 biologic initiators with 1,967 non-initiators from **OPCRD (UK)**. Multivariable generalized linear models were used.

Results

Likelihood of achieving low or zero OCS

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx vs Non-Bx) [95% CI]	P-value
Low Dose (0-5mg)	1st year	0.63 [0.62,0.65]	0.70 [0.68,0.72]	1.62 [1.40,1.86]	<0.001
	2nd year	0.71 [0.69,0.73]	0.73 [0.71,0.75]	1.40 [1.21,1.61]	<0.001
Zero Dose (0mg)	1st year	0.19 [0.17,0.21]	0.28 [0.26,0.30]	2.38 [1.87,3.04]	<0.001
	2nd year	0.25 [0.23,0.27]	0.33 [0.31,0.35]	2.11 [1.65,2.70]	<0.001



Likelihood of achieving optimal (>75%) total OCS reduction*

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx v Non-Bx) [95% CI]	P-value
Optimal Reduction*	1st year	0.21 [0.19,0.23]	0.37 [0.35,0.40]	2.35 [2.06,2.68]	<0.001
	2nd year	0.37 [0.34,0.40]	0.46 [0.44,0.49]	1.53 [1.35,1.73]	<0.001

Conclusions

Biologic initiation led to **substantial reduction in total OCS exposure**, particularly in the first year. Personalized OCS tapering strategies and early biologic intervention are needed.

*Optimal reduction: ≥75% reduction in total OCS daily dose from baseline (12 months prior to index date) to first or second year of follow-up.

Bx = Biologic; CI = Confidence interval; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids; OPCRD = Optimum Patient Care Research Database; OR = Odds ratio; Pr = Probability

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Aim and Methods

Rationale

For severe asthma (SA) management, real-world evidence on the effects of biologic therapies in reducing oral corticosteroid (OCS) use is limited.

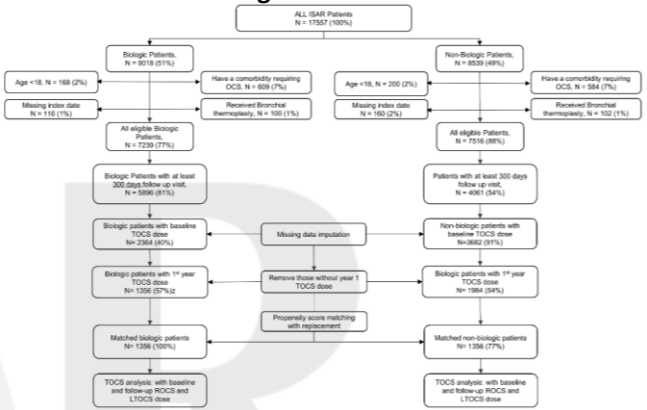
Aim

To estimate the effect of biologic initiation on total OCS (TOCS) exposure in SA patients from real-world specialist and primary care settings.

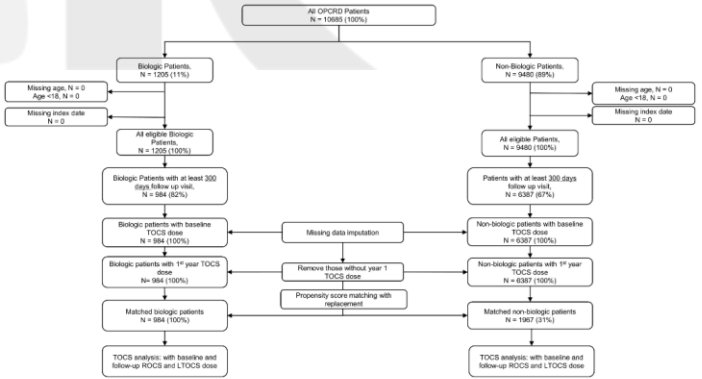
Methods

- **Data source:** The International Severe Asthma Registry (ISAR) and the Optimum Patient Care Research Database (OPCRD, primary care, UK)
- **Study population:** SA patients ≥ 18 years of age with adult biologic initiators propensity-score matched (PSM) with non-initiators (ISAR, 1:1; OPCRD, 1:2).
- **Statistical analyses:** Impact of biologic initiation on TOCS daily dose in the 1st and 2nd year follow-up period was estimated using multivariable generalized linear models.

Flow diagram of ISAR cohort



Flow diagram of OPCRD cohort



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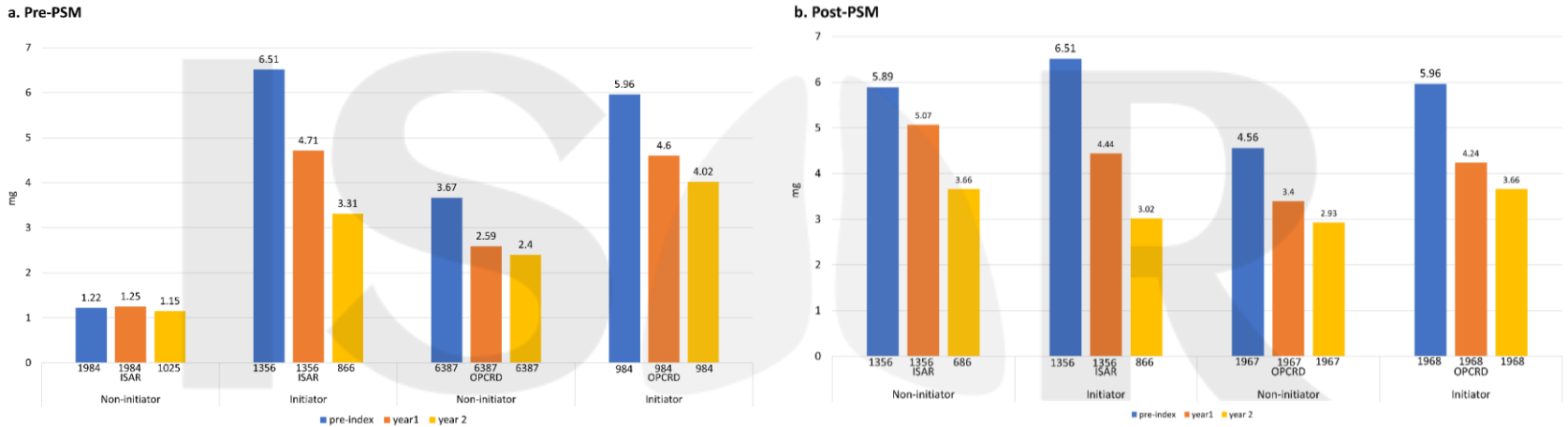
Biologic initiators had higher baseline TOCS daily doses compared to non-initiators in both ISAR and OPCRD cohorts

Distributions of mean OCS daily dose over time for patients with baseline and at least 1 year of follow-up period before and after propensity score matching.



- **Baseline Differences in TOCS Use**: In the matched sample, biologic initiators had higher baseline TOCS daily doses than non-initiators and these differences were adjusted for in regression analyses.
  - ISAR: 6.5 mg/day vs 5.9 mg/day (SMD = -0.09)
  - OPCRD: 6.0 mg/day vs 4.6 mg/day (SMD = -0.23)

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Balanced baseline characteristics after PSM and higher baseline TOCS daily doses among biologic initiators in both ISAR and OPCRD cohorts

Post-matching patient characteristics* for ISAR and OPCRD cohorts						
Demographics and disease characteristics	ISAR cohort			OPCRD cohort		
	Bx not initiated (n=1356)	Bx initiated (n=1356)	SMD	Bx not initiated (n=1967)	Bx initiated (n=984)	SMD
Age, y, mean (SD)	54.1 (15.7)	53.4 (13.8)	0.05	49.4 (16.8)	50.2 (15.4)	-0.05
Gender, n (%)			0.04			0.02
Male	533 (39.3%)	561 (41.4%)		767 (39.0%)	392 (39.8%)	
Female	823 (60.7%)	795 (58.6%)		1200 (61.0%)	592 (60.2%)	
BMI, mean (SD)	28.8 (6.3)	28.4 (5.9)	0.08	29.8 (7.9)	29.9 (8.2)	-0.01
Symptom control in the past 4 weeks, n (%)			0.08			0.06
Well controlled	148 (10.9%)	183 (13.5%)		96 (4.9%)	36 (3.7%)	
Partially controlled	220 (16.2%)	225 (16.6%)		683 (34.7%)	343 (34.9%)	
Uncontrolled	989 (72.9%)	948 (69.9%)		1188 (60.4%)	605 (61.5%)	
Blood eosinophil count (highest), mean (SD), mL	510.6 (429.1)	586.3 (494.8)	-0.16	838.8 (556.3)	825.7 (518.2)	-0.02
Percent of predicted FEV_1, mean (SD), %	73.2 (23.5)	73.3 (22.8)	0.00	74.5 (23.7)	74.7 (22.8)	-0.01
FEV_1/FVC Ratio, mean (SD)	0.7 (0.1)	0.7 (0.1)	0.04	0.7 (0.2)	0.7 (0.2)	0.04
Nasal polyps, n (%)	508 (37.5%)	551 (40.6%)	0.06	380 (19.3%)	204 (20.7%)	0.04
Use of LTRA, n (%)	354 (26.1%)	332 (24.5%)	0.04	53 (2.7%)	24 (2.4%)	0.02
Use of LAMA, n (%)	338 (24.9%)	287 (21.2%)	0.09	867 (44.1%)	464 (47.2%)	0.06
Use of long-term OCS, n (%)	654 (48.2%)	555 (40.9%)	0.15	437 (44.2%)	438 (44.5%)	0.01
Use of Anti-biotics, n (%)	----------	----------	----------	1400 (71.2%)	697 (70.8%)	0.01
Exacerbations in the past 12 months, mean (SD)	2.7 (2.9)	2.9 (2.8)	-0.04	2.8 (2.3)	3.1 (2.6)	-0.11
Severe exacerbations, mean (SD)	0.7 (1.7)	0.6 (1.4)	0.09	0.2 (0.5)	0.2 (0.5)	0.01
Pre-index daily OCS use, mean (SD), mg	5.9 (6.9)	6.5 (7.0)	-0.09	4.6 (5.1)	6.0 (7.0)	-0.23
1st year daily OCS use, mean (SD), mg	5.2 (7.5)	4.7 (8.0)	0.07	3.5 (4.9)	4.6 (7.0)	-0.18
2nd year daily OCS use, mean (SD), mg	3.7 (6.3)	3.3 (7.2)	0.07	3.1 (6.3)	4.0 (6.8)	-0.16

- **Balanced Baseline Characteristics**: After PSM, biologic initiators and non-initiators in both ISAR and OPCRD cohorts were well-balanced across most demographic and clinical characteristics, with SMDs generally <0.1
- **Higher Baseline and Follow-up OCS Use in Initiators**: Biologic initiators had slightly higher baseline daily OCS doses than non-initiators in both cohorts (ISAR: 6.5 vs 5.9 mg; OPCRD: 6.0 vs 4.6 mg), with these differences diminishing over time

SMD, standardized mean difference, BMI, body mass index, Bx, biologic, FEV_1, forced expiratory volume at 1 second, FVC, forced vital capacity, LAMA, Long-Acting Muscarinic Antagonists, LTRA, Leukotriene Receptor Antagonists, OCS, oral corticosteroids, SD, standard deviation.

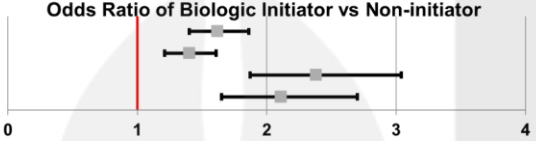
Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Biologic initiators were more likely to achieve low or zero OCS compared to non-biologic initiators during the 1st and 2nd year of follow-up

Association of biologic initiation on daily TOCS in the 1st and 2nd year among SA patients for low dose and zero dose outcome.

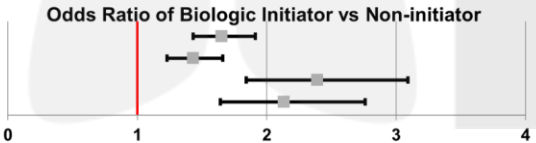
a. Original Result

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx vs Non-Bx) [95% CI]	P-value
Low Dose (0-5mg)	1st year	0.63 [0.62,0.65]	0.70 [0.68,0.72]	1.62 [1.40,1.86]	<0.001
	2nd year	0.71 [0.69,0.73]	0.73 [0.71,0.75]	1.40 [1.21,1.61]	<0.001
Zero Dose (0mg)	1st year	0.19 [0.17,0.21]	0.28 [0.26,0.30]	2.38 [1.87,3.04]	<0.001
	2nd year	0.25 [0.23,0.27]	0.33 [0.31,0.35]	2.11 [1.65,2.70]	<0.001



b. Result after removing Anti-IgE

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx vs Non-Bx) [95% CI]	P-value
Low Dose (0-5mg)	1st year	0.63 [0.61,0.65]	0.70 [0.67,0.72]	1.65 [1.43,1.91]	<0.001
	2nd year	0.70 [0.68,0.72]	0.73 [0.71,0.76]	1.43 [1.23,1.66]	<0.001
Zero Dose (0mg)	1st year	0.19 [0.17,0.20]	0.29 [0.27,0.31]	2.39 [1.84,3.09]	<0.001
	2nd year	0.24 [0.22,0.26]	0.34 [0.31,0.37]	2.13 [1.64,2.76]	<0.001



- **Higher Odds of Achieving Low TOCS**: Biologic initiators had significantly higher odds of reaching a low daily OCS dose (≤5 mg/day) compared to non-initiators in both the 1st (OR: 1.62; 70% vs 63%) and 2nd year (OR: 1.40; 73% vs 71%) of follow-up
- **Greater Chance of TOCS Cessation**: Biologic use was associated with a markedly higher likelihood of achieving zero TOCS use in both years—1st year: OR 2.38 (28% vs 19%), 2nd year: OR 2.11 (33% vs 25%); excluding Anti-IgE initiators had minimal impact on these estimates.

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Biologics had a significantly higher likelihood of achieving optimal reduction with stronger effects observed without Anti-IgE

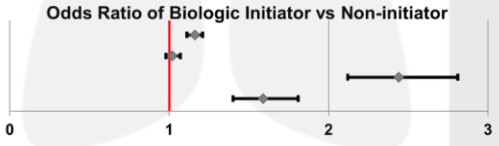
Association of biologic initiation on daily TOCS in the 1st and 2nd year among SA patients for any reduction and optimal reduction result

a. Original Result

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx v Non-Bx) [95% CI]	P-value
Any Reduction*	1st year	0.68 [0.66,0.70]	0.76 [0.73,0.78]	**1.13 [1.09,1.19]**	**<0.001**
	2nd year	0.79 [0.76,0.81]	0.78 [0.76,0.80]	1.00 [0.96,1.05]	0.896
Optimal Reduction†	1st year	0.21 [0.19,0.23]	0.37 [0.35,0.40]	**2.35 [2.06,2.68]**	**<0.001**
	2nd year	0.37 [0.34,0.40]	0.46 [0.44,0.49]	**1.53 [1.35,1.73]**	**<0.001**

b. Result after removing Anti-IgE

		No Bx, Pr [95%CI]	Bx, Pr [95%CI]	OR (Bx v Non-Bx) [95% CI]	P-value
Any Reduction*	1st year	0.69 [0.67,0.71]	0.78 [0.76,0.80]	**1.16 [1.11,1.21]**	**<0.001**
	2nd year	0.79 [0.76,0.81]	0.80 [0.78,0.82]	1.02 [0.98,1.07]	0.304
Optimal Reduction†	1st year	0.21 [0.19,0.22]	0.38 [0.35,0.41]	**2.44 [2.12,2.81]**	**<0.001**
	2nd year	0.37 [0.34,0.40]	0.48 [0.44,0.51]	**1.59 [1.40,1.81]**	**<0.001**



- **Higher Likelihood of Optimal Reduction**: Biologic users had significantly greater odds of achieving >75% reduction in TOCS use than non-users—OR: 2.35 (37% vs 21%) in Year 1 and OR: 1.53 (46% vs 37%) in Year 2.
- **Stronger Effect Without Anti-IgE**: Excluding Anti-IgE users further increased the odds—Year 1 OR: 2.44; Year 2 OR: 1.59—indicating a more pronounced benefit in non–Anti-IgE biologic users.

*Any reduction: any reduction in TOCS daily dose from baseline (12 months prior to index date) to 1st or 2nd year of follow-up. †Optimal reduction: ≥75% reduction in TOCS daily dose from baseline (12 months prior to index date) to 1st or 2nd year of follow-up.

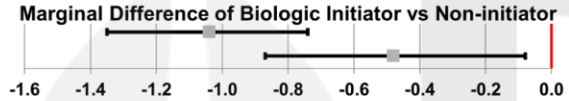
Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Biologics was associated with a greater and continuous reduction in the TOCS daily dose in both the 1st and 2nd year, with stronger effects observed without Anti-IgE

Association of biologic initiation on daily TOCS in the 1st and 2nd year among SA patients for absolute change.

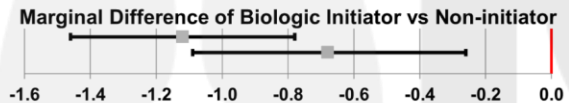
a. Original Result

		No Bx, mg/d [95%CI]	Bx, mg/d [95%CI]	MD (Bx vs Non-Bx) [95% CI]	P-value
Absolute Change	1st year	-1.40 [-1.57,-1.22]	-2.44 [-2.70,-2.18]	-1.04 [-1.35,-0.74]	<0.001
	2nd year	-2.64 [-2.95,-2.33]	-3.12 [-3.40,-2.84]	-0.48 [-0.87,-0.08]	0.017



b. Result after removing Anti-IgE

		No Bx, mg/d [95%CI]	Bx, mg/d [95%CI]	MD (Bx vs Non-Bx) [95% CI]	P-value
Absolute Change	1st year	-1.46 [-1.63,-1.29]	-2.58 [-2.87,-2.29]	-1.12 [-1.46,-0.78]	<0.001
	2nd year	-2.67 [-2.99,-2.36]	-3.35 [-3.66,-3.04]	-0.68 [-1.09,-0.26]	0.002

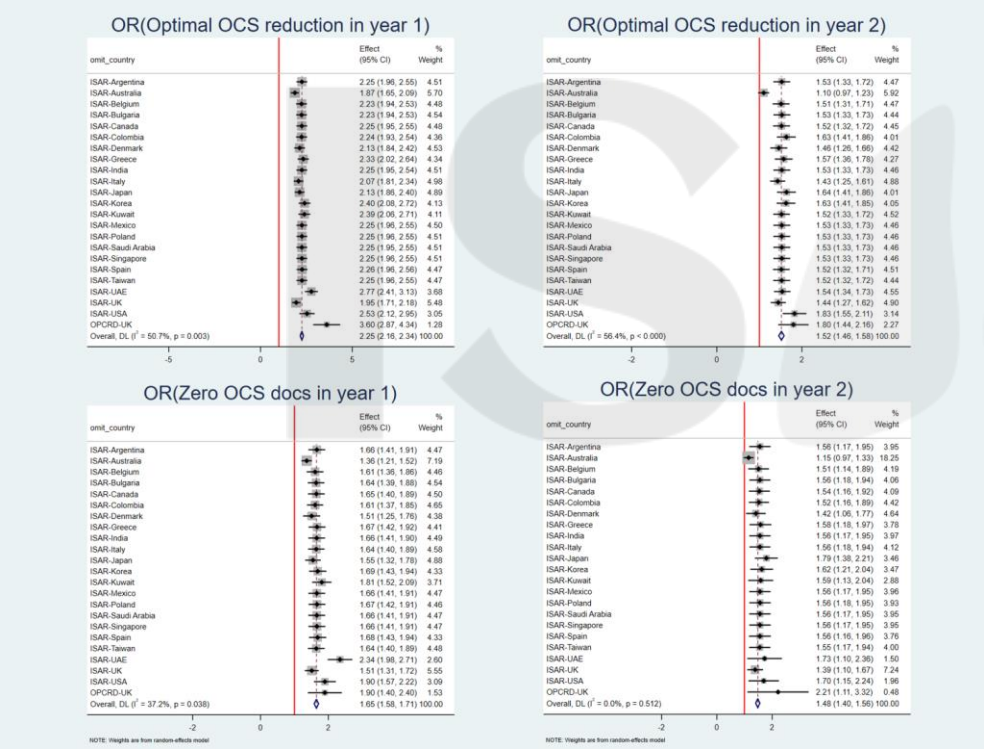


- **Greater TOCS Reduction with Biologics**: Biologic initiators experienced a larger reduction in daily TOCS dose compared to non-initiators—1st year: -2.44 mg/day vs -1.40 mg/day (excess reduction: -1.04 mg/day), and 2nd year: -3.12 mg/day vs -2.64 mg/day (excess reduction: -0.48 mg/day).
- **Impact of Excluding Anti-IgE Initiators**: Removing Anti-IgE users slightly increased the excess TOCS reductions—1st year: -1.12 mg/day, 2nd year: -0.68 mg/day—suggesting even greater benefit among non–Anti-IgE biologic users.

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Robustness across countries: Benefits of biologic initiation in achieving zero OCS and optimal reduction (>75%)

Jackknife sensitivity for zero OCS and optimal reduction (>75%) in the 1st and 2nd year.



- **Consistent Findings Across Settings**: Leave-one-country-out sensitivity analysis confirmed the robustness of biologic-associated OCS reduction, with no single country materially influencing the results.
- **Sustained Effects**: Pooled ORs for complete TOCS cessation were 1.65 (1st year) and 1.48 (2nd year), and for optimal reduction were 2.25 (1st year) and 1.52 (2nd year)—closely matching the main analysis.

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032

Conclusions

- **Biologics significantly reduce OCS use**: Biologic initiation in severe asthma patients led to sustained reductions in TOCS intake, with 2–3 times higher odds of achieving optimal reduction or complete cessation across real-world settings.
- **Need for optimized tapering strategies**: Findings support the development of pragmatic trials and updated clinical guidelines to implement biologic-facilitated, personalized OCS tapering strategies in routine care.
- **Broaden access and explore alternatives**: For patients not eligible or with limited access to biologics, revisiting eligibility criteria and addressing steroid-masking effects are essential, alongside identifying alternative therapies to reduce long-term OCS burden.

Chen W et al. Impact of biologic initiation on oral corticosteroid use in the International Severe Asthma Registry and the Optimum Patient Care Research Database: a pooled analysis of real-world data. *JACI: In Practice* 2025; doi: 10.1016/j.jaip.2025.04.032


ORIGINAL ARTICLE

Prevention of Cardiovascular and Other Systemic Adverse Outcomes in Patients with Asthma Treated with Biologics

Abstract

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SOLAR II: Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics

Mohsen Sadatsafavi, Trung N. Tran, Ghislaine Scelo, Ming-Ju Tsai, John Busby, Benjamin Emmanuel, Liam G. Heaney, Christine Jenkins, Flavia Hoyte, Giorgio Walter Canonica, Rohit Katial, Enrico Heffler, Eileen Wang, Francesca Puggioni, Michael E. Wechsler, Ledit R. F. Ardusso, Jorge Máspero, Martin Sivori, Cathy Emmas, Andrew N. Menzies- Gow, Neda Stjepanovic, Sinthia Z. Bosnic-Anticevich, Belinda Cochrane, Eve Denton, Peter G. Gibson, Mark Hew, Peter G. Middleton, Matthew J. Peters, Guy G. Brusselle, Renaud Louis, Florence Schleich, George C. Christoff, Todor A. Popov, Celine Bergeron, Mohit Bhutani, Kenneth R. Chapman, Andréanne Côté, Simon Couillard, Delbert R. Dorscheid, Libardo Jiménez- Maldonado, Ivan Solarte, Carlos A. Torres-Duque, Susanne Hansen, Celeste M. Porsbjerg, Charlotte Suppli Ulrik, Alan Altraja, Arnaud Bourdin, Konstantinos P. Exarchos, Athena Gogali, Konstantinos Kostikas, Michael P. Makris, Andriana I. Papaioannou, Patrick D. Mitchell, Takashi Iwanaga, Tatsuya Nagano, Yuji Tohda, Mona S. Al-Ahmad, Désirée Larenas-Linnemann, Bernt Bøgvald Aarli, Piotr Kuna, Cláudia Chaves Loureiro, Riyad Al-Lehebi, Adeeb A. Bulkhi, Wenjia Chen, Yah Ru Juang, Mariko Siyue Koh, Anqi Liu, Chin Kook Rhee, Borja G. Cosio, Luis Perez-de-Llano, Diahn-Warng Perng, Chau- Chyun Sheu, Hao-Chien Wang, Bassam Mahboub, Laila Salameh, David J. Jackson, Pujan H. Patel, Paul E. Pfeffer, Njira Lugogo, Roy Alton Pleasants, Aaron Beastall, Lakmini Bulathsinhala, Victoria Carter, Nevaashni Eleangovan, Kirsty Fletton, John Townend, Ruth B. Murray and David B. Price, on behalf of the ISAR SOLAR II Working Group

Sadatsafavi M, Tran TN, Scelo G, Tsai M-J, Busby J, Emmanuel B, et al; on behalf of the ISAR SOLAR II Working Group. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Summary of the SOLAR II study

Objective

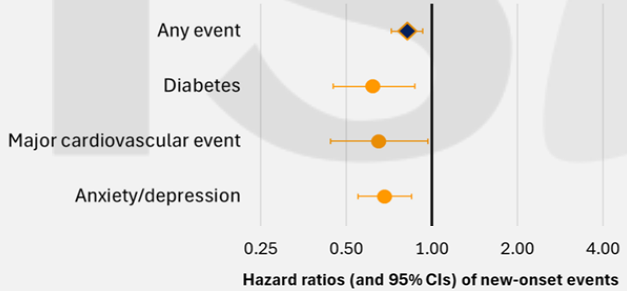
To compare the risk of developing **new-onset OCS-related adverse outcomes** between biologic initiators and non-initiators

Methods

5,690 biologic initiators and 37,218 non-initiators from **ISAR (16 countries) and OPCRD (UK)** were included. Inverse probability of treatment weighting and weighted Cox proportional hazard models were used.

Results

Association between biologic initiation and risk of OCS-related adverse outcomes*



New-onset adverse outcomes	Group	N (total)	N (events)	Median time at risk (yrs)	HR (95% CI)	p
Any event	Non-initiators	36,845	7,062	1.59	0.82 (0.72-0.93)	0.002
	Biologic initiators	5,633	736	1.95		
Diabetes	Non-initiators	31,650	1,139	1.99	0.62 (0.45-0.87)	0.006
	Biologic initiators	5,010	90	2.23		
Major cardiovascular event	Non-initiators	36,779	883	1.99	0.65 (0.44-0.97)	0.034
	Biologic initiators	5,258	63	2.25		
Anxiety/depression	Non-initiators	24,004	2,966	1.71	0.68 (0.55-0.85)	0.001
	Biologic initiators	4,517	170	2.09		

Major cardiovascular event includes heart failure, myocardial infarction, or cerebrovascular accident.

Conclusions

Biologics **prevent new-onset OCS-related adverse outcomes** in patients with severe asthma. Timely biologic initiation is needed to minimize OCS use and withdraw long-term OCS.

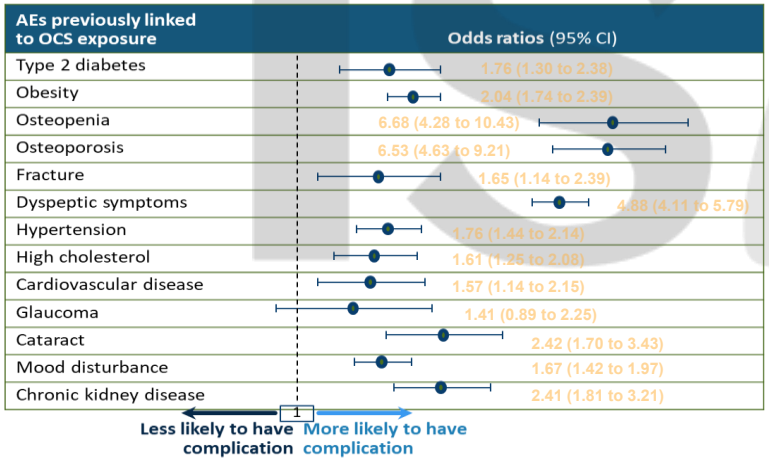
*Covariates: age, sex, smoking status, BMI, LTOCS status, exacerbation rate, asthma control, blood eosinophil count, nasal polyposis, percent predicted FEV1, FEV1/FVC ratio, index date, data source (OPCRD vs. ISAR), data collection system (EMR vs. eCRF), and country. BMI = Body mass index; CI = Confidence interval; eCRF = Electronic case report form; EMR = Electronic medical record; FEV1 = Forced expiratory volume in 1 second; FEV1/FVC = FEV1 to forced vital capacity (FVC) ratio; HR = Hazard ratio; IPTW = Inverse probability of treatment weighting; ISAR = International Severe Asthma Registry; LTOCS = Long-term oral corticosteroids; OCS = Oral corticosteroids; OPCRD = Optimum Patient Care Research Database

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

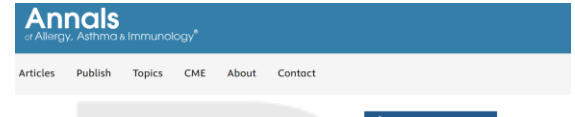
Background and Rationale: OCS exposure and association with health conditions

opcrd OPTIMUM PATIENT CARE RESEARCH DATABASE + **BTS Difficult Asthma Registry (now the UKSAR)**

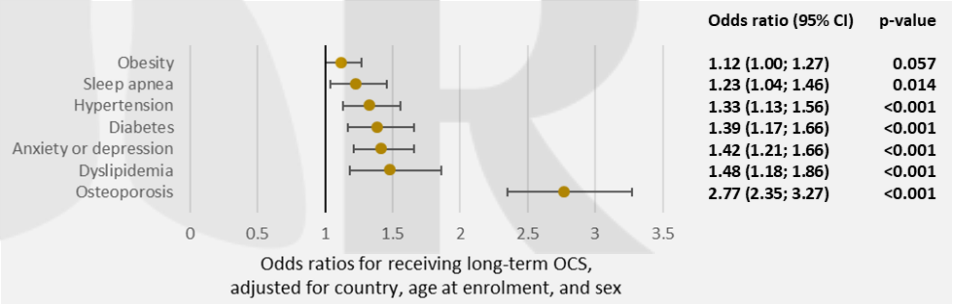
Severe asthma cohort requiring frequent OCS (n=808) **compared with non-asthma controls** (n=2412)



ISAR



Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry

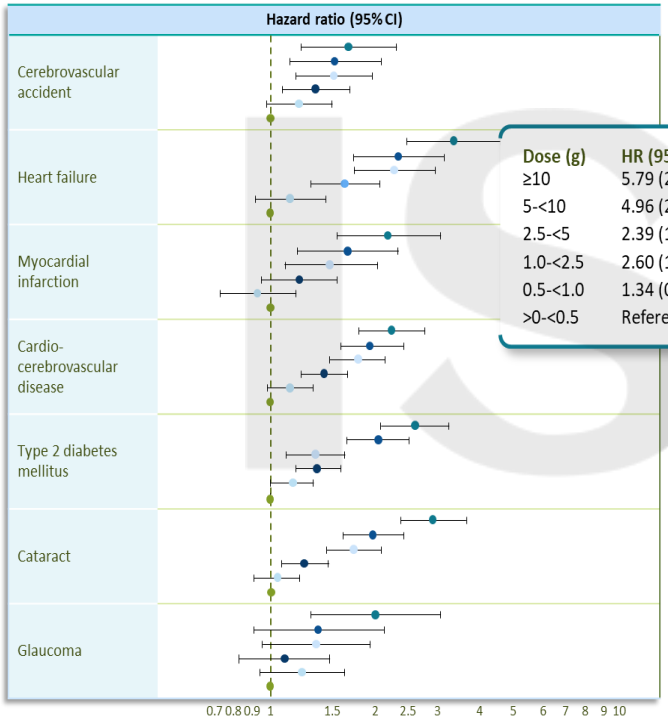


67% of patients had **at least 1 potentially OCS-related comorbidity**.

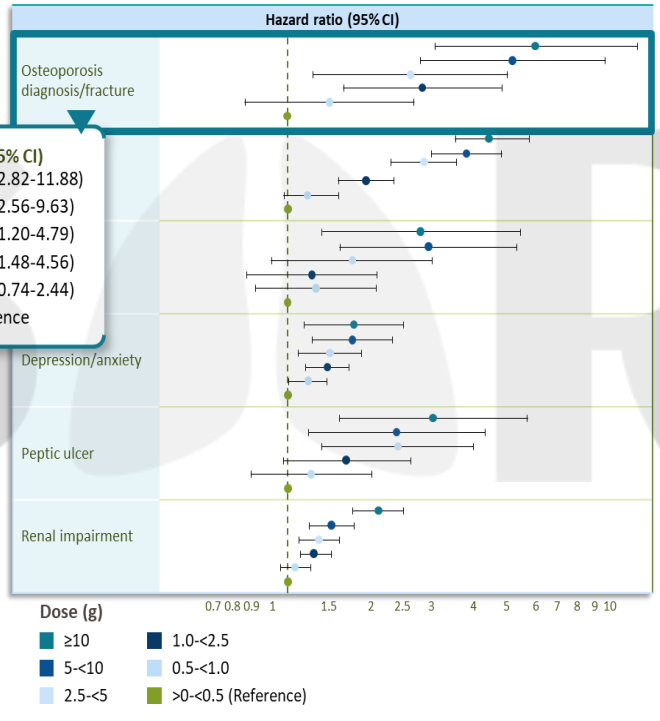
AE = Adverse event; BTS = British Thoracic Society; CI = Confidence interval; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroid; OPCRD = Optimum Patient Care Research Database; UKSAR = UK Severe Asthma Registry

Sweeney J, et al. Thorax 2016;71:339–346; [2]Price D, et al. J Asthma Allergy 2018;11:193–204; Scelo G et al., Ann. Allergy Asthma Immunol 2023,132, issue 1, 42-53, DOI https://doi.org/10.1016/j.anai.2023.08.021

Background and Rationale: Dose-response OCS exposure and adverse events



Dose (g)	HR (95% CI)
≥10	5.79 (2.82-11.88)
5-<10	4.96 (2.56-9.63)
2.5-<5	2.39 (1.20-4.79)
1.0-<2.5	2.60 (1.48-4.56)
0.5-<1.0	1.34 (0.74-2.44)
>0-<0.5	Reference



opcrd + CPRD

GLOBAL INITIATIVE FOR ASTHMA

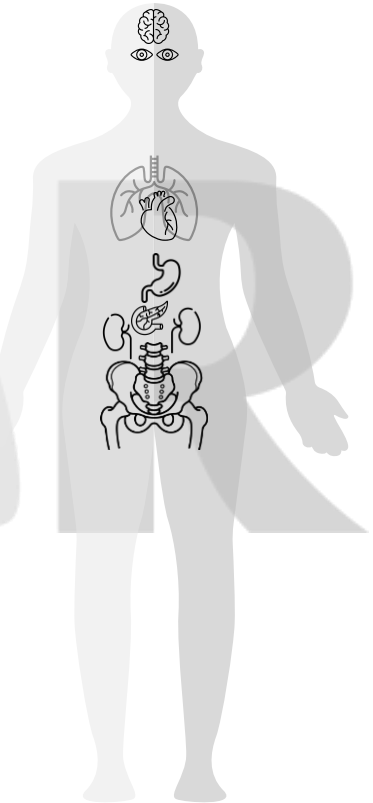
"Even occasional short courses of OCS are associated with **increased risk** (osteoporosis, diabetes, cataract etc)"[1]

AE = Adverse event; CI = Confidence interval; CPRD = Clinical Practice Research Datalink; GINA = Global Initiative for Asthma; OCS: Oral Corticosteroids; OPCRD = Optimum Patient Care Research Database

[1]GINA. What's new in GINA 2021? Available from: https://ginasthma.org/wp-content/uploads/2021/04/Whats-new-in-GINA-2021_final.pdf (Accessed 16 May 2025); [2]Price D, et al. *J Asthma Allergy* 2018;11:193–204

Study Aim

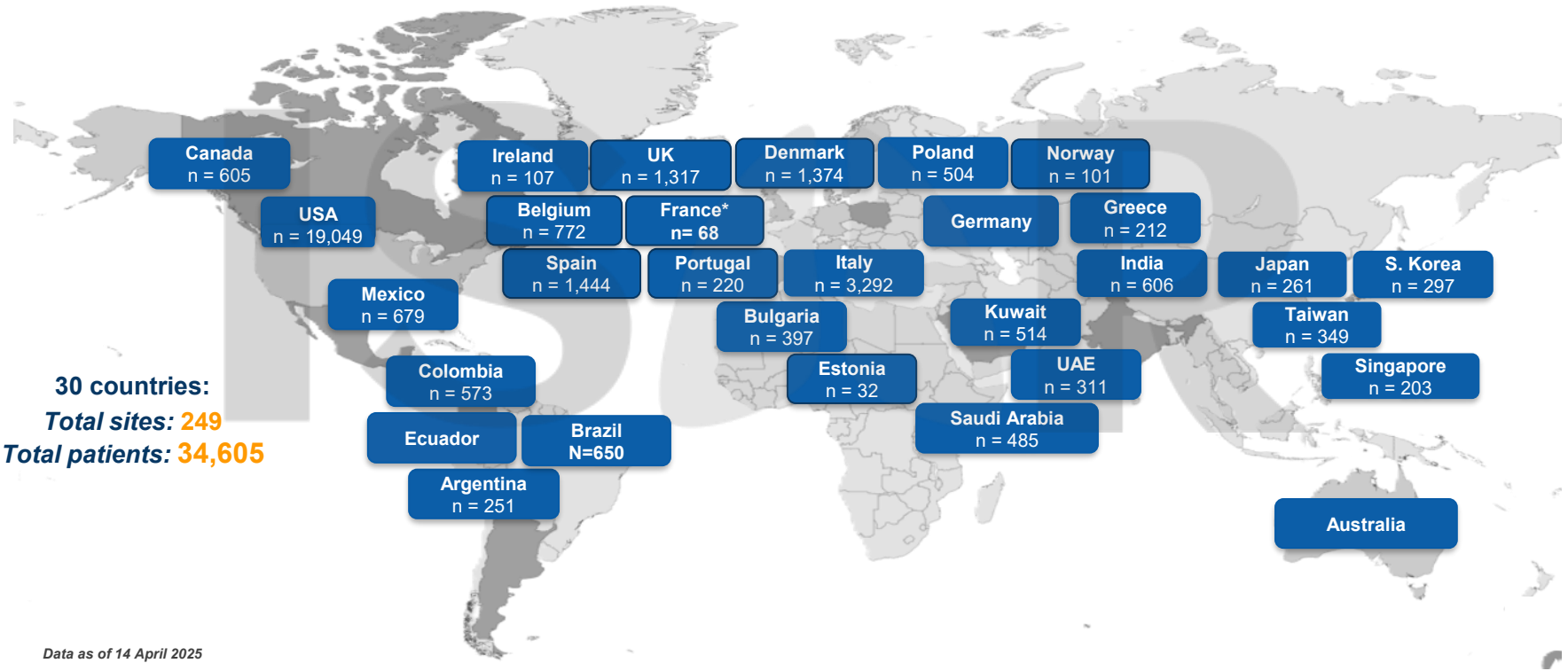
To investigate whether initiating biologics **mitigates risk of developing OCS-related adverse outcomes** in patients with severe asthma in real life



OCS = Oral corticosteroids

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

The International Severe Asthma Registry (ISAR), 2017 – today



30 countries:

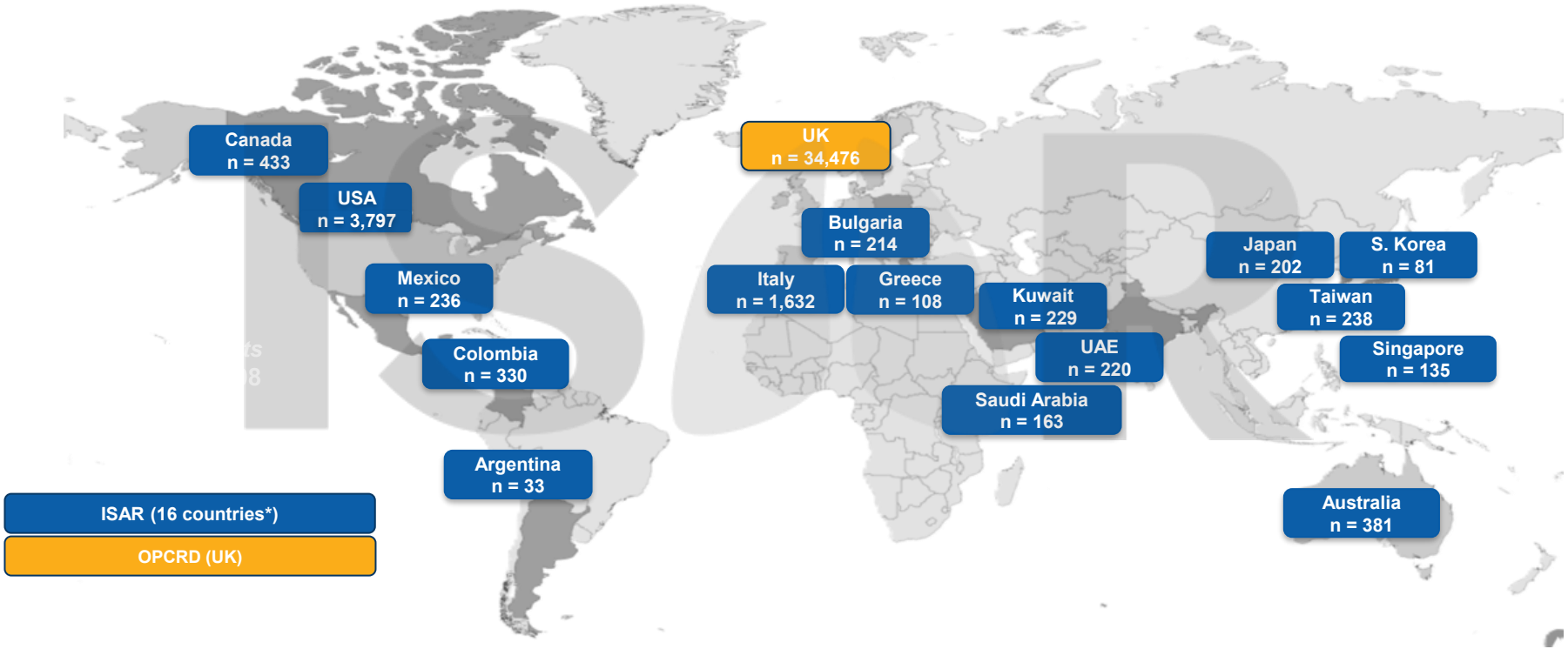
Total sites: **249**

Total patients: **34,605**

Data as of 14 April 2025

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

SOLAR study data sources: ISAR and OPCRD



*ISAR countries specifically collecting OCS-related adverse event data

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Study design

Index date (2008 – 2024)

- Biologic initiation for biologic initiators
- Earliest clinical visit at which severe asthma criteria met for non-initiators

≥1 follow-up visit

- New OCS-related adverse outcome
- Loss to follow-up
- Censored at 5-years post-index date

ISAR + opcrd

- **Inclusion criteria:**
  - ≥18 years of age at index date
  - Severe asthma
- **Exclusion criteria:**
  - Confounding medical conditions requiring systemic corticosteroids*

New-onset OCS-related adverse outcomes (*a priori* defined):

- Diabetes
- Major cardiovascular event (heart failure, myocardial infarction, cerebrovascular accident)
- Anxiety/depression
- Cataract
- Sleep apnea
- Pneumonia
- Pulmonary embolism/ venous thromboembolism
- Glaucoma
- Renal failure
- Osteoporosis
- Peptic ulcer

*Confounding medical conditions included cystic fibrosis, alpha-1-antitrypsin deficiency, systemic lupus erythematosus, Crohn's disease or ulcerative colitis or inflammatory bowel disease, dermatomyositis, giant cell arteritis, immune deficiency, myasthenia gravis, pemphigus, polymyalgia rheumatica, sarcoidosis, vasculitis. ISAR: International Severe Asthma Registry; OCS: Oral Corticosteroids; OPCRD: Optimum Patient Care Research Database

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Statistical analyses

Baseline characteristics summarized descriptively

Inverse probability of treatment weighting (IPTW) to improve comparability between groups

- Variables: age, sex, smoking, BMI, LTOCS status, annual exacerbation rates, asthma control, BEC, nasal polyposis, percent predicted FEV_1, FEV_1/FVC ratio, index date, data source (ISAR, OPCRD), and data collection system (EMR, eCRF)

Weighted Cox proportional hazard models

- To estimate the HRs and 95% CIs of developing any OCS-related adverse outcome
- Covariates: all variables used in the IPTW computations plus country

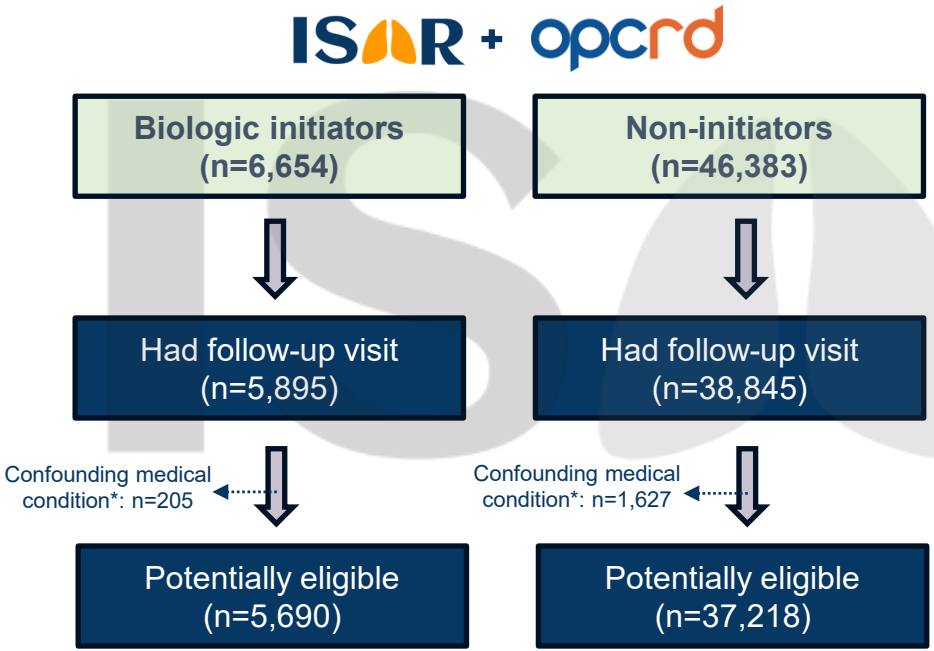
Statistical testing

- Comparisons were 2-sided, significance at a p-value level of 0.05

BEC = Blood eosinophil count; BMI = Body mass index; CI = Confidence interval; eCRF = Electronic case report form; EMR = Electronic medical record; FEV1 = Forced expiratory volume in 1 second; FEV1/FVC = FEV1 to forced vital capacity (FVC) ratio; HR = Hazard ratio; IPTW = Inverse probability of treatment weighting; LTOCS = Long-term oral corticosteroids; OCS = Oral corticosteroids

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Patient flow



Median (Q1, Q3) follow-up duration:

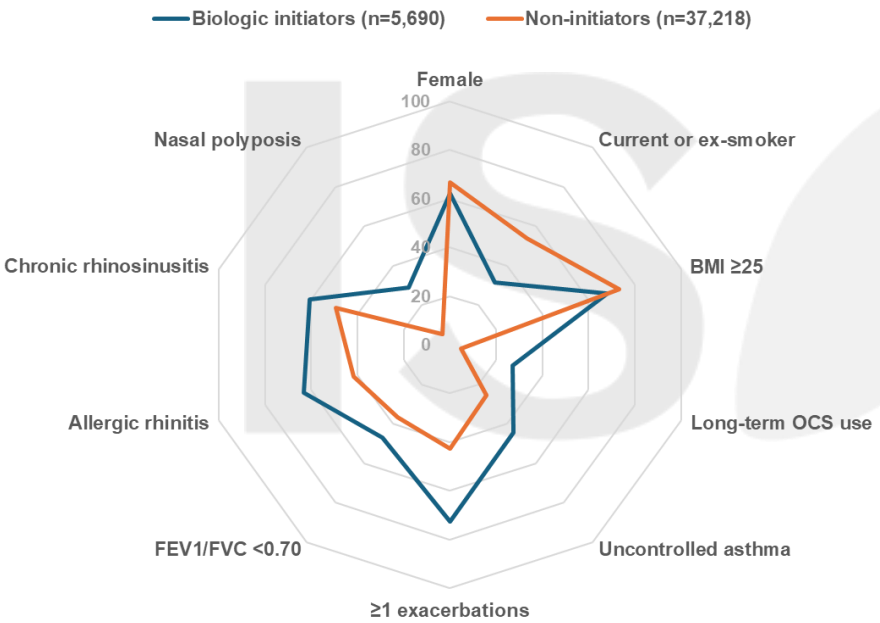
- Biologic initiators: 2.8 (1.3, 4.7) years
- Non-initiators: 2.0 (1.0, 3.8) years

*Confounding medical conditions included cystic fibrosis, alpha-1-antitrypsin deficiency, systemic lupus erythematosus, Crohn's disease or ulcerative colitis or inflammatory bowel disease, dermatomyositis, giant cell arteritis, immune deficiency, myasthenia gravis, pemphigus, polymyalgia rheumatica, sarcoidosis, vasculitis. ISAR = International Severe Asthma Registry; OPCRD = Optimum Patient Care Research Database

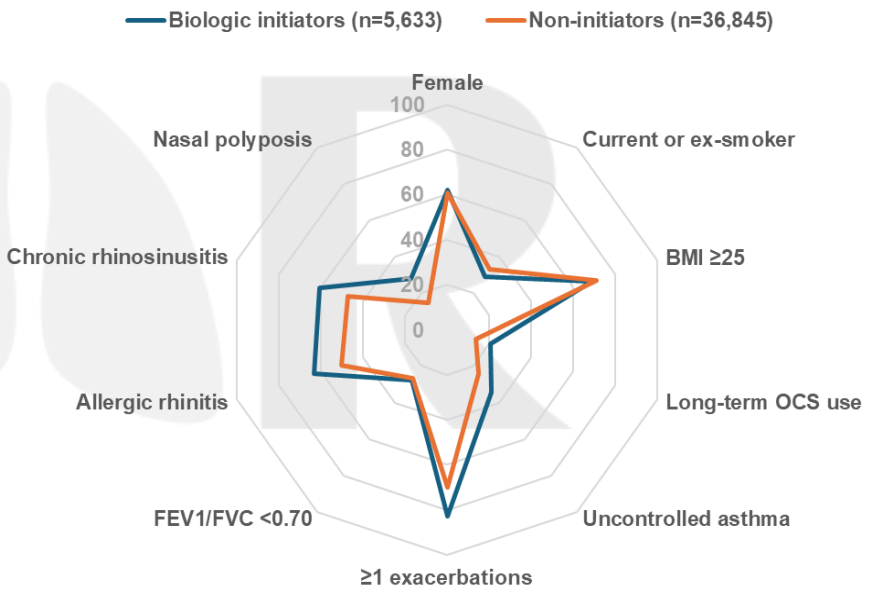
Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Results: Baseline characteristics (pre- and post-IPTW)

Pre-IPTW



Post-IPTW



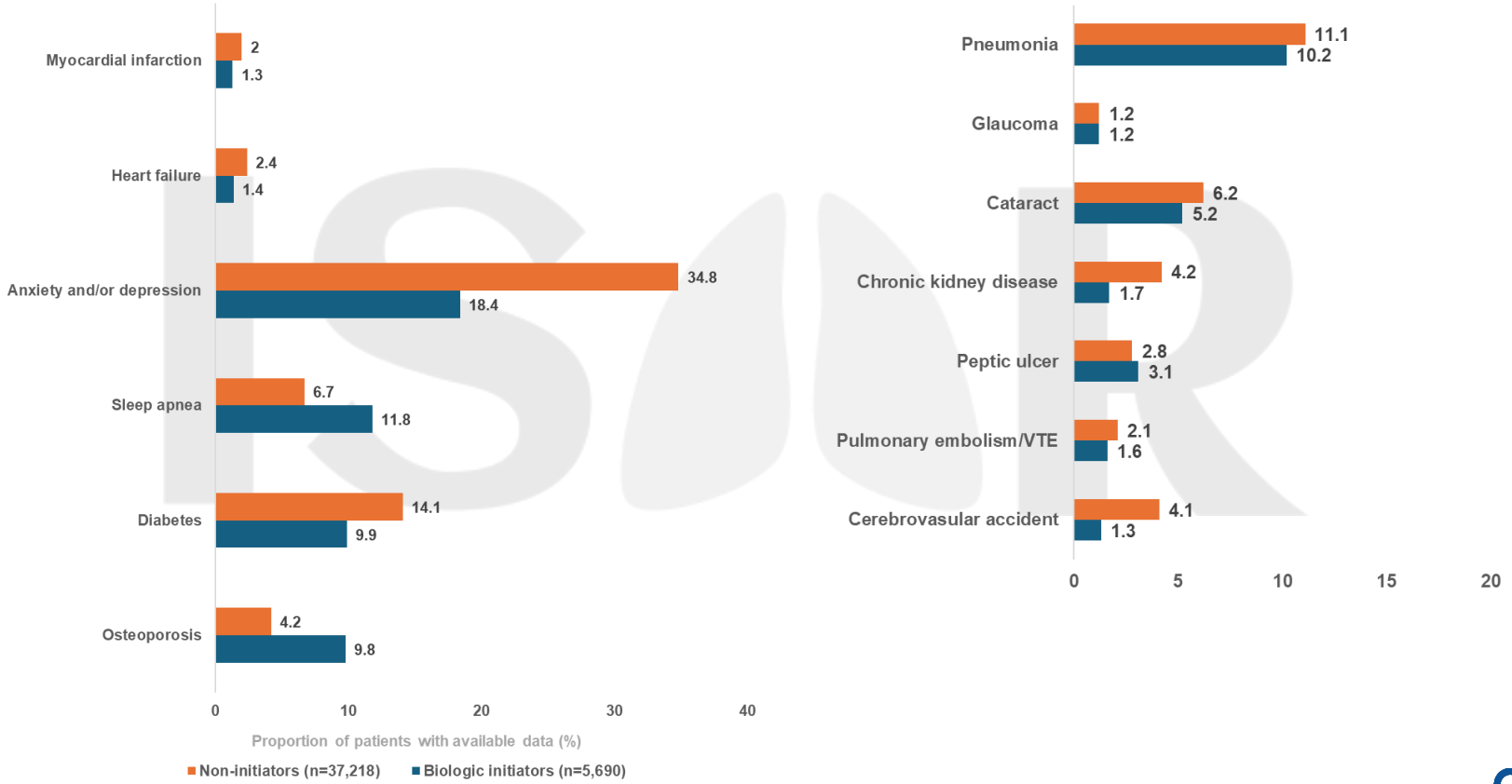
Age (mean, SD):

- Biologic initiators: 51.3 (14.4) years
- Non-initiators: 48.9 (15.7) years

BMI: Body mass index; FEV1: Forced expiratory volume in one second; FVC = Forced vital capacity; IPTW = Inverse probability of treatment weighting; OCS = Oral corticosteroids; SD = Standard deviation; T2 = Type 2

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

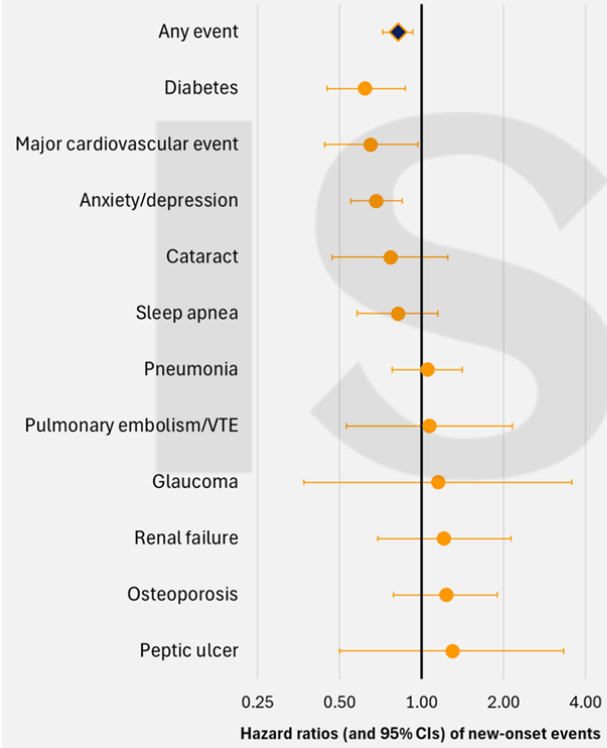
Results: Baseline characteristics



Prevalent (historical) cases of OCS-related adverse events at the index date were excluded from the study analyses. VTE = Venous thromboembolism

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Results: Association between biologic initiation and risk of OCS-related adverse outcomes



New-onset adverse outcomes	Group	N (total)	N (events)	Median time at risk (yrs)	HR (95% CI)	p
Any event	Non-initiators	36,845	7,062	1.59	0.82 (0.72-0.93)	0.002
	Biologic initiators	5,633	736	1.95		
Diabetes	Non-initiators	31,650	1,139	1.99	0.62 (0.45-0.87)	0.006
	Biologic initiators	5,010	90	2.23		
Major cardiovascular event	Non-initiators	36,779	883	1.99	0.65 (0.44-0.97)	0.034
	Biologic initiators	5,258	63	2.25		
Anxiety/depression	Non-initiators	24,004	2,966	1.71	0.68 (0.55-0.85)	0.001
	Biologic initiators	4,517	170	2.09		
Cataract	Non-initiators	34,542	463	2.03	0.77 (0.47-1.25)	0.293
	Biologic initiators	5,224	69	2.23		
Sleep apnea	Non-initiators	34,281	720	1.97	0.82 (0.58-1.15)	0.242
	Biologic initiators	4,863	102	2.23		
Pneumonia	Non-initiators	36,803	881	2.00	1.05 (0.78-1.41)	0.752
	Biologic initiators	5,383	154	2.23		
Pulmonary embolism/VTE	Non-initiators	35,994	211	2.03	1.07 (0.53-2.16)	0.840
	Biologic initiators	5,162	23	2.24		
Glaucoma	Non-initiators	36,361	87	2.03	1.15 (0.37-3.56)	0.810
	Biologic initiators	5,447	15	2.28		
Renal failure	Non-initiators	35,275	437	2.03	1.21 (0.69-2.13)	0.514
	Biologic initiators	5,480	36	2.29		
Osteoporosis	Non-initiators	35,238	329	2.03	1.23 (0.79-1.90)	0.352
	Biologic initiators	4,885	103	2.18		
Peptic ulcer	Non-initiators	35,791	113	2.03	1.30 (0.50-3.33)	0.600
	Biologic initiators	5,396	17	2.28		

CI: confidence interval; OCS: oral corticosteroid, HR: hazard ratio; VTE: venous thromboembolism, yrs: years;
Major cardiovascular event includes heart failure, myocardial infarction, or cerebrovascular accident.

Covariates: age, sex, smoking status, BMI, LTOCS status, exacerbation rate, asthma control, blood eosinophil count, nasal polyposis, percent predicted FEV_1, FEV_1/FVC ratio, index date, data source (OPCRD vs. ISAR), data collection system (EMR vs. eCRF), and country.

BMI = Body mass index; CI = Confidence interval; eCRF = Electronic case report form; EMR = Electronic medical record; FEV1 = Forced expiratory volume in 1 second; FEV1/FVC = FEV1 to forced vital capacity (FVC) ratio; HR = Hazard ratio; IPTW = Inverse probability of treatment weighting; ISAR = International Severe Asthma Registry; LTOCS = Long-term oral corticosteroids; OCS = Oral corticosteroids; OPCRD = Optimum Patient Care Research Database

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Results: Benchmarking, implications for payors

Disease	Reduced risk of disease with available disease-specific agents	Reduced risk of disease with biologics (SOLAR II results[1])
Major adverse cardiovascular events (MACE)	Statins[2] CVD: 25%; CHD: 27%; Stroke: 22%	Biologics Major cardiovascular events: 35%
Diabetes	Metformin[3] 35%*	Biologics 38%

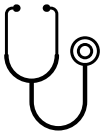
*Metformin significantly reduces the odds of developing diabetes mellitus by 35% among individuals with pre-diabetes versus control groups. CHD = Coronary heart disease; CVD = Cardiovascular disease; OCS = Oral corticosteroids

[1]Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med.* 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.; [2]Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013, Issue 1. Art. No.: CD004816; [3]Patel D, Ayesha IE, Monson NR, et al. The Effectiveness of Metformin in Diabetes Prevention: A Systematic Review and Meta-Analysis. *Cureus* 2023;15(9):e46108

Conclusions

Biologic initiators had 18% lower risk of developing any OCS-related adverse outcome (versus non-initiators)

Short follow-up time (median ~2 years) might explain the lack of signal for outcomes like osteoporosis and cataract

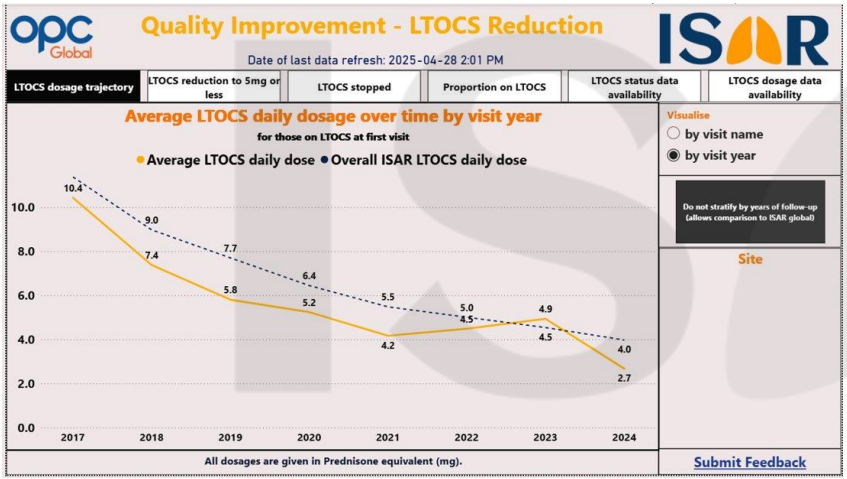


Timely biologic initiation to minimise OCS use required and withdraw long-term OCS

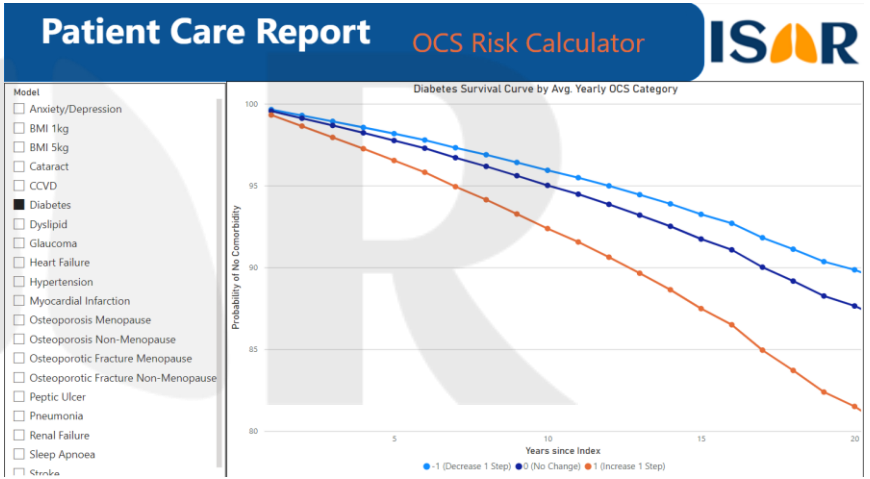
OCS = Oral corticosteroids

Sadatsafavi M et al. Prevention of cardiovascular and other systemic adverse outcomes in patients with asthma treated with biologics. *Am J Respir Crit Care Med*. 2025 May 19. doi: 10.1164/rccm.202501-0246OC. Online ahead of print.

Clinical implications of SOLAR I & II: New tools within ISAR



Identification of long-term OCS (LTOCS) use



Prediction of health risks linked to OCS use

LTOCS = Long-term oral corticosteroids; OCS = Oral corticosteroids
ISAR: https://www.isar.opcglobal.org/

Thank you!

Canada
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•Vancouver General Hospital, University of British Columbia
•University of Alberta Hospital, University of Alberta
•Rockyview Hospital, University of Calgary
•Toronto Western Hospital, University of Toronto
•University Institute of Cardiology and Respirology of Quebec, Université Laval
•McGill University Health Centre, McGill University
•The Ottawa Hospital
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Ecuador
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•Hospital General Monte Sinaí, Guayaquil

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•Hospital da Criança de Brasília José Alencar
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•Aseer Central Hospital

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United Arab Emirates
•Rashid Hospital, Dubai

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•China Medical University Hospital
•Kaohsiung Medical University Hospital

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•Aarhus University Hospital
•Hvidovre University Hospital
•Vejle Hospital
•Aalborg University Hospital
•Odense University Hospital
•Gentofte Hospital
•University Hospital Zealand

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•Medical University of Gdańsk
•National Institute of Tuberculosis and Lung Diseases
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•Narayana Hrudayalaya, Bengaluru, Karnataka
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•Surabhi Hospital, Mumbai

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•Osaka University Hospital
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•Juntendo University Hospital
•Tohoku University Hospital
•Fukuoka University Hospital
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South Korea
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•Seoul National University Hospital
•Samsung Medical Center
•Chonnam National University Hospital
•Pusan National University Hospital
•Korea University Guro Hospital
•Yonsei University Severance Hospital

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•Kirsty Fletton
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•Freya Tyrer
•Karen Hosking
•Celine Goh
•Dominic Friston
•Aaron Beastall
•Angelica Tatam
•Pui Yee Lai
•Harika Gosala
•Veronica Mendez Moro

Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR)

Florence Schleich, Désirée Larenas-Linnemann, Alan Altraja, Luis Pérez de Llano, Konstantinos Kostikas, Mohsen Sadatsafavi, Arnaud Bourdin, Roy Alton Pleasants, Mark Hew, Wenjia Chen, Libardo Jiménez-Maldonado, Simon Couillard, Charlotte Suppli Ulrik, Adeeb A. Bulkhi, Ming-Ju Tsai, George C. Christoff, Nikolaos G. Papadopoulos, Paul E. Pfeffer, Dermot Ryan, Celine Bergeron, Mona S. Al-Ahmad, Delbert R. Dorscheid, Eileen Wang, John D. Blakey, Belinda Cochrane, Matthew J. Peters, Todor A. Popov, Carlos A. Torres-Duque, Susanne Hansen, Francesca Puggioni, Kirsty Fletton, Laila Salameh, Peter G. Middleton, Paulo Márcio Pitrez, Chin Kook Rhee, Eve Denton, Kenneth R. Chapman, Lauri Lehtimäki, Ruth B. Murray, Chau-Chyun Sheu, David J. Jackson, Riyad AL-Lehebi, Mariko Siyue Koh, Bassam Mahboub, Ledit R. F. Ardusso, Athena Gogali, Giorgio Walter Canonica, Piotr Kuna, Martin Sivori, Renaud Louis, Shelley Abercromby, Giuseppe Guida, Bernt Bøgvald Aarli, Aaron Beastall, Victoria Carter, Ghislaine Scelo, John Townend, Borja G. Cosio, Pujan H. Patel, Celine Yun Yi Goh, Zsuzsanna Csoma, John W. Upham, João A. Fonseca, Peter G. Gibson, Christine Jenkins, Guy G. Brusselle, Anne Chèvremontca, Andréanne Côté, Carlos Andrés Celis-Preciado, Ivan Solarte, Celeste M. Porsbjerg, Asger Sverrild, Paula Kauppi, Stelios Loukides, Michael P. Makris, Andriana I. Papaioannou, Enrico Heffler, Jeffrey Shi Kai Chan, Hyonsoo Joo, Liam G. Heaney, Wei-Han Cheng, Njira Lugogo, Michael E. Wechsler, Cláudia Chaves Loureiro, Bellanid Rodríguez- Cáceres, Tatsuya Nagano, Zhixiao Wang, Hao-Chien Wang, Jorge Máspero, Fernando Saldarini, Ana María Stok, Anahi Yañez, Philip G. Bardin, Sinthia Z. Bosnic-Anticevich, Vidya Navaratnam, Mohit Bhutani, M. Diane Lougheed, Lyle Melenka, Petros Bakakos, Konstantinos P. Exarchos, Aggelos A. Ladias, Dóra Lúdvíksdóttir, Takashi Iwanaga, Elvia Angelica Contreras Contreras, Sverre Lehmann, José Alberto Ferreira, Rebecca Gall, Pin-Kuei Fu, Diahn-Warng Perng, Flavia Hoyte, Rohit Katial, Unnur S. Björnsdóttir, Camille Taillé, Christian Taube, Breda Cushen, Lakmini Bulathsinhala, Leif Bjermer, and David B. Price, on behalf of the ISAR STAR Working Group

Summary of the STAR study

Aim

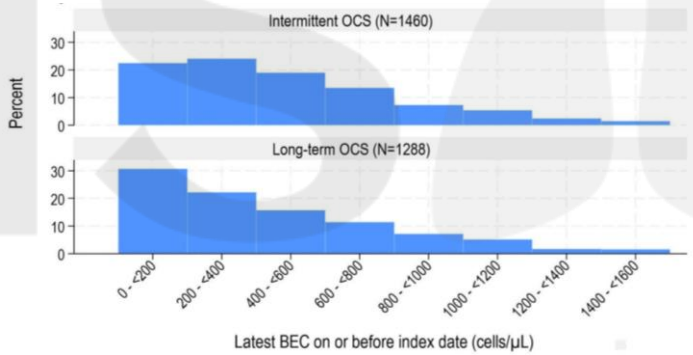
- To study the effect of **OCS use** prior to biologic initiation on SA phenotype and **biomarker profile**
- To characterize the **burden of SA** among **long-term OCS users** by biomarker profile

Methods

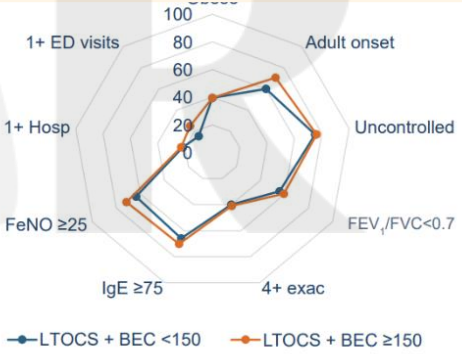
4,305 patients from 23 countries in **ISAR** (2003-2023) were included. **Biomarker distributions** were described according to OCS use*. **Long-term OCS** users were characterized according to BEC.

Results

Pre-biologic BEC distribution according to OCS use



Disease characteristics of long-term OCS users by BEC



Conclusions

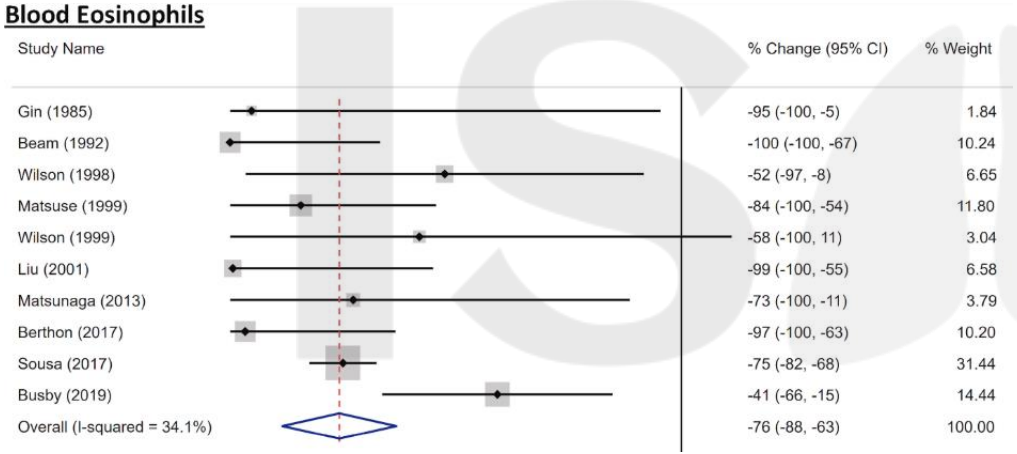
- **OCS (intermittent and long term) affect BEC** distribution.
- Biologic access criteria should consider **long-term OCS users with low BEC**, who have high disease burden.

*3 cohorts: (i) no prescription for OCS, (ii) prescription(s) for intermittent OCS (i.e, 90 days in previous 12 months, usually short courses for exacerbations), and (iii) prescriptions for long-term OCS (i.e, >90 days in previous 12 months)
BEC = Blood eosinophil count; ED = Emergency department; FeNO = Fractional exhaled nitric oxide; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; IgE = Immunoglobulin E; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids; SA = Severe asthma

Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

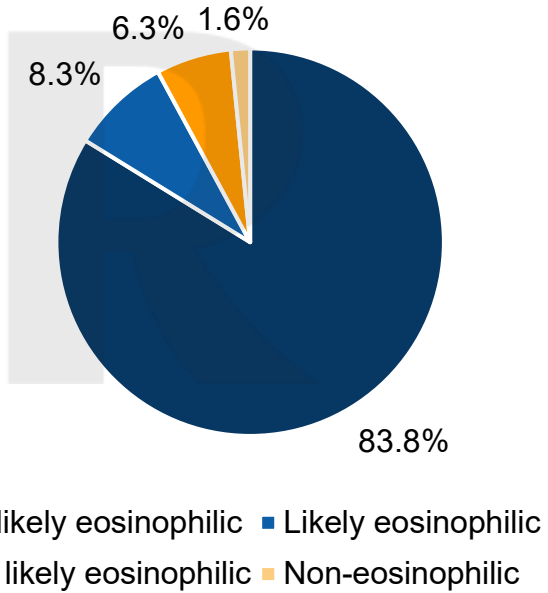
Background and Rationale

Weighted % change in BEC following OCS in stable asthma[1]



BEC was reduced by 76% across all studies in this meta-analysis

Proportion of asthma phenotypes in ISAR (n=1,716)[2]



BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids

[1]Busby J et al. The effects of oral corticosteroids on lung function, type-2 biomarkers and patient-reported outcomes in stable asthma: A systematic review and meta-analysis. *Respir Med* 2020;173:106156. [2]Heaney LG et al. Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. *CHEST* 2021;160(3):814-830

Aim

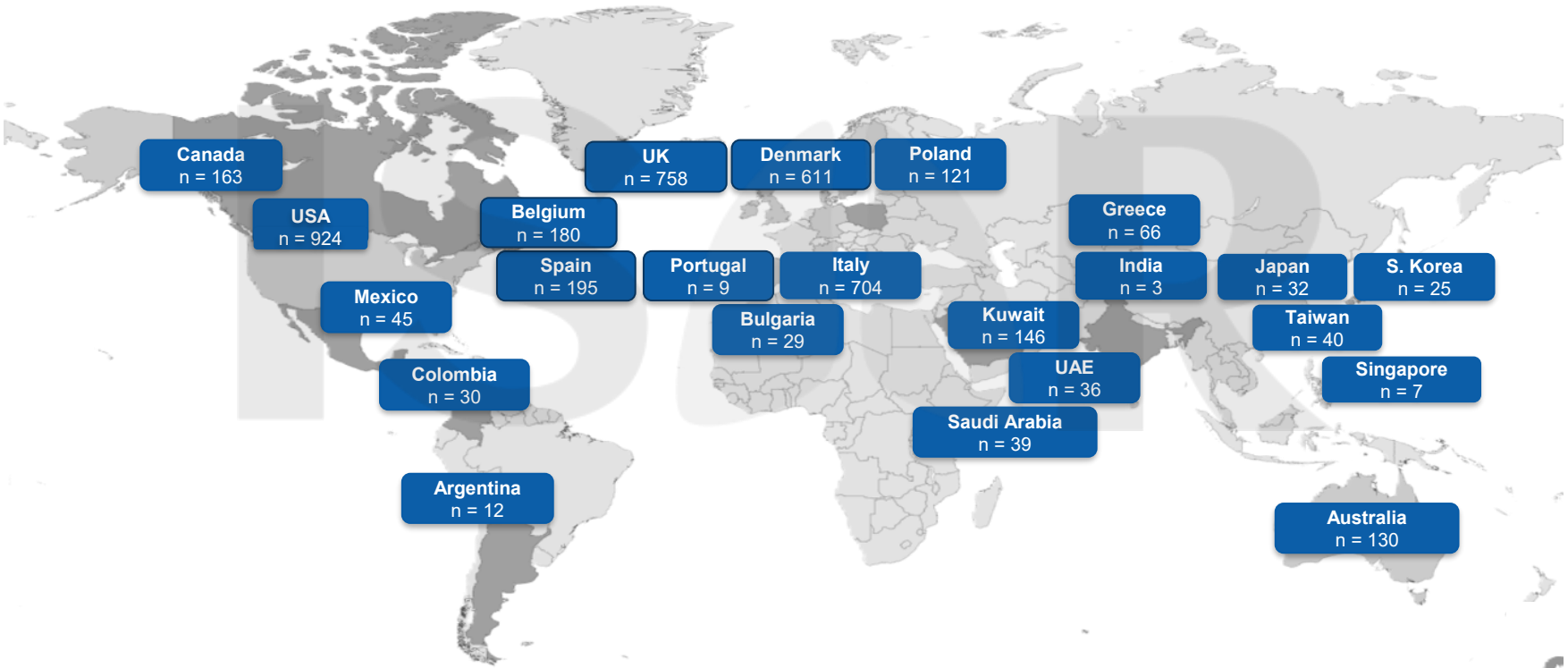
To explore the effect of OCS (intermittent and long-term) prior to biologic initiation on severe asthma phenotype and biomarker profile

To characterize the burden of severe asthma among patients prescribed long-term OCS by biomarker profile

BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; OCS = Oral corticosteroids

Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

STAR study data source: ISAR (23 countries)



Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Methods

Patients

Inclusion criteria
- ISAR patients ≥18 years old, severe asthma*
- Initiated biologic therapy
- Data for ≥1 year prior to biologic initiation

Exclusion criteria
- Received bronchial thermoplasty
- Missing biologic initiation date
- No pre-biologic assessment
- Comorbidity conventionally treated with long-term OCS

Variables

Demographics

Biomarkers:
- BEC, FeNO, IgE

Disease characteristics:
- Asthma onset and duration
- Eosinophilic phenotype
- Exacerbations
- Asthma control
- Lung function
- Asthma treatment pattern
- HCRU

Statistical analyses

Continuous and **categorical** variables were summarized.

Comparisons between groups:
- T-tests
- Mann-Whitney tests
- Poisson regression
- Chi-square tests

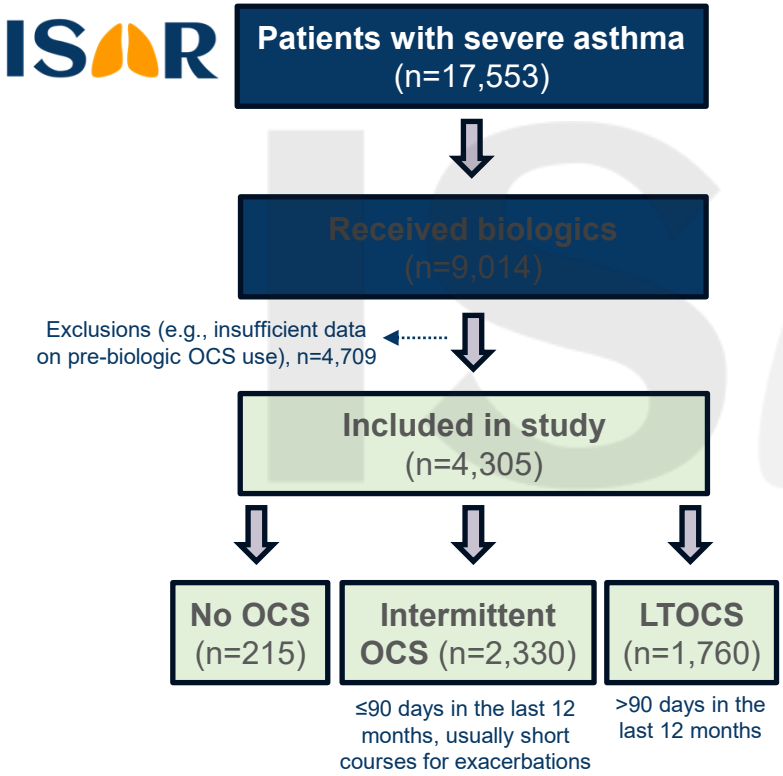
***P* values ≤0.05** were considered statistically significant.

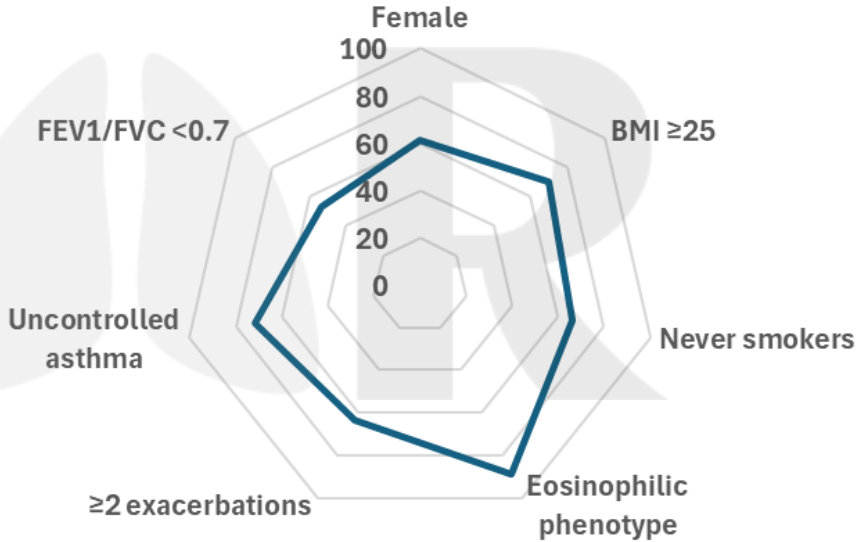
*Severe asthma is defined as receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4

BEC = Blood eosinophil count; FeNO = Fractional exhaled nitric oxide; HCRU = Healthcare resource utilization; IgE = Immunoglobulin E; ISAR = International Severe Asthma Registry; OCS = Oral corticosteroids

Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Patient flow and overall phenotypic characterization

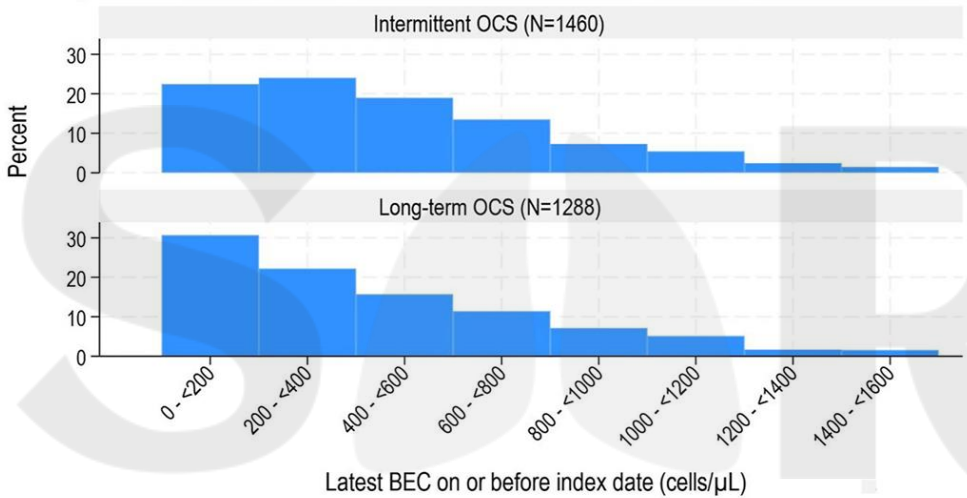




BMI = Body mass index; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; HCRU = Healthcare resource utilization; ISAR = International Severe Asthma Registry; LTOCS = Long-term OCS; OCS = Oral corticosteroids

Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

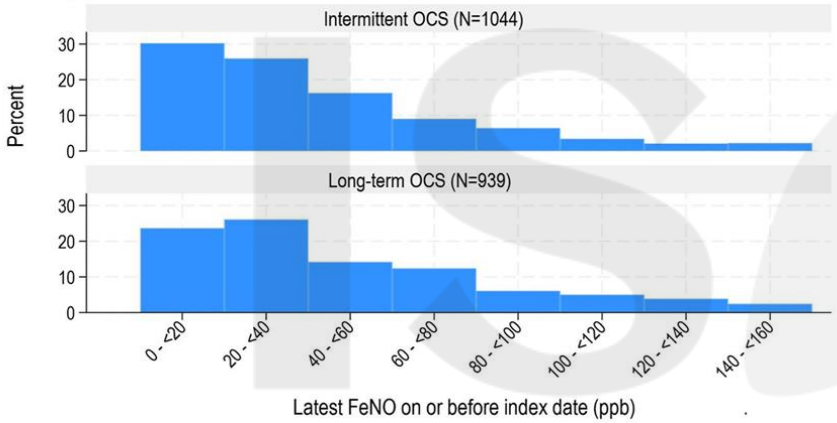
Pre-biologic BEC according to OCS use



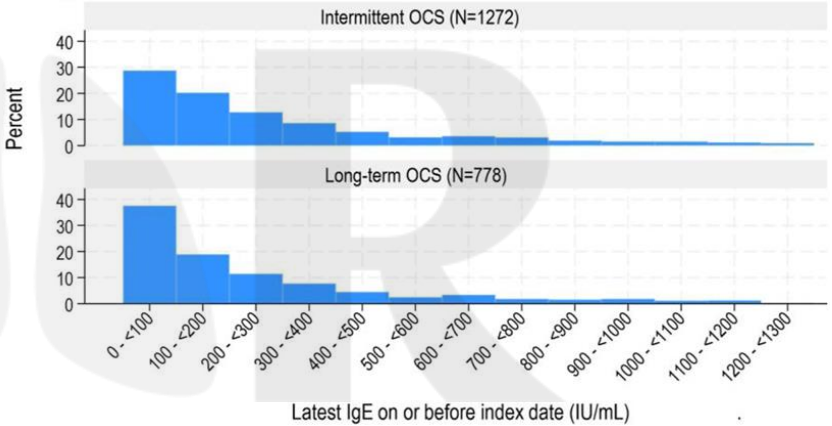
Median BEC was **lower** in the long-term OCS vs intermittent OCS group (**310** vs **400 cells/µL**; *p* <0.001).

Intermittent: OCS use for ≤90 days; Long-term: OCS use for >90 days
BEC = Blood eosinophil count; OCS = Oral corticosteroids
Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Pre-biologic FeNO and IgE according to OCS use



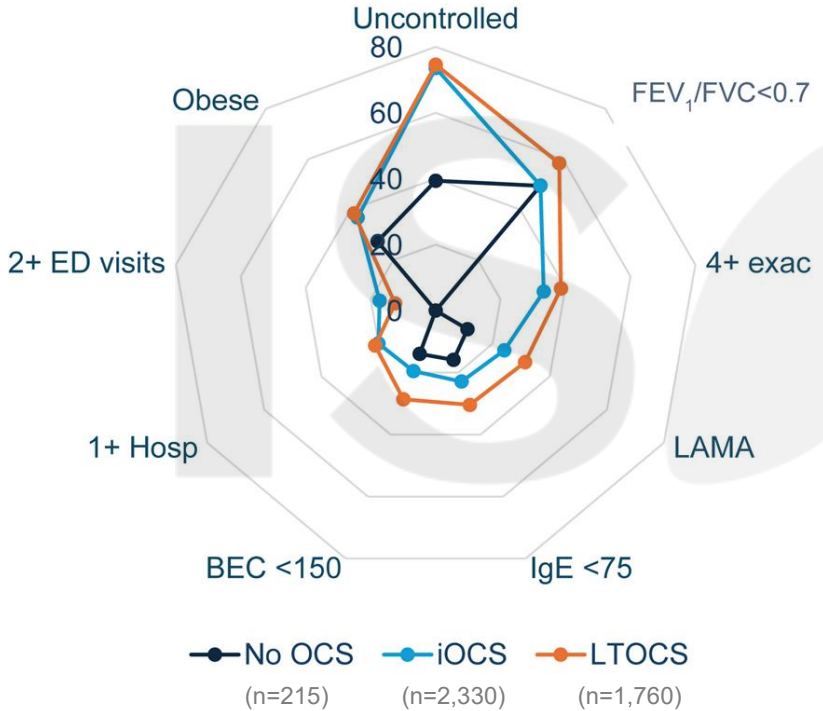
Median **FeNO** was significantly **higher** in long-term OCS vs intermittent OCS group (**40** vs **34 ppb**; *p* <0.001).



Median **IgE** was significantly **lower** in the long-term OCS vs intermittent OCS group (**154** vs **206 IU**; *p* <0.001).

Intermittent: OCS use for ≤90 days; Long-term: OCS use for >90 days
FeNO = Fractional exhaled nitric oxide; IgE = Immunoglobulin E; OCS = Oral corticosteroids
Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Severe asthma phenotypes by pattern of OCS use

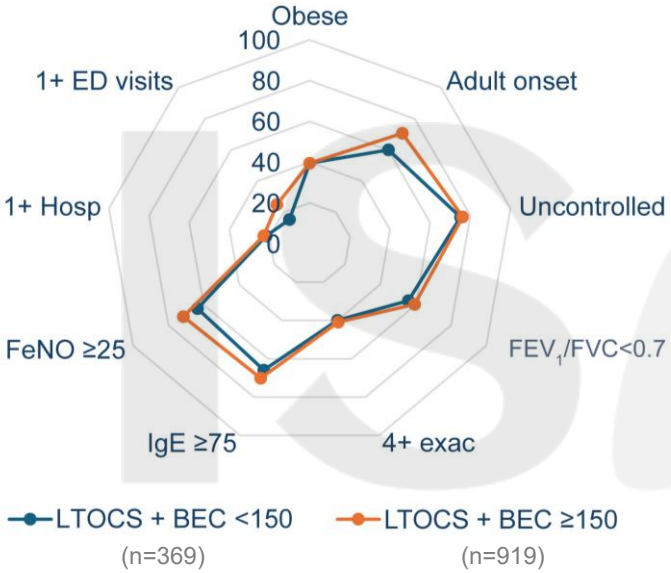


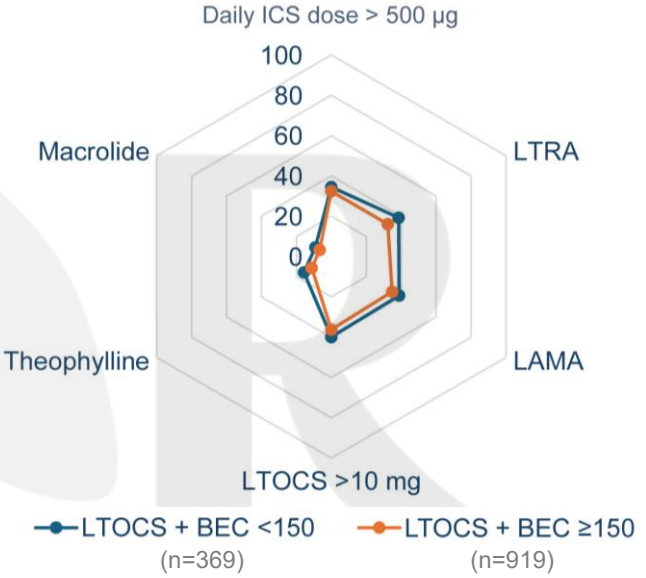
Intermittent and long-term OCS users were more likely than non-OCS users to have:

- BMI ≥30
- Uncontrolled asthma
- Impaired FEV_1
- ≥4 exacerbations
- Received LAMA add-on therapy
- Been hospitalized
- Visited the ED for asthma

iOCS = Intermittent OCS use (for ≤90 days); LTOCS = Long-term OCS use (for >90 days). Denominators for variables in the figure may vary depending on data availability.
BEC = Blood eosinophil count; ED Emergency department; FVC = Forced vital capacity; FEV_1 = Forced expiratory volume in 1 second; IgE = Immunoglobulin E; LAMA = Long-acting muscarinic antagonists; OCS = Oral corticosteroids
Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Disease characteristics of LTOCS users by BEC





- The low BEC group had **younger asthma onset** (26.5 vs 29.9 yrs; p = 0.021) and **longer asthma duration** (26.0 vs 23.2 yrs; p = 0.036).
- **Disease burden remained high** among LTOCS users, irrespective of BEC.

Denominators for variables in the figures may vary depending on data availability.
BEC = Blood eosinophil count; ED: Emergency department; FeNO = Fractional exhaled nitric oxide; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; IgE = Immunoglobulin E; LTOCS = Long-term oral corticosteroids; LAMA = Long-acting muscarinic antagonists; LTRA = Leukotriene receptor antagonists
Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Clinical implications for LTOCS users with low BEC

Biologic prescribing criteria worldwide (BACS[1])

BEC

- Mepolizumab: 64% of countries use BEC ≥300 cells/µL
- Benralizumab: 43% of countries use BEC ≥300 cells/µL
- Reslizumab: 67% of countries use BEC ≥400 cells/µL
- Dupilumab: 55% of countries use BEC ≥150 cells/µL

Background OCS use

- 0% (reslizumab) to 21% (omalizumab) of countries use LTOCS

Unmet need of LTOCS users with low BEC (STAR[2])

Disease burden:

- LTOCS users with low BEC were as likely as those with high BEC to have uncontrolled asthma, exacerbations and irreversible airflow obstruction

Clinical implications:

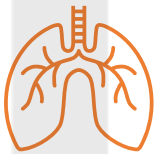
- Biologic access criteria should consider LTOCS users with low BEC (<150 cells/µL)

BACS = Biologic accessibility score; BEC = Blood eosinophil count; LTOCS = Long-term oral corticosteroids

[1]Porsbjerg C et al. Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma. *JACI: In Practice* 2022;10(5):1202-1216. [2]Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Conclusions

OCS (intermittent and long-term) affect BEC distribution.



Disease burden remained high among LTOCS users, irrespective of BEC.

OCS use should be considered when characterizing severe asthma.
Earlier phenotyping (prior to initiation of LTOCS) is recommended.

Biologic access criteria should consider LTOCS users with low BEC,
who have high disease burden but do not qualify for most biologics.

BEC = Blood eosinophil count; LTOCS = Long-term oral corticosteroids; OCS = Oral corticosteroids

Schleich F et al. Biomarker profile and disease burden associated with intermittent and long-term oral corticosteroid use in patients with severe asthma prior to biologic initiation in real-life (STAR). *World Allergy Organ J* 2025;18:101066

Prediction pathway for severe asthma exacerbations: a Bayesian Network analysis

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Aim and Methods

Rationale

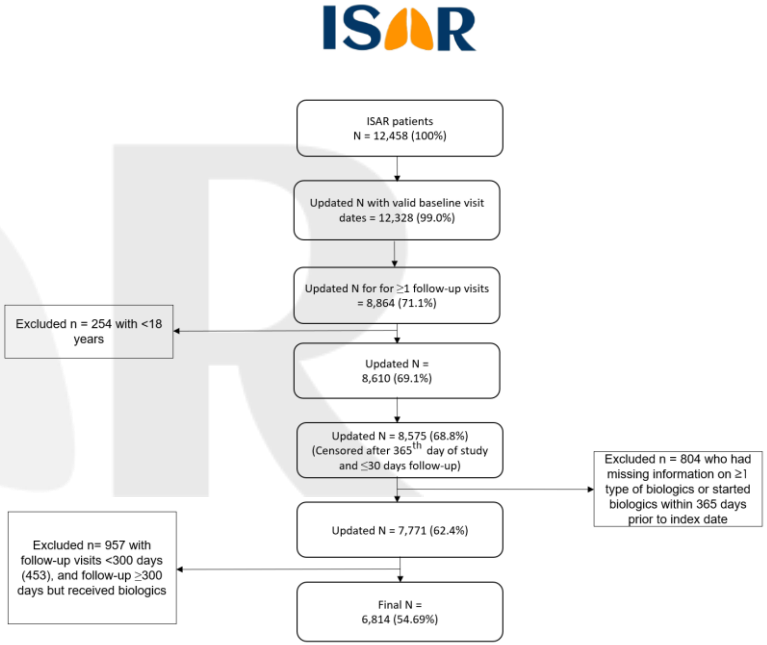
Accurate risk prediction of exacerbations is pivotal in severe asthma management. Multiple risk factors are at play, but the pathway of risk prediction remains unclear.

Aim

To examine how key clinical predictors interact to drive severe asthma exacerbations, supporting more informed clinical decision-making.

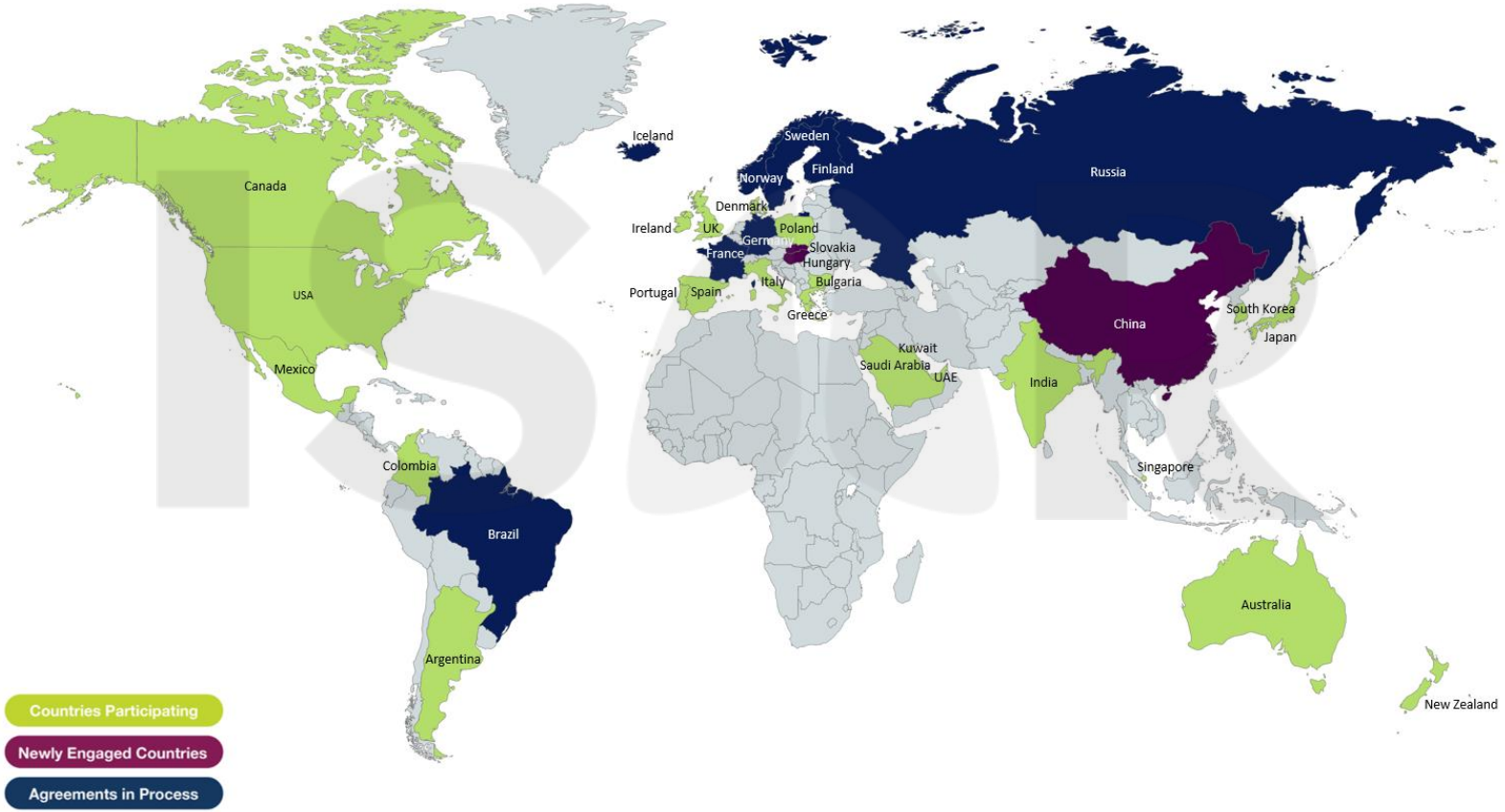
Methods

- **Data source:** The International Severe Asthma Registry (ISAR).
- **Study population:** Patients ≥ 18 years of age who did not initiate any biologics before the baseline visit.
- **Statistical analyses:** A Bayesian network, developed using expert input and machine learning, identified key pathways leading to severe exacerbations, complemented by an influence diagram incorporating decision and utility nodes.



Flow diagram of the International Severe Asthma Registry cohort

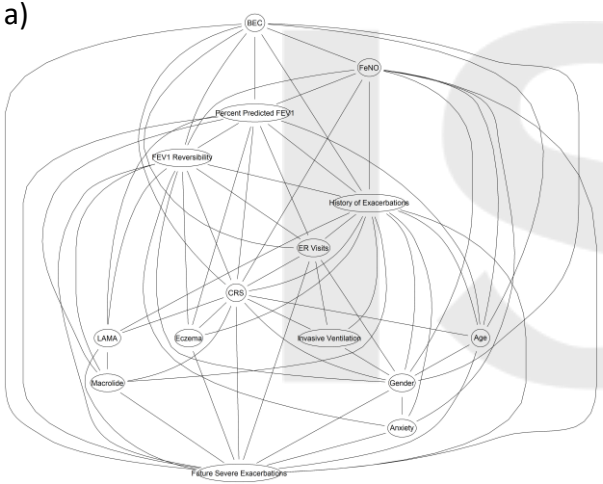
ISAR participating countries



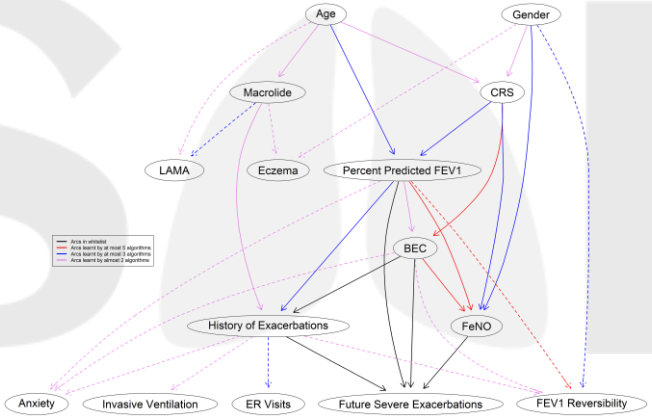
The comprehensive local neighborhood network of relevant predictors

Bayesian Network plots: Initial parent-child relationship learnt, machine learning with expert knowledge integration, and final model with clinically relevant arcs.

a)



b)



c)

Key Predictors Identified:

- Among 14 LASSO-selected predictors, those most connected included prior severe exacerbations, FeNO, % predicted FEV1, BEC, macrolide use, and CRS.

Machine-Learned BN Structure:

- ML algorithms consistently identified core arcs—CRS → BEC, FEV1 → FeNO, and BEC → FeNO—while predictors like anxiety and ER visits were peripheral.

Final Expert-Tuned BN (2 main pathways):

- (1) CRS impacts biomarkers and lung function leading to future exacerbations;
- (2) Age and sex influence CRS and macrolide use, which in turn affects exacerbation risk.

Model discrimination was moderate in 10-fold cross-validation and leave-one-country-out cross-validation, and model calibration was high in train-test data.

Validation results

Performance Metrices	10-fold cross-validation	
AUC[1]	0.65	
Specificity[2]	0.75	
Precision[3]	0.50	
Recall[4]	0.50	
Accuracy[5]	0.63	
Calibration using 70:30 train-test data		
Calibration intercept[6]	risk of ≥1 severe exacerbations	0.130
	risk of ≥2 severe exacerbations	-0.018
Calibration slope[6]	risk of ≥1 severe exacerbations	0.804
	risk of ≥2 severe exacerbations	0.949

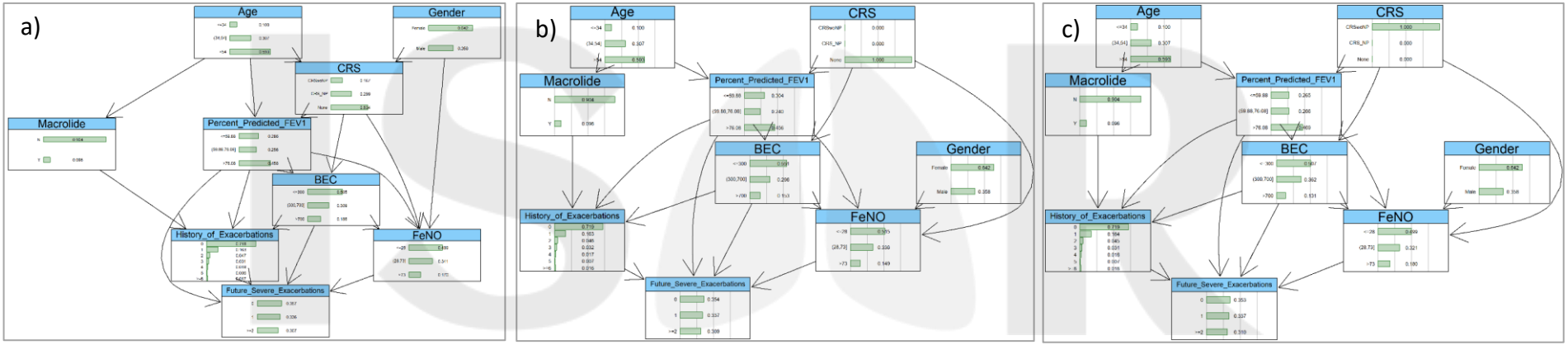
1. AUC (Area Under the Curve): Range between 0 and 1, indicating the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one.
2. Specificity: Range between 0 and 1, measures the proportion of actual negatives that are correctly identified as such by the classifier.
3. Precision: Range between 0 and 1, denotes the proportion of true positive predictions among all positive predictions made by the classifier.
4. Recall: Range between 0 and 1, represents the proportion of actual positives that are correctly identified as such by the classifier.
5. Accuracy: Range between 0 and 1, measures the proportion of correct predictions made by the classifier over all predictions.
6. A calibration slope near 1 and an intercept close to zero signify well-calibrated models with accurate risk estimation across different individuals.

Findings

- **Discrimination**: The BN model showed moderate predictive performance with AUCs of 0.65 (10-fold CV) and 0.62 (leave-one-country-out), supported by consistent specificity, precision, recall, and accuracy.
- **Calibration**: Good model calibration was observed with calibration intercepts (0.130, -0.018) and slopes (0.804, 0.949) in test data for predicting ≥1 and ≥2 severe exacerbations.

The conditional probability table of BN and counterfactual analysis

Conditional probability and counterfactual analysis



Conditional Probability Plot:

- BN model estimates future severe exacerbation risk based on levels of upstream clinical predictors.

CRS Impact Simulation:

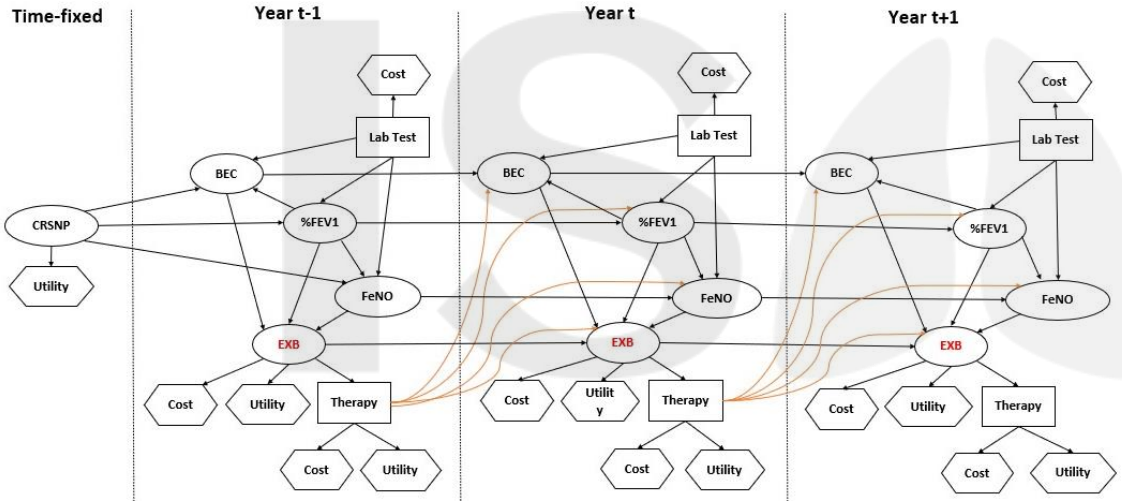
- Changing CRS status to “CRS without NP” alters downstream biomarkers (FEV1, BEC, FeNO).

Prediction Shift:

- These biomarker shifts lead to a change in the predicted probability of future severe exacerbations.

Influence diagram identified CRS-Biomarker-Lung Function pathway driving future severe exacerbations

Influence diagram integrating nodes, cost and utility



Findings

- **CRS–Biomarker–Lung Function Pathway**: The model emphasized how CRS influences biomarkers (BEC, FeNO) and lung function (% predicted FEV1), which drive the transition from current to future severe exacerbations.
- **Treatment Decision Integration**: Treatment was modeled as a decision node post-exacerbation, influencing biomarker levels and lung function, thus shaping future exacerbation risk and costs.

Conclusions

- An essential prediction pathway of severe exacerbation was identified, which involves the **influence of CRS on the immediate predictors** of risk transition from current to future severe asthma exacerbations.

- The BN also reveals heterogeneity in predicted risks, with **macrolide use linked to the transition from past to future exacerbations** through a separate, non-T2 pathway.

- Findings provided significant insights for **asthma risk prediction** and potentially support the **cost-effectiveness analysis** of interventions related to T2 inflammations and/or CRS.

EMBER: Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach

Eileen Wang, William Henley, Désirée Larenas-Linnemann, Lakmini Bulathsinhala, Trung N. Tran, Michael E. Wechsler, Shawn D. Aaron, Mona Al-Ahmad, Riyad Al-Lehebi, Alan Altraja, Peter Barker, Aaron Beastall, Andrey S. Belevskiy, Celine Bergeron, Leif Bjermer, Unnur S. Björnsdóttir, Sinthia Z. Bosnic-Anticevich, Arnaud Bourdin, Guy G. Brusselle, John Busby, Giorgio Walter Canonica, Victoria Carter, Kenneth R. Chapman, Nicholas Chapman, George C. Christoff, Borja G. Cosio, Richard W. Costello, James Fingleton, João A.ioa Fonseca, Mina Gaga, Peter G. Gibson, Susanne Hansen, Liam G. Heaney, Enrico Heffler, Mark Hew, Takahiko Horiguchi, Flavia Hoyte, Richard B. Hubbard, Takashi Iwanaga, David J. Jackson, Rohit Katial, Mariko Siyue Koh, Konstantinos Kostikas, Piotr Kuna, Sverre Lehmann, Lauri Lehtimäki, Renaud Louis, Dóra Lúdvíksdóttir, Njira Lugogo, Bassam Mahboub, Neil Martin, Jorge Máspero, Andrew N. Menzies-Gow, Arjun Mohan, Ruth B. Murray, Tatsuya Nagano, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Pujan H. Patel, Luis Perez-de-Llano, Diahn-Warng Perng, Matthew J. Peters, Paul E. Pfeffer, MRCP(UK), Paulo Márcio Pitrez, Roy Alton Pleasants, Todor A. Popov, Celeste M. Porsbjerg, Francesca Puggioni, Anna Quinton, Chin Kook Rhee, Mohsen Sadatsafavi, Sundeep Salvi, Giulia Scioscia, Chau-Chyun Sheu, Concetta Sirena, Camille Taillé, Christian Taube, Carlos A. Torres-Duque, Ming-Ju Tsai, Alf Tunsäter, Charlotte Suppli Ulrik, and David B. Price, on behalf of the ISAR EMBER Working Group

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Summary of the EMBER study

Objective

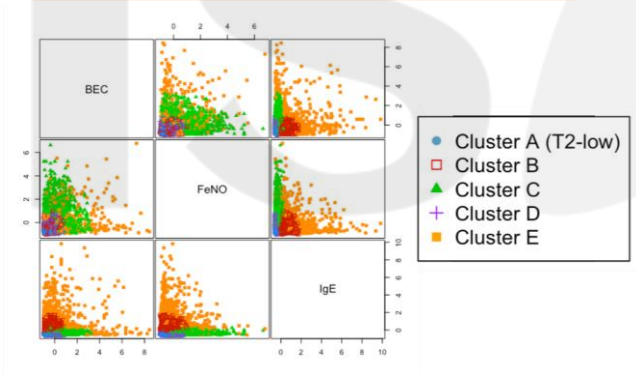
To characterize severe asthma phenotypes and compare pre- to post-biologic change in outcomes along a gradient of **T2-involvement**.

Methods

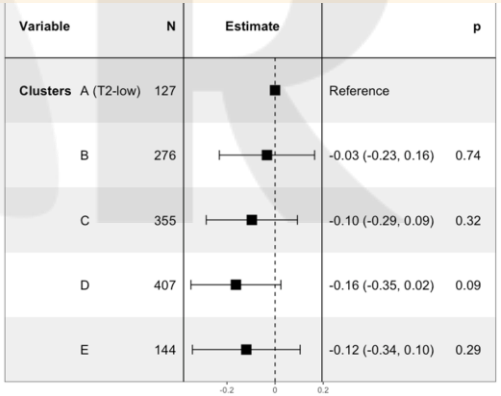
3,675 patients (23 countries) in **ISAR** were included; of these, 2,276 received biologics (Anti-IgE, Anti-IL5/5R, Anti-IL4Rα). **Clusters** were identified using a five-component Gaussian finite mixture model. **Change in outcomes** between 1 year pre- and post-biologic initiation were compared between clusters and by biologic class.

Results

Biomarker clusters identified using Gaussian finite mixture model (n=3675)



Change in annualized exacerbation rate pre- to post-biologic relative to Cluster A (T2-low)



Conclusions

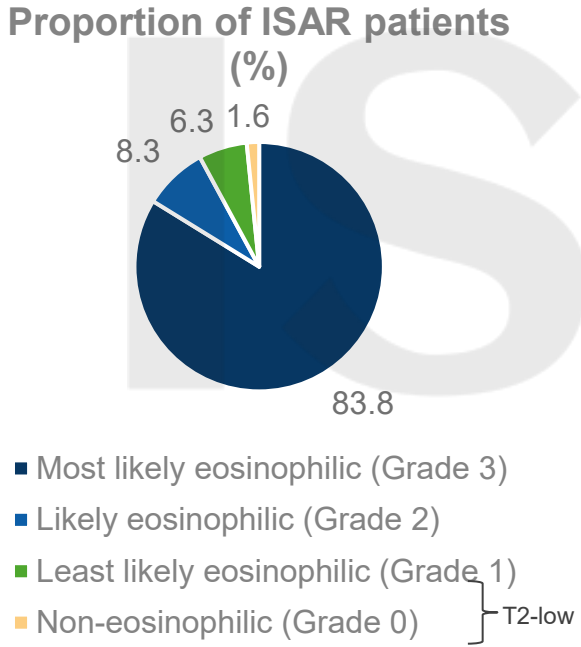
Five biomarker clusters along a gradient of T2 involvement were identified using a **data-driven approach.** Biologic use was associated with **improved outcomes** in all clusters but tended to be better at the higher end of the T2 spectrum.

BEC: Blood eosinophil count; IgE: Immunoglobulin E; IL4Rα: Interleukin 4-receptor-alpha; IL5/5R: Interleukin 5/5-receptor; FeNO: Fractional exhaled nitric oxide; T2: Type 2

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Background and Rationale

~8% of patients in ISAR are T2-low



Much remains unknown about T2-low asthma

- **No agreed definition** or clinical biomarker profile, other than the absence of T2 inflammation
- ICS and OCS suppress T2 biomarkers, **confounding** T2-low categorization
- T2-low asthma is **less responsive to biologics**, which target T2-related pathways
- **Limited effective treatment options** for T2-low asthma

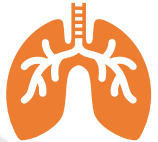
ICS: Inhaled corticosteroids; OCS: Oral corticosteroids; T2: Type 2

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Aim

Describe **distributions of biomarkers** in patients with severe asthma along a gradient of T2 involvement

Phenotypically **characterize** patients along this gradient



Compare the **pre- to post-biologic initiation change in asthma outcomes** and HCRU across the gradient

Using a data-driven approach instead of pre-defined clinical biomarker cut-offs

HCRU: Healthcare resource utilization; T2: Type 2

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Data source: ISAR

23 countries

Total patients: **3,675**

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Methods

Patients

Inclusion criteria

- ISAR patients ≥18 years old, severe asthma*

Assessment of biomarker distributions

- Pre-biologic data for BEC, FeNO and IgE

Assessment of change in outcomes

- Received a biologic
- Data for ≥1 asthma outcomes with ≥24 weeks follow-up

Exclusion criteria

- Missing outcome data
- Outlier biomarker values†

Variables

Pre-biologic demographic and clinical characteristics

Pre-biologic biomarkers

- BEC, FeNO, IgE

Asthma outcomes:

- Annual exacerbation rate
- Highest post-bronchodilator FEV_1
- Asthma control
- HCRU

Statistical analyses

Biomarker clusters were identified using Gaussian finite mixture models.

Multivariable analysis was conducted with cluster A (T2-low) as reference.

- All models were adjusted for pre-biologic outcome, age, sex, pre-biologic long-term OCS use and country.

*Receiving treatment at Global Initiative for Asthma (GINA) 2018 Step 5 or with uncontrolled asthma at GINA Step 4; †BEC >5000 cells/μL; FeNO >500 ppb; IgE >10,000 IU/mL

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; HCRU: Healthcare resource utilization; IgE: Immunoglobulin E; OCS: Oral corticosteroids

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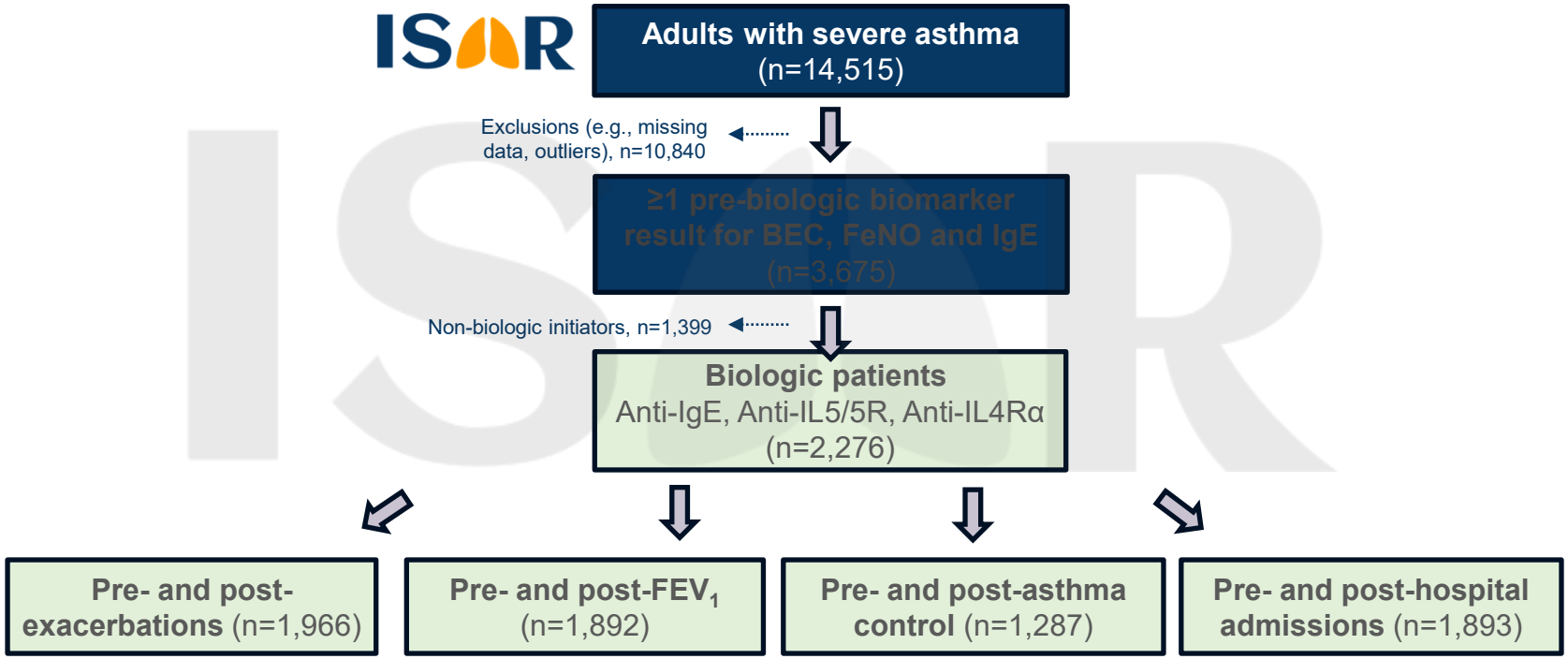
Patient Flow



*Receiving treatment at Global Initiative for Asthma (GINA) 2018 Step 5 or with uncontrolled asthma at GINA Step 4; †BEC >5000 cells/μL; FeNO >500 ppb; IgE >10,000 IU/mL
BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; IgE: Immunoglobulin E; IL4Rα: Interleukin 4-receptor-alpha; IL5/5R: Interleukin 5/5-receptor; OCS: Oral corticosteroids
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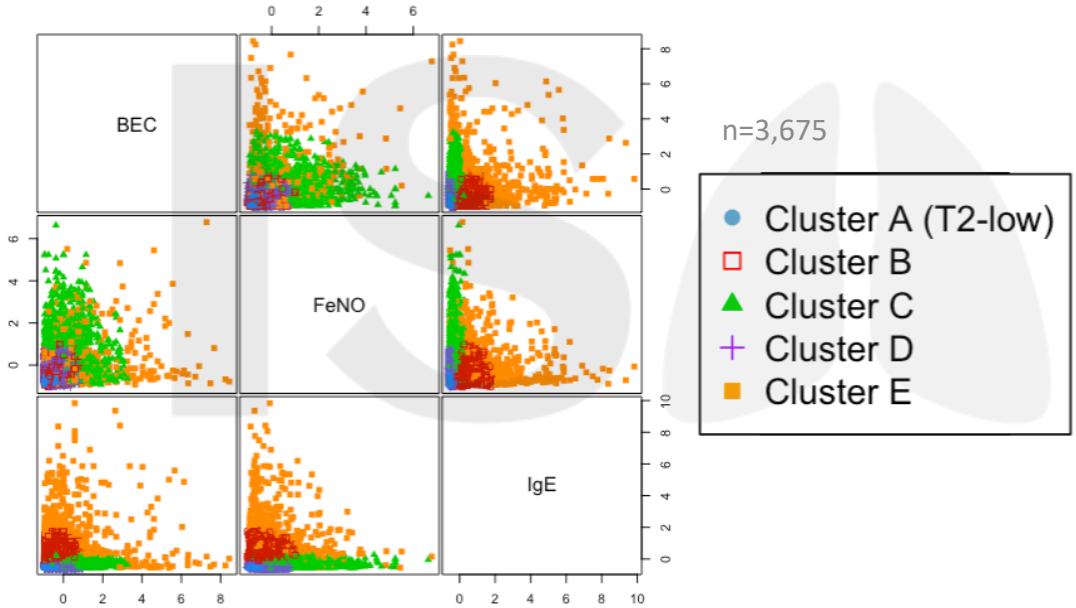
Five biomarker clusters (identified using Gaussian finite mixture models)



n=3,675

- Cluster A (T2-low)
- Cluster B
- Cluster C
- Cluster D
- Cluster E

Cluster A (16.4%)
- T2-low, triple-biomarker-low

Cluster B (20.4%)
- High IgE, intermediate BEC

Cluster C (22.9%)
- High BEC + FeNO

Cluster D (30.3%)
- Triple-biomarker-intermediate

Cluster E (10.0%)
- Triple-biomarker-high

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; IgE: Immunoglobulin E; T2: Type 2

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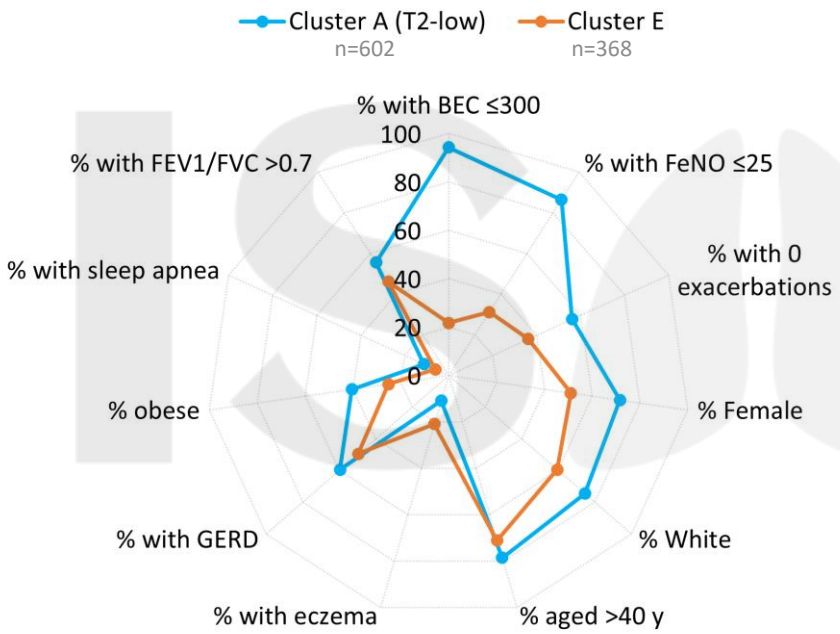
Demographic and clinical characteristics of Clusters A and E



Cluster A (vs Cluster E)

- Tended to be female, White, and have a lower exacerbation rate
- More likely to have GERD and other potentially OCS-related comorbidities

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GERD: Gastroesophageal reflux disease; IgE: Immunoglobulin E; T2: Type 2

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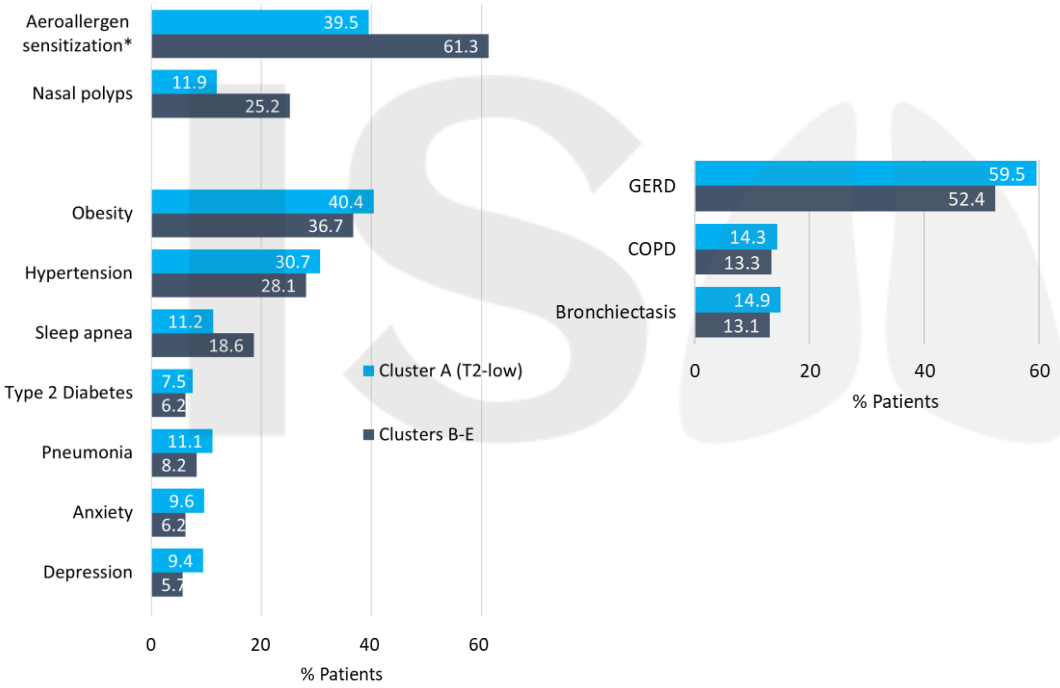
Demographic and clinical characteristics of biomarker clusters (N=3,675)



Cluster A (vs other clusters)

- More likely to have potentially OCS-related comorbidities
- Less likely to have any diagnosed allergy* and nasal polyps

*Aeroallergen sensitization by skin prick testing or serum allergen testing

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GERD: Gastroesophageal reflux disease; IgE: Immunoglobulin E; T2: Type 2

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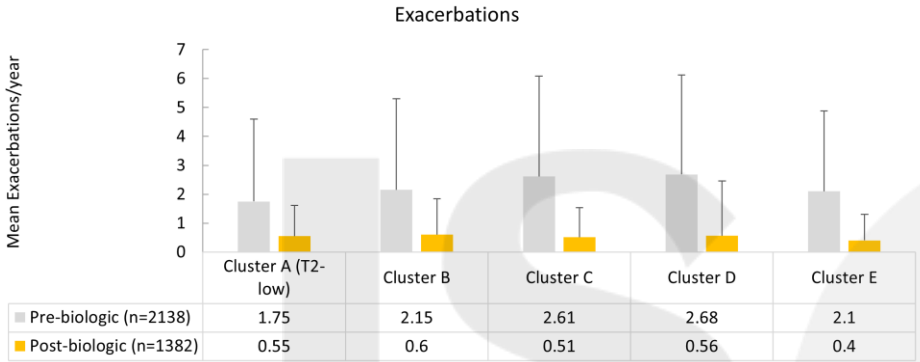
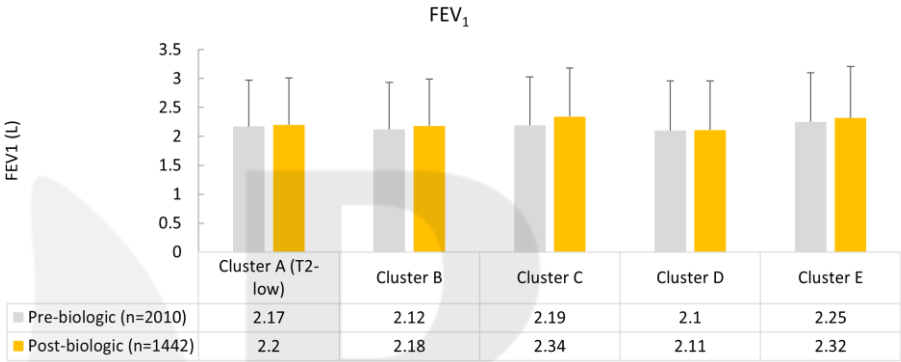
Pre- to post-biologic change in asthma outcomes for each cluster (univariate analysis)

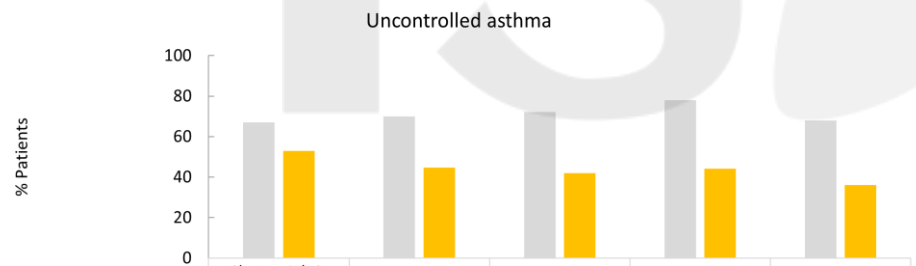


	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=2138)	1.75	2.15	2.61	2.68	2.1
Post-biologic (n=1382)	0.55	0.6	0.51	0.56	0.4



FEV$_1$

	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=2010)	2.17	2.12	2.19	2.1	2.25
Post-biologic (n=1442)	2.2	2.18	2.34	2.11	2.32



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1221)	67	70	72.1	78	68
Post-biologic (n=1227)	53	44.6	42	44.1	36

Pre- to post-biologic improvements *were shown for exacerbations, lung function and asthma control,* ***irrespective of the degree of T2 involvement***

FEV$_1$: Forced expiratory volume in 1 second; T2: Type 2

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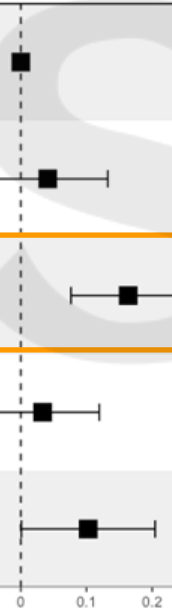
Pre- to post-biologic change in lung function relative to Cluster A (T2-low)

Variable		N	Estimate	p
Clusters	A (T2-low)	131	Reference	
	B	279	0.04 (-0.05, 0.13)	0.38
	C	367	0.16 (0.08, 0.25)	<0.001
	D	414	0.03 (-0.05, 0.12)	0.45
	E	154	0.10 (0.00, 0.20)	0.05



*Patients in **Cluster C (high BEC + FeNO)** had a **significantly greater increase in FEV_1** vs Cluster A*

BEC: Blood eosinophil count; FeNO: Fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in 1 second; T2: Type 2

Wang E et al. on behalf of the ISAR EMBER Working Group. Response to biologics along a gradient of T2 involvement in patients with severe asthma: a data-driven biomarker clustering approach, *JACI: In Practice* 2025; in press

Pre- to post-biologic change in asthma outcomes relative to Cluster A (T2-low) for patients who received Anti-IL5/5R

Exacerbations

Variable	N	Estimate	p
Clusters A (T2-low)	67	Reference	
B	126	-0.08 (-0.38, 0.22)	0.59
C	254	-0.30 (-0.56, -0.03)	0.03
D	280	-0.31 (-0.58, -0.05)	0.02
E	93	-0.15 (-0.46, 0.16)	0.35

FEV_1

Variable	N	Estimate	p
Clusters A (T2-low)	71	Reference	
B	125	0.10 (-0.02, 0.23)	0.1
C	265	0.22 (0.11, 0.33)	<0.001
D	272	0.09 (-0.02, 0.20)	0.1
E	101	0.06 (-0.07, 0.20)	0.4

Uncontrolled asthma

Variable	N	Odds ratio	p
Clusters A (T2-low)	56	Reference	
B	106	0.55 (0.26, 1.16)	0.1
C	182	0.60 (0.30, 1.19)	0.1
D	223	0.67 (0.34, 1.30)	0.2
E	57	0.48 (0.20, 1.14)	0.1

Lower exacerbation rates *and* ***greater improvements in lung function and asthma control*** *were noted for Anti–IL5/5R (but not Anti-IgE or Anti-IL4Rα) for all clusters relative to cluster A*

FEV_1: Forced expiratory volume in 1 second; IgE: Immunoglobulin E; IL4Rα: Interleukin 4-receptor-alpha; IL5/5R: Interleukin 5/5-receptor; T2: Type 2

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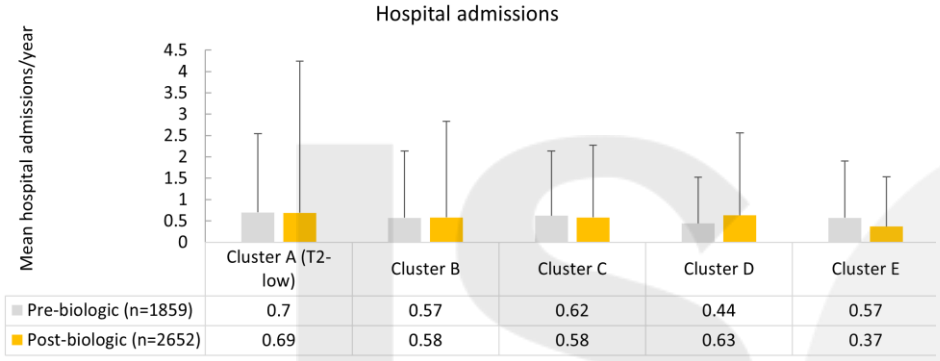
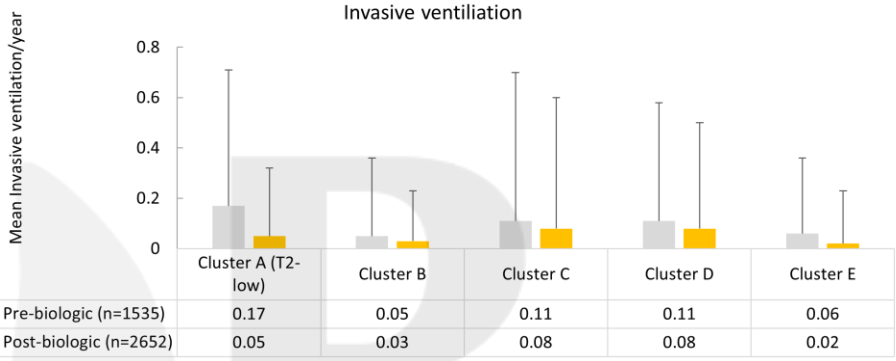
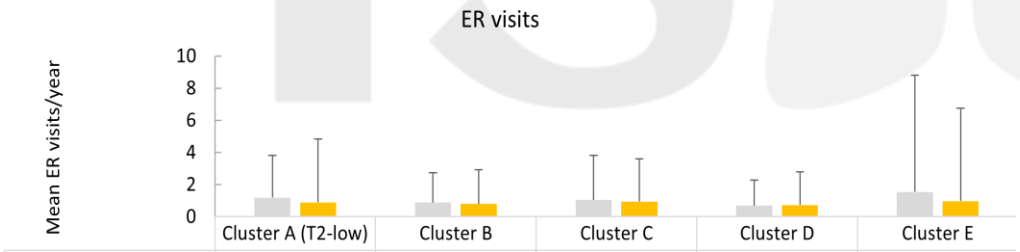
Pre- to post-biologic change in HCRU for each cluster (univariate analysis)



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1859)	0.7	0.57	0.62	0.44	0.57
Post-biologic (n=2652)	0.69	0.58	0.58	0.63	0.37



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1535)	0.17	0.05	0.11	0.11	0.06
Post-biologic (n=2652)	0.05	0.03	0.08	0.08	0.02



	Cluster A (T2-low)	Cluster B	Cluster C	Cluster D	Cluster E
Pre-biologic (n=1850)	1.19	0.87	1.04	0.69	1.53
Post-biologic (n=2652)	0.89	0.79	0.94	0.73	0.97

Pre- to post-biologic reductions *were shown for hospitalizations, ER visits and invasive ventilation,* ***irrespective of the degree of T2 involvement***

ER: Emergency room; HCRU: Healthcare resource utilization; T2: Type 2

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Pre- to post-biologic change in hospital admissions relative to Cluster A (T2-low)

Variable		N	Estimate	p
Clusters	A (T2-low)	68	Reference	
	B	197	0.54 (0.42, 0.68)	<0.001
	C	222	0.63 (0.50, 0.79)	<0.001
	D	315	0.75 (0.61, 0.94)	0.01
	E	77	0.57 (0.41, 0.77)	<0.001

*Patients in clusters B, C, D and E had **significantly greater reductions in hospital admissions for asthma** vs Cluster A*

T2: Type 2

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Pre- to post-biologic change in ER visits relative to Cluster A (T2-low)

Variable		N	Estimate	p	
Clusters	A (T2-low)	68		Reference	
	B	196		0.53 (0.43, 0.65)	<0.001
	C	224		0.68 (0.57, 0.83)	<0.001
	D	313		0.60 (0.50, 0.73)	<0.001
	E	76		0.37 (0.27, 0.49)	<0.001

*Patients in clusters B, C, D and E had **significantly greater reductions in ER visits** vs Cluster A*

ER: Emergency room; T2: Type 2

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Conclusions

Five biomarker clusters along a gradient of T2 involvement were identified using a data-driven approach.

Biologic use was associated with improved outcomes in all clusters but tended to be better at the higher end of the T2 spectrum.

T2-targeted biologics have utility in the management of triple-biomarker-low asthma, but more effective therapies are needed.

Further research is needed to identify pathways specific to T2-low asthma that can be targeted by treatment.

T2: Type 2

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