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

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# Background and aims

[ Asthma Original Research ] CHEST

Characterization of Severe Asthma Worldwide

Data From the International Severe Asthma Registry

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**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.

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**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

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## 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;<br>• 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<br>• For the United States, comorbidity data were captured using International Classification of Diseases, Tenth Revision codes for active diagnosis of comorbidity<br>• 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.

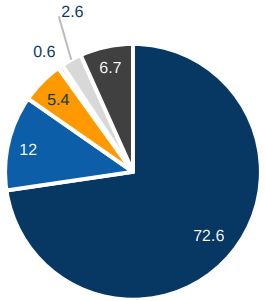
# Results: Patient demographics

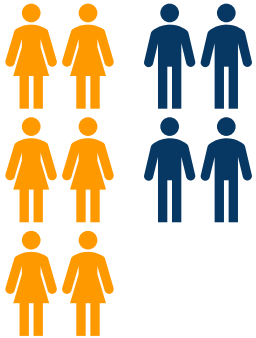
**4,990**
**ELIGIBLE PATIENTS**

**MEAN AGE OF**
**55**
**YEARS**

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

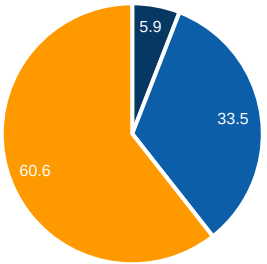
## ETHNICITY



**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**

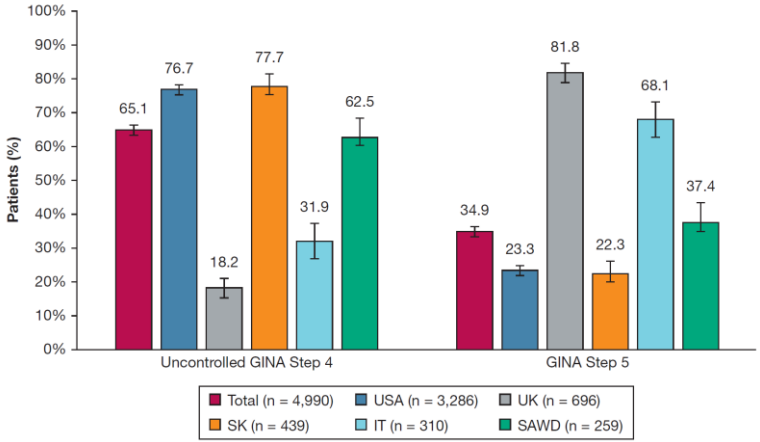
SK had the oldest patients, the lowest prevalence of patients who were overweight or obese, and the highest prevalence of current smokers.

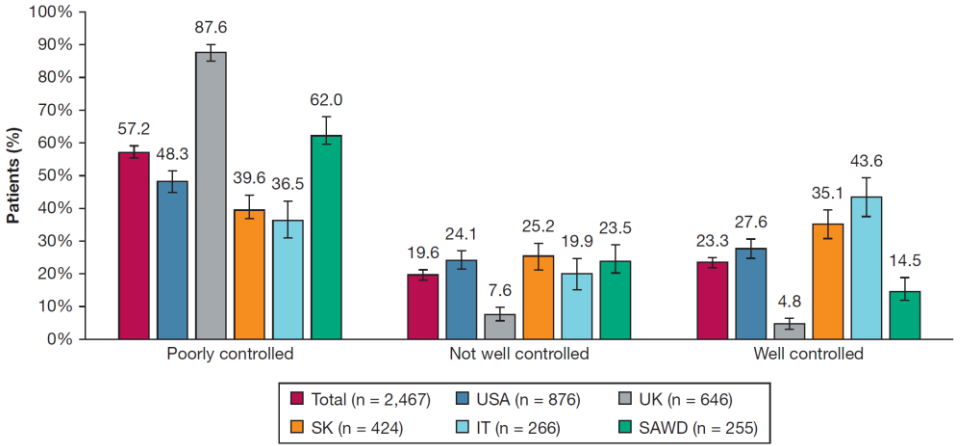
USA: United States of America; SK: South Korea; SAWD: Severe Asthma Web-based Database

# Results: Demographic characteristics

## Asthma Control

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



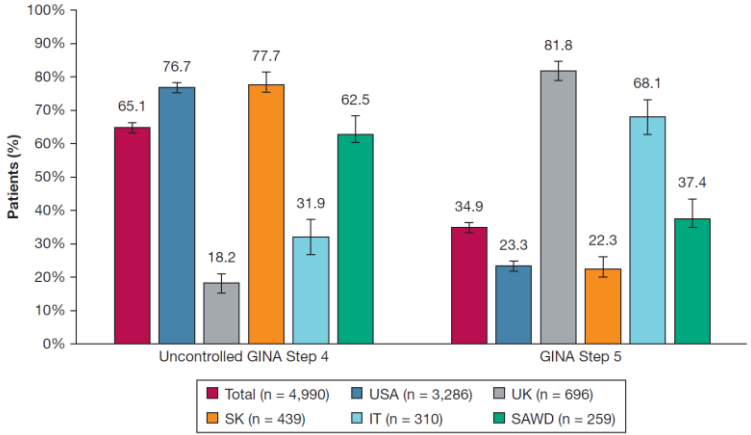

USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

# 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.

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# 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

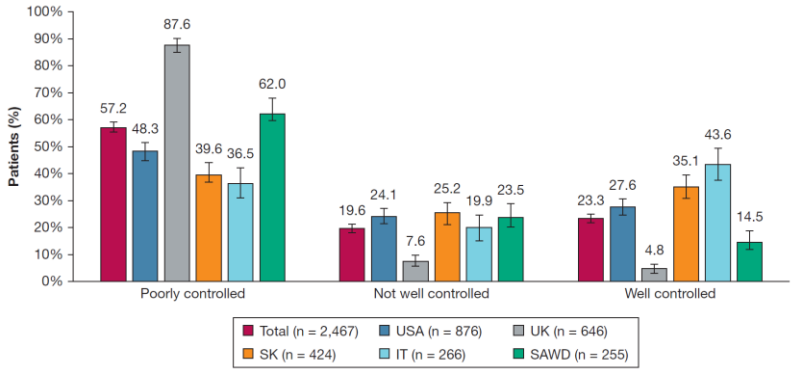
- The mean (SD) age at onset was **30.7** (17.7) **years**.
- 77.5% of patients developed asthma after the age of 12 years, and 34.4% developed it after the age of 40 years.
- Patients from the UK and the SAWD registry developed asthma slightly earlier than this, and those from South Korea and Italy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

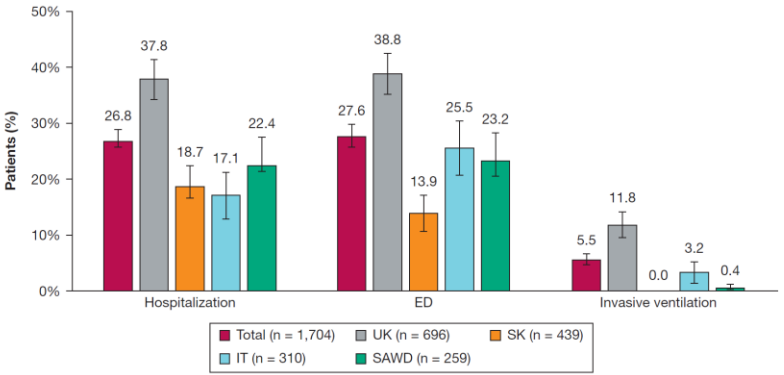
USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

# 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.



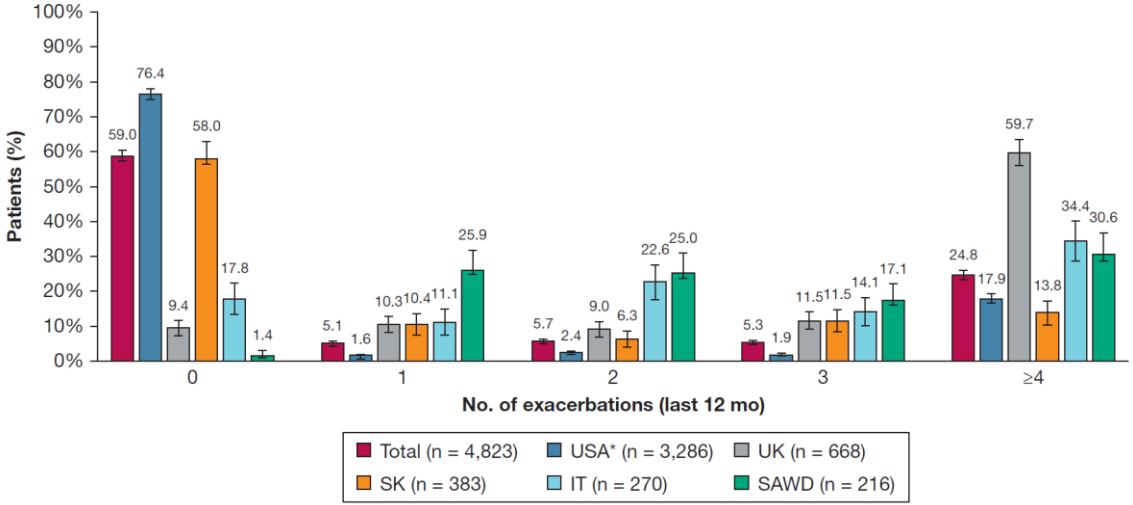




USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

# 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.

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# Results: Clinical characteristics

## Immunoglobulin E (IgE) Concentration

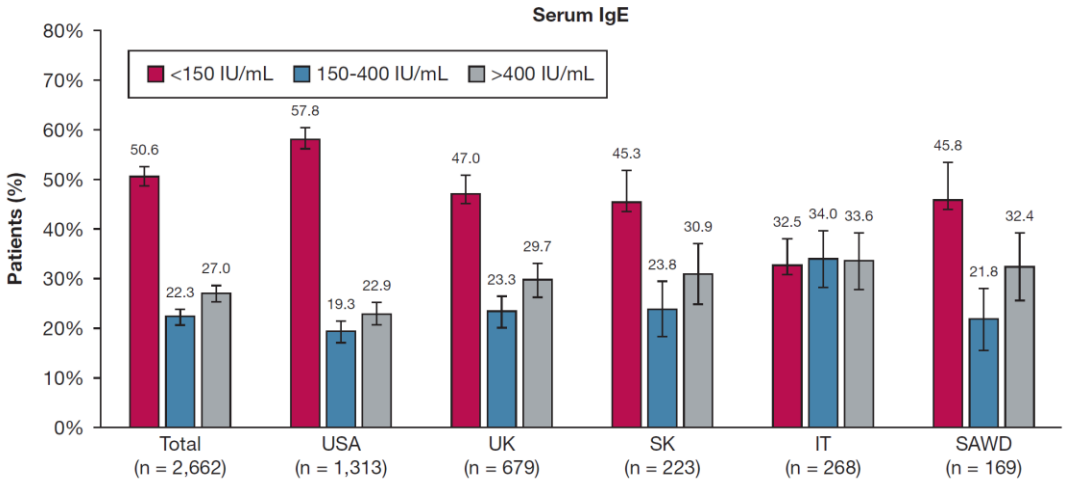
1. Overall, o**ne-half** of the patient population with severe asthma had **low IgE** concentrations, and IgE profile varied according to **severity**.

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.

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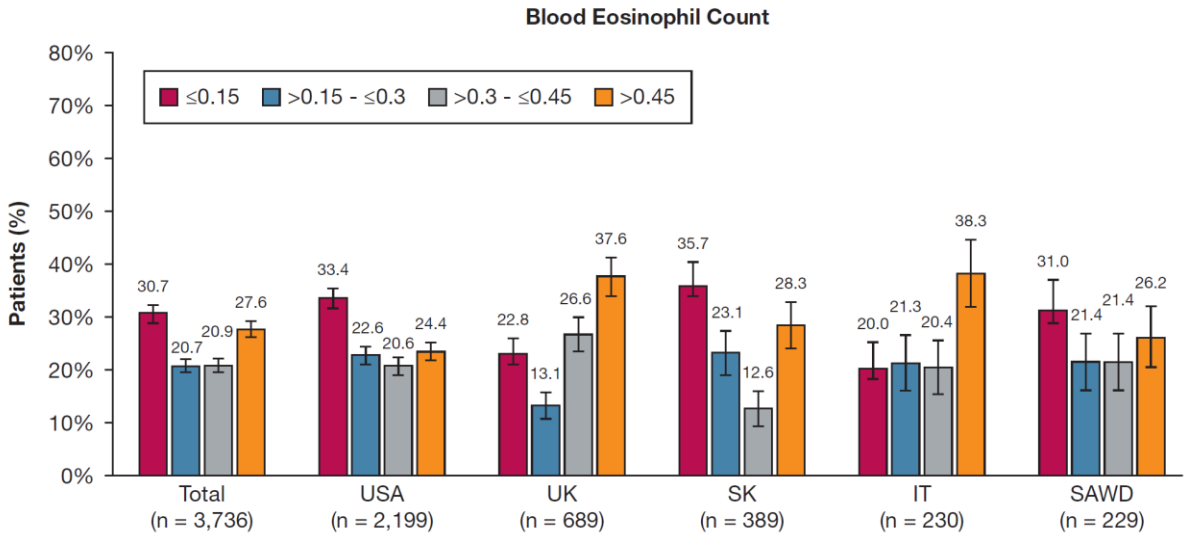
# Results: Clinical characteristics

## Blood Eosinophil Count (BEC)

- 48.5% of patients had a BEC > 0.3x10$^9$/L.
  - This comprises mostly patients from the UK and IT.
- Most patients had a BEC ≤ 0.3x10$^9$/L.

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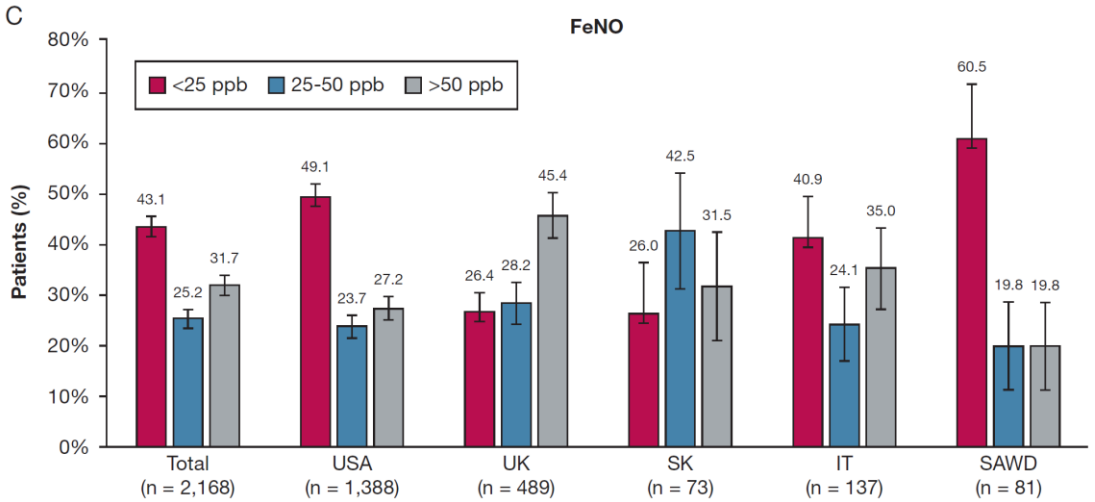
# Results: Clinical characteristics

## 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.

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# 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%): 

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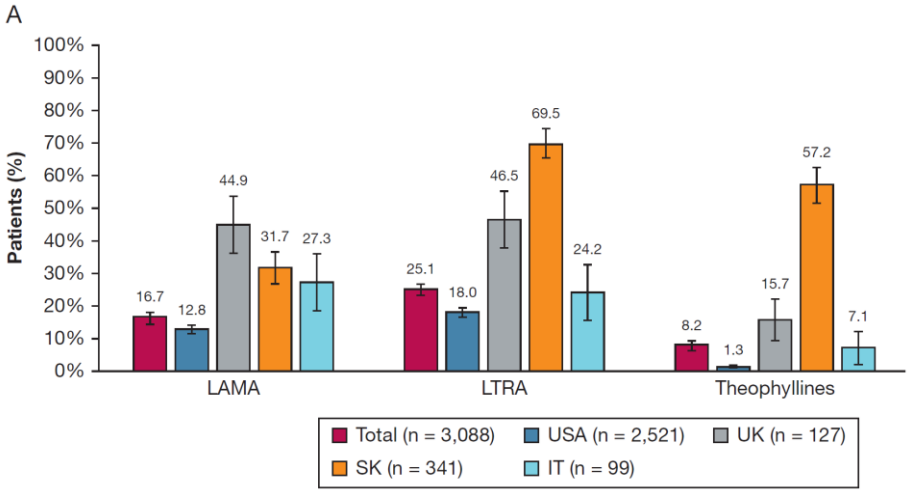
# Results: Clinical characteristics

## 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).

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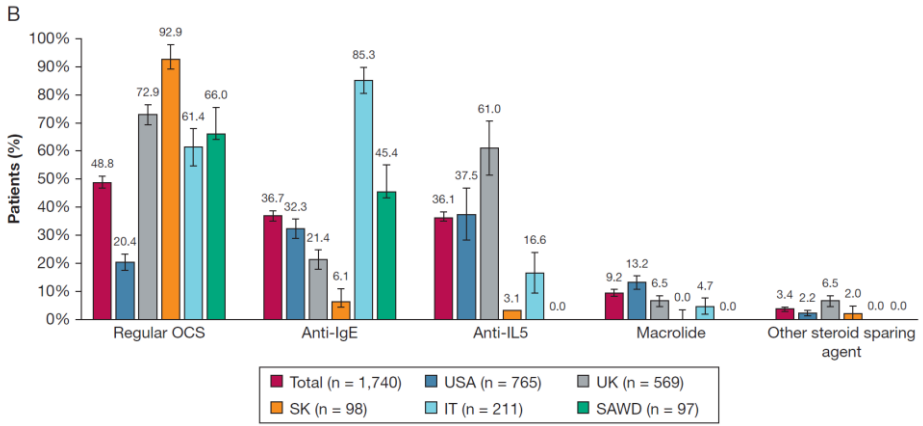
# Results: Clinical characteristics

## 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.

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# 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