# Biomarker relatability in the International Severe Asthma Network

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# Disclosure

Giorgio Walter Canonica has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi93 Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas.

# Background

- Severe asthma accounts for 5-10% of all asthma[1] but accounts for the majority of asthma-related morbidity and economic burden
- Severe asthma is composed of different inflammatory phenotypes[2]
- Clinical inflammatory biomarkers may be used to identify patients with type 2 inflammation suitable for targeted therapy
- These biomarkers are now measured and used routinely for severe asthma management around the world
- Little is known about the relationship between commonly used clinical biomarkers including IgE, blood eosinophils and FeNO


1. *Chung et al, ERJ, 2014*
2. *Wenzel et al, Nature Med, 2012*

# Background

- International Severe Asthma Registry: multicentre, observational data repository
- To date, data from 10 countries: United States, Canada, Greece, Italy, Ireland, South Korea, Bulgaria, Kuwait, the United Kingdom and Spain
- Person-level data from approximately 7,000 severe asthma patients
- Enrolment criteria:
  - Patients ≥ 18 years receiving GINA Step 4 treatment and remaining uncontrolled (with presence of severe asthma symptoms or exacerbations) or GINA Step 5 treatment

  Uncontrolled if:
  - Poor symptom control (ACQ >1.5, ACT <20, or 3 GINA symptoms in the past 4 weeks)
  - Airflow limitation ($FEV_1$ <80%)
  - Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the past year
  - Frequent, severe asthma exacerbations (2 or more as per ATS/ERS criteria)

# Aim

- To describe the prevalence and overlap of the three clinically used biomarkers in a large international cohort of severe asthma patients in the context of increasing numbers of targeted therapies

- To characterise and compare severe asthma patients positive for different combinations of asthma biomarkers

# Study Design

- Cross-sectional study
- Baseline at the point of enrolment in ISAR
- Inclusion criteria:
  - Patients ≥ 18 years receiving GINA Step 4 treatment and remaining uncontrolled (with presence severe asthma symptoms or exacerbations) or GINA Step 5 treatment
  - AND
  - All three biomarkers measured and available at baseline
- Cut points for biomarker positivity are as follows:
  - Blood eosinophils ≥ 300 cells/uL
  - FeNO ≥ 25ppb[1]
  - Total IgE ≥ 75 kilounits per litre (kU/L)[2]
- Patients classified into 8 possible groups based on biomarker combination (Figure 1)

# Study Design

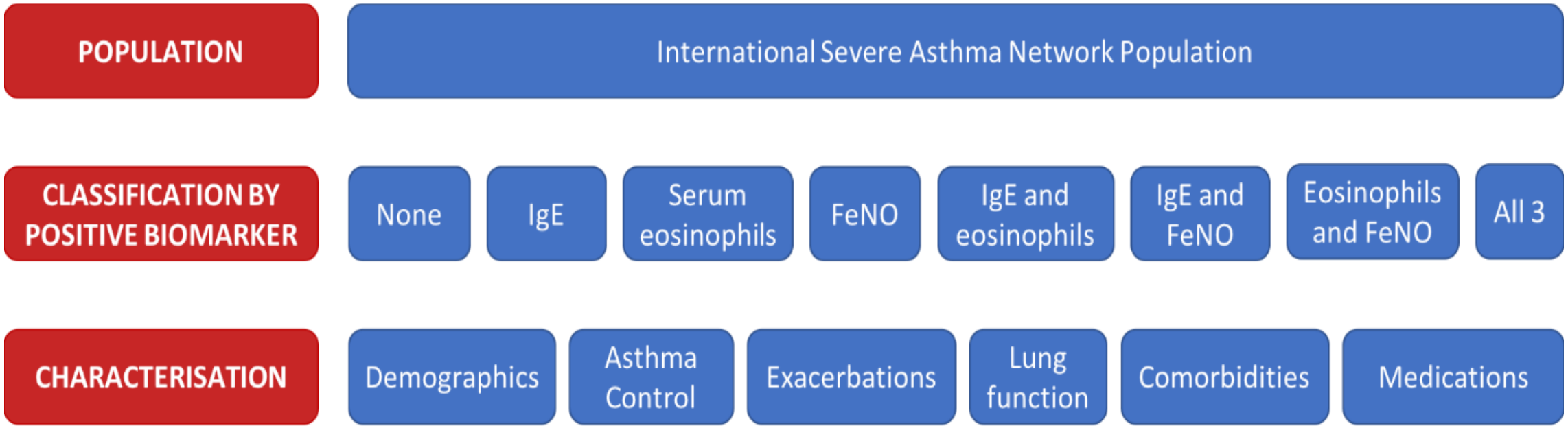



*Figure 1: Biomarker Relatability in the International Severe Asthma Registry (BRISAR) Study Design*

# Results

- 961 adult severe asthma patients met inclusion
- 10 countries in North America, Europe and Asia
- 61% female
- Mean age 54 years (SD ±16)
- BMI 30 (SD ±7.6)
- Post bronchodilator $FEV_1$ 2.3 L (SD ±0.83)*

Overall:

- 57% eosinophil positive
- 54% FeNO positive
- 63% IgE positive

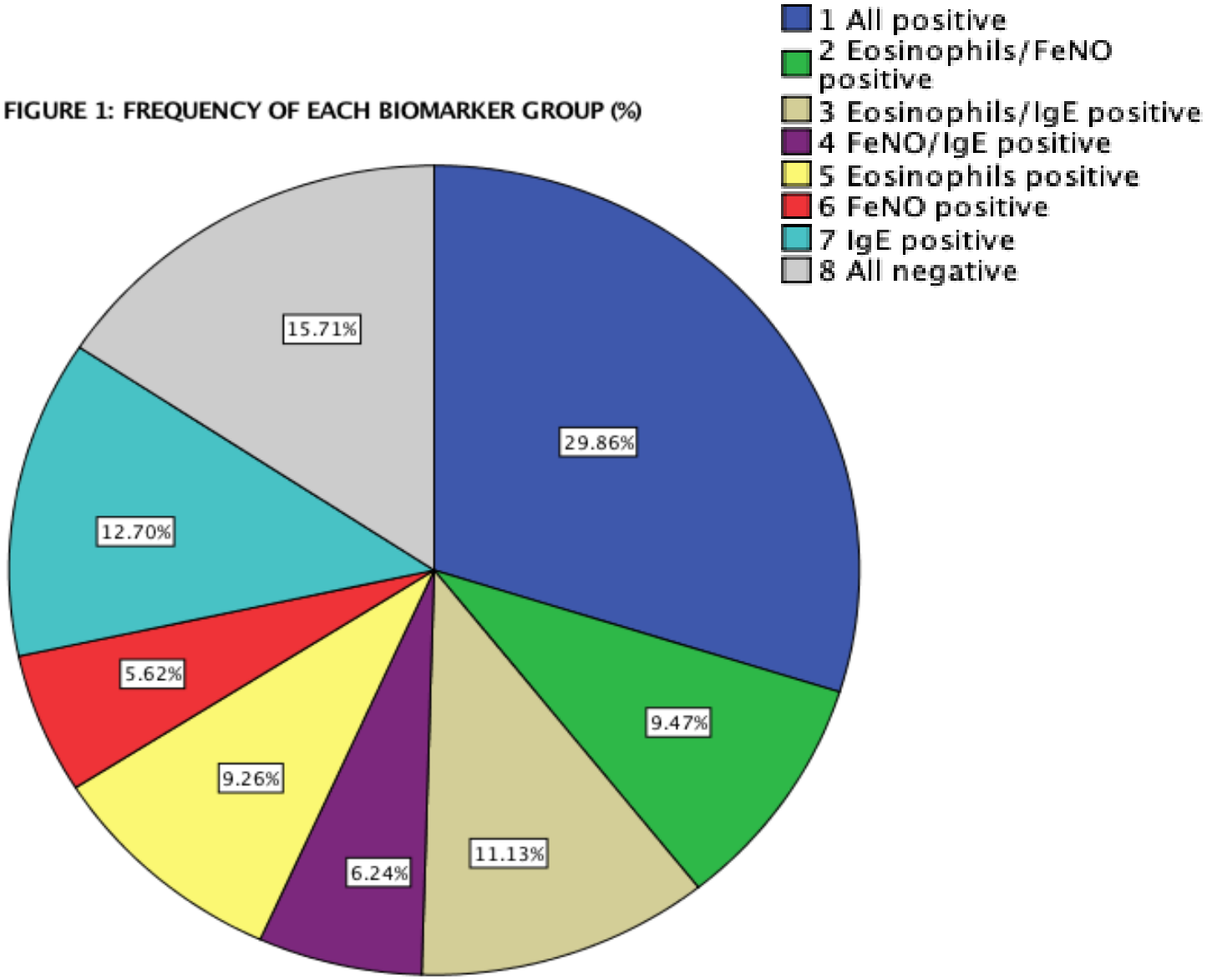
| Positive biomarkers | Eos FeNO IgE | Eos FeNO | Eos IgE | Eos | FeNO IgE | FeNO | IgE | None | P value |
|---|---|---|---|---|---|---|---|---|---|
| **Point prevalence of each group: % of total (number, 961)** | 30% (287) | 10% (91) | 11% (107) | 6% (60) | 9% (89) | 6% (54) | 13% (122) | 16% (151) | |
| **% female** | 55%* | 56% | 65% | 75% | 46% | 54% | 62% | 75%* | *<0.0001 |
| **% asthma not controlled** | 47% | 67% | 56% | 68% | 63% | 85% | 72% | 80% | NS |
| **Exacerbations past 12 months (mean)** | 1.4 | 1.8 | 1.1 | 2.1 | 0.65 | 0.75 | 1.1 | 1.5 | 0.4 |
| **Post bronchodilator FEV1 (litres)** | 2.5* | 2.3 | 2.2 | 2.3 | 2.5 | 2.5 | 2.2 | 2.2* | *0.036 |
| **Oral corticosteroids (number)** | 138 | 52 | 41 | 26 | 30 | 25 | 51 | 67 | N/A |
| **Number of patients prescribed Anti IgE (number)** | 59 | 5 | 33 | 3 | 20 | 6 | 36 | 11 | N/A |
| **Number of patients prescribed Anti IL5 (number)** | 86 | 31 | 22 | 21 | 17 | 10 | 18 | 11 | N/A |
| **Number of patients prescribed Anti IL4/13** | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | N/A |

*Table: Characteristics of biomarker groups*

*% predicted not available for this analysis

# Results

FIGURE 1: FREQUENCY OF EACH BIOMARKER GROUP (%)



# Results

- The triple negative group (compared to the triple positive group) had:
  - More females:
    - 75% versus 55%, p<0.0001
  - Worse lung function:
    - Post bronchodilator FEV1 2.2 versus 2.5 litres, p=0.04
  - Worse asthma control (non-significant)
    - 80% versus 47%
- Proportion on long term oral corticosteroids was similar in both groups: 48% versus 44%

# Limitations

- Only 975 patients (of >7000 total) had all three biomarkers measured at baseline
- Female sex may have confounded the lung function findings
- Where possible baseline biomarkers were measured prior to initiation of biologics but it remains a possibility that treatments may have confounded the results

# Conclusion

- One third of this large international severe asthma cohort were triple positive while 16% were triple negative
  - Impacting on biologic eligibility

- The triple negative group had a higher proportion of females and greater airflow obstruction representing an unmet burden of disease