What have we learned from the UK severe asthma registry and ISAR?

Andrew Menzies-Gow

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Conflicts of interest

- I am an employee of and own shares in AstraZeneca
- Attended advisory boards: AstraZeneca, GlaxoSmithKline, Novartis, Regeneron, Sanofi, Teva
- Speaker fees: AstraZeneca, Novartis, Sanofi, Teva
- Participated in research: AstraZeneca
- Consultancy agreements: AstraZeneca, Sanofi

Agenda

- Why we started UK SAR and what did it show?
- ISAR: What have we learnt with global collaboration?
- The future of severe asthma registries

The burden of severe asthma

262M people have asthma worldwide[1,2,3]

1 in 10 people

have **severe** asthma, requiring:

High-dose ICS-based therapy

Other asthma medications

640k severe asthma patients in EU5

Severe asthma patients have poorer outcomes[4,5]

Uncontrolled **severe asthma*** patients:

8x risk of death

(15k per year in EU[6])

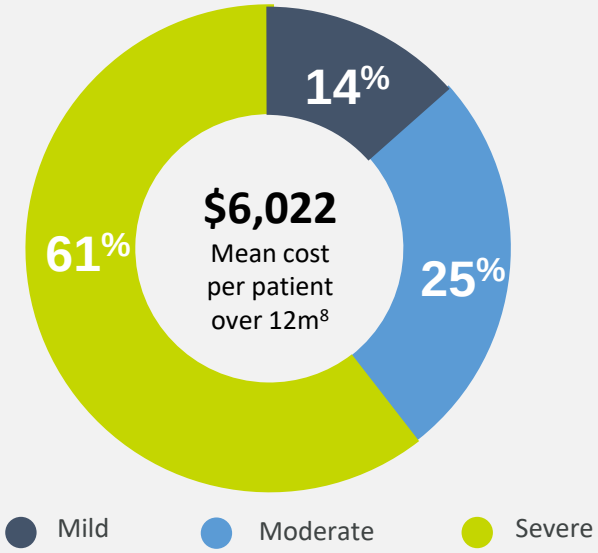
10x risk of hospital stays

(500k per year in EU[6])

Major impact on **quality of life**

Severe asthma accounts for majority of asthma costs[7]

Share (%) of total direct cost of asthma



* Compares severe uncontrolled asthma with severe controlled asthma

1. Chung KF et al. Eur Respir J. 2014 Feb;43(2):343-73. 2. To T et al. BioMed Central Public Health. 2012: 12(204). 3. Hekking PPW et al. J Allergy Clin Immun. 2015:135(4):896-902. 4. Price D et al. NPJ Prim Care Respir Med 2014; 12; 24: 14009., 5. Fernandes AG et al, J Bras Pneumol. 2014; 40(4): 364-372, 6. http://www.asthma.org.uk/News/asthma-experts-form-new-partnership-to-halve-european-asthma-deaths [Accessed 5 November 2014] 7. Sadatsafavi M et al. Can Respir J 2010; 17: 74-80. 8. Sullivan SD, Rasouliyan L, Russo PA, et al. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy 2007;62:126–33.

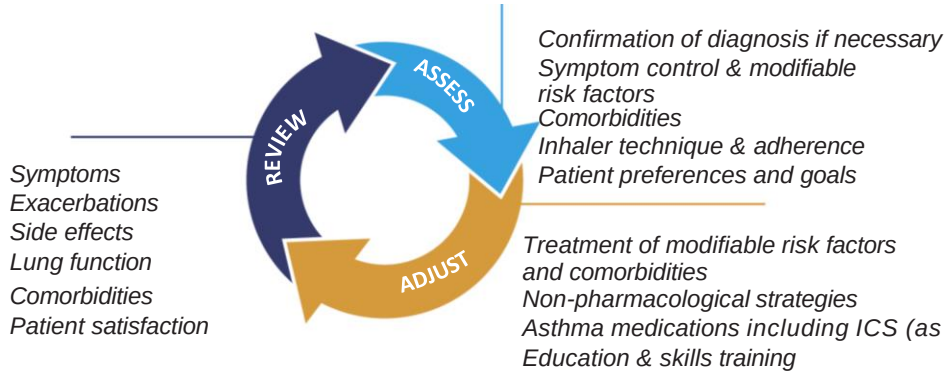
GINA Recommends Stepwise Treatment Escalation with biologics at Step 5

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review

For individual patient needs



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

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

See GINA severe asthma guide

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

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken[a]	Low dose maintenance ICS[a]	Low-dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: As-needed SABA				
Low-dose ICS whenever SABA taken[a], or daily LTRA[b], or add HDM SLIT		Medium dose ICS, or add LTRA[b], or add HDM SLIT	Add LAMA or LTRA[b] or HDM SLIT, or switch to high dose ICS-only	Add azithromycin (adults) or LTRA[b]. As last resort, consider adding low dose OCS but consider side-effects

GINA = Global Initiative for Asthma; HDM = house dust mite; ICS = inhaled corticosteroid(s); IgE = immunoglobulin E; IL4Rα = interleukin 4 receptor alpha; IL5 = interleukin 5; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid(s); SABA = short-acting β_2-agonist; SLIT = sublingual immunotherapy
TSLP = thymic stromal lymphopoietin

[a]Anti-inflammatory reliever; [b]If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.
GINA. Global Strategy for Asthma Management and Prevention. 2024.

Why is severe asthma important in the UK?

- Patients with difficult to control asthma have:
  - Decreased quality of life
  - Side effects from high-dose steroids
  - Increased risk of death?

Royal College of Physicians

Why asthma still kills

The National Review of Asthma Deaths (NRAD)

Report prepared by:

Dr Mark L Levy	NRAD clinical lead, Royal College of Physicians (RCP)
Rachael Andrews	NRAD programme coordinator, Royal College of Physicians (RCP)
Rhona Buckingham	Operations director, Clinical Effectiveness and Evaluation Unit (CEEU), Royal College of Physicians (RCP)
Hannah Evans	Medical statistician, Royal College of Physicians (RCP)
Caia Francis	Senior lecturer in adult nursing, University of the West of England, and former chair, respiratory forum, Royal College of Nursing (RCN)
Rosie Houston	NRAD programme manager, Royal College of Physicians (RCP) (until February 2013)
Derek Lowe	Medical statistician, Royal College of Physicians (RCP)
Dr Shuaib Nasser	Consultant allergist and respiratory physician; British Society for Allergy and Clinical Immunology (BSACI); Eastern Region Confidential Enquiry of Asthma Deaths
Dr James Y Paton	Reader in paediatric respiratory medicine, Royal College of Paediatrics and Child Health (RCPCH)
Navin Puri	Programme manager for respiratory medicine (asthma and lung cancer), Royal College of Physicians (RCP)
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Professor Mike Thomas	Professor of primary care research, University of Southampton; Primary Care Respiratory Society UK (PCRS-UK)

7 Special situations

7.1 DIFFICULT ASTHMA

D

Patients with difficult asthma should be systematically evaluated, including:

- confirmation of the diagnosis of asthma and
- identification of the mechanism of persisting symptoms and assessment of adherence with therapy.

D

This assessment should be facilitated through a dedicated multidisciplinary difficult asthma service, by a team experienced in the assessment and management of difficult asthma.

Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry

Liam G Heaney,[1] Chris E Brightling,[2] Andrew Menzies-Gow,[3] Michael Stevenson,[4] Rob M Niven,[5] on behalf of the British Thoracic Society Difficult Asthma Network

Thorax 2010;**65**:787–794.

Table 4 Healthcare utilisation and medication

	All (382)	Belfast (95)	Brompton (99)	Leicester (79)	Manchester (109)	
Unscheduled visits in preceding 12 months (n)	4 (2–6) (372)	5 (2–9) (91)	4 (1–6) (99)	4 (2–6) (79)	3 (2–5) (103)	p=0.007
Rescue steroid courses in the previous year (n)	4 (2–6) (352)	5 (1–6) (84)	5 (2.75–7) (86)	4 (2–6) (79)	2 (0–4) (103)	p<0.001
Hospital admissions in preceding 12 months (n)	0 (0–2) (377)	0 (0–1) (93)	1 (0–3) (99)	0 (0–1) (79)	0 (0–1) (106)	p<0.001
Total number of ICU admission (range) (n)	0 Range (0–11) (379)	0 Range (0–4) (95)	0 Range (0–11) (99)	0 Range (0–1) (79)	0 Range (0–10) (106)	p=0.012
Maintenance oral steroids (%)	158 of 379 (41.7)	32 of 95 (33.7)	57 of 98 (58.2)	30 of 79 (38.0)	39 of 107 (36.4)	p=0.002
Oral steroid dose (mg) (n)	15 (10–20) (154)	13 (6–20) (31)	15 (10–20) (57)	10 (7.5–15) (30)	15 (10–30) (36)	p=0.021
BDP equivalent dose (μg) (n)	2000 (1000–2000) (362)	1800 (1000–2000)m (93)	2000 (2000–2000) (94)	2000 (1600–2000) (78)	1500 (1000–2000) (97)	p<0.001
SABA use per day	6 (4–8) (262)	8 (4–10) (31)	4 (6–8) (75)	4 (2–6) (62)	8 (4.75–10) (94)	p=0.001
Theophylline (n)	146 of 375 (37.9)	40 of 95 (42.1%)	52 of 97 (53.6%)	25 of 77 (32.5%)	29 of 106 (27.4%)	p=0.001
Nebuliser use (%)	165 of 376 (43.9)	45 of 94 (47.9)	64 of 97 (66.0)	19 of 79 (24.0)	37 of 106 (34.9)	p<0.001
Steroid-sparing meds						
None	7 of 372	91	95	78	101	p=0.361
Methotrexate	(1.9)	1	0	0	3	
Ciclosporin		0	1	1	0	
Azathioprine		0	0	0	1	
Anti-IgE treatment	3 of 378 (0.8)	0	0	0	3	p=0.054
PPI (%)	111 of 360 (29.7)	28 of 95 (29.5)	32 of 97 (32.9)	18 of 79 (22.8)	33 of 107 (30.8)	p=0.498
Aspirin/NSAID sensitivity (%)	36 of 378 (9.5)	8 of 93 (8.6)	8 of 92 (8.7)	10 of 76 (13.2)	10 of 105 (9.5)	p=0.741
Antihistamine (%)	89 of 374 (23.8)	17 of 94 (18.1)	26 of 96 (27.1)	16 of 78 (20.5)	30 of 106 (28.3)	p=0.271
Nasal steroids (%)	96 of 374 (25.7)	27 of 94 (28.7)	24 of 96 (25.0)	17 of 78 (21.8)	28 of 106 (26.4)	p=0.77
Leukotriene receptor antagonists (%)	141 of 375 (37.6)	52 of 94 (55.3)	42 of 96 (43.8)	25 of 79 (31.6)	22 of 106 (20.8)	P<0.001

Group data (mean±SD or median (IQR) unless stated otherwise) for all subjects are presented in column 2 followed by data for individual centres. Between-centre comparisons for continuous variables were made using one-way analysis of variance or Kruksal–Wallis test (for posthoc comparisons, see text) and for categorical variables using χ^2 exact testing.
Significance was taken as $p<0.01$.
BDP, beclomethasone dipropronate; ICU, intensive care unit; IgE, immunoglobulin E; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SABA, short-acting β-agonist.

Table 5 Lung function

	All (382)	Belfast (95)	Brompton (99)	Leicester (79)	Manchester (109)	
Prebronchodilator spirometry (n) FEV_1 (litres)	(371)	(95)	(96)	(77)	(103)	
% predicted	1.94±0.81	1.92±0.70	1.86±0.078	2.21±0.86	1.84±0.87	p=0.013
	65.9±23.6	65.7±24.0	60.4±20.4	75.3±22.8	64.7±25.0	p=0.001
FVC (litres) % predicted	3.07±1.01	3.07±0.87	3.26±1.07	3.11±1.10	2.90±1.00	p=0.081
	81.9±19.8	82.5±20.2	82.4±20.4	83.1±21.1	79.1±19.6	p=0.424
FEV_1/FVC ratio %	63.1±15.2	62.7±14.8	56.2±14.5	71.1±13.3	63.4±14.8	p<0.001
Subjects with baseline postbronchodilator study (n)	(261)	(62)	(43)	(75)	(81)	
Prebronchodilator FEV_1 (litres) (% predicted)	1.90±0.83	1.69±0.63	1.83±0.80	2.22±0.87	1.81±0.87	p=0.001
	(64.0±23.1)	(56.9±18.6)	(58.6±20.5)	(75.4±23.0)	(62.7±24.3)	p<0.001
Prebronchodilator FVC (litres) (% predicted)	3.05±1.05	2.99±0.94	3.36±1.15	3.11±1.10	2.89±1.02	p=0.128
						p=0.220
	(80.6±19.8)	(79.0±19.3)	(84.1±18.1)	(83.3±21.4)	(77.8±19.3)	
Postbronchodilator FEV_1 (litres) (% predicted)						p=0.020
	2.18±0.88	1.93±0.70	2.29±1.03	2.36±0.86	2.14±0.89	p=0.004
	(73.6±24.2)	(65.3±21.4)	(73.6±26.3)	(80.7±22.5)	(74.2±24.7)	
Postbronchodilator FVC (litres) (% predicted)						p=0.246
	3.29±1.06	3.21±0.97	3.60±1.26	3.30±1.11	3.23±0.95	p=0.664
	(87.4±19.1)	(85.2±19.9)	(90.9±21.1)	(87.8±20.3)	(87.4±16.4)	
Postbronchodilator FEV_1/FVC ratio (%)						p<0.001
	65.0±14.6	60.6±12.4	61.44±15.82	71.6±12.3	65.0±15.6	
Total lung capacity % predicted (n)	104.9±16.8 (265)	107.8±17.8 (80)	109.1±13.9 (96)		98.0±16.6 (89)	p<0.001
Residual volume % predicted (n)	134.4±42.0 (263)	127.8±44.2 (80)	151.0±40.1 (97)		121.8±35.9 (86)	p<0.001
K_{CO} % predicted (n)	101.5±17.5 (256)	97.3±17.7 (79)	98.0±13.8 (94)		110.04±18.5 (83)	p<0.001

Group data (mean±SD) for all subjects are presented in column 2 followed by data for individual centres. Between-centre comparisons for continuous variables were made using one-way analysis of variance (for posthoc comparisons, see text).
Significance was taken as $p<0.01$.
FEV_1, forced expiratory volume in 1 s. FVC, forced vital capacity, K_{CO}, carbon monoxide transfer coefficient.

Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry

Joan Sweeney,[1] Chris E Brightling,[2] Andrew Menzies-Gow,[3] Robert Niven,[4] Chris C Patterson,[5] Liam G Heaney,[1] on behalf of the British Thoracic Society Difficult Asthma Network

Thorax 2012;**67**:754–756.

Table 1 Lung function and healthcare outcomes for cohort

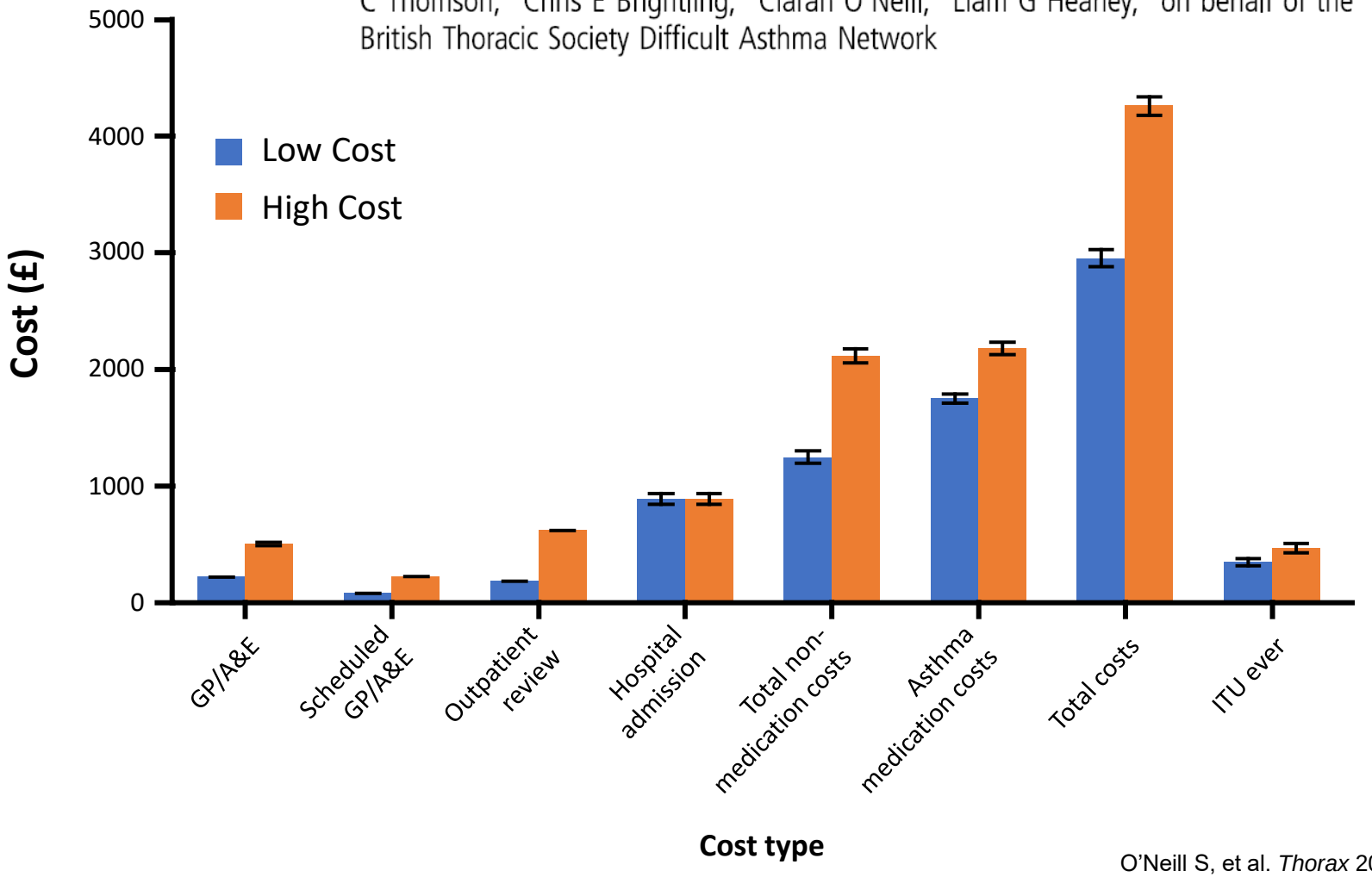
	Baseline	Follow-up	p Value
Pre-bronchodilator FEV_1 % predicted (259)	66.4±23.7	72.7±26.8	<0.001
Pre-bronchodilator FVC % predicted (242)	82.7±20.3	86.5±21.5	0.002
Post-bronchodilator FEV_1 % predicted (77)	79.2±21.5	77.6±30.7	0.61
Post-bronchodilator FVC % predicted (72)	90.6± 19.8	86.3± 25.9	0.08
Rescue oral steroids in previous 12 months (302)	4 (2–6)	2 (0–4)	<0.001
Hospital admissions in previous 12 months (324)	0 (0–2)	0 (0–1)	<0.01
Unscheduled visits in previous 12 months (315)	4 (2–6)	2 (0–6)	<0.05
Inhaled steroid dose, BDP equivalent (327)	2000 (1000–2000)	2000 (1200–2000)	0.80
Average daily SABA use (205)	6 (4–9)	8 (4–10)	0.058
Blood eosinophils (206)	0.33 (0.11–0.60)	0.20 (0.09–0.43)	<0.001
FeNO (112)	40 (18–69)	89 (77–102)	<0.001
Body mass index	29.2±6.5	30.2±6.4	<0.001

Group data (mean±SD or median (IQR)) for all subjects are presented in column 1 followed by data for individual centres. Comparisons were made using paired samples t tests or Wilcoxon signed rank tests; significance was taken as $p<0.05$.
BDP, beclometasone dipropionate; FeNO, fractional expiratory nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SABA, short-acting β agonist.

AUDIT, RESEARCH AND GUIDELINE UPDATE

The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry

Stephen O'Neill,[1] Joan Sweeney,[2] Chris C Patterson,[3] Andrew Menzies-Gow,[4] Rob Niven,[5] Adel H Mansur,[6] Christine Bucknall,[7] Rekha Chaudhuri,[8] Neil C Thomson,[8] Chris E Brightling,[9] Ciaran O'Neill,[1] Liam G Heaney,[2] on behalf of the British Thoracic Society Difficult Asthma Network



O'Neill S, et al. *Thorax* 2015: 70: 376–8

CHEST™

Dedicated Severe Asthma Services Improve Health-care Use and Quality of Life

David Gibeon, MBChB; Liam G. Heaney, MD; Chris E. Brightling, PhD, FCCP; Rob Niven, MD; Adel H. Mansur, PhD; Rekha Chaudhuri, MD; Christine E. Bucknall, MD; and Andrew N. Menzies-Gow, PhD; on behalf of the British Thoracic Society Difficult Asthma Network

- 493 patients referred with difficult asthma to regional severe asthma referral centres
- Prospective data collection for 12 months after entry into severe asthma service compared with 12 months prior to referral
- 397 (81%) diagnosed with severe asthma

[148#4 **CHEST** OCTOBER 2015]

TABLE 2] Comparison of Health-care Use and Lung Function at Baseline and Follow-up

Health-care Use/Lung Function	Baseline	Follow-up	Days Between Visits	No.	*P* Value
Overall	...	...	286 (248-376)	346	...
Health-care use (≥1 visit in past year)					
Primary care or ED, %	201 (87.8)	152 (66.4)	286 (247-386)	229	<.0001
Hospital admissions, %	131 (48.0)	90 (33.0)	285 (249-380)	273	.0005
Of those with ≥1 visit in past year					
Primary care or ED	4 (2-6)	1 (0-3)	286 (247-386)	...	<.0001
Hospital admissions	2 (1-3)	2 (1-3)	285 (249-380)	...	.28
Total IgE, kU/L	230 (58-690)	178 (54-620)	296 (251-411)	83	.045
Blood eos count × 10^9/L	0.3 (0.15-0.6)	0.27 (0.11-0.6)	281 (251-376)	133	.38
FENO, ppb	34.5 (15.3-74.3)	28.5 (15.3-69)	276 (246-333)	76	.22
Lung function					
Pre-BD FEV_1, L	1.92 (1.42-2.51)	2.03 (1.6-2.61)	285 (251-385)	219	.091
Pre-BD FEV_1 % predicted	71 (51-88)	75 (58-89)	283 (250-382)	207	.0071
Pre-BD FEV_1/FVC ratio	66 (55-75)	70 (61-77)	285 (251-391)	207	<.0001
Post-BD FEV_1, L	1.93 (1.65-2.87)	2.2 (1.43-2.87)	266 (243-301)	50	.20
Post-BD FEV_1 %	78 (54-89)	79 (57-96)	259 (241-299)	47	.17

Data are presented as No. (%) or median (interquartile range). BD = bronchodilator; eos = eosinophil; FENO = fraction of exhaled nitric oxide; ppb = parts per billion.

TABLE 4] Comparison of QoL Scores at Baseline and Follow-up

Score	Baseline	Follow-up	Days Between Visits	No.	*P* Value
AQLQ					
Overall score	3.0 (2.5-3.9)	3.7 (2.8-5.1)	294 (259-433)	106	<.0001
Symptomatic	3 (2.2-4.0)	3.6 (2.6-4.9)	293 (259-435)	109	<.0001
Activity	3.3 (2.5-4.4)	4 (2.6-5)	295 (262-436)	112	<.0001
Emotional	3.1 (1.8-4.4)	3.6 (2.8-5.5)	294 (261-438)	114	<.0001
Environmental	3.3 (2.3-5.3)	4.3 (2.7-5.8)	295 (261-441)	114	<.0001
ACQ	3.4 (2.5-4.1)	2.8 (1.9-4.0)	292 (256-448)	118	.001

Data are presented as median (interquartile range). ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; QoL = quality of life.

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

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**

Background and aims

Original Article

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

Lakmini Bulathsinhala, MPH[a], Nevaashni Eleangovan, BSC[a], Liam G. Heaney, MD[b], Andrew Menzies-Gow, PhD, FRCP[c], Peter G. Gibson, MBBS, FRACP[d,e], Matthew Peters, PhD, MD[f], Mark Hew, MBBS, PhD, FRACP[g], Job F. M. van Boven, PharmD, PhD[h], Lauri Lehtimäki, MD[i], Eric van Ganse, MD, PhD, FRCP[j], Manon Belhassen, PhD[j], Erin S. Harvey, PhD[d,e], Luis Perez de Llano, MD, PhD[k], Anke H. Maitland-van der Zee, PharmD, PhD[l], Nikolaos G. Papadopoulos, MD, PhD[m,n], J. Mark FitzGerald, MB, MD, FRCPI, FERS, FRCPC[o], Celeste Porsbjerg, MD, PhD[p], G. Walter Canonica, MD[q,r], Vibeke Backer, MD, DMSci[s], Chin Kook Rhee, MD, PhD[t], Katia M. C. Verhamme, MD, PhD[u], Roland Buhl, MD[v], Borja G. Cosio, MD, PhD[w], Victoria Carter, BSc[a], Chris Price, LLB[a], Thao Le, BComm[a], Martina Stagno d'Alcontres, PhD[a], Gokul Gopalan, MD[a], Trung N. Tran, MD, PhD[a], and David Price, FRCGP[a,w,x]

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

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

Background and aims

[Asthma Original Research] CHEST

Characterization of Severe Asthma Worldwide

Data From the International Severe Asthma Registry

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 Mod; 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

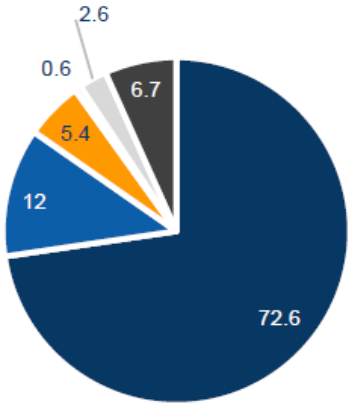
Results: Patient demographics

4,990
ELIGIBLE PATIENTS

MEAN AGE OF
55
YEARS

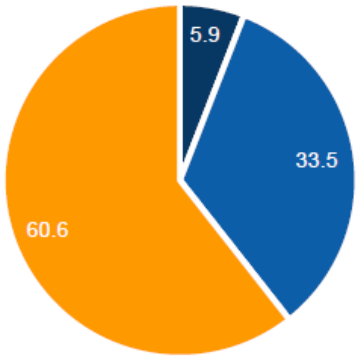
MEAN AGE OF
30.7
YEARS AT ASTHMA ONSET

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

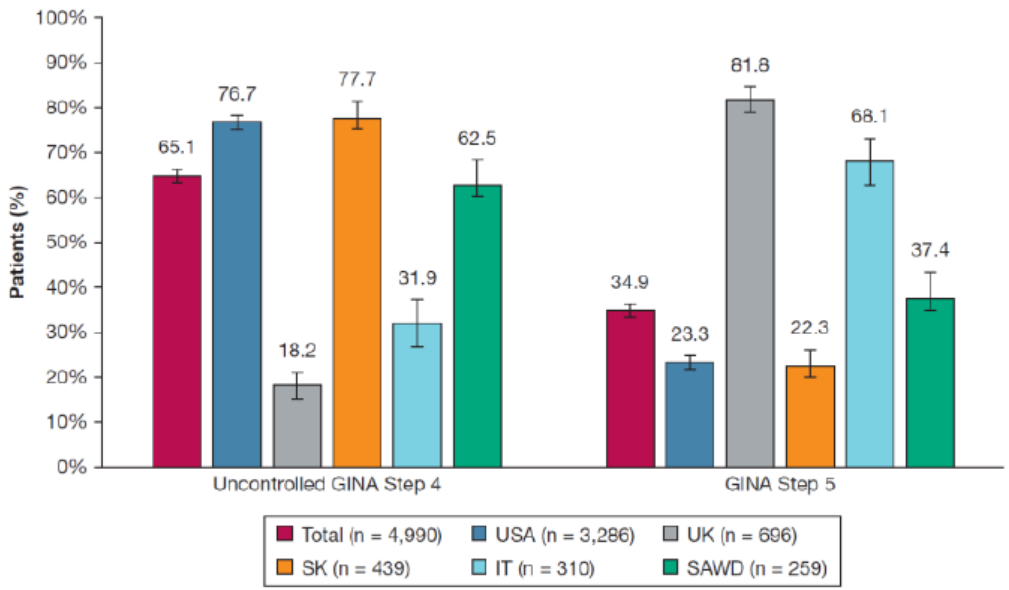
SK had the oldest patients, the lowest prevalence of patients who were overweight or obese, and the highest prevalence of current smokers.

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

Results: 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.

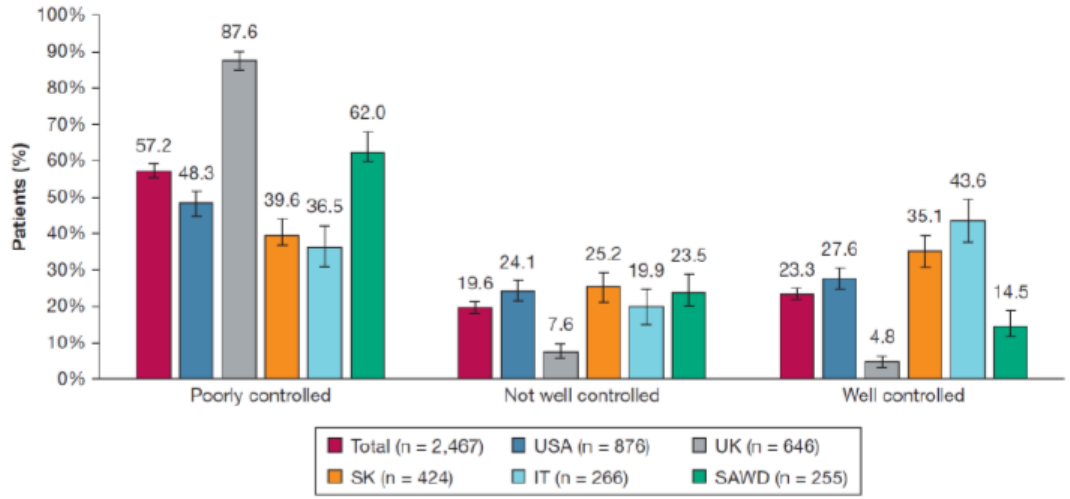


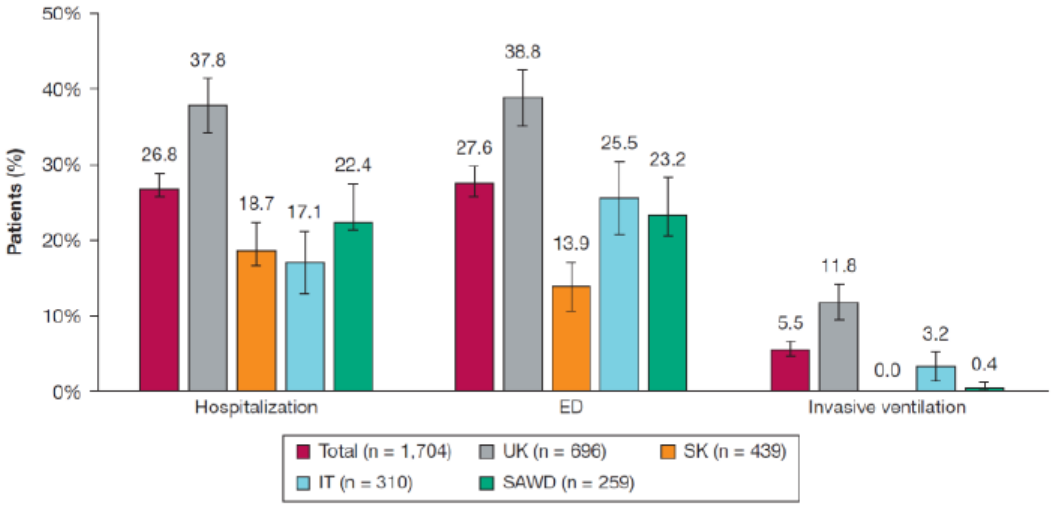
USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

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.



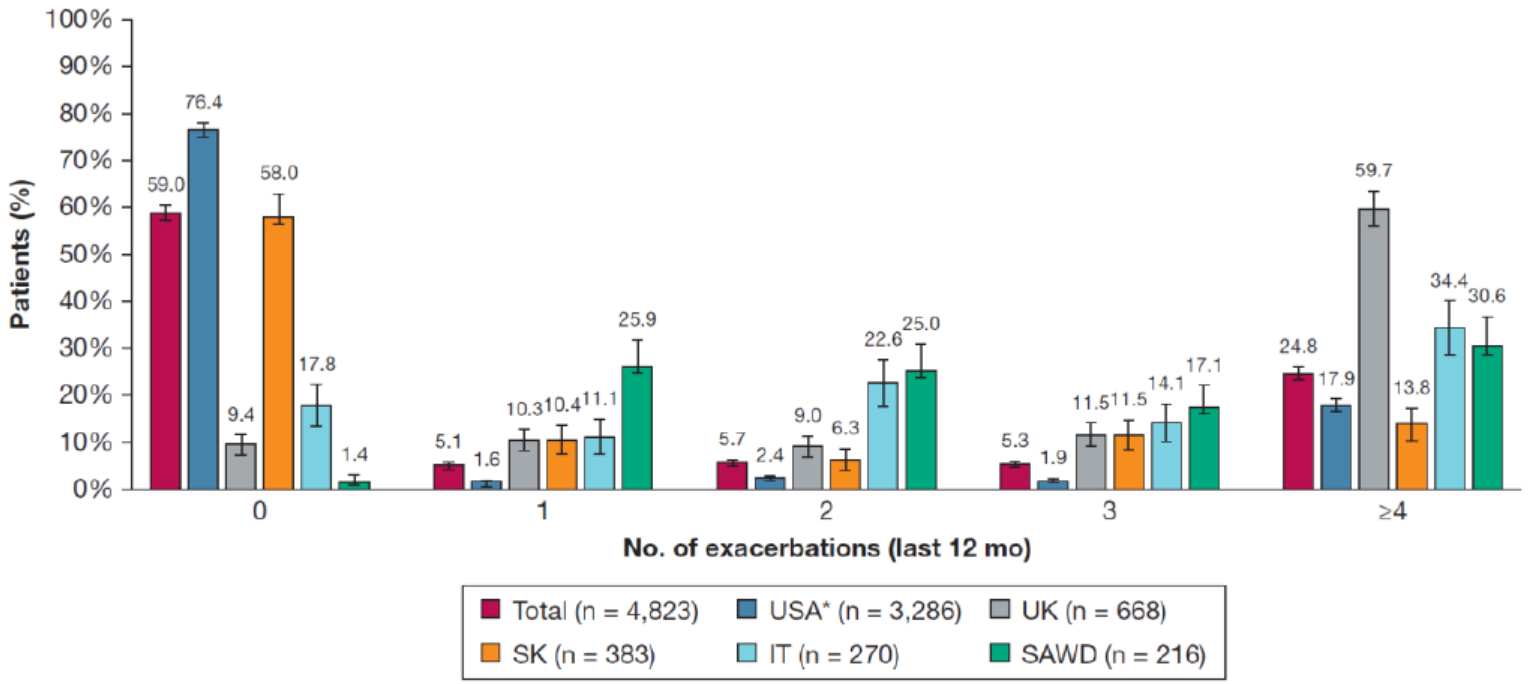


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

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.

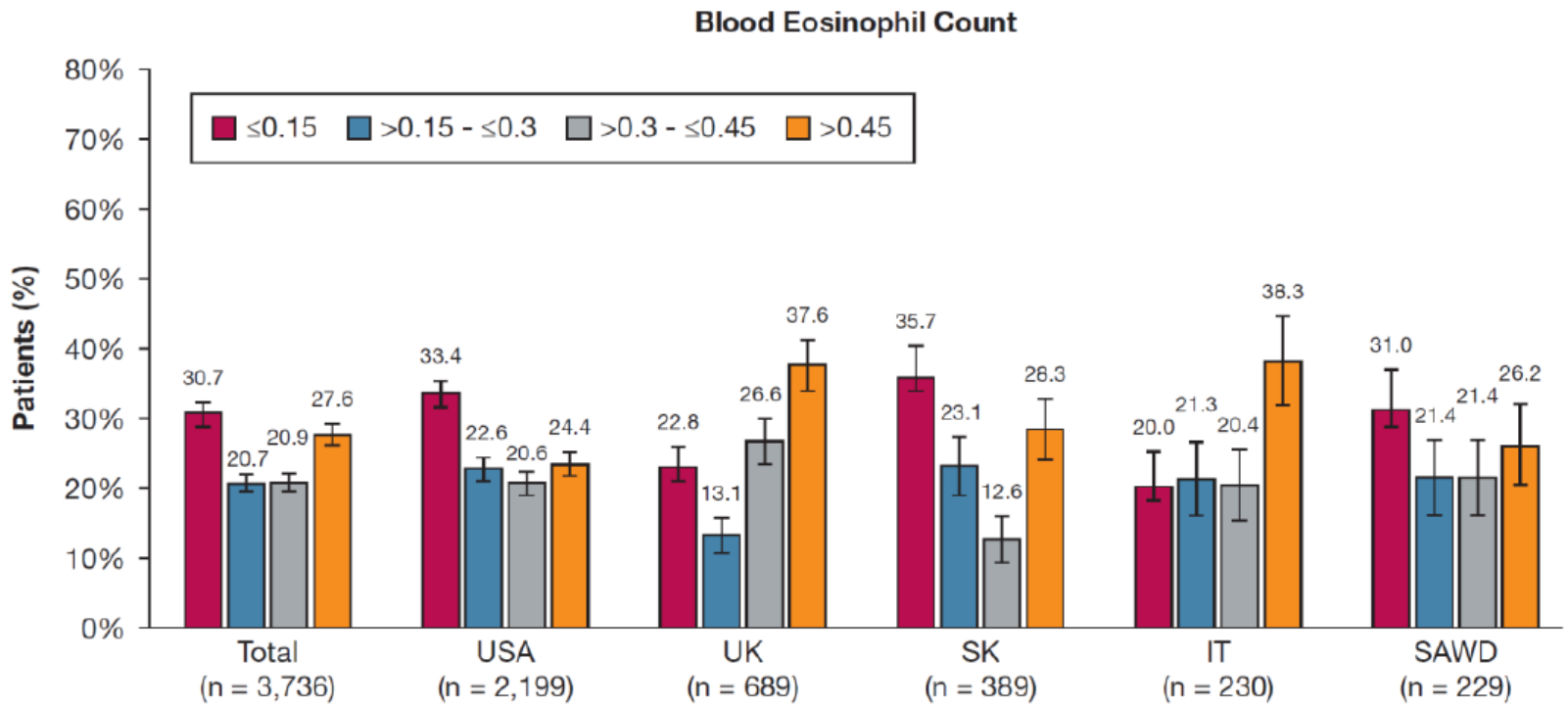


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

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.

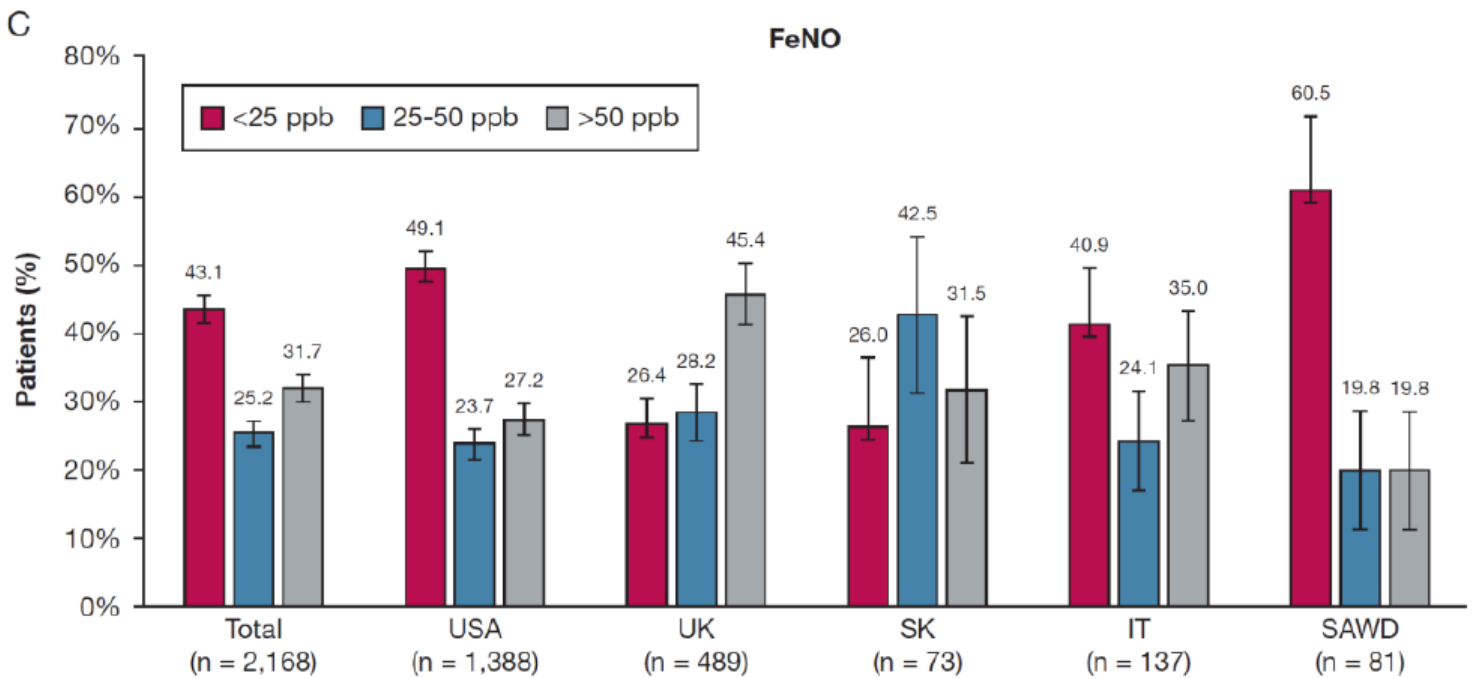


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

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.

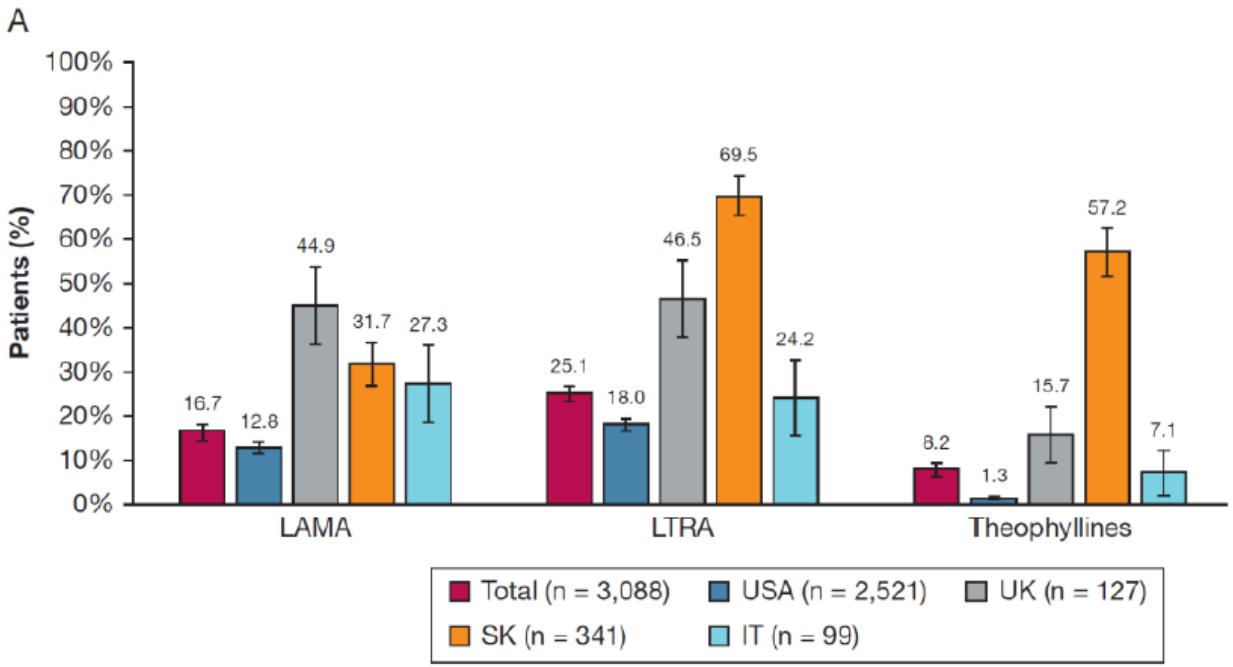


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

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).

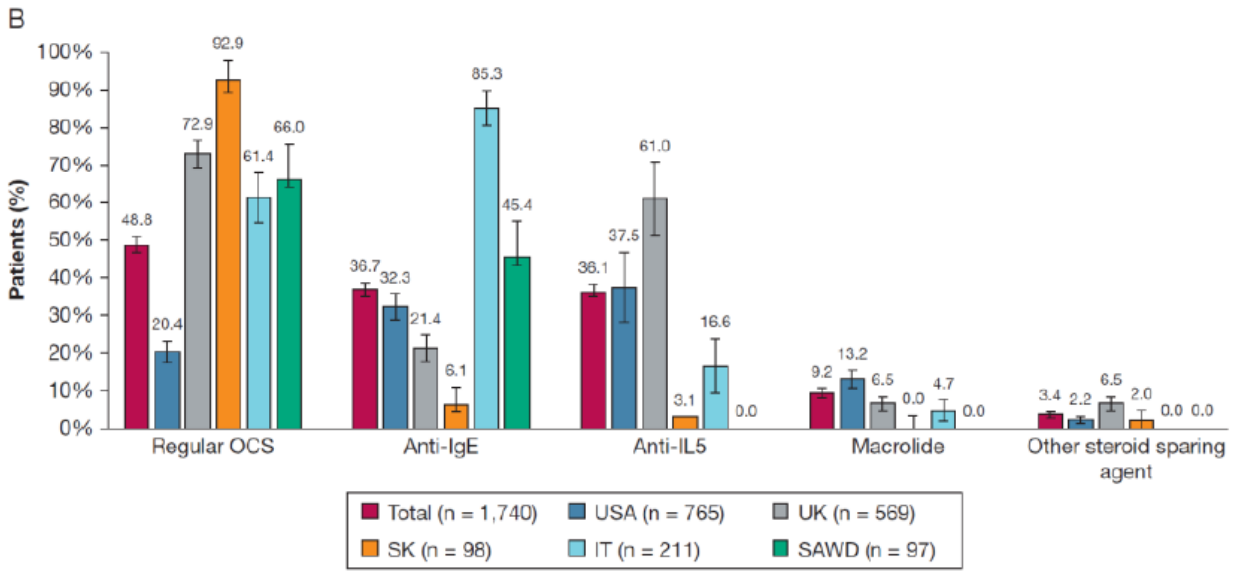


USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

Results: Clinical characteristics

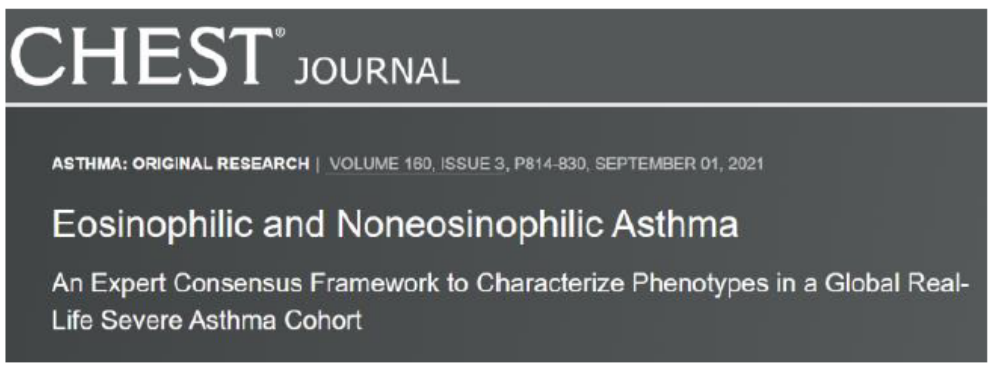
Treatment

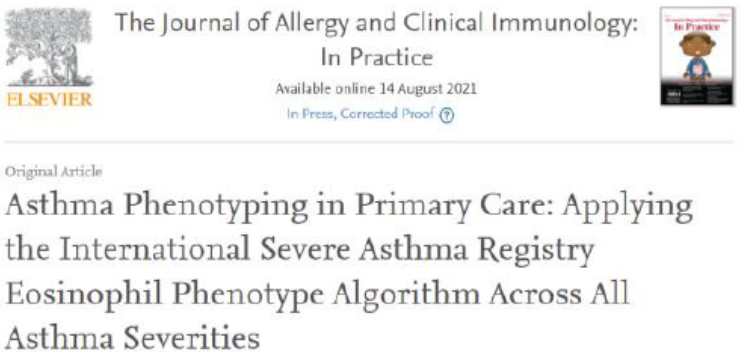
- Add-on regular OCS was used by almost one-half of the patients at GINA Step 5.
  - A wide range of intercountry variability was noted for regular OCS use.
- Anti-IgE and anti-IL-5 were each used by approximately one-third of patients, and macrolides were prescribed for a minority.
- Overall, 72.6% 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.



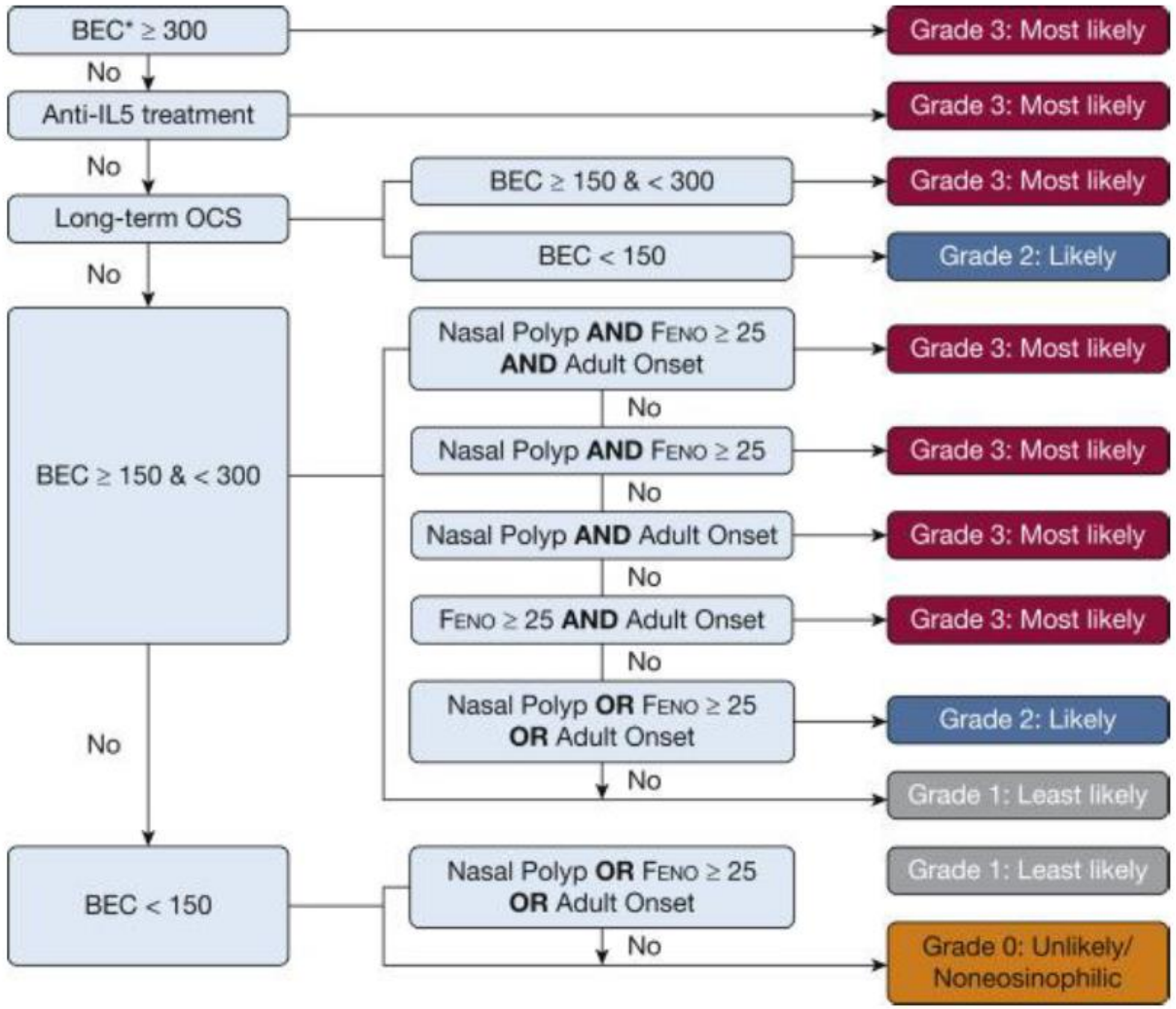
USA: United States of America; UK: United Kingdom; SK: South Korea; IT: Italy; SAWD: Severe Asthma Web-based Database

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





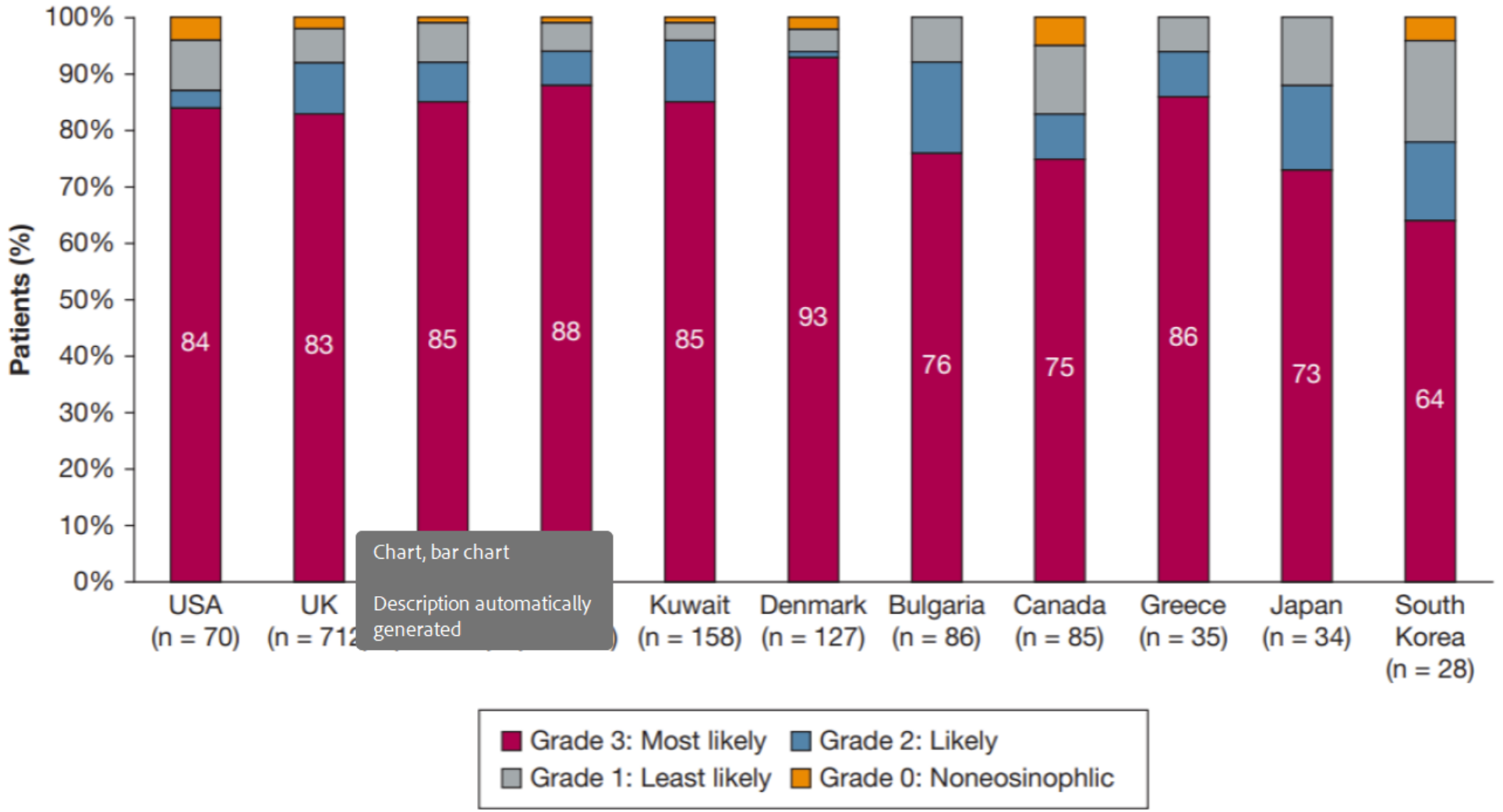
ISAR eosinophilic severe asthma phenotype algorithm



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

Eosinophilic severe asthma was the most common phenotype globally

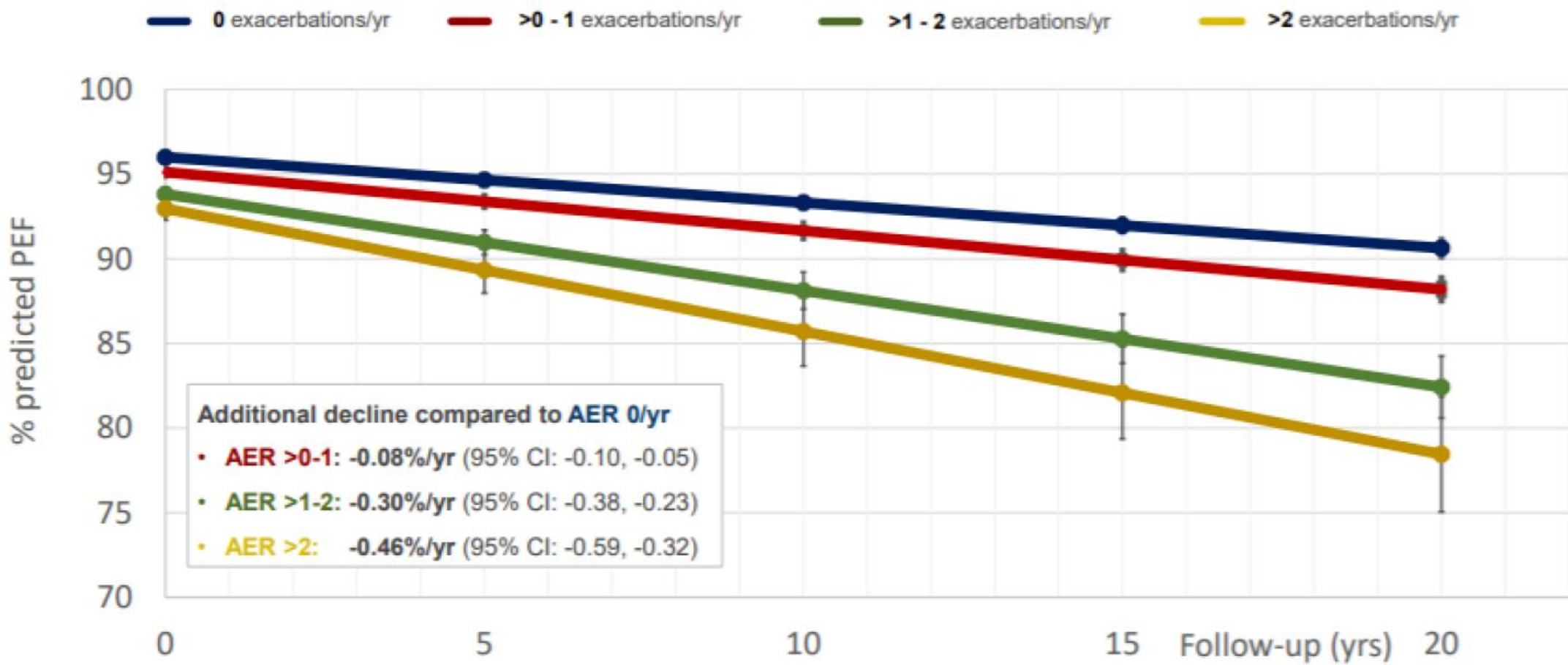


Heaney LG, Price D et al. *CHEST* 2021;3:814-830

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

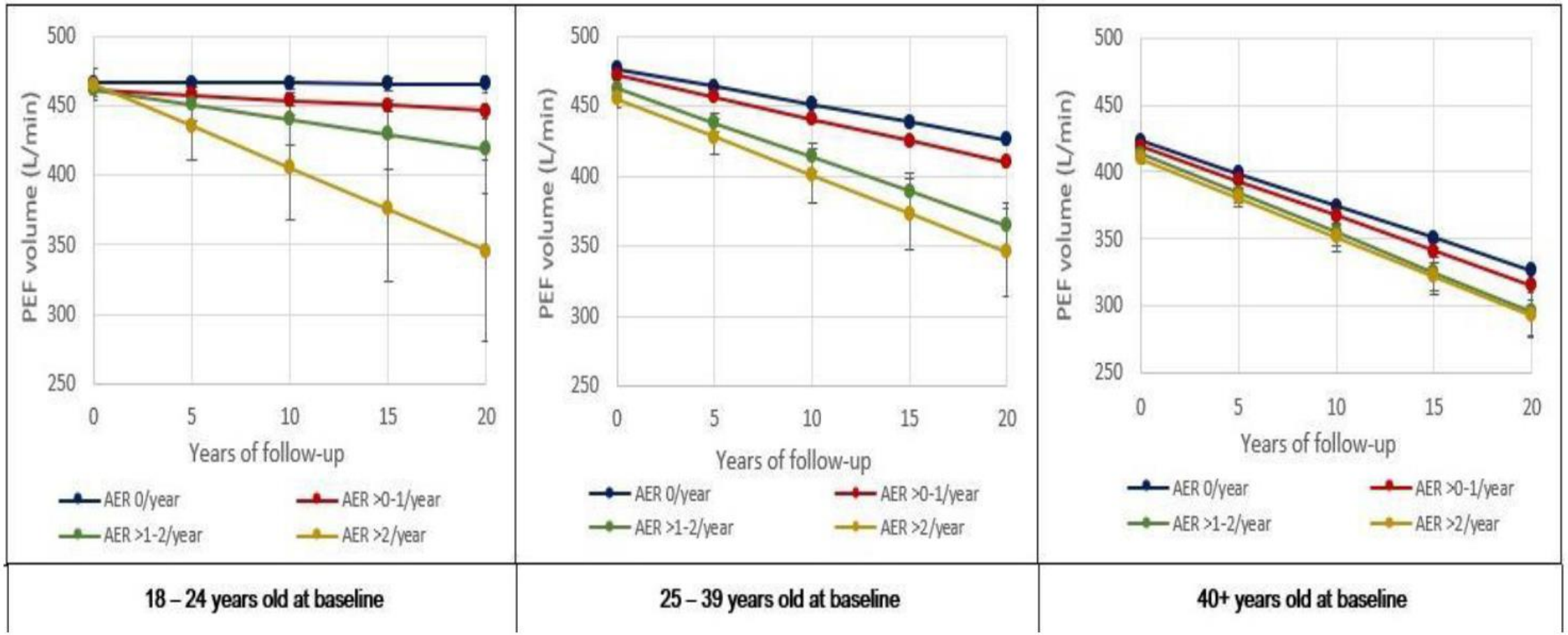
Exacerbations and lung function decline in asthma



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

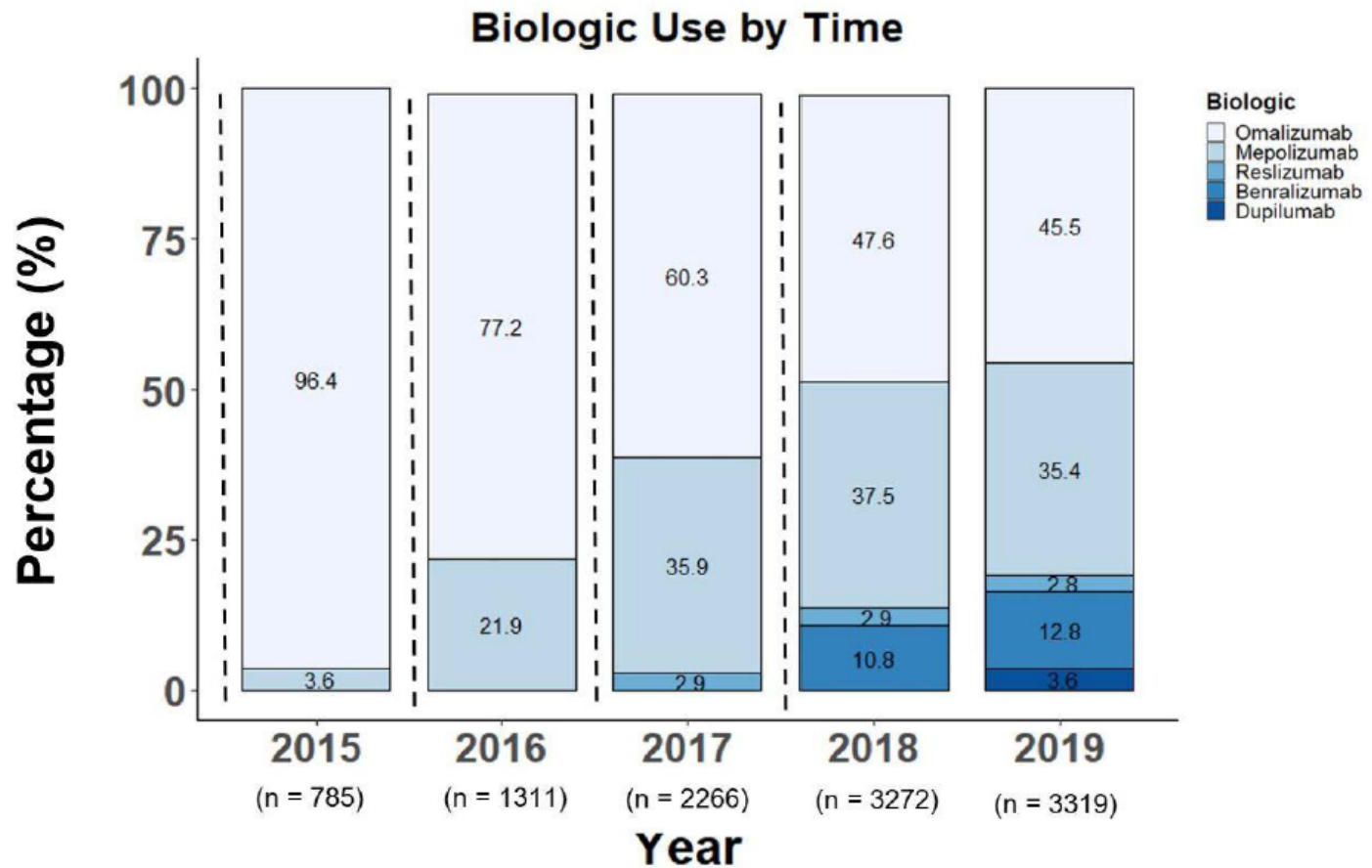
Soremekun S et al. Thorax 2022; 10.1136/thorax-2021-217032

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

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 ↑.

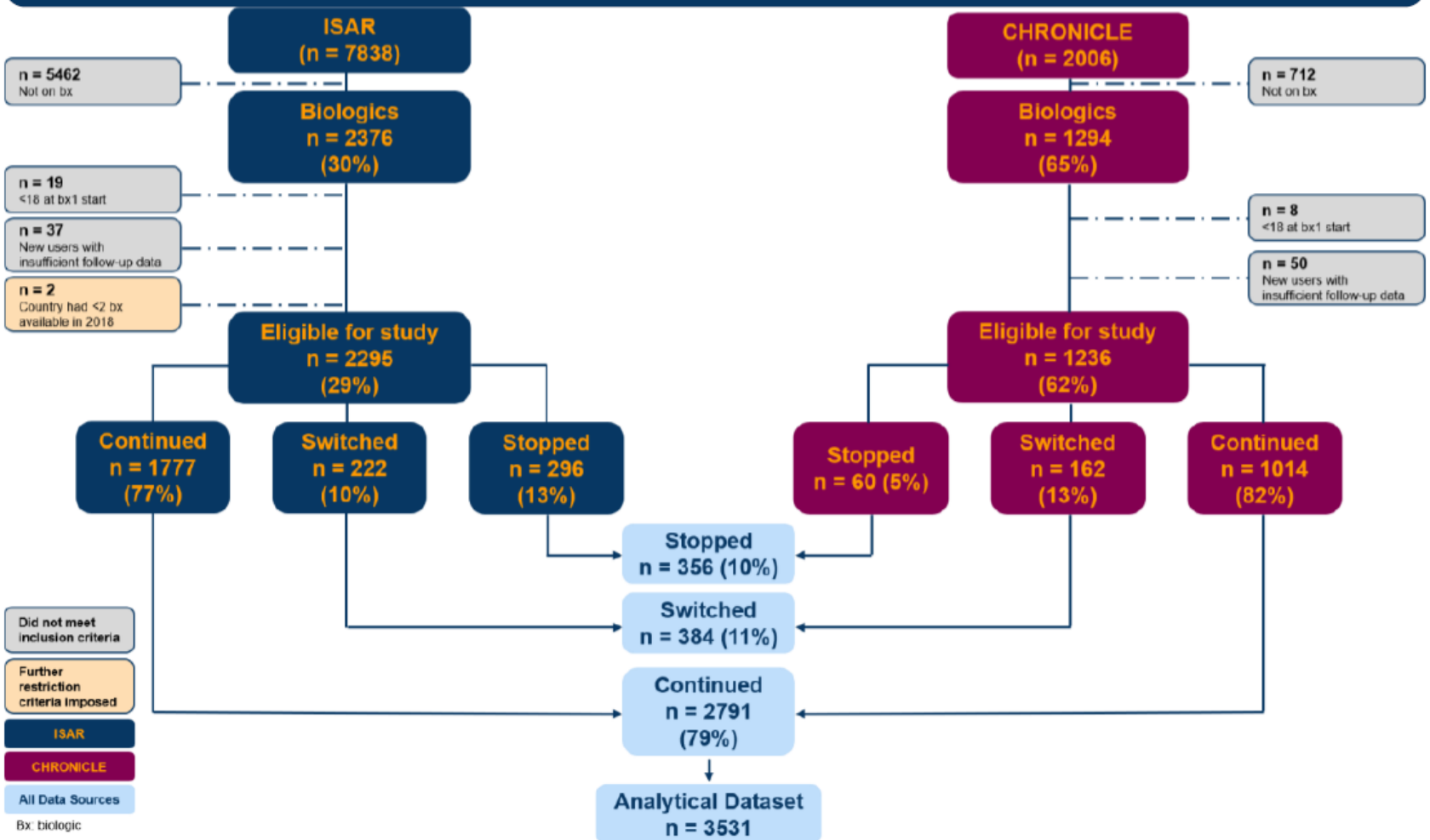


IgE = Immunoglobulin E; IL5/5R = Interleukin 5/5 receptor

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.

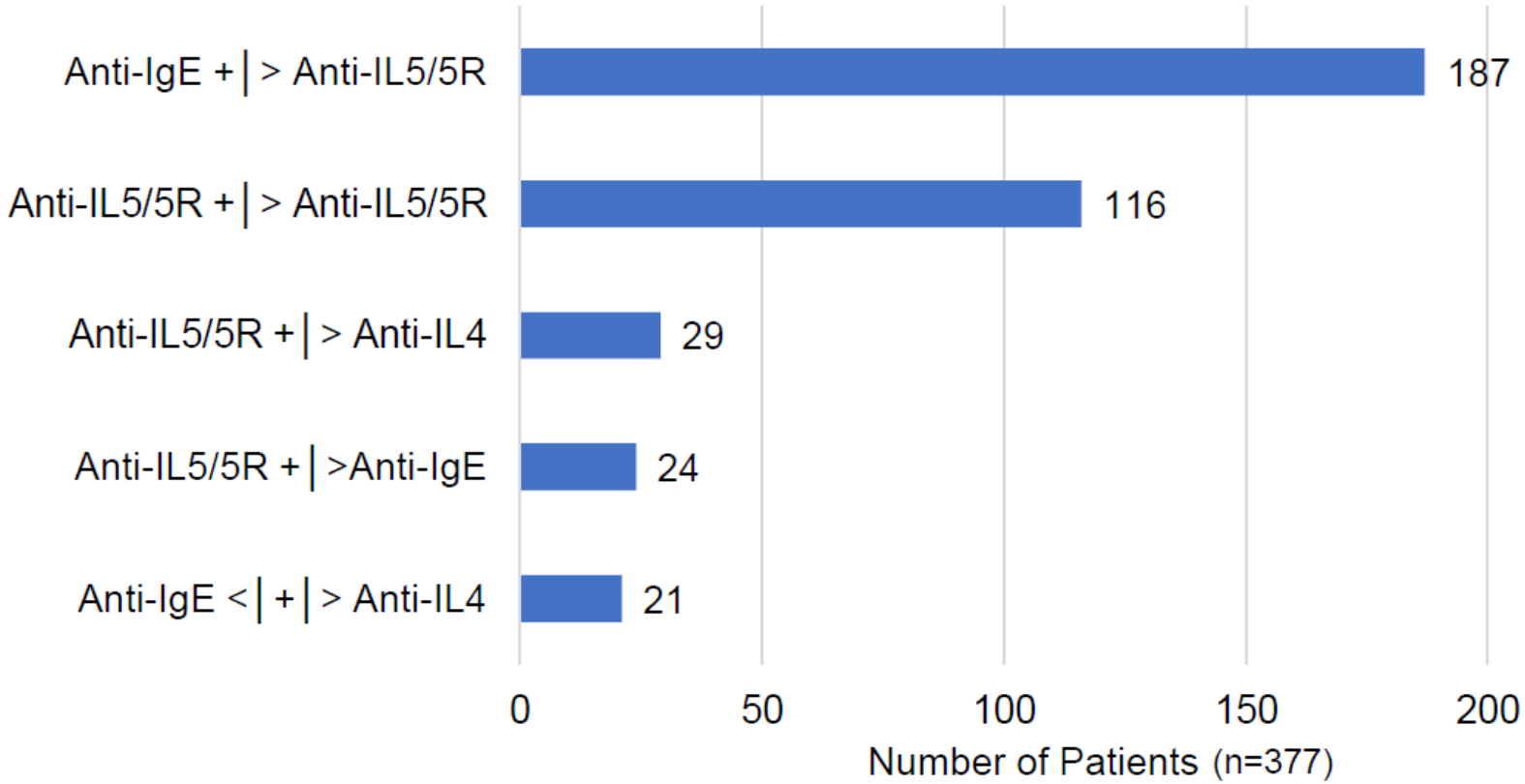


ISAR = International Severe Asthma Registry; CHRONICLE = Observational Study of Characteristics, Treatment and Outcomes With Severe Asthma in the United States

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

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.

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.

Exploring definitions and predictors of severe asthma clinical remission post-biologic in adults

Definitions	Exacerbations/year	LTOCS daily dose*	Asthma control†	ppFEV$_1$‡
Strict	0	0 mg	Partly/well controlled	≥80%
Relaxed	≤1 (not requiring hospitalization)	≤5mg		

Figure 1: Definitions of remission post-biologic therapy using strict and relaxed domain cut-offs.

Am J Respir Crit Care Med 2024; in press

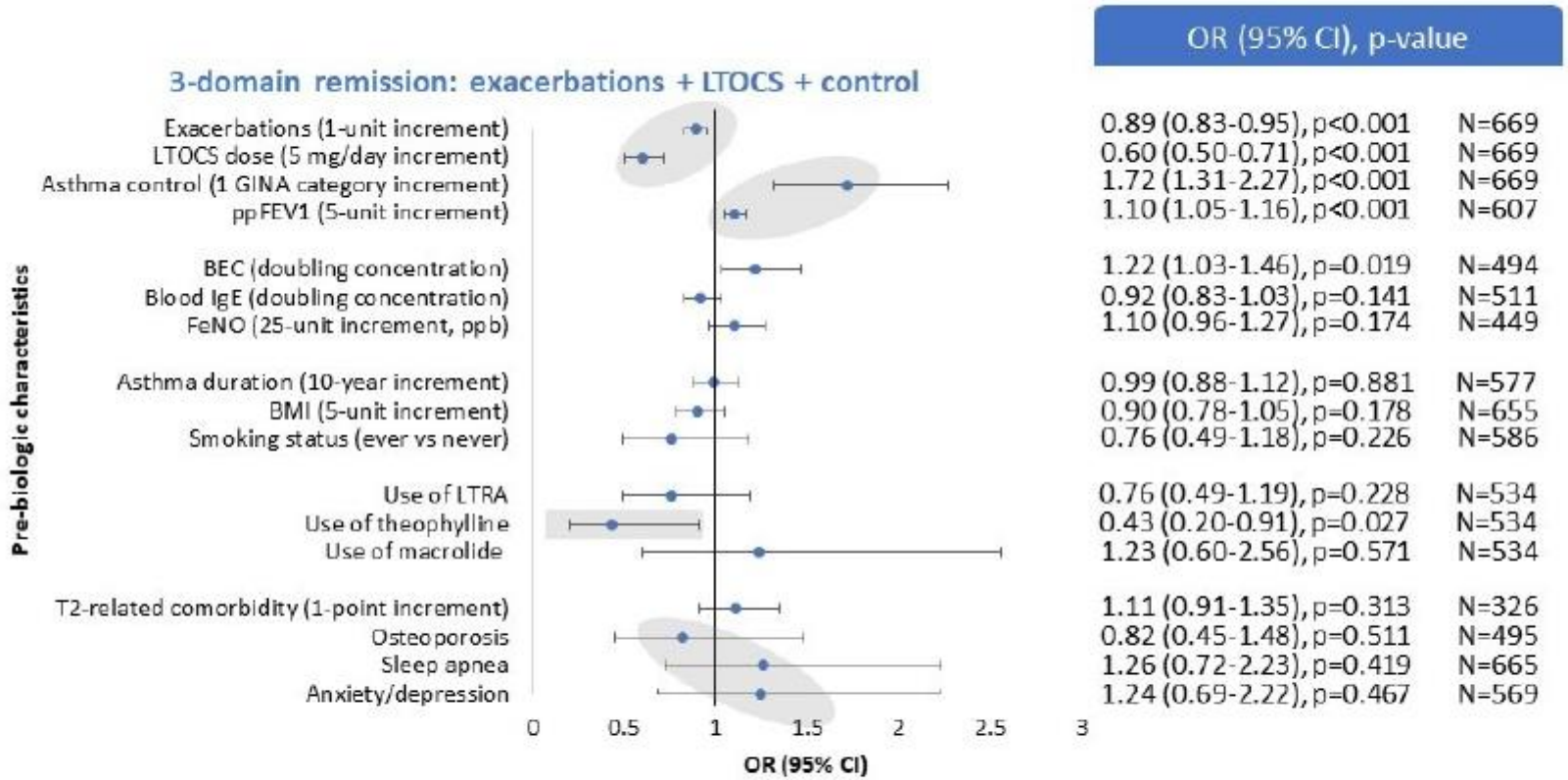


Figure 4A: Association between selected pre-biologic characteristics and 3-domain asthma remission in patients with severe asthma.

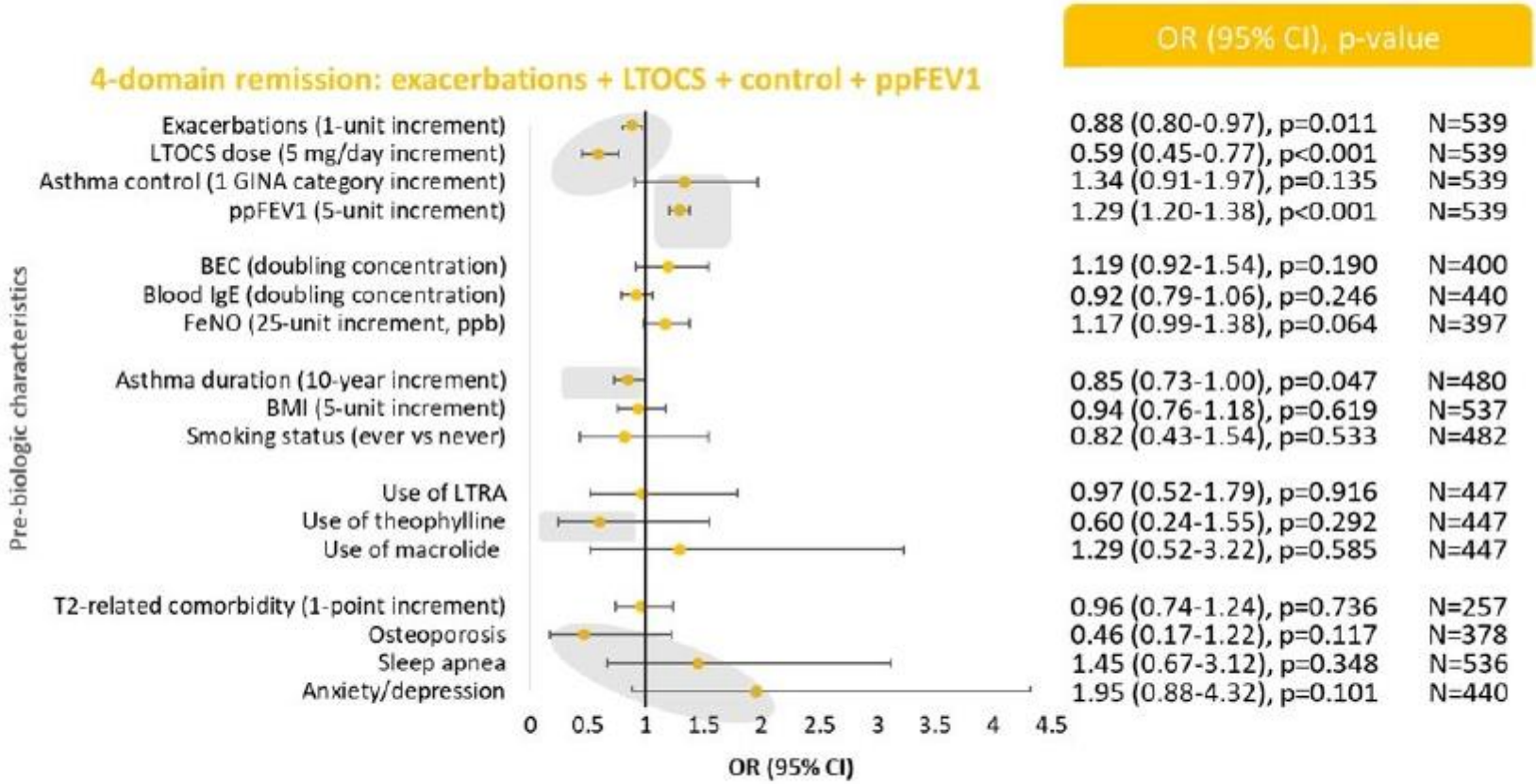


Figure 4B: Association between selected pre-biologic characteristics and 4 domain asthma remission in patients with severe asthma.

Summary

- Country specific severe asthma registries are key to understanding current services and improving future care
- By pooling resources in ISAR it has been possible to have datasets large enough to answer clinically relevant questions
- Moving forward the focus will be on leveraging these datasets to allow for earlier intervention and drive quality improvement across healthcare