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Use of long-acting muscarinic antagonists for severe asthma: insights from clinicians in the SHARP network

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Abstract

Background There is limited real-world evidence on the use and positioning of inhaled long-acting muscarinic antagonists (LAMAs) for treating severe asthma.

Objective We aimed to assess the differences in clinicians' perspectives on prescribing LAMA for severe asthma across Europe.

Methods Within the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) network, we conducted a multi-country survey of 470 respiratory clinicians in 2023-24.

Results Most participants were pneumonologists (83%). 68% reported using specific criteria for prescribing LAMA for severe asthma, primarily fixed bronchial obstruction (68%), frequent asthma exacerbations (65%), and a history of smoking (53%). Improved quality of life, lung function improvement, and reduction of asthma exacerbations were the three expected outcomes of LAMA treatment that showed the largest agreement across clinicians (85–95%). As compared to non-severe asthma specialists (about 50% of the sample), severe asthma specialists were more likely to report always prescribing LAMA before biologics (54 vs. 41%) and before oral corticosteroids (OCS) (51 vs. 40%). Approximately 90% of participants prioritised tapering or discontinuing OCS before stopping LAMA. Overall, participants in Northern ($n = 73$) and Western Europe ($n = 71$) appeared less prone to prescribe LAMA and less confident in their benefits compared to those from Eastern ($n = 88$) and Southern Europe ($n = 238$). In particular, most participants from Latvia (91%) and Lithuania (67%) reported that LAMAs are not reimbursed for severe asthma in their countries. Most participants who expressed their opinion favoured triple therapy ($n = 236$) over single inhaler therapy ($n = 91$).

Conclusion Our findings show that barriers and heterogeneous approaches still limit LAMA prescription for severe asthma in Europe, potentially leading to the underuse of this treatment option. Establishing a clear role for LAMA within a precision medicine framework is crucial; this aspect is not yet firmly supported by current international recommendations.

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Highlights

What is already known about this topic? Long-acting muscarinic antagonists (LAMA) are approved for treating severe asthma, but the best responder profile is unclear.

What does this article add to our knowledge? Our survey documents heterogeneous perspectives and barriers to LAMA use across Europe, examining the background of different prescription behaviours.

How does this study impact current management guidelines? The findings highlight the need for international recommendations to specify which patient profiles are most likely to benefit from LAMA treatment and to clarify LAMA positioning within the step-up and step-down approach to asthma management.

Keywords Asthma care, Bronchodilators, Clinical guidelines, Controller medication, Geographical variability, Real-world evidence, Severe asthma, Survey-based research

Introduction

Long-acting muscarinic antagonists (LAMAs) are a class of bronchodilators approved for treating severe asthma (SA). Their mechanism of action targets specifically the cholinergic tone, which is a key contributor to asthma pathobiology. An increased cholinergic tone amplifies airways inflammation, hyperresponsiveness, remodelling, mucus hypersecretion, and cough [1]. Besides relaxation of the airway smooth muscle, inhibition of the muscarinic receptors of the bronchioles has been shown to reduce inflammation and asthma-related airway remodelling in preclinical asthma models [2]. The impact of LAMAs on the asthma pathobiological background and clinical burden is more beneficial when a combined anti-muscarinic and inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) therapy is provided. In fact, Tiotropium, as an add-on option, showed benefits over LABA/ICS alone in reducing the need for rescue oral steroids in patients with SA, improving lung function and asthma control [3]. Tiotropium Respimat was the first LAMA approved for asthma use in 2014. Subsequently, an increasing research interest in the field focused on single-inhaler ICS/LABA/LAMA triple therapy, providing robust evidence for their positioning in asthma treatment [4].

Beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide (BDP/FF/GB), fluticasone furoate/umeclidinium/vilanterol (FF/U/V), and indacaterol/glycopyrrolate/mometasone furoate (I/GB/MF) are currently licensed for asthma, although with heterogeneous distribution. In Europe, BDP/FF/GB and more recently I/GB/MF have been approved [1]. Starting from the 2021 update, GINA recommendations included Tiotropium for SA (Steps 4 and 5) as an add-on treatment to medium-to-high dose ICS/LABA in patients aged ≥ 12 years before considering the use of biologics or prescribing oral corticosteroids (OCS) [5]. Nonetheless, an analysis of the SA Italian Network (SANI) found that only 35% of patients with SA were using LAMA [6]. Notably, 12.7% of patients were prescribed off-label antimuscarinic agents, highlighting that LAMA prescription is not well established among physicians treating SA. In addition,

a substantial proportion of LAMA non-users were still on long-term OCS therapy (36.9%) or biologic agents (54.1%). This trend may vary in other countries depending on national recommendations and guidelines. Identifying which patients would benefit most from LAMA therapy remains an unmet need, as does determining specific contraindications or conditions that increase the risk of side effects. Considering the high costs and limited global availability of biologic treatments, this issue is especially relevant for treatment sustainability and equity.

This study aimed to describe clinicians' perspectives on prescribing LAMA for SA in real-life practice and to evaluate differences across Europe. To this end, we surveyed clinicians participating in the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) network. SHARP is an international Clinical Research Collaboration within the European Respiratory Society that brings together clinicians and researchers working to improve mild-to-severe asthma care [7]. As of January 2025, SHARP has established a network of over 300 members, including clinicians, researchers, patients with SA, and industry partners from 28 European countries. Together, these members collaborate on research and dissemination activities.

The survey collected general data on clinicians' routine practice. It examined their points of view on the patient traits and characteristics influencing LAMA prescription in SA, the positioning of LAMA treatment, preferences for single vs. triple inhaler therapy, expected outcomes, and side effects. In this analysis of the survey data, we focused on regional differences and, secondarily, on differences between clinicians who self-identified as SA specialists and those who did not.

Methods

Development of the survey tool

We developed a survey tool to gather real-world opinions from clinicians prescribing LAMA across Europe (Additional file 1, Figure S1). The tool was created in English, as all participating clinicians were expected to possess proficiency in the language, given their involvement in

SHARP. The first draft was reviewed in the “Investigators-led initiatives” working group meetings and pilot-tested by four clinicians to assess its clarity, simplicity, and face validity.

Following revisions, the updated version was validated by ten SHARP national leads, who were surveyed and provided feedback for further refinement. Analyses of responses confirmed that the survey tool effectively captured variability in perspectives across European countries (Additional file 2). Most response options were utilised, underscoring the diversity of opinions. The final survey tool is included in Additional file 3.

The survey was implemented through the SurveyMonkey system (<https://uk.surveymonkey.com/>) and distributed via an online link. Participants were required to answer each question to proceed, as unanswered questions triggered error messages. It was initially circulated among respiratory clinicians through the national societies of SHARP-participating countries on November 17, 2023. Then, it was shared with SA experts in these countries through the National Leads in April 2024. The survey period concluded on June 7, 2024. Participation was anonymous.

Statistical analysis

We classified clinicians as “SA specialists” based on their self-identification, distinguishing them from those who identified as “general respiratory physicians” or selected “other” qualifications (question 2, Additional file 3). We adopted a data-driven classification of study areas because the number of participants was small in most countries. We grouped countries into five regions following the United Nations classification: Eastern Europe, Northern Europe, Southern Europe (excluding Italy and Spain), Italy and Spain (analysed separately due to the large number of participants), and Western Europe. Turkey was included in Southern Europe due to its geographical proximity.

Data on expected outcomes, treatment step-down approach, and reasons to favour triple or single therapy were collected using a 4-point Likert scale of agreement (Additional file 3). For the main analysis, responses were dichotomised into “agreement” (strongly or somewhat agree) and “disagreement” (strongly or somewhat disagree). Additionally, multiple correspondence analyses (MCA) were performed to explore the internal structure of the responses on the original 4-point scale.

We compared study outcomes across regions by reporting frequency distributions as counts and percentages and tested differences using Fisher’s exact test (crude analysis). Since the proportion of SA specialists varied by region (possibly reflecting the organisation of the national registries and the participation in SHARP), we adjusted the analysis by including SA specialist self-identification

as a covariate in logistic regression models. Separate models were fitted for each outcome, with regions as a covariate. We used Wald tests to compute adjusted p -values for the joint null hypothesis of no regional heterogeneity (i.e., all regression coefficients for regions equalling zero). In cases of perfect separation (0% or 100% in one or more areas), we applied Firth’s penalised likelihood logistic regression and assessed regional heterogeneity using likelihood ratio tests comparing models with and without regression coefficients for regions constrained to zero [8]. We performed statistical analyses using STATA 18.0 (StataCorp, College Station, Texas).

Results

General characteristics of the clinicians surveyed

After excluding 26 clinicians whose main country of practice was unclassified, the total number of participants in the survey was 470. The distribution of participants by main country of practice is reported in Table S1 in Additional file 1. Most participants were from Southern Europe.

The primary specialty reported by the participants was pneumology (82.5%) (Table 1). Two out of three clinicians (67.9%) reported 10 years or longer experience as specialists. The clinicians in centres treating at least 100 patients with SA were 39.5%, and those who reported seeing at least 50 patients with SA in a typical month were 16.2%. Around half of the participants (49.4%) identified themselves as SA specialists, and 33.4% reported working in SA clinics.

The proportion of clinicians reporting to be SA specialists was highest in Italy and Spain (82.2%). In the remaining regions, the distribution was as follows: 34.1% in Eastern Europe, 39.4% in Western Europe, 41.1% in Northern Europe, and 44.5% in the other Southern European countries. The clinicians reporting to work in SA clinics were 68.3% in Italy and Spain, while the proportion ranged from 10.2% (Eastern Europe) to 31.5% (Northern Europe) in the other regions.

Prescription of LAMA by SA specialists and non-SA specialists

SA specialists reported having longer experience in the field and treating more patients with SA than non-SA specialists (Table 1). SA specialists were more likely to report prescribing LAMA to all their patients with SA (36.6 vs. 21.0%, respectively, $p=0.001$) (Table 2). Among the clinicians who reported treating only selected patients with LAMA, SA specialists were more likely to consider fixed bronchial obstruction, frequent asthma exacerbations, non-eosinophilic asthma, and LABA/short-acting beta agonist (SABA) intolerance to favour their decision to prescribe LAMA.

Table 1 Characteristics of the clinicians, by SA specialist status

Characteristic		Non-SA specialist (n = 238)	SA specialist (n = 232)	Overall (n = 470)
		N (%)	N (%)	N (%)
Region	Eastern Europe	58 (24.4)	30 (12.9)	88 (18.7)
	Northern Europe	43 (18.1)	30 (12.9)	73 (15.5)
	Italy and Spain	18 (7.6)	83 (35.8)	101 (21.5)
	Southern Europe, other*	76 (7.6)	61 (26.3)	137 (29.2)
	Western Europe	43 (18.1)	28 (12.1)	71 (15.1)
Specialty	Pneumology	194 (81.5)	168 (72.4)	362 (77.0)
	Allergy/Immunology	38 (16.0)	44 (19.0)	82 (17.4)
	Both specialties	6 (2.5)	20 (8.6)	26 (5.5)
Years of practice	less than 1	23 (9.7)	4 (1.7)	27 (5.7)
	1–4	30 (12.6)	19 (8.2)	49 (10.4)
	5–9	45 (18.9)	30 (12.9)	75 (16.0)
	10–14	35 (14.7)	39 (16.8)	74 (15.7)
	15–19	29 (12.2)	30 (12.9)	59 (12.6)
	20 or more	76 (31.9)	110 (47.4)	186 (39.6)
Number of patients treated for SA in the clinic	less than 50	129 (54.2)	45 (19.4)	174 (37.0)
	50–99	54 (22.7)	57 (24.6)	111 (23.6)
	100–149	20 (8.4)	34 (14.7)	54 (11.5)
	150–199	14 (5.9)	29 (12.5)	43 (9.2)
	200 or more	21 (8.8)	67 (28.9)	88 (18.8)
Number of patients with SA seen in a typical month	less than 25	207 (87.0)	100 (43.1)	307 (65.3)
	25–49	22 (9.2)	65 (28.0)	87 (18.5)
	50–74	7 (2.9)	37 (16.0)	44 (9.4)
	75–99	2 (0.8)	16 (2.9)	18 (3.8)
	100 or more	0 (0.0)	14 (6.0)	14 (3.0)
Report working in SA clinic	yes	18 (7.6)	139 (59.9)	157 (33.4)

*Excluding Italy and Spain, and including Turkey

Table 2 Distribution of traits and characteristics usually driving LAMA prescription to patients with SA, by SA specialist status

	Severe asthma specialist		
	no	yes	p-value
Number of clinicians	238	232	
Usually treated with LAMA, n (%)			
All patients	50 (21.0)	85 (36.6)	0.001
Selected patients	179 (75.2)	138 (59.5)	
No patients	9 (3.8)	9 (3.9)	
<i>Traits driving LAMA prescription to selected patients</i>			
Fixed bronchial obstruction, n (%)	114 (63.7)	104 (74.8)	0.039
Frequent asthma exacerbations (2 per year or more), n (%)	104 (58.1)	102 (73.4)	0.006
Current or past smoking history, n (%)	89 (49.7)	81 (58.3)	0.142
Non-eosinophilic asthma, n (%)	71 (39.7)	74 (53.2)	0.017
LABA/SABA-related side effects (e.g., arrhythmias, tachycardia), n (%)	58 (32.4)	62 (44.6)	0.027
Chronic cough, n (%)	52 (29.0)	45 (32.6)	0.54
Chronic sputum, n (%)	47 (26.3)	42 (30.2)	0.45
Abuse of SABA, n (%)	46 (25.7)	34 (24.6)	0.90
Factors limiting LAMA prescription, n (%)			
No	134 (79.3)	111 (81.6)	0.67
Yes	35 (20.7)	25 (18.4)	

Twenty-three clinicians (two SA specialists and 21 non-SA specialists) reported that none of their patients received biologics. SA specialists were more likely to agree that LAMA treatment helps reduce OCS doses among patients under biologics (76.5 vs. 67.2%, $p = 0.037$) and the risk of asthma exacerbations among biologic-naïve patients (93.6 vs. 88.2%, $p = 0.065$) (Table 3).

Compared to non-SA specialists, SA specialists were more likely to position LAMA before biologics (53.8 vs. 40.6%, $p = 0.006$) and before OCS (51.1 vs. 39.7%, $p = 0.017$) in treatment step-up (Table 4). None of them positioned LAMA after OCS, unlike 5.9% of non-SA specialists ($p < 0.001$). No apparent differences emerged regarding LAMA stepping down (Table 4) or preferences for single vs. triple inhaler therapy (Table S2 in Additional file 1).

These findings indicate that being a SA specialist influences specific characteristics, though not all of them. Importantly, adjusting for the qualification as SA specialists did not change the distribution of outcomes across different regions, suggesting no substantial confounding due to imbalanced distribution among regions. Therefore, only the results from the unadjusted analysis are

Table 3 Proportion (%) of clinicians strongly/somewhat agreeing on the expected outcomes of LAMA treatment in patients with SA, by SA specialist status

	SA specialist		
	no	yes	p-value
<i>Patients already under biologics</i>			
Number of clinicians	219	221	
improved health-related quality of life, n (%)	182 (93.3)	206 (94.9)	0.53
lung function improvement, n (%)	166 (85.1)	186 (85.7)	0.89
reduction of asthma exacerbations, n (%)	160 (82.0)	190 (87.6)	0.13
reduction of OCS dose, n (%)	131 (67.2)	166 (76.5)	0.037
reduction of infection-driven exacerbations, n (%)	114 (58.5)	126 (58.1)	0.99
reduction of ICS dose, n (%)	101 (51.8)	125 (57.6)	0.28
<i>Biologic-naïve patients*</i>			
Number of clinicians	198	219	
improved health-related quality of life, n (%)	199 (93.9)	210 (96.7)	0.17
lung function improvement, n (%)	195 (92.0)	200 (92.2)	0.99
reduction of asthma exacerbations, n (%)	187 (88.2)	203 (93.6)	0.065
reduction of OCS dose, n (%)	153 (72.2)	164 (75.6)	0.44
reduction of infection-driven exacerbations, n (%)	132 (62.3)	141 (65.0)	0.62
reduction of ICS dose, n (%)	127 (59.9)	131 (60.4)	0.99

*Information collected only from clinicians managing patients on biologics

reported below, although adjusted *p*-values can be found in Tables S3–S5 in Additional file 1.

Traits and characteristics usually driving LAMA prescription

Clinicians in Italy and Spain were most likely to treat all their patients with SA using LAMA (45.5%), while those in Northern Europe were the least likely (11.0%) (Table 5).

Among the clinicians who reported prescribing LAMA to specific patients based on their phenotypes, two out of three indicated that fixed bronchial obstruction and frequent asthma exacerbations influenced their decisions (Table 5). A smoking history and non-eosinophilic asthma were mentioned by about half of the clinicians. The other characteristics were reported less frequently by clinicians, ranging from 37.5% for LABA/SABA intolerance to 25.2% for SABA abuse. Regional variation in these proportions was primarily observed for fixed bronchial obstruction and frequent asthma exacerbations, which were selected more often by clinicians in Italy and Spain (> 80%) compared to those from the other regions (50–70%).

Overall, 60 (19.7%) clinicians indicated that certain factors limited their ability to prescribe LAMA (Table 5). About half of these were from Northern Europe. Specifically, 10 (90.9%) clinicians from Latvia and 14 (66.7%)

Table 4 Positioning of LAMA in the treatment of patients with SA, by SA specialist status

	SA specialist		p-value
	no	yes	
Number of clinicians	219	221	
<i>Positioning of LAMA in treatment step-up</i>			
Add-on to maximal ICS/LABA dose, n (%)	143 (65.3)	128 (57.9)	0.11
Add-on to ICS/LABA depending on phenotype, n (%)	96 (43.8)	115 (52.0)	0.087
Always before biologics, n (%)	89 (40.6)	119 (53.8)	0.006
Always before OCS, n (%)	87 (39.7)	113 (51.1)	0.017
Before starting stepping up OCS, n (%)	58 (26.5)	74 (33.5)	0.12
Add-on to ICS/LABA plus LTRA, n (%)	56 (25.6)	55 (24.9)	0.91
Add-on to ICS/LABA before LTRA, n (%)	45 (20.6)	32 (14.5)	0.10
Usually after OCS, n (%)	13 (5.9)	0 (0.0)	< 0.001
<i>Strongly/somewhat agree on options before stepping down LAMA</i>			
Taper down OCS dose, n (%)	177 (90.3)	198 (93.4)	0.28
Stop OCS, n (%)	165 (84.2)	189 (89.2)	0.15
Taper down ICS dose, n (%)	91 (46.4)	107 (50.5)	0.43
Stop LTRA, n (%)	85 (43.4)	92 (43.4)	0.99
Stop biologics, n (%)	33 (16.8)	26 (12.3)	0.21
Stop LABA, n (%)	22 (11.2)	15 (7.1)	0.17
Stop ICS, n (%)	16 (8.2)	11 (5.2)	0.24

clinicians from Lithuania reported that the lack of reimbursement affected their willingness to prescribe LAMA.

Expected outcomes of LAMA treatment

Figure 1 illustrates clinicians' agreement regarding the expected outcomes of LAMA treatment (refer to Table S3 in Additional file 1 for details). Among patients already receiving biologics (Fig. 1, A), the highest level of overall agreement across all the regions combined was for improvement in quality of life (94.2%), while the lowest was for reduction in ICS dose (54.8%).

Notably, there was considerable variation in agreement across different regions, with Western Europe generally showing lower levels of consensus than other regions. The most extensive heterogeneity was observed for lung function improvement (ranging from 70.8% in Northern Europe to 90.3% in Eastern Europe), reduction of OCS dose (~ 52% in Northern and Western Europe and ~ 80% in the other regions), and reduction of ICS dose (33.8%, Western Europe to 64.0%, other Southern European countries). A similar pattern of overall agreement was observed for expected outcomes among biologic-naïve patients (Fig. 1, B), where the lowest agreement was found in Western Europe. The geographical variation in the agreement was most pronounced for reducing OCS dose, infection-driven exacerbations, and ICS dose.

Table 5 Distribution of traits and characteristics usually driving LAMA prescription to patients with SA, by region

	Overall	Region					p-value, unadjusted	p-value, adjusted†
		Eastern Europe	Northern Europe	Italy and Spain	Southern Europe, other*	Western Europe		
Number of clinicians	470	88	73	101	137	71		
Usually treated with LAMA, n (%)								
All patients	135 (28.7)	21 (23.9)	8 (11.0)	46 (45.5)	50 (36.5)	10 (14.1)	<0.001	<0.001
Selected patients	317 (67.5)	65 (73.9)	58 (79.4)	51 (50.5)	84 (61.3)	59 (83.1)		
No patients**	18 (3.8)	2 (2.3)	7 (9.6)	4 (4.0)	3 (2.2)	2 (2.8)		
<i>Traits driving LAMA prescription to selected patients</i>								
Fixed bronchial obstruction, n (%)	217 (68.4)	37 (56.9)	37 (63.8)	45 (88.2)	55 (65.5)	43 (72.9)	0.003	0.027
Frequent asthma exacerbations (2 per year or more), n (%)	205 (64.7)	39 (60.0)	31 (53.4)	41 (80.4)	62 (73.8)	32 (54.2)	0.004	0.018
Current or past smoking history, n (%)	169 (53.3)	33 (50.8)	34 (58.6)	25 (49.0)	44 (52.4)	33 (55.9)	0.85	0.70
Non-eosinophilic asthma, n (%)	144 (45.4)	26 (40.0)	29 (50.0)	19 (37.2)	39 (46.4)	31 (52.5)	0.43	0.18
LABA/SABA-related side effects (e.g., arrhythmias, tachycardia), n (%)	119 (37.5)	22 (33.8)	26 (44.8)	22 (43.1)	31 (36.9)	18 (30.5)	0.46	0.64
Chronic cough, n (%)	97 (30.6)	22 (33.8)	23 (39.7)	15 (29.4)	24 (28.6)	13 (22.0)	0.31	0.30
Chronic sputum, n (%)	88 (28.0)	17 (26.2)	24 (41.4)	10 (19.6)	24 (28.6)	13 (22.0)	0.10	0.073
Abuse of SABA, n (%)	80 (25.2)	23 (35.4)	11 (19.0)	12 (23.5)	20 (23.8)	14 (23.7)	0.31	0.30
Factors limiting LAMA prescription, n (%)								
No	245 (80.3)	47 (79.7)	28 (50.0)	44 (88.0)	73 (90.1)	53 (89.8)	<0.001	<0.001
Yes	60 (19.7)	12 (20.3)	28 (50.0)	6 (12.0)	8 (9.9)	6 (10.2)		

* excluding Italy and Spain, and including Turkey
** these individuals were excluded prior to testing due to sparse data issues
† Wald test after logistic regression adjusted for SA specialist (no/yes)

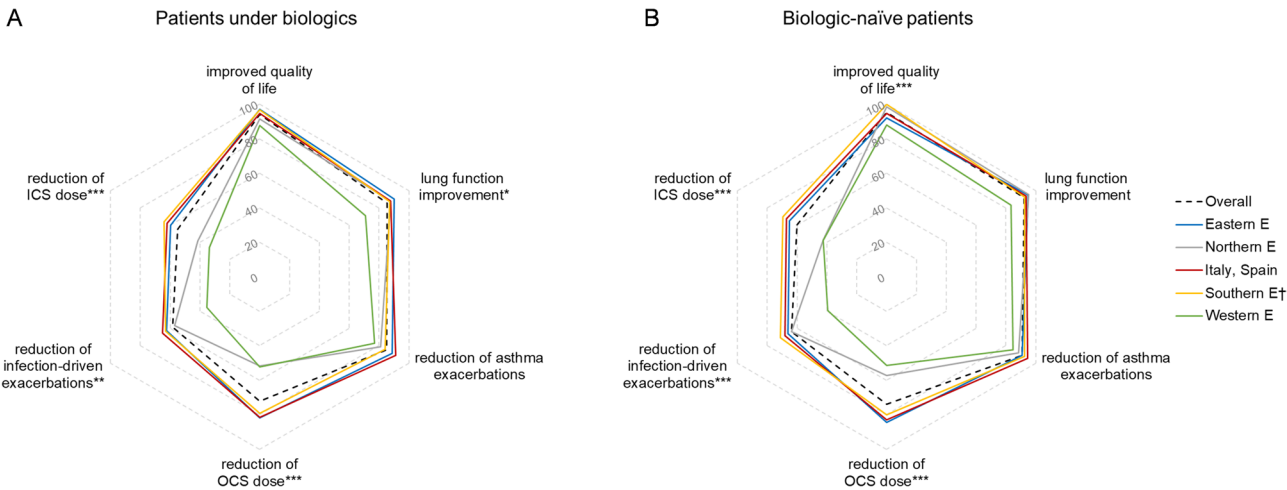


Fig. 1 Proportion (%) of clinicians strongly/somewhat agreeing on the expected outcomes of LAMA treatment in patients with SA already under biologics (panel **A**) and biologic-naïve patients (panel **B**), by region. † excluding Italy and Spain, and including Turkey. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ for the overall comparison of agreement across regions

Results from the MCA highlighted that the primary source of variation in clinicians’ opinions on the expected outcomes was their level of agreement (Figure S2 in Additional file 1). The response categories followed an ordinal structure from strong agreement to strong disagreement reasonably well, supporting the validity of dichotomising responses into ‘agreement’ versus ‘disagreement’ for the main analysis. Clinicians tended to cluster based on their level of agreement across the expected outcomes. Additionally, the MCA identified a distinct group of clinicians who strongly disagreed that LAMA treatment improves lung function, health-related quality of life, and reduces asthma exacerbations among patients under biologics.

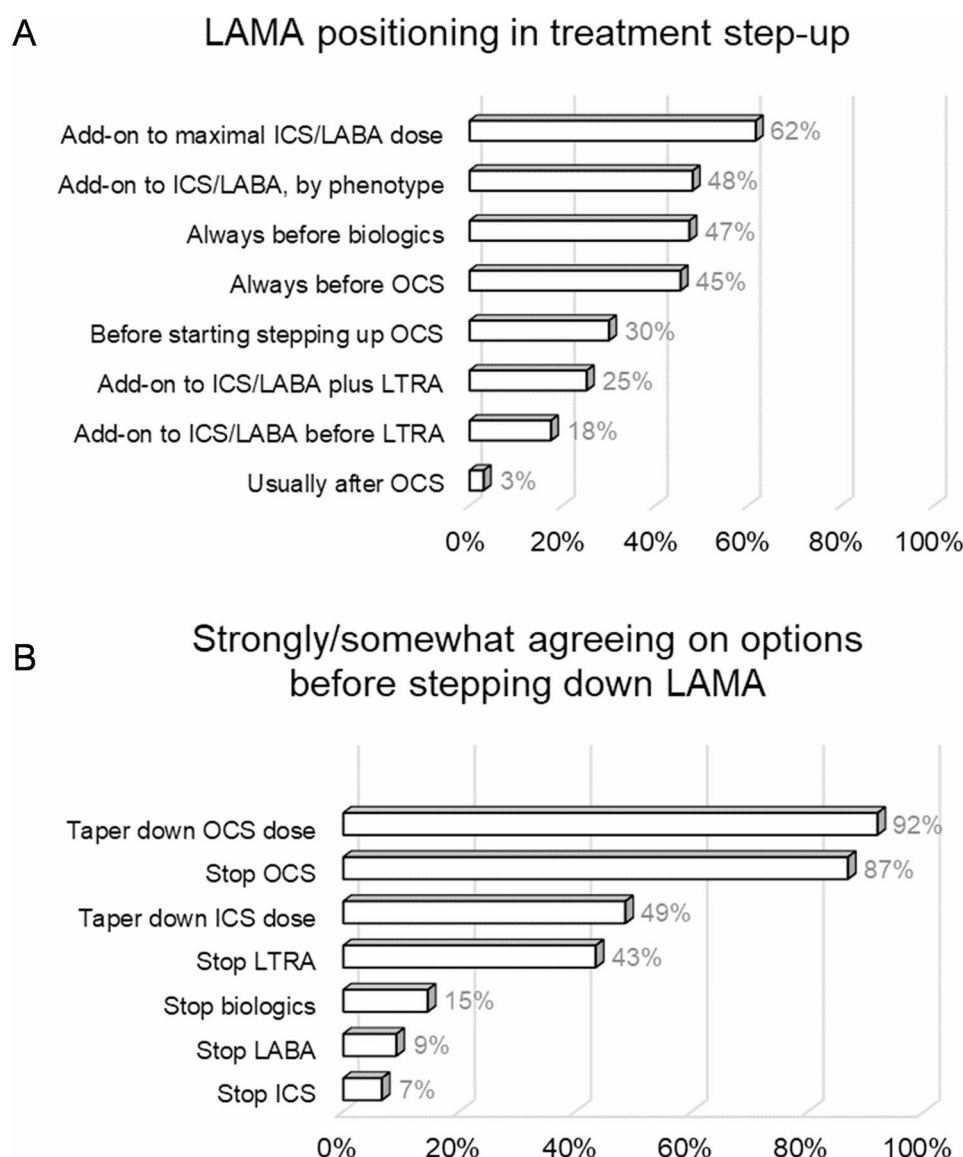


Fig. 2 Positioning of LAMA in the treatment of patients with SA across all regions combined. * **Panel **A**, treatment step-up: proportion (%) of clinicians selecting each response; panel **B**, treatment step-down: proportion (%) of clinicians strongly/somewhat agreeing on each option.

Positioning of LAMA treatment

In the treatment step-up, 62% of the clinicians reported prescribing LAMA as an add-on to the maximal ICS/LABA dose (Fig. 2, panel A). About half of them prescribed LAMA as an add-on to ICS/LABA based on a patient's phenotype. This was reported more frequently in Western and Northern Europe than in other regions (Table S4 in Additional file 1). Approximately half of the clinicians reported prescribing LAMA before biologics, which was more common in Italy, Spain, and other Southern European countries. Additionally, about half of the clinicians reported that they always prescribe LAMA before OCS. Only 3% indicated that they usually prescribe LAMA after OCS.

Most of the clinicians (~90%) agreed on trying to stop OCS or taper down OCS dose before stepping down LAMA (Fig. 2, panel B); clinicians from Northern and Eastern Europe showed a slightly lower agreement on this (Table S4 in Additional file 1). Almost half of the clinicians reported tapering down ICS before stepping down LAMA. A minority reported trying to stop ICS (6.6%), LABA (9.1%), or biologics (14.5%) before stepping down LAMA.

Preference for single or triple inhaler therapy

Out of 406 clinicians who responded to the question, more than half (236, 58.1%) preferred triple therapy. In contrast, 91 (22.4%) favoured single therapy, and 46

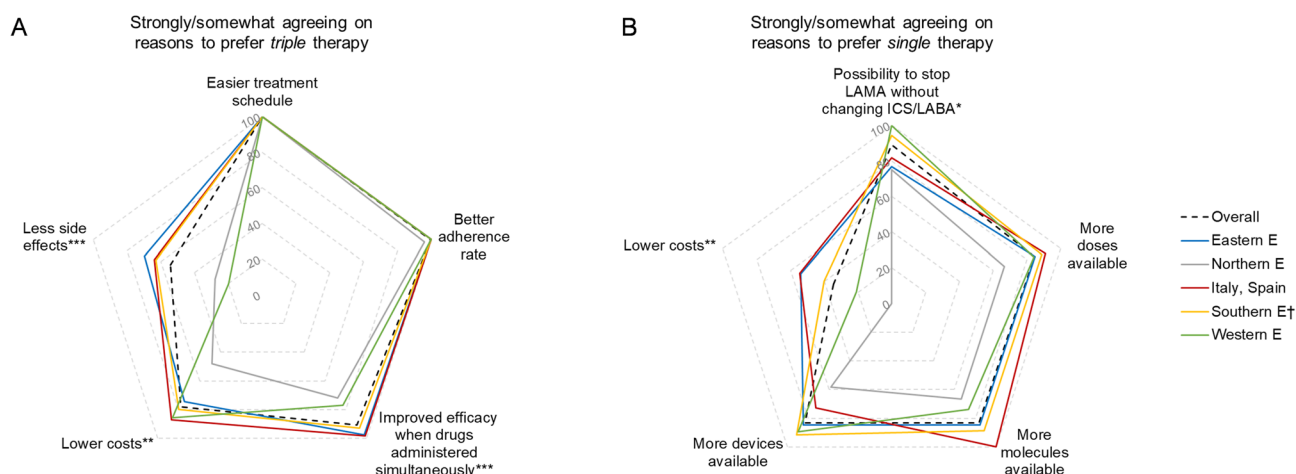


Fig. 3 Proportion (%) of clinicians strongly/somewhat agreeing on reasons to prefer triple (panel **A**) or single (panel **B**) therapy with LAMA for SA, by region. † excluding Italy and Spain, and including Turkey * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for the overall comparison of agreement across regions

(11.3%) had no preference between single and triple therapy. Additionally, 33 clinicians (8.1%) stated that LAMAs were unavailable, or not marketed for SA, in their countries; 18 were in Northern Europe.

Among the clinicians preferring triple therapy, the following reasons for their choice were reported (Fig. 3 and Table S5 in Additional file 1): easier treatment schedule (100%), better adherence rate (99.6%), improved efficacy when the drugs are administered simultaneously (90.6%), lower costs (78.2%), and fewer side effects (54.3%). Among the clinicians preferring single therapy, the reasons reported were: the possibility of stopping LAMA treatment without changing ICS/LABA therapy (89.0%), more options in terms of doses available (84.4%), molecules available (83.3%), and devices available (83.3%), lower costs (34.4%), and fewer side effects (24.4%). There were some differences in agreement across regions, with a general tendency for Northern Europe and, to a minor extent, Eastern Europe, to show a lower degree of agreement.

Discussion

Our study investigated how LAMAs are prescribed for SA across Europe by gathering real-world opinions from clinicians involved in the international SHARP project. Overall, a quite heterogeneous approach to LAMA can be described in terms of target patients, expected outcomes, positioning with respect to other SA treatment options, and preferred formulation.

The main international documents on asthma management indicate the use of LAMA for moderate-to-severe asthma. GINA updated its recommendations in 2021 to include tiotropium for patients at step 4–5 asthma [5], similarly to the National Asthma Education and Prevention Program [9]. European Respiratory Society/American Thoracic Society guidelines published in 2019

also strongly recommend the addition of tiotropium for severe uncontrolled asthma [10]. Following the publication of the Trimaran and Trigger trials, a single inhaler combining beclomethasone, formoterol, and glycopyrronium was also approved for use in SA [11]. Despite this background, some grey shades persist regarding prescribing LAMA in clinical practice, according to our survey.

A first controversial point relates to the best eligible patient for LAMA therapy. In Italy and Spain, the surveyed clinicians are most inclined to treat all their SA patients with LAMA, whilst the drug prescription is managed more selectively in Northern Europe. On the other hand, around half of participating clinicians reported prescribing LAMA as a systematic step before initiating biologic treatment, with this trend being more common in Italy, Spain, and the other Southern European countries. The heterogeneous prescribing behaviours observed across European countries align with findings from a previous study from the SHARP network, where differences in biological treatment initiation and administration were observed [12].

When looking at the literature, a 2020 report from the Severe Asthma Italian network (SANI) described an ongoing LAMA therapy for a small proportion (35%) of patients [6]. At the time of data collection, only tiotropium was licensed for SA, but 12.7% of patients were still prescribed off-label anti-muscarinic agents. Juntunen et al. [13] showed that LAMA-containing inhalers are seldom prescribed, even for asthma cases where these drugs are indicated. Additionally, a study from the US analysing Health Plan Claims Data (October 2014 - December 2016) highlighted that only around 50% of patients on biologic therapy had previously received LAMA as part of a single inhaler or triple therapy regimen [14]. These findings may reflect the heterogeneous approach to LAMA use in terms of positioning, especially with

respect to biological treatment. Our report echoes this variability, even though the data collection was conducted several years later. In fact, about half of the clinicians reported that they always prescribe LAMA before biologics, a practice more common in Italy, Spain, and the other Southern European countries. Notably, 23 clinicians reported that none of their patients were on biologic treatment. Among these clinicians, 21 were non-SA asthma specialists, which may explain this finding. In fact, according to the regulatory guidelines, biologic prescription is usually limited to specialists working in severe asthma referral centres. About half of the clinicians also indicated that they always prescribe LAMA before OCS.

The substantial variability in agreement on drivers for LAMA prescription may account for their controversial positioning. Heterogeneity was observed mainly for fixed bronchial obstruction and frequent asthma exacerbations, which were selected more frequently by clinicians from Italy and Spain (>80%) compared to the clinicians from the other regions (50–70%). On the other hand, the outcomes expected from LAMA use remain a topic of debate. In fact, we observed substantial heterogeneity for lung function improvement, reduction of OCS dose, and reduction of ICS dose, in both biologic-naïve patients and those undergoing monoclonal antibody therapy. An additional source of variability within our survey is related to the self-reported qualification of participating physicians as SA or non-SA specialists, suggesting that the individual background and work setting might impact the treatment approach to asthma patients. In fact, SA specialists seemed to be more confident with LAMA prescription and with its drivers, including fixed bronchial obstruction, frequent asthma exacerbations, non-eosinophilic asthma, and LABA/SABA intolerance.

To date, international recommendations do not provide a straightforward step-up approach for SA regarding specific treatments, including LAMA, nor do they define specific SA phenotypes for which step 5 treatments are recommended. This might explain the lack of a univocal perspective on LAMA prescription drivers and defined expected outcomes. When looking at COPD, which represents a traditional indication of LAMA treatment and a potential paradigm, escalation to triple therapy (ICS-LABA-LAMA) was driven by factors such as exacerbation history and symptom severity, though in the absence of clear-cut indications from guidelines [15, 16]. Some authors suggested persistent airflow limitation and smoking history, associated with recurring symptoms and frequent exacerbations refractory to inhaler therapy with an ICS/LABA, as potential criteria for LAMA prescription [17].

A greater consensus was noted on the step-down approach in asthma therapy management, without clear differences emerging when comparing SA and non-SA

specialists. Approximately 90% of the surveyed clinicians converged on prioritising stopping or tapering OCS before stepping down LAMA, although clinicians from Northern and Eastern Europe showed a slightly lower agreement on this. Nearly half of the clinicians indicated a preference for tapering down ICS before stepping down LAMA. A minority reported attempting to discontinue ICS (7%), LABA (9%), or biologics (15%) before deciding to step down LAMA. The international documents on asthma highly recommend the step-down approach, and OCSs are considered for extremely selected cases as a temporary option. However, no details have so far been provided about step-down protocols, especially in prioritising the decrease or discontinuation of ICS vs. LAMA.

Our study aligns with others highlighting critical gaps in asthma management, physician awareness, and adherence to guidelines, emphasising the need for improved education and structured interventions to optimise patient outcomes. A study on asthma management in Italy and Spain revealed significant variability in how general practitioners implemented asthma management protocols, including inconsistent use of ICSs and LABAs [18], often leading to suboptimal asthma control among patients. Another study reported marked inconsistencies in guideline adherence among Italian paediatricians, particularly in the underuse of ICSs for asthma management, suggesting systemic barriers such as inadequate training or poor familiarity with up-to-date recommendations [19].

This study has limitations. Due to the small number of clinicians participating in each country, we could not perform separate analyses and grouped the countries according to the internationally recognised United Nations classification. Our findings reflect average patterns across groups of geographically close countries. Survey participants represent a self-selected group of motivated clinicians, as they were not recruited through random sampling, and their engagement with the SHARP network may have led to a selection bias, potentially limiting the generalizability of our findings to routine clinical practice. Nevertheless, our conclusions were not affected by regional differences in the proportion of SA specialists, as adjustment for this characteristic did not alter the results. It is also important to note that our study captures clinicians' perspectives and opinions, which are inherently subjective. As with other surveys, reporting bias, including social desirability bias, cannot be excluded. Finally, we could not access patient-level data to correlate with clinician perspectives. Integrating objective real-world data on LAMA prescriptions, along with patient insights, would enhance the comprehensiveness and the validity of future research.

In conclusion, although the indication of LAMA treatment in SA is supported by robust evidence and

recommended by international documents on asthma management, this real-world validated survey highlights substantial variability in prescription behaviours related to anticholinergic treatments for SA among clinicians from different European regions, regardless of their declared degree of experience in the field. The absence of specific algorithms in current international recommendations for positioning LAMA relative to inhaled steroids in the step-up and step-down approaches, or for prioritising LAMA over biologic therapy, may reflect this heterogeneity. In addition, there is currently no data available to identify the best responder patients or those who should be excluded due to specific contraindications. Our survey indicates that patients with fixed bronchial obstruction, frequent asthma exacerbations, and a history of smoking are more likely to benefit from LAMA prescription, which should be considered an ICS and OCS sparing strategy and be prioritised over biologic drugs. Our findings support further discussion on the topic at a broader level, for example, by promoting Delphi-based consensus statements and a focused update of international guidelines and recommendations.

Abbreviations

BDP/FF/GB	beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide
FF/U/V	fluticasone furoate/umeclidinium/vilanterol
GINA	Global Initiative for Asthma
I/GB/MF	indacaterol/glycopyrrolate/mometasone furoate
ICS	inhaled corticosteroid
LABA	long-acting beta-2-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonists
MCA	multiple correspondence analysis
OCS	oral corticosteroid
SA	severe asthma
SABA	short-acting beta-agonist
SHARP	Severe Heterogeneous Asthma Research collaboration, Patient-centred

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-025-03378-4>.

Additional files 1: Supplementary data. Additional results.

Additional files 2: Responses from the National Leads who participated in the survey validation. Information collected from SHARP National Leads for validation of the survey tool.

Additional files 3: Positioning LAMA in severe asthma treatment: the perspective of clinicians in the SHARP network. Validated survey tool.

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Authors' contributions

AM, MC, and LM conceived the idea for the study, drafted the first versions of the survey tool and manuscript. EB coordinated contacts with national societies, SHARP National Leads, and the SHARP "Investigators-led initiatives" working group. AM, LM, and PM conducted the statistical analysis. All authors contributed to the design of the survey tool and interpretation of the results. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

Clinical trial number

Not applicable.

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While preparing this work, the authors used Grammarly and ChatGPT to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the publication's content.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study involved the participation of clinicians who completed an anonymous questionnaire. Participants were not recruited individually but were reached via emails by national societies or SHARP National Leads, without access to their personal information. Participation was voluntary, and informed consent was explicitly obtained at the beginning of the questionnaire (Additional file 3).

Consent for publication

Not applicable.

Competing interests

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