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The ALPACA study: (In)Appropriate LAMA prescribing in asthma: A cohort analysis

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ABSTRACT

Introduction: Since long-acting muscarinic antagonists (LAMA) are only indicated as add-on therapy in subjects with moderate-to-severe asthma, there are concerns whether LAMA monotherapy is associated with worse asthma control.

Aim: To study the prevalence of LAMA monotherapy and its potential association with severe asthma exacerbations (SAE) in patients with asthma.

Methods: A cohort study (2007–2017) in the IPCI primary care database, in asthma patients aged 6–50, using LAMA during follow-up. Respiratory prescriptions were retrieved from the electronic medical records based on ATC code. Asthma treatment periods were created and categorized as LAMA mono, dual (LAMA + ICS), or triple therapy (LAMA + ICS + LABA). Relative rates (RR) of SAE, adjusting for patient characteristics, were estimated to compare treatments.

Results: From a total of 66,508 asthma patients, 1236 (1.9%) LAMA users were identified. Median age was 41 years, 65.9% were females. LAMA users were responsible for 3596 LAMA treatment periods of which 1390 (38.7%) were LAMA monotherapy, 553 (15.4%) dual therapy and 1653 (46.0%) triple therapy. The RR of SAE during LAMA monotherapy compared to dual therapy was 1.5 (95% CI 0.6–3.8). In patients alternating between mono and dual therapy (but never triple therapy), the RR for LAMA monotherapy increased to 5.7 (95% CI 1.4–23.6).

Conclusions: This observational study shows that when LAMA is prescribed, it is often prescribed without concurrent ICS (LAMA monotherapy). LAMA monotherapy was associated with an increased risk of exacerbations when not used concurrently with ICS. This emphasizes the importance that LAMA should never be prescribed without concomitant ICS use in patients with asthma.

1. Introduction

Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment. However, in some patients additional medication is required to control symptoms, prevent exacerbations and improve the quality of life. The preferred add-on medication in asthmatic patients is a long-acting beta2 agonist (LABA). Other options are leukotriene receptor antagonists (LTRA) or long-acting muscarinic antagonists (LAMA) [1]. LAMA is most commonly used in patients with COPD, however since 2014 it is also registered for treatment in patients with severe asthma aged 6 years or older [2]. Trials have shown that LAMA - as an add-on to ICS in uncontrolled asthma - reduces the risk of an asthma exacerbation and improves lung function, but no significant effect on asthma control questionnaires or quality of life has been observed [3,4]. Since most evidence on the use of LAMA in asthmatic patients is based on tiotropium, tiotropium is currently the only LAMA indicated for use in asthma. The Global Initiative for Asthma (GINA) recommends the use of tiotropium in step 4 and 5 of asthma treatment, as an add-on treatment

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only, when asthma control cannot be achieved with a combination of ICS and LABA [1].

Treatment adherence is often suboptimal in asthmatic patients [5]. One study using a US claims database reported that amongst asthma patients using tiotropium, in almost one out of five patients this use consisted of tiotropium monotherapy, i.e. without a concurrent ICS prescription [6]. This is alarming, as studies have shown that LABA, also a controller therapy, if used in monotherapy increases the risk of asthma exacerbations and even asthma-related death [7,8]. The effect of LAMA monotherapy on asthma control is not yet known. The aim of this study is to examine the use of LAMA monotherapy in asthmatic patients and to investigate whether LAMA monotherapy increases the risk of severe asthma exacerbations using data from a primary care electronic healthcare database.

2. Methods

2.1. Data source and study design

A retrospective cohort study was conducted using data from the Integrated Primary Care Information (IPCI) database. IPCI is a primary care database containing the complete electronic patient records from approximately 2.5 million patients in the Netherlands [9]. The study period was from January 1, 2007 to December 31, 2017. Patients were included if they were 6–50 years old during the study period, with physician diagnosed asthma (ICPC = R96) in combination with at least two asthma drug prescriptions (Anatomical Therapeutic Chemical Classification System (ATC) code R03) within one year of any available asthma diagnosis code In addition, patients had at least one year of database history, and at least one LAMA prescription during the study period. Patients with a COPD diagnosis code (ICPC = R95) were excluded. The follow-up started on the date of database entry, asthma diagnosis, reaching the age of 6 years or study start, whichever came last. The follow-up ended at the age of 50 years, death, lost-to-follow up, or end of study period, whichever came first.

2.2. Exposure

From the individual prescriptions, treatment periods were created from consecutive prescriptions within 30 days. At the start of each treatment period, a washout-period of 30 days was applied (see online supplements) implying that follow-up only started after 30 days treatment. This washout was applied to reduce the effect of previous treatment periods on subsequent treatment periods. Since the washout reduced the duration of the follow-up period sensitivity analyses without wash-out periods were also conducted.

For the analysis the treatment periods were categorized into three types of LAMA-therapy use, and patients were categorized into four types of LAMA-users based on all their treatment periods during follow-up.

1. Treatment period types

LAMA-therapy treatment periods were classified in 3 categories: 1) monotherapy (LAMA): a treatment period of a LAMA exposure with no simultaneous ICS exposure; 2) dual therapy (LAMA + ICS): a treatment period of LAMA exposure overlapping with a treatment period of ICS, but with no simultaneous LABA exposure; 3) triple therapy (LAMA + ICS + LABA): a treatment period of LAMA prescription overlapping with ICS and LABA exposure (Fig. 1).

2. Patient types

Patients were categorized into four patient types based on their respective treatment periods during complete follow-up: 1) only LAMA mono use: patients only using LAMA monotherapy; 2) only LAMA dual use: patients using only dual therapy (LAMA + ICS); 3) mixed: patients using both mono and dual therapy; 4) triple: patients using at least once triple therapy.

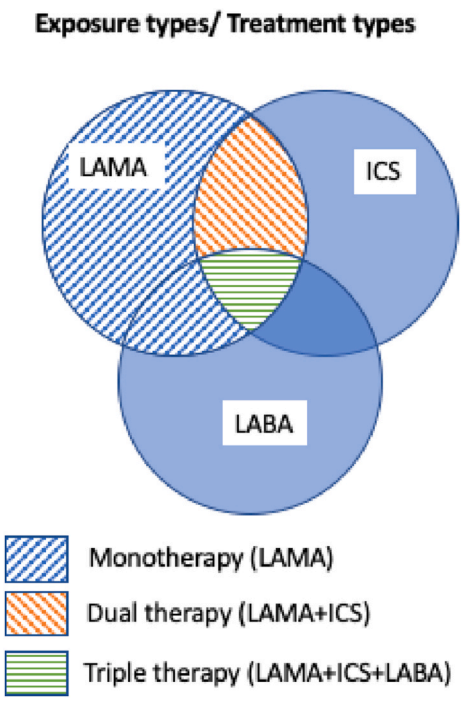

Fig. 1. Visualization of types of treatment periods. Exposure was divided into three categories: LAMA monotherapy (LAMA), dual therapy (LAMA + ICS) and triple therapy (LAMA + ICS + LABA). Periods with other exposure combinations were not considered in the analysis.

2.3. Outcome measures

Our primary outcome was the occurrence of severe asthma exacerbations (SAE). SAE were defined as a burst of systemic corticosteroids for at least 5 days and maximum 30 days (ATC-code starting with H02AB), an emergency department visit or a hospitalization, all for reason of asthma [10,11]. A cut-off of a minimum of 5 days of systemic corticosteroids was chosen as this is in alignment with the Dutch guidelines [12]. All potential exacerbations were automatically selected from the electronic medical records and validated by two researchers (EB and CH). Initially we also aimed to study the effect on mortality however as the number of asthma patients who died in our study population was (fortunately) too small (n = 0), this analysis could not be conducted.

2.4. Covariates

Patient characteristics (age, sex, SAE in the previous year, smoking and comorbidities) were determined at the start of each treatment period. The number of SAEs were determined in the year before each treatment period and used as a continuous variable to be able to adjust for the history of asthma exacerbations. Comorbidities were identified based on an ICPC specific search. Details of these ICPC codes are described in the online supplement.

2.5. Analysis

We described the characteristics of patients by patient type (mono, dual, mixed, or triple) and calculated p-values for the differences in characteristics between the groups (chi-square test or fisher exact test for dichotomous and categorical variables, and Kruskal-Wallis or

ANOVA for continuous variables as applicable). Crude exacerbation rates were calculated as the number of exacerbations divided by the total follow-up time. A Poisson regression analysis was performed to study the relative risk of asthma exacerbations for LAMA monotherapy exposure periods using LAMA + ICS dual therapy as reference category, adjusting for patient characteristics. Furthermore, subgroup analyses were performed based on patient type as these patient types are likely to reflect the severity of asthma. For these analyses the AER package for GEE modeling was used to allow for repeated measures as one patient could be exposed to multiple treatment periods during follow-up. In case the correlation matrix coefficient was low (indicating that there is a low correlation between repeated measures of patients), a GLM Poisson model was used instead. All analyses were done with R version 3.6.1 using packages: AdhereR, AER, dplyr, gee, glm, lme4, MASS, nlme, pglm, reshape, reshape2, tableone, tidyr). The risk window for exacerbations was defined as the duration of the treatment episodes (Fig. 2) after the wash-out period. A sensitivity analysis was done to evaluate outcomes without washout period.

3. Results

In total, there were 66,508 asthma patients aged between 6 and 50 years in the period from 2007 to 2017, of which 1236 (1.9%) patients used LAMA. The median age was 43 years and 65.9% were females. A total of 3596 LAMA treatment periods were generated, of which 1390 (38.7%) were LAMA mono therapy with a median duration of 38 days, 553 (15.4%) LAMA and ICS dual therapy with a median of 58 days and 1653 (46.0%) triple therapy with a median of 60 days (Table 1). LAMA prescription consisted for 93% of tiotropium. The majority of LAMA patients used at least once triple therapy (n = 852, 69.0%), 74 (6.0%) patients used both monotherapy and dual therapy, 89 (7.2%) patients used only LAMA + ICS dual therapy, and 221 (17.9%) patients only used monotherapy (Table 1).

3.1. Patient characteristics by type of LAMA use

Patient characteristics according to type of LAMA use are described in Table 2. The proportion of females differed significantly between the different patient user types (p = 0.045) ranging from 64.4% in the triple therapy users to 76.4% in the LAMA and ICS dual users. The median age of patients was 43 years, with no significant difference across the groups.

The most common comorbidities were allergic rhinitis (range 24.3–31.2%), eczema (range 10.8–20.2%), and depression (range 9.0–18.1%). Patients exposed to triple therapy (ICS + LAMA + LABA) had slightly more comorbidities than patients on mono, dual or mixed therapies. However, for none of the comorbidities this difference was significant. Smoking status was significantly different across the groups, with more current (46.5%) and past (13.8%) smokers in patients who only used LAMA in monotherapy compared to the other three exposure types. Patients who were exposed to triple therapy more often had a SAE in the year before treatment with 30% having at least one severe exacerbation in the year prior. In contrast, the proportion of patients with a history of SAE was much lower in patients who only used LAMA in monotherapy where 14% had at least one SAE in the year before LAMA treatment.

Table 1
Number of treatment periods per patient type. All categories are mutually exclusive. Total duration of treatment periods were: LAMA monotherapy: 127,660 patient days; Dual therapy: 74,728 patient days; Triple therapy: 312,259 patient days.

		Patient type			
		Only Mono n = 221	Only Dual (LAMA and ICS) n = 89	Mixed n = 74	Triple n = 852
Treatment period	**Monotherapy (n=1390)**	340	0	165	885
	Dual therapy (n=553)	0	116	164	273
	Triple therapy (n=1653)	0	0	0	1653

3.2. Differences in risk of exacerbations

A total of 201 severe asthma exacerbations occurred during LAMA treatment periods (either in monotherapy or in combination with ICS or ICS + LABA). The absolute risk was highest during treatment periods consisting of triple therapy (0.56/1000 treatment days; 95% CI 0.48–0.65/1000 treatment days), followed by monotherapy (0.21/1000 treatment days; 95% CI 0.15–0.31/1000 treatment days) and LAMA and ICS dual therapy (0.15/1000 treatment days; 95% CI 0.08–0.27/1000 treatment days). The relative risk (RR) of SAE, after adjustment for confounders such as smoking, during LAMA monotherapy compared to dual therapy was 1.50 (p = 0.387) (Table 3). The risk of SAE was significantly higher during triple therapy than dual therapy with an RR of 3.80 (p < 0.001). After adjusting for potential confounders such as prior exacerbation rate, the RR remained significant at 2.75 (p = 0.025) (Table 3).

Next the analysis was repeated but now in a more homogenous group of patients with both exposure periods of LAMA monotherapy and exposure periods of dual therapy. None of these patients had been prescribed triple therapy during the study period, and all had at least once a concomitant prescription of ICS + LAMA. Compared to periods of dual therapy, during monotherapy patients had a relative risk of SAE of 2.1 (p = 0.045) and after adjusting for potential confounders 5.7 (p = 0.016) (Table 3).

We performed a sensitivity analysis in which treatment periods were determined without washout period. Results were comparable to those when considering a washout-period. The risk of exacerbations was higher during triple and monotherapy periods compared to dual therapy

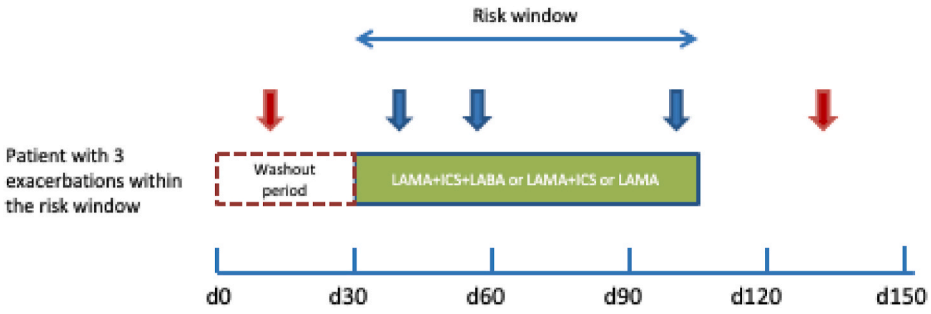

Fig. 2. Risk window. The risk window is defined as the duration of treatment excluding the washout period. Blue arrows represent exacerbations within the risk window and are counted in the exacerbation rate. Red arrows represent exacerbations outside the risk window and are thus excluded. The exacerbation rate during the treatment period is 3/75 patient days = 0.04.

Table 2
Patient characteristics (determined at the start of first treatment period of interest) of all patients included in the study cohort stratified by patient type. Patients are categorized into four types of LAMA exposure.

	Patient type				
	Only mono	Only dual	Mixed	Triple	p-value
Number of patients	221	89	74	852	
Female gender (%)	158 (71.5)	68 (76.4)	49 (66.2)	549 (64.4)	0.045
Age (median (Q1-Q3))	44.3 (38.9–47.2)	43.4 (34.5–47.6)	42.9 (34.3–46.2)	42.7 (35.6–46.4)	0.261
GERD[a] (%)	18 (8.1)	8 (9.0)	2 (2.7)	95 (11.2)	0.086
Obesity (%)	20 (9.0)	7 (7.9)	3 (4.1)	94 (11.0)	0.206
Diabetes Mellitus (%)	7 (3.2)	3 (3.4)	2 (2.7)	59 (6.9)	0.069
Allergic rhinitis (%)	64 (29.0)	27 (30.3)	18 (24.3)	266 (31.2)	0.619
Chronic rhinosinusitis (%)	14 (6.3)	6 (6.7)	3 (4.1)	45 (5.3)	0.817
Nasal polyposis (%)	1 (0.5)	0 (0.0)	0 (0.0)	7 (0.8)	0.661
Eczema (%)	29 (13.1)	18 (20.2)	8 (10.8)	125 (14.7)	0.320
Allergic conjunctivitis (%)	6 (2.7)	2 (2.2)	0 (0.0)	29 (3.4)	0.391
Depression (%)	40 (18.1)	8 (9.0)	9 (12.2)	127 (14.9)	0.197
Number of patients with ≥1 lower respiratory tract infections in previous year	36 (16.3)	10 (11.2)	16 (21.6)	135 (15.8)	0.351
Smoking (%)					0.033
Never	65 (40.6)	36 (60.0)	35 (57.4)	355 (55.1)	
Current	74 (46.5)	17 (28.3)	19 (31.1)	215 (33.4)	
Past	22 (13.8)	7 (11.7)	7 (11.5)	74 (11.5)	
Severe asthma exacerbations in previous year (%)					<0.001
0	190 (86.0)	69 (77.5)	62 (83.8)	596 (70.0)	
1	21 (9.5)	17 (19.1)	10 (13.5)	167 (19.6)	
≥2	10 (4.5)	3 (3.4)	2 (2.7)	89 (10.4)	

[a] GERD = Gastro-oesophageal reflux disease.

Table 3
Full model to estimate the relative risk of severe asthma exacerbations in all patients and in mixed patients (patients who had exposure to LAMA mono as well as exposure to LAMA + ICS, but never triple therapy (LAMA + ICS + LABA).

	Treatment exposure periods (n = 3596) considering all patients (n = 1236)			Treatment exposure periods (n = 329) considering mixed patients (n = 74) only		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Mono therapy	1.50	0.60-3.80	0.387	**5.72**	**1.39-23.62**	**0.016**
Dual therapy	Ref	Ref	–	Ref	Ref	–
Triple therapy	**2.75**	**1.13-6.68**	**0.025**	N/A	N/A	N/A
Female sex	**1.60**	**1.05-2.44**	**0.028**	0.77	0.22-2.69	0.677
Age	0.98	0.96-1.00	0.097	0.95	0.89-1.00	0.065
History of exacerbations	**1.72**	**1.54-1.91**	**<0.001**	2.14	0.92-5.01	0.079
Allergic rhinitis	0.98	0.64-1.51	0.931	0.86	0.27-2.70	0.793
Sinusitis	0.77	0.32-1.92	0.587	0.00	0.00-∞	1.00
Depression	1.53	0.87-2.68	0.142	**5.09**	**1.27-20.35**	**0.021**
Lower respiratory tract infection	0.66	0.40-1.09	0.103	**6.04**	**1.53- 23.90**	**0.011**
Smoking: never	ref			ref		
Smoking: current	0.72	0.44-1.17	0.183	0.24	0.048-1.20	0.083
Smoking: past	**0.43**	**0.19-0.98**	**0.044**	0.00	0.00-∞	1.000
Smoking: unknown	0.85	0.52-1.37	0.498	0.00	0.00-∞	1.000

periods, though this was only statistically significant for triple therapy. In mixed patients only, the risk of exacerbations was again significantly higher during monotherapy compared to dual therapy (RR 4.9, p-value 0.015). For details see online supplements.

To investigate whether the increased risk of exacerbations was driven by LABA use, we also repeated the analyses for LAMA monotherapy prescriptions without concurrent LABA prescriptions. While the risk of exacerbations seemed to be higher during LAMA monotherapy without concurrent LABA prescription, the results were not statistically significant. Details on these analysis can be found in the online supplements.

A stratified analysis on history of severe asthma exacerbation showed an increased risk of SAE during LAMA monotherapy for mixed patients without a SAE in the year prior (RR: 2.68 (CI 95% 1.49–4.82)), and for all patients with a SAE in the year prior (RR = 16.36, CI 95% 1.68–159.18). Details on these analyses can be found in the online supplements.

4. Discussion

In this cohort study, we describe real-life prescription patterns of LAMA therapy in asthmatic patients. In this Dutch cohort, less than 2% of asthmatic patients were prescribed LAMA therapy. However, in almost 4 out of 10 LAMA prescriptions a co-prescription of ICS was lacking in the database. Yet 14% of patients prescribed LAMA monotherapy already experienced severe asthma exacerbations in the year prior. This again confirms that these patients had an indication to receive inhaled corticosteroids. We observed a predominance in female gender in our study population, which is in line with the occurrence of asthma in adulthood [13]. Importantly, in this study we have shown that patients using LAMA monotherapy have an increased risk of severe asthma exacerbations compared to using LAMA with an ICS. This was observed in patients with and without a history of severe asthma exacerbations.

Interpretation of the risk of asthma exacerbations is complex. We know from literature that the a-priori risk of exacerbations depends on the severity of asthma, as well as the adherence to medication and life style changes such as smoking. Asthma treatment step-up is driven by

asthma severity and control [1]. Unfortunately, we lack information on asthma control as measurements such as the asthma control questionnaire are not routinely collected in primary care. However, exacerbations in the previous year could be seen as a proxy for asthma control, since the most important known risk factor for an exacerbation is a previous exacerbation [14,15]. The lowest rate of previous asthma exacerbations was observed for LAMA monotherapy treatment, and the highest for triple therapy. This suggests that patients being prescribed triple therapy have more severe asthma, and patients prescribed LAMA monotherapy have less severe asthma. This further aligns with a potential difference in asthma control. To investigate the relationship between asthma control, therapy and exacerbation risk in more detail a stratified analysis for history of exacerbation was conducted. This analysis showed an increased risk of SAE during LAMA monotherapy for mixed patients without a SAE in the year prior, and for all patients with a SAE in the year prior. However, in other subgroups numbers were too small to perform an analysis. This stratified analysis supports the findings in the manuscript that LAMA monotherapy increases the risk of SAE, regardless of history of exacerbations.

Interestingly, only when investigating a group of patients intermittently using monotherapy and dual therapy, the risk of SAE was significantly higher during monotherapy. When comparing treatment periods for all asthma patients being prescribed a LAMA, a modest (50% increase) risk of asthma exacerbations was observed but this difference in exacerbation risk was not statistically significant. An explanation of these conflicting results could be that we did not completely adjust for asthma severity. It is expected that for worsening of respiratory symptoms the patient would contact the physician and would add an ICS on top of LAMA. Yet this assumption could not be investigated further in this dataset as the exact indication of use is missing in the database.

The frequency of monotherapy is similar to that mentioned in a previous study by Averell et al. [6] In this US claims database study, 34% of the tiotropium dispensing was without a concomitant ICS. Similar to our study, those with LAMA monotherapy had less often a history of asthma exacerbations. This suggests a milder or better controlled asthma than in patients who are prescribed a LAMA in combination with an ICS. Unfortunately, this study did not investigate differences in the risk of exacerbation by type of LAMA exposure (mono vs dual). The fact that in their as well as in our study many of the patients being prescribed LAMA monotherapy had a history of a severe asthma exacerbation confirms that a prescription of ICS definitely was indicated.

To our knowledge, we are the first to investigate the risk of severe asthma exacerbations during LAMA monotherapy in asthmatic patients. An increased risk of asthma exacerbations when ICS coverage is inadequate, especially in a population where part of the patients had an asthma exacerbation in the previous year, is not surprising. ICS is the corner stone of asthma management, as it is the most effective drug to prevent exacerbations [1]. Whether the risk of exacerbations is increased by LAMA treatment is not clear. The benefit of tiotropium as add-on therapy on top of ICS use has been demonstrated in randomized controlled trials as well as in a few real-life studies [16,17]. National and international guidelines are clear on the place of LAMA therapy in asthma management, as it is only recommended as add-on therapy in severe uncontrolled asthma [1,18,19]. The warning of the FDA on LABA monotherapy and several studies showing the danger of SABA overuse have cautioned not to use reliever therapy without a concomitant controller in asthma [8,20]. In this study, we have shown that many asthmatic patients are not prescribed controller therapy which is in conflict with current guidelines. We know from literature that asthmatic patients are often non adherent, especially to controller medication [5]. The proportion of actual (correct) ICS use will even be lower than our estimates based on prescribed ICS amount. Therefore, increasing adherence of patients to ICS should always be supported by education, electronic or face-to face reminders, and simplified regimens [21,22].

As all studies, there are strengths and limitations to this study. This observational cohort study provides important insight in real-life asthma management. The strengths of this study is multiple. First, we had access to a large cohort of asthmatic patients, being able to capture sufficient LAMA prescriptions even though the prevalence of LAMA use in asthma patients is low. Secondly, in the Netherlands every inhabitant is registered with a general practitioner (GP) who acts as a gatekeeper to specialist health care and all data is registered as part of usual care. Therefore, the risk of information bias is minimal. Thirdly, all exacerbations were manually validated by reviewing the patient's file (free text validation) to minimize misclassification of the outcome. Lastly, in the Netherlands, the drugs mentioned in the study are included in all standard health insurance packages. Therefore, the choice of drug does not depend on differences in health insurance.

However, as with all observational studies there are limitations inherent to the study design. Indeed, data on asthma control such as asthma control questionnaires or lung function tests were not routinely collected. Since the study was conducted in a primary care database, prescriptions by specialists might be missed. Importantly, misclassification of asthma diagnosis was possible since asthma diagnosis was based on asthma diagnostic codes in combination with use of respiratory drugs. However, to reduce the potential of misclassification between asthma and COPD – which could be a concern as LAMA monotherapy is indicated for the treatment of COPD (GOLD stage II), we excluded patients with both a disease code of asthma and COPD and limited the population to individuals younger than 50 years. Moreover, stratified analyses according to smoking status showed that the risk of SAE in non-smokers (where the risk of misclassification of COPD is rare) was still significantly increased for patients using LAMA monotherapy (see online supplements). This is an important clinical message for patients and physicians.

What is the clinical relevance of our finding? In this cohort study, we found that – although use of LAMA in asthma is low - many patients are prescribed a LAMA without concomitant ICS, despite that this is clearly discouraged in national and international asthma guidelines. Moreover, although the absolute risks remain low, we found an increased risk of exacerbations during periods of LAMA monotherapy in patients alternating between mono and dual therapy. This was found in both patients with a history of severe asthma exacerbations and without a history of severe asthma exacerbations. These findings emphasize that monitoring of ICS use when prescribing LAMA should be a key strategy to improve asthma care. Developing fixed combinations of LAMA and ICS, or using triple inhaled therapy (LAMA + LABA + ICS) might prevent the use of LAMA as monotherapy in patients with asthma.

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CRediT authorship contribution statement

E.J. Baan: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **C.E. Hoeve:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **M. De Ridder:** Conceptualization, Methodology, Writing – review & editing. **L. Demoen:** Validation, Investigation. **L. Lahousse:** Writing – review & editing. **G.G. Brusselle:** Supervision, Writing – review & editing. **K.M.C. Verhamme:** Conceptualization, Supervision, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pupt.2021.102074.

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