

Seventeen-Year Nationwide Trends in Use of Long-acting Bronchodilators and Inhaled Corticosteroids among Adults – A Danish Drug Utilization Study

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Abstract: Long-acting bronchodilators and inhaled corticosteroids (ICS) are the cornerstones in treatment of chronic obstructive and inflammatory pulmonary diseases. However, non-adherence to guidelines is widespread. Detailed information on real-life treatment patterns is needed to promote rational use. We aimed to investigate nationwide time trends in individual-level treatment patterns of long-acting bronchodilators and ICS. Using nationwide Danish health registries, we identified all Danish adults with a prescription for long-acting bronchodilators and/or ICS from 2000 to 2016. We investigated the total use of long-acting bronchodilators and ICS, the proportion of current users and the rate of new users over time. Finally, we assessed treatment persistence. We included 23,061,681 prescriptions for long-acting bronchodilators and ICS issued to 805,860 individuals from 2000 to 2016. Over this period, the total annual amount of prescribed long-acting bronchodilators and ICS increased by 39%. Similarly, the proportion of adult users increased from 2.6% to 4.5%, mainly driven by the introduction of combination therapy and long-acting muscarinic antagonist (LAMA). Although the rate of new users of fixed-dose combination drugs increased substantially over time, the overall rate of new users was stable. In general, the proportion of patients on therapy after 1 year was low (25–53%), especially among young individuals and users of ICS. We document a pronounced increase in the total use of long-acting bronchodilators and ICS over time, mainly driven by the introduction of combination drugs and LAMA. Special attention should be paid to the low level of persistence, especially among young individuals and users of ICS.

Long-acting bronchodilators and inhaled corticosteroids (ICS) constitute the cornerstones in the medical treatment of chronic obstructive and inflammatory pulmonary diseases [1,2]. According to the World Health Organization (WHO), asthma and chronic obstructive pulmonary disease (COPD) affect more than 300 million people worldwide [3,4], and the prevalence is expected to increase over the following decades [5].

A range of new devices and long-acting bronchodilators has been marketed within the last decade. The first long-acting muscarinic antagonist (LAMA) was authorized by The European Medicines Agency (EMA) in 2002, whereas combinations of ICS and long-acting beta-2-agonists (LABA), that is ICS + LABA, and combinations of long-acting bronchodilators (LAMA + LABA) were authorized in 1999 and 2013, respectively. ICS and LABA in monotherapy have been on the market even longer. This development in pharmacological treatment certainly has an influence on health expenditures, emphasized by the fact that costs related to use of drugs targeting obstructive pulmonary diseases in Denmark have doubled in the last 20 years [6].

These concerns for the rising financial costs are supplemented by concerns for both inadequate treatment and

inappropriate overuse of medication targeting chronic obstructive and inflammatory pulmonary diseases [7]. Similarly, adverse effects are of interest. While some long-acting bronchodilators like LAMAs are suspected to increase the risk of major adverse cardiac events [8], ICS is known to increase the risk of pneumonia [9,10] and osteoporotic fractures [11,12].

To guide future initiatives on optimal and rational use of medication for stable chronic obstructive and inflammatory pulmonary diseases, there is a need for detailed information on real-life utilization patterns of these drugs over time. In this study, we therefore aimed to investigate nationwide time trends in the individual-level treatment patterns of long-acting bronchodilators and ICS.

Materials and Methods

In this nationwide, registry-based utilization study, we described the use of long-acting bronchodilators and ICS among Danish adults from January 2000 to December 2016.

Data sources. In Denmark, it is possible to conduct accurate population-based studies based on registries covering the entire population due to the unique Civil Person Registry number and the Danish National Health Service which provides tax-supported health care for the entire Danish population [13].

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We retrieved data from two large population-based registries: The Registry of Medicinal Products Statistics and The Danish Civil Registration System.

The Registry of Medicinal Products Statistics contains data on all redeemed prescription drugs by Danish citizens at outpatient pharmacies since 1995 and onwards [14]. Prescription data include the date of dispensing, the substance, brand name and quantity. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) code, developed by WHO for purposes of drug use statistics [15]. The quantity in each prescription is expressed by the defined daily dose (DDD) measure, also developed by WHO [15].

The Danish Civil Person Registry covers every Danish citizen and contains data on vital status (date of birth and death) and migrations to and from Denmark [16].

Study population. We identified all Danish adults (≥ 18 years) who had filled a prescription for long-acting bronchodilators and/or ICS between 1 January 2000 and 31 December 2016. The adult population increased from 4.18 million in 2000 to 4.54 million in 2016.

Study drugs. We subcategorized long-acting bronchodilators according to pharmacological drug class into LABA, LAMA, ICS, combinations of LABA and ICS, and combinations of LABA and LAMA. ATC codes and corresponding DDDs are shown in table 1.

The duration of each prescription was estimated as the number of doses dispensed in DDDs, that is assuming a consumption of one DDD per day, while adding a grace period of 25% to account for irregular prescription refills and/or minor non-compliance. Current users were defined as individuals who had filled a prescription for the

Table 1.

Long-acting bronchodilators and ICS.

Drug	ATC codes	DDD
Long-acting β_2 -agonists (LABA) ¹		
Salmeterol	R03AC12	0.1
Formoterol	R03AC13	0.024
Indacaterol	R03AC18	0.15
Olodaterol	R03AC19	0.005
Bambuterol	R03CC12	20
Long-acting anticholinergics (LAMA) ¹		
Tiotropium bromide	R03BB04	0.005/0.010
Aclidinium bromide	R03BB05	0.644
Glycopyrronium bromide	R03BB06	0.044
Umeclidinium bromide	R03BB07	0.055
Inhaled corticosteroids (ICS) ¹		
Beclomethasone	R03BA01	0.8/1.5
Budesonide	R03BA02	0.8/1.5
Flunisolide	R03BA03	1
Fluticasone	R03BA05	0.6/1.5
Mometasone	R03BA07	0.4
Ciclesonide	R03BA08	0.16
Combinations(LABA+ICS) ²		
Salmeterol + fluticasone	R03AK06	2/4
Formoterol + budesonide	R03AK07	2/4
Formoterol + beclomethasone	R03AK08	4
Vilanterol + fluticasone furoate	R03AK10	1
Formoterol + fluticasone	R03AK11	2/4
Combinations (LAMA + LABA) ²		
Vilanterol + umeclidinium bromide	R03AL03	1
Indacaterol + glycopyrronium bromide	R03AL04	1
Formoterol + aclidinium bromide	R03AL05	2
Olodaterol + tiotropium bromide	R03AL06	2

¹DDD is expressed in mg.

²DDD for combined products are expressed in unit dose (UD).

drug of interest with enough doses in DDDs to cover a specific day. New (incident) users were defined as such, if they had no fillings of the drug of interest since the establishment of the Registry of Medicinal Products Statistics in 1995.

Analysis. To examine time trends in the utilization of long-acting bronchodilators and ICS, we used the following three approaches:

- 1 Firstly, we calculated the overall annual use of long-acting bronchodilators and ICS (measured as amount of dispensed DDDs) on a nationwide level during the study period, specified by pharmacological subclass.
- 2 Secondly, we investigated the proportion of current users on each day during the study period (point prevalence proportion) and the rate of new users per 1000 persons in a specific year (annual incidence rate) from 2000 to 2016. The total Danish adult population on 1 January in the specific year was used as the denominator. To be able to account for differences according to sex and age on treatment patterns and to evaluate changes over time, we additionally determined the sex- and age-specific point prevalence proportions by the end of 2000, 2004, 2008, 2012 and 2016. All analyses were performed as specified by the pharmacological subclass. We used Cuzick's test for trends in overall annual use, prevalence and incidence per study year.
- 3 Thirdly, we assessed the overall persistence to therapy over time by determining the proportion of patients covered by treatment (PPC). The advantage of this approach is the minimal sensitivity to variations in the grace period as the PPC allows patients to have a short break in therapy without being excluded from the analysis. We followed all new users for up to 12 months from the date of their first prescription for long-acting bronchodilators or ICS. Over time, we estimated the proportion of individuals still alive and not migrated that were still using the same pharmacological subclass of long-acting bronchodilators or ICS at a given day regardless of prior treatment breaks, relative to the date of their first prescription (i.e. had filled enough doses in DDD to cover that given day). An individual could be regarded as dropped out of treatment at one point in time and later be reclassified as users upon filling a new prescription. In a post hoc analysis, we further investigated the persistence to therapy stratified by sex and age groups (18–39, 40–64, 65–79, +80 years).

Other. Stata version 14.1 (StataCorp, College Station, TX, USA) was used for all analyses.

The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on registry data do not require approval from an ethics review board [17].

Results

In total, 805,860 adults filled 23,061,681 prescriptions for long-acting bronchodilators and ICS from 2000 to 2016. Of all individuals included, 25% ($n = 197,335$) filled only one prescription for either a long-acting bronchodilator or an ICS from 2000 to 2016, while 19% and 56% filled 2–4 and 5+ prescriptions, respectively. The median number of filled prescriptions per person within the study period was 7 (interquartile range (IQR): 2–33). LAMA was the drug subclass with the highest median number of prescriptions (12; IQR: 3–33), whereas ICS had the lowest (3; IQR: 1–13).

Prevalence, Incidence and amount dispensed.

The total amount (in DDD) of prescribed long-acting bronchodilators and ICS increased by 39% in the study period,

from 42.1 million DDDs in 2000 to 69.4 million in 2016 (fig. 1, p for trend <0.001). The increase was more pronounced for combinations of LABA + ICS and LAMA + LABA, while the amount of ICS outside combination treatment was reduced by half by the end of the study period (from 31.3 million DDDs in 2000 to 15.2 million DDDs in 2016, p for trend <0.001). However, the overall use of LABA and ICS (in combined and single substance devices) remained largely stable in the study period.

Similarly, the overall proportion of all Danish adults currently using long-acting bronchodilators and/or ICS (point prevalence proportion) increased throughout the study period. As such, 2.6% of the adult Danish population was currently using any kind of long-acting bronchodilators and/or ICS by the end of 2000, which increased to 4.5% by the end of 2016 (p for trend <0.001). The most pronounced increase was seen among current users of LABA + ICS (0.1% in 2000 to 1.8% in 2016, p for trend <0.001; fig. 2). For all subclasses, the point prevalence of use increased with age until the age of 80 years. Hereafter, we observed a steep decrease in current users, most pronounced among women. In general, we did not observe any sex-specific difference in use except for a tendency towards a higher point prevalence among female users of ICS and LABA + ICS below the age of 80 years (fig. 3). This pattern was consistent throughout the study period. An increasing or decreasing prevalence of use of subclasses over time seems to be driven by use in individuals older than 50 years (Figure S1).

The overall rate of new users each year (annual incidence rate) was more or less stable throughout the study period (fig. 4). However, as specified by drug class, we found a more than three times increase in incident use of LABA + ICS from two new users per 1000 persons per year in 2000 to more than seven new users per 1000 persons per year in 2005 (p for trend = 0.03). From 2006 onwards, the annual incidence rate settled around five new users per 1000 persons per year (p for trend = 0.004). After the introduction of LABA + LAMA in 2013, we similarly observed a steep increase in the rate of new users of this drug to more than three new users per 1000

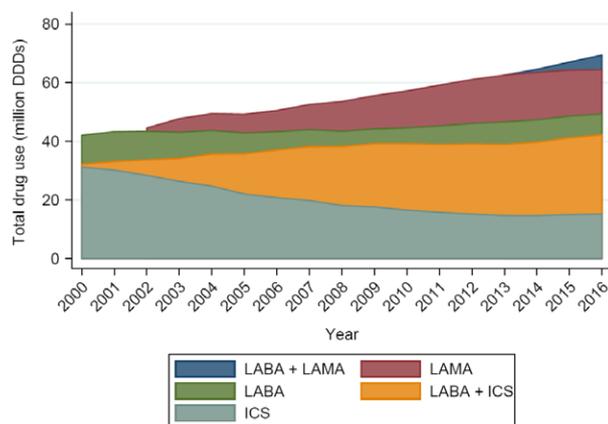


Fig. 1. Total amount of dispensed defined daily doses, specified by type of inhalation therapy and calendar year.

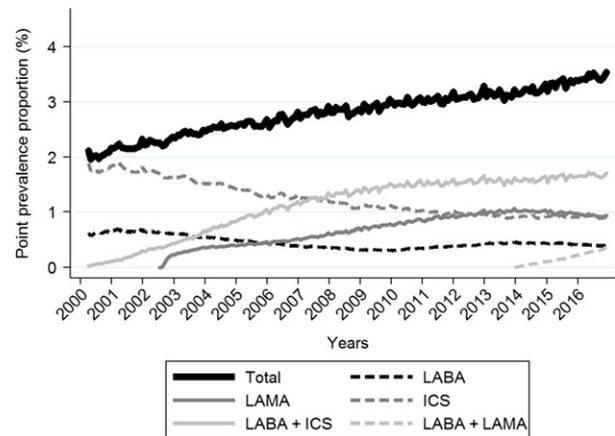


Fig. 2. Proportion of current users of long-acting bronchodilators and ICS at any date, that is point prevalence proportion, in the total Danish adult population from 2000 to 2016. The total Danish adult population on 1 January in the specific year was used as the denominator. Overall and stratified by drug class.

persons per year in 2016. Of note, the annual incidence rate of ICS and LABA decreased in the first half of the study period but reached a stable level from 2008 to 2009 onwards (fig. 4).

Persistence to treatment.

Consistently for all drug subclasses, we observed a pronounced decrease in the proportion of new users covered by the therapy of interest after 1 month of therapy. The proportion of patients on therapy after 12 months was highest among users of LABA + LAMA and LAMA (around 50%) and lowest among users of ICS, LABA and LABA + ICS (25–32%) (fig. 5). When stratifying by age groups, we consistently found a higher proportion of patients on therapy after 12 months among individuals older than 65 years of age, compared to young individuals aged 18–39 years (Figure S2).

Discussion

In this nationwide drug utilization study, we investigated time trends in individual-level treatment patterns of long-acting bronchodilators and ICS in the adult Danish population from 2000 to 2016. Overall, we observed a substantial increase in the amount of redeemed long-acting bronchodilators and ICS as well as in the proportion of current adult users. Fixed-dose combinations (ICS + LABA and LAMA + LABA) and LAMA accounted for the majority of this increase, while use of ICS non-combination inhalers decreased. Of note, we observed that after 12 months of initiation of therapy, only a small proportion of patients alive were on therapy with long-acting bronchodilators and ICS. This tendency was especially pronounced among users of ICS and LABA and individuals younger than 40 years.

The principled strength of this study is the nationwide and register-based approach. The Danish health registries cover the entire Danish population regardless of demographic and

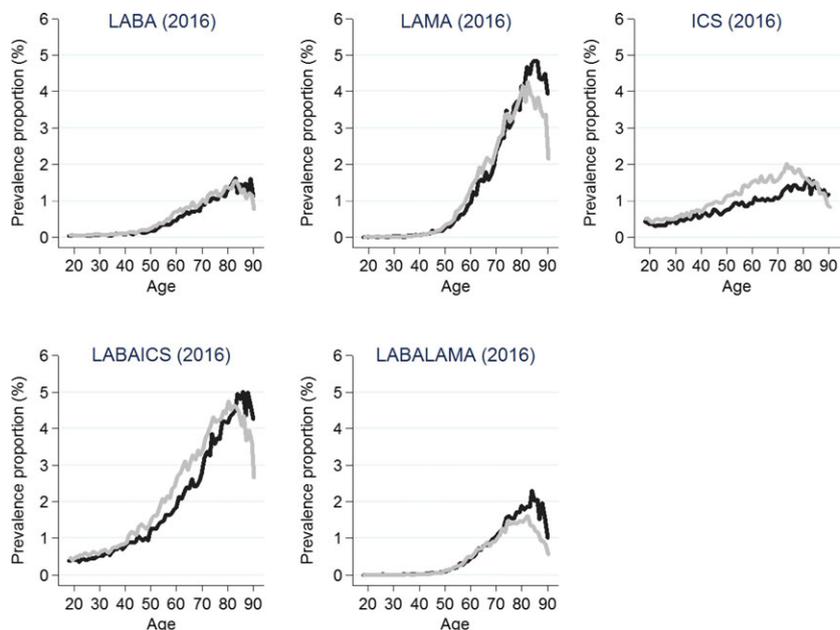


Fig. 3. Age- and sex-specific point prevalence proportions by the end of 2016, specified by subclasses of inhalation therapy. Females: light grey; males: dark grey.

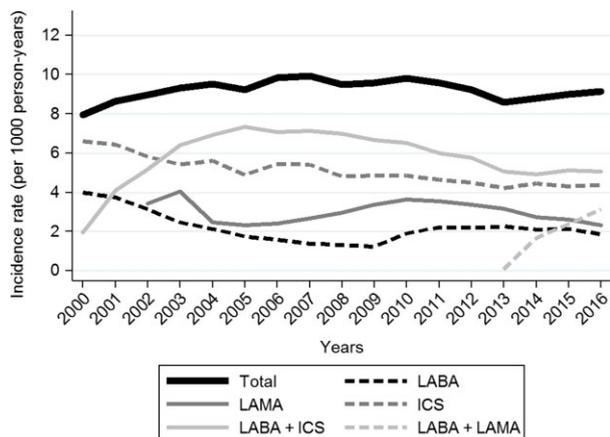


Fig. 4. Rate of new adult users of long-acting bronchodilators and ICS per 1000 persons in a specific year, that is the annual incidence rate, in Denmark from 2000 to 2016. The total Danish adult population on 1 January in the specific year (excluding current users) was used as the denominator. Overall and stratified by drug class.

socio-economic characteristics providing a unique opportunity to evaluate the use of drugs in the general population with no selection bias. In Denmark, long-acting bronchodilators and ICS are not available over the counter, enabling complete individual-level identification of all users of these drugs prescribed for home use by general practitioners and hospital physicians [18]. Further, our data represent medication that has actually been bought at the pharmacy, eliminating bias from primary non-adherence [19].

An important limitation of this study is the lack of information about the underlying indication for prescribing inhalation therapy, as this has not been recorded systematically in the

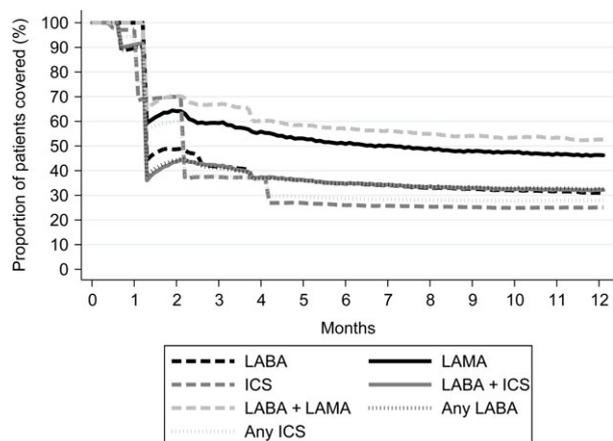


Fig. 5. Persistence patterns of long-acting bronchodilators and ICS at a population level, that is the proportion of patients alive covered by treatment at a given point in time after their first prescription, specified by drug class.

National Prescription Registry. Such information could improve our understanding of initiation and persistence to therapy as well as choice of treatment. However, we consider this to be beyond the scope of this specific study in which we aimed at providing an overview of drug utilization patterns. Further, we did not have information on the intended daily dosage but relied on the assumption of one DDD per day. This assumption may, at least among heavy users, overestimate the length of the period covered by a prescription, but on the other hand underestimate the length among those who used less than one DDD per day.

Use of long-acting bronchodilators became increasingly widespread during the study period. As seen in fig. 1, the

increase is primarily driven by LAMA, which was introduced in Denmark in 2000 and apparently promptly accepted as a new treatment in COPD among healthcare professionals and patients. Though more modest, a slight increase was similarly found after the introduction of fixed-dose combinations of LABA + LAMA in 2013.

The overall amount of filled long-acting bronchodilators and the proportion of current users increased concurrently in Denmark along with a stable incidence rate. As such, the observed changes in use over time seem likely caused by a tendency to add more drugs following the diagnosis of a respiratory disease supplemented by a reluctance towards discontinuing therapy [20]. Further, an extended survival among patients with chronic diseases resulting in a prolonged treatment duration may contribute to the observed pattern [21]. As the rate of new adult users was more or less stable throughout the study period, our results do not intuitively support that raised awareness and campaigns on chronic respiratory diseases by healthcare providers and authorities influenced on the incidence of disease. However, as such intensified focus may contribute to more appropriate use of drugs, the observed pattern might reflect that an increase in correctly diagnosed asthma and COPD patients is cancelled out by a decrease in off-label use.

A previous Danish study demonstrated a substantial increase in ICS use (alone and in fixed-dose combinations with LABA) among young asthma patients from 2000 to 2006 [22]. Though not evident in our study, we do not consider this conflicting to our study in which all adult users of long-acting bronchodilators in the general population are represented. The largely stable use of ICS and fixed-dose combinations containing ICS may reflect a decline in the use of ICS among COPD patients caused by enhanced awareness of side effects related to ICS treatment [23] and an improved adherence to guidelines.

The safety of LABA has been debated extensively in the last decade due to a suspected increase in mortality and exacerbation risk among asthma patients with mono-therapeutic use of LABA. This resulted in a safety communication issued by FDA in 2010 [24]. Despite this, we found an increase in the overall use of LABA in Denmark, which has also been reported from other European countries [25]. Of note, the observed increase is not necessarily contrary to guidelines as it may reflect an increase in combination use with separate inhalers rather than mono-therapeutic use of LABA.

The overall low level of persistence to long-acting bronchodilators and especially ICS therapy is striking though it corresponds to the findings of previous studies. In a Scottish study by Covvey *et al.*, [26] 1-year persistence was found to be as low as 12% and 16% among asthma and COPD patients, respectively. Based on German data, Mueller *et al.* [27] demonstrated that 35% of COPD patients persisted to treatment. Similarly, a Danish study restricted to patients with a first-time hospitalization due to COPD found that 20% of patients were persistent 12 months after initiation of therapy [28].

As we do not take switching to other pharmacological drug classes into account, our findings may reflect both a switch to other drugs containing ICS as well as discontinuation of ICS. It is, however, of note that users of combination drugs

containing LABA + ICS reach a comparably low persistence level after 12 months. As the persistence among users of LAMA and LABA + LAMA is substantially higher, the observed pattern most likely reflects a higher persistence among COPD patients compared to asthma patients. The higher persistence among older users further supports such conclusion. This finding is in agreement with previous studies [29,30] and plausibly explained by the more consistent and severe symptomatology in COPD [26,31].

Emphasized by the initial steep decline in the PPC in our study and the rather stable PPC until the end of 12 months, most of the observed non-persistence to long-acting bronchodilator therapy seems caused by discontinuation within the first 1–3 months after the first-ever prescription for a given drug. This is supported by the fact that 25% of individuals filled only one prescription for long-acting bronchodilators within the 17-year study period. Early discontinuation of respiratory therapy is well known [26,29] and the reason behind this is debated. Firstly, long-acting bronchodilators and especially ICS are in some cases prescribed as a diagnostic tool [32] as well as off-label without sufficient pre-diagnosing [33]. If use does not support the diagnosis of respiratory disease or relief symptoms, therapy will be discontinued shortly after initiation. Secondly, expenditures related to long-acting bronchodilators may affect patients' inclination to continue treatment. Finally, both lack of perceived necessity and benefit from treatment, concerns about adverse effects, and the episodic nature of symptoms are known reasons for discontinuation [34]. Thus, the low degree of persistence may reflect both justified discontinuation and unjustified discontinuation of therapy, representing two very different aspects of treatment.

This study raises important concerns about the utilization patterns of long-acting bronchodilators and inhaled corticosteroids. In accordance with the chronic nature of chronic obstructive and inflammatory pulmonary diseases, the low persistence within the first 12 months after initiation of therapy indicates suboptimal prescribing and use patterns. Future initiatives should investigate the potential underlying causes. Similarly, it needs to be elucidated whether the increase in the number of prevalent users reflects a rational use or perhaps reluctance towards discontinuing ineffective or irrelevant therapy.

In conclusion, we found a pronounced increase in the overall use of combination drugs and LAMA over time, while the use of ICS dropped. Persistence to therapy was low, especially among young individuals and users of ICS. To optimize treatment in everyday clinical practice, attention should be paid to improving persistence to therapy in these patients and only initiating therapy when indicated. Future initiatives should be targeted at elucidating causes behind the increase in use.

Conflict of interests

Mette Reilev reports participation in research projects funded by LEO Pharma, all with funds paid to the institution where she was employed (no personal fees) and with no relation to the work reported in this study. Anton Pottgård reports participation in research projects funded by Alcon,

Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this study. Jens Søndergaard reports personal fees from Boehringer Ingelheim without relation to the work reported in this study. Jesper Rømhild Davidsen, Daniel Pilsgaard Henriksen, Christian B. Laursen and Lotte Rasmussen report no potential conflict of interests.

Author Contribution

Daniel Pilsgaard Henriksen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mette Reilev, Daniel Pilsgaard Henriksen, Lotte Rasmussen, Jens Søndergaard, Jesper Rømhild Davidsen, Christian Laursen and Anton Pottegård conceived and designed the study. Daniel Pilsgaard Henriksen and Anton Pottegård acquired and analysed the data. Mette Reilev, Daniel Pilsgaard Henriksen, Lotte Rasmussen, Jens Søndergaard, Jesper Rømhild Davidsen, Christian Laursen and Anton Pottegård interpreted the data. Mette Reilev and Daniel Pilsgaard Henriksen drafted the manuscript. Mette Reilev, Daniel Pilsgaard Henriksen, Lotte Rasmussen, Jens Søndergaard, Jesper Rømhild Davidsen, Christian Laursen and Anton Pottegård made critical review of the manuscript for important intellectual content. Daniel Pilsgaard Henriksen performed the statistical analysis.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Age- and sex specific point-prevalence proportions by the end of 2000 (A), 2004 (B), 2008 (C) and 2012 (D), specified by subclasses of inhalation therapy. Females: light grey; males: dark grey.

Figure S2. Persistence patterns of long-acting bronchodilators and ICS at a population level i.e., the proportion of patients alive covered by treatment at a given point in time after their first prescription, specified by drug class and stratified by age groups.