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Short title: *Non-adherence and non-persistence in asthma patients*

Extent of non-adherence and non-persistence in asthma patients: Analysis of a large claims data set

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Abstract

Introduction

The objective of this study was to assess non-adherence (NA) and non-persistence (NP) to long-acting asthma medications in Germany by differentiating between measurement of NA in periods of therapy continuation and measurement of NP in therapy-naïve patients.

Methods

We analyzed treatment adherence to long-acting asthma medication using German claims data for periods of treatment continuation based on the medication possession ratio (MPR) and the proportion of days covered. Persistence was assessed in treatment-naïve patients. Outcomes were observed from the date of the first to the last prescription within a 12-month period. Both NA and NP analyses considered prescription supply, using either defined daily dosages, or prescribed daily dosages derived from a medical chart review.

Results

We identified 52,508 asthma patients (mean age: 40.1, 58.4% female) who received at least two long-acting asthma prescriptions within 12 months; 50,660 treatment-naïve patients were included in the NP analysis (mean age: 39.7, 58.8% female).

The mean 12-month MPR was 38.5% (89.4% NA according to $MPR \leq 80\%$) and the average proportion of days covered was 40.4% (85.9% NA). Agent-specific MPR and NA rates varied between 31.8% (91.8% NA) and 56.2% (71.6% NA). The average weighted-MPR increased to 53.1% when using the prescribed daily dosage.

Based on a > 90 -day gap definition, 86.7% of patients were considered non-persistent after 12 months (>180 : 72.3%). When using prescribed daily dosages, NP rates ranged from 66.7-78.5%.

Conclusion

High levels of treatment NA and NP indicate a substantial need to improve adherence and persistence to long-acting asthma medication in Germany.

Keywords adherence, persistence, asthma, long-acting asthma medication, medication possession ratio, claims data set, health-insurance records, Germany

Introduction

Asthma is a common chronic disorder of the airways, characterized by reversible airflow obstruction caused by a variable combination of bronchial hyperresponsiveness and underlying inflammation [1]. According to the World Health Organization (WHO), 235 million people around the world suffer from asthma [2]. In Germany, the prevalence of asthma in adults is estimated to be 6.2% [3]. Various treatment options for asthma patients exist, including long-term use of controller drugs taken daily, and rescue bronchodilators, for use as needed [4], [5]. However, non-adherence, the mismatch between a patient's drug-taking behavior and a healthcare provider's instructions for proper use of a medication [6], and non-persistence, the general discontinuation of a therapy [7], [8], pose a real-world challenge to the implementation of effective and safe asthma therapy. Non-adherence and non-persistence often result in poor real-world outcomes such as a higher asthma burden and a lower quality of life, as well as higher healthcare resource utilization and treatment costs [9]–[12].

Within the existing body of pharmaceutical literature [13], [14], various measures are used to determine levels of non-adherence using prescription-related claims data. The most common approaches for measuring non-adherence include the Medical Possession Ratio (MPR) and the Proportion of Days Covered (PDC). The time window used for measuring treatment adherence may be set using either a fixed interval (hereafter referred to as the interval-based approach) or the window between the first and last prescription fill during a pre-defined observation period (hereafter referred to as the prescription-based approach). The utility of a prescription-based approach derives from its measurement of adherence during periods where some level of treatment persistence has been documented (i.e. multiple prescription fills for the same agent or agent class). Slight distinctions in the calculation of MPR and PDC are noted below:

$$MPR = \frac{\text{Sum of } \textbf{days' supply} \text{ in observed time frame}}{\text{Number of days in observed time frame}} \times 100$$

$$PDC = \frac{\text{Number of days } \textbf{covered} \text{ in observed time frame}}{\text{Number of days in observed time frame}} \times 100$$

For PDC, the term *covered* refers to the availability of a prescribed medication on a given day. In our calculation remaining stock of a prescribed treatment may be allocated to a subsequent period when the recent prescription supply has been exhausted. Furthermore, when calculating PDC, the oversupply of medication is truncated when the specified observation period ends. Since the number of days covered cannot exceed the number of days in the observation window, the PDC may not exceed 100%.

In contrast, the MPR measures the sum of the daily dosages that have been received by a patient during the specified observation window. Here, the supply of daily doses for all prescription fills will be summed up, regardless of the day a specific medication was dispensed during the

observational period. Thus, if a patient continues to receive early refills prior to exhausting their existing stock of a medication, it is possible that the sum of all daily doses will exceed the number of days in the observation period. Consequently, it is possible to obtain an MPR value of over 100% [13], [14]. However, MPR values are generally truncated to 100% when population averages are reported.

Ultimately, there are considerable discrepancies in non-adherence and non-persistence figures reported by previous studies. Retrospective studies using claims data/dispensing records suggest that treatment non-adherence among asthma patients can range from 20% to 84% [15]–[17]. Other studies relying on patient-reported information identified non-adherence rates of 60% to around 85% [18]–[21]. With regard to non-persistence, retrospective studies reported low to moderate 12-month medication persistence rates (1% to 30%) among asthma patients [22]–[24].

While many factors such as patient selection and treatment patterns could explain these heterogeneous findings, the large variation in results may be partially attributable to the applied methodology. Specifically, when using claims data on prescriptions and refills, many authors did not differentiate between therapy discontinuation (non-persistence) and poor implementation of a generally continued therapy (non-adherence), when using an interval-based approach. Examples from other diseases show that a lack of differentiation often leads to an overestimation of non-adherence rates, due to low MPR rates resulting from early discontinuation of therapy instead of poor implementation [16], [25], [26]. Consequently, the main objective of this study was to address this gap, by using a large claims dataset provided by a statutory sickness fund, which contains anonymized patient-level data on all filled prescriptions and details information about the prescribed medications. Therefore, compared to other studies, this method is not subject to a high level of study site and patient selection bias, and is generally less susceptible to missing data, since German claims include information on all filled prescriptions/refills at the patient level, irrespective of the prescribing health care professional. In particular, we measured the extent of non-adherence and non-persistence to long-acting medication among German asthma patients, by differentiating between poor implementation of therapy (non-adherence) and therapy discontinuation (non-persistence).

Methods

This study consisted of a retrospective, non-interventional cohort analysis based on anonymized claims data provided by a German statutory health insurance fund (AOK PLUS; 3.2 million insured in the German federal states of Saxony and Thuringia) from 2011–2016.

The analysis included all continuously insured patients with a diagnosis of asthma [at least one inpatient or confirmed outpatient diagnosis of asthma using the International Classification of Disease, Tenth Revision coding framework (ICD-10: J45.-)] from 2012–2016. Additionally, to ensure that only patients with asthma were observed, all patients who received a diagnosis of chronic obstructive pulmonary disease (COPD) (ICD-10 J44) from 2012–2016, as well as all patients who received a prescription for a long-acting muscarinic antagonist (LAMA)¹ were excluded. No age-related eligibility criteria were applied.

We analyzed treatment persistence and adherence to long-acting asthma medication therapy, recommended for use by the German treatment guideline, when the study was conducted [27]. Specifically, we addressed the following agents: inhaled long-acting beta2-agonists (LABA;

¹ ATC code: R03BB04/ R03BB05/ R03BB06 ; not approved for the use in patients with asthma at time of study initiation

Formoterol and Salmeterol)², leukotriene receptor antagonist (LTRA; Montelukast³), inhaled corticosteroids (ICS; Beclometasone, Budesonide, Flunisolide, Fluticasone, Triamcinolone, Mometasone, Ciclesonide)⁴, and single-device combinations of ICS+LABA (Fluticasone/Salmeterol, Budesonide/Formoterol, Beclometasone/Formoterol, Mometasone/Formoterol, Fluticasone furoate/Vilanterol, Fluticasone/Formoterol)⁵.

Our analysis looked at all patients who received at least one prescription for the above-mentioned long-acting asthma medications from 01/01/2012 until 31/12/2016. The date of the first prescription during the patient inclusion period was defined as the index date. From the general cohort of patients identified in this first step, two analysis cohorts were defined. The first, **Cohort 1**, consisted of patients with at least two long-acting asthma prescriptions for the same agent or at least two different agents from the same agent class (within 12 months of the index prescription), and was used to analyze treatment non-adherence. The second, **Cohort 2**, was used to analyze treatment non-persistence and consisted of only treatment-naïve patients who initiated therapy with one of the specified long-acting agents between 01/01/2012 until 31/12/2016. Therefore, patients in Cohort 2 must not have received any previous prescriptions for a long-acting asthma medication within 12 months before their index prescription. For both analyses, 2011 was included as a baseline period.

Assessment of treatment adherence

Treatment adherence was analyzed for periods of treatment continuation only, using a prescription-based approach. In this study, treatment continuation was assumed if there were more than two filled prescriptions for treatments from the same agent class within 12 months (Figure 1). Adherence was measured from the date of the first prescription to the date of the last prescription/refill (within a maximum period of 12 months). The MPR was calculated separately for each agent class (ICS, ICS/LABA, LABA, LTRA) as described in the formula below:

$$MPR = \frac{\text{Sum of days' supply received during the observation period (excluding the supply of the last fill)}}{\text{Number of days between the first and last prescription (excluding hospitalization days in same period)}}$$

In addition to the agent-class specific calculation, an overall MPR was calculated on a patient level, weighing the agent class-specific MPRs by the number of days these agent classes were prescribed (days between first prescription and last prescription/refill for each agent class). To measure treatment coverage during the observation period for each patient irrespective of the prescribed agent, a PDC was calculated, to provide a more comprehensive perspective on treatment adherence, since treatment switches between different classes of long-acting asthma medication may have been recommended by clinicians. Moreover, the PDC considers the timing of fillings throughout the observational period by assessing available stock on each day, rather than simply summing the supply of all prescriptions/refills within the observational period (MPR). Ultimately, we described adherence in two ways: as a mean MPR/PDC and as the percentage of patients with an MPR/PDC $\leq 80\%$. In cases where the MPR was above 100%, it was truncated to 100%.

² ATC codes: R03AC13/R03AC12.

³ ATC code: R03DC03. Montelukast was the only LTRA included in the study, since it is approved for usage as a long-term asthma medication, according to the German treatment guidelines.

⁴ ATC codes: R03BA01/R03BA02/R03BA03/R03BA05/R03BA06/R03BA07/R03BA08.

⁵ ATC codes: R03AK06/R03AK07/R03AK08/R03AK09/R03AK10/R03AK11.

We used the claims data standard of defined daily dosage (DDD) formulated by the WHO and the German AOK Research Institute (WIdO) [9] as a proxy for the prescribed daily dosage (PDD). In a sensitivity analysis, we also used real-world agent-specific prescribed dosages which were derived from a separate medical chart review. For this analysis, the medical charts of 641 German asthma patients (including those who satisfied the eligibility criteria for the general cohort of patients with at least one prescription for long-acting asthma agents from 01/01/2012 until 31/12/2016) were analyzed with the goal of assigning a real-world prescribed daily dosage (hereafter referred to as the PDD) to each of the respective agents. Physicians reported package size and recommended dosage per day for each agent prescribed to patients in the chart review; the derived daily dosage is outlined in Supplementary Table 1 and was based on an overall number of 1,610 prescriptions/refills for long-term asthma medication.

In the MPR calculation, stockpiling of medications in the same agent class (but not across different agent classes) was taken into account, while for PDC stockpiling across agent-classes was considered. As Figure 1 illustrates, in the case of overlapping medications, we assumed that the previous supply was taken fully before the new supply was initiated. Additionally, we excluded hospitalization periods from observation in our adherence calculations since it was assumed that medications would be provided to patients by hospitals during these inpatient stays.

Assessment of treatment persistence

Treatment persistence for long-acting agents was recorded in the treatment-naïve patients only (*Cohort 2*) and was reported separately for the following classes: ICS, LABA, ICS+LABA, and LTRA. In the main analysis, non-persistence was defined as having a lapse in the supply of the prescribed agent for >90 days, whereas in the sensitivity analysis a lapse in treatment supply for >180 days was used to define non-persistence. For non-persistence reporting per agent class, drug switches within agent classes were interpreted as a continuation of therapy, while switches to another agent class were considered non-persistence. Patients were observed for 12 months from the date of the index prescription until the event of non-persistence (i.e. >90-day treatment gap) or until death (whichever came first).

The DDD for respective agents was used to calculate medication coverage and adherence, while the chart review-based PDD was used in the sensitivity analysis. Furthermore, assumptions around stockpiling and drug coverage during inpatient stays were also considered when calculating treatment persistence.

In addition to reporting non-persistence rates for each drug class, we also reported treatment persistence related to use of any long-acting asthma treatments mentioned above, assuming non-persistence only in the case of a sustained lapse in the prescribed drug supply (hereafter referred to as a treatment gap). Thus, when reporting on the use of any long-term agent, drug switches from one long-acting agent class to another class were not considered non-persistence (Figure 2). The percentage of patients that could be classified as non-persistent 12 months after the initiation of a long-term asthma therapy was reported (both compositely and disaggregated by agent class) as a study outcome.

All descriptive analyses were carried out using Microsoft SQL Server 2008 and Microsoft Excel 2010. All other statistical analyses were carried out using STATA MP13.

Ethical and institutional approval

The study was approved by the ethics committee of the Rostock University Medical Center (Germany) as well as by the Saxon State Ministry for Social Affairs and Consumer Protection.

Results

Observed patient samples

We identified 207 930 patients with a diagnosis of asthma, who satisfied all general inclusion criteria; from the base cohort, 71 569 patients with at least one prescription for a long-acting asthma treatment were identified (Supplementary Figure 1).

In **Cohort 1**, 52 508 (of the above 71 569) patients received at least one additional prescription/refill for a treatment from the same agent class, in the 12-month period following their index prescription. Thus, individuals who satisfied these criteria were eligible for inclusion in the non-adherence analysis (mean age: 40.1, 58.4% female). The percentage of patients from Cohort 1 who received at least two prescriptions for medications from the same agent class was 47.7% for ICS, 6.1% for LABA, 53.0% for LABA+ICS combinations, and 13.8% for LTRA.

Cohort 2 consisted of 50 660 treatment-naïve patients who initiated at least one long-acting therapy in the observational period. We observed a mean age of 39.7 years, and 58.8% were female. Within the respective agent classes, the percentage of patients starting a therapy was 47.8% (ICS), 4.3% (LABA), 57.7% (LABA+ICS combinations), and 11.6% (LTRA). Furthermore, 9,597 patients (18.9%) started more than one new long-acting therapy (different agent classes) during the observational period. Patient characteristics for each group are outlined in Table 1.

Assessment of treatment adherence

Table 2 describes the results of the treatment adherence analysis on a patient level as well as on an agent class level. For Cohort 1, the 12-month MPR across all agent classes considering the DDD for each respective agent was 38.5%. Accordingly, 89.4% of patients are classified as non-adherent ($MPR \leq 80\%$). Agent-specific mean MPR/non-adherence rates ($MPR \leq 80\%$) were 31.8/91.8% for ICS, 48.6/80.9% for LABA, 42.9/86.7% for ICS+LABA, and 56.2/71.6% for LTRA. The average PDC for patients in Cohort 1 was 40.4% and 85.9% of patients were classified as non-adherent ($PDC \leq 80\%$) to any kind of observed long-term asthma medication. Within the sensitivity analysis, which considered the chart-review based PDD instead of the DDD, the weighted MPR (for all agent classes) increased to 53.1% and the percentage of non-adherent patients decreased to 74.6%. Similarly, for the sensitivity analysis, the average PDC increased to 54.5% while non-adherence decreased to 65.2%.

Assessment of non-persistence

Table 3 presents the results of the treatment non-persistence analysis for the 50 660 asthma patients in **Cohort 2**. Using a > 90-day treatment gap and consideration of DDD (rather than PDD), the percentage of non-persistent patients was 86.7% after 12 months. Mean drug survival time after treatment initiation for the entire sample of newly treated patients in the first 12 months was estimated to be 114.6 days. The agent-specific rates for non-persistence over the first 12 months in the base-case (treatment lapse >90 days; coverage: DDD) for **Cohort 2** were as follows: 94.5% for ICS, 86.7% for LABA, 80.6% for ICS+LABA, and 85.6% for LTRA. For the sensitivity analysis, changing the treatment gap definition to >180 days (based on the DDD) resulted in a non-persistence

rate of 72.3% and a mean drug survival time of 159.6 days. Figures 3 and 4 present Kaplan-Meier curves to illustrate treatment persistence among patients receiving long-acting asthma medication, within a 12-month period following initiation of treatment, calculated based on a lapse in the supply of treatment of >90 days and >180 days, respectively. Moreover, Table 3 also provides non-persistence rates based on the sensitivity analysis conducted using the chart-review based PDD. Use of the PDD instead of the DDD was found to result in a higher rate of treatment persistence. Depending upon the applied method, the percentage of non-persistent patients after 12 months was found to vary between 66.7% and 86.7%.

Discussion

Our study addressed two major challenges in the literature, by assessing both the level of non-adherence and non-persistence among individuals receiving treatment with long-acting asthma agents in Germany. One key strength of this study is the use of a large claims dataset to observe treatment non-adherence and non-persistence in the German population. This method is not subject to a high level of study site and patient selection bias, as in other studies, and is generally less susceptible to missing data, since German claims generally include information on all filled prescriptions/refills at the patient level, irrespective of the prescribing physician. Secondly, potential uncertainty around real-world dosing for observed agents was addressed by conducting a sensitivity analysis to measure treatment coverage based on real-world prescribing behavior, as compared to clinically approved dosing.

Extent of non-adherence

We observed considerable deficits in drug therapy implementation, defined as an $MPR/PDC \leq 80\%$ during periods of therapy continuation. These results are generally comparable to findings from previous research. In Sweden, one study observed a similar non-adherence rate of 73–99% and reported a higher level of adherence among patients using combination products than among ICS users [28]. US claims data analyses have revealed low adherence rates ($MPR > 80\%$) of 8.3% within a 12-month follow-up period [29] and 14–16% for a 6-month follow-up [30], among patients initiating long-acting asthma therapy.

In this analysis, ICS use was associated with the lowest adherence (8.2% of patients), whereas LTRA users had the highest adherence (28.4%). LABA and ICS+LABA combination users had adherence rates of 19.1% and 13.3%, respectively. Differences in adherence between ICS and ICS+LABA therapy users aligned with findings from previous claims data studies performed in the US [30]. In turn, low adherence among ICS users in our study (median MPR 24.4%) and higher adherence among LTRA users (median MPR 58.8) is comparable to findings from another claims data analysis which observed a median MPR of 15% for ICS and 39% for LTRA (measured over 2 years instead of 1 year) [31]. Most analyses applied an interval-based approach to measure treatment adherence. Thus, high non-adherence rates within the literature may also reflect a certain level of non-persistence since treatment continuation was not always guaranteed. However, even when we used a prescription-based approach to assess adherence, we identified very low adherence among patients receiving long-acting asthma treatment.

One possible reason for differences in treatment adherence among patients using ICS versus those using an ICS+LABA combination is that LABA is associated with immediate symptom relief, meaning that it may be easier for patients to internalize the benefit of its long-term use [18], [32]. Furthermore, according to the treatment guidelines, ICS is commonly used as a first line treatment for asthma, whereas ICS+LABA is generally used to treat patients with more severe forms of asthma

that have not been well controlled using ICS or LTRA alone [4], [18]. Therefore, fundamental differences between patients (e.g. with regard to asthma severity and the associated need for (and experience with) reliever and/or controller medication) might drive the observed differences in medication adherence between agent classes, or vice versa. Moreover, higher average MPR values among LTRA users may suggest that the mode of administration matters, and that use of pills may play a role in optimizing treatment adherence.

Extent of non-persistence

Treatment discontinuation is a real-world phenomenon that needs to be assessed, explained, and addressed in a different manner than treatment adherence, when considering use of a generally continued therapy. Treatment discontinuation may have multiple causes, including patient behavior and a physician's decision to halt therapy due to limited effectiveness or safety concerns. In contrast, treatment non-adherence is almost exclusively attributable to patients [23], [33].

Overall, treatment persistence was generally low in our study. Approximately 86.7% of newly treated asthma patients experienced a treatment gap of >90 days in their first year of treatment with any long-acting drug therapy. However, variations between different classes of medication and between the applied methods used to define prescribed dosing were observed. Treatment with ICS was associated with the highest discontinuation rate, as only 5.5% of those initiating ICS treatment were persistent with this therapy for more than 12 months. In contrast, combination drugs (ICS+LABA) were associated with the lowest discontinuation rate in this analysis (19.4% of treatment starters remained on combination therapy for at least 12 months). These findings align with those from other treatment persistence studies in asthma, including a Canadian study that used administrative healthcare data and found that only 10% of asthma patients initiating a combination regime (ICS+LABA) exhibited treatment persistence one year after therapy initiation [34]. Another study based on the same database concluded that persistence to LTRA therapy was significantly better than persistence to ICS therapy alone [35]. Due to the nature of our dataset, we could not identify the share of treatment non-persistence that was patient- and physician-driven.

To address uncertainty related to dosing in both the adherence and persistence analyses, we used a sensitivity analysis to test assumptions derived from a medical chart review. By comparing the DDD (used for our base-case) with the chart-review based PDD, we found that physicians tended to recommend lower daily dosages of long-acting asthma medications than was generally assumed by the DDD. Thus, lower adherence rates might reflect physicians' recommendations which do not always conform with clinical guidelines on dosing [36], [37]. Still, despite these variations in assumed dosing, the medical chart review based PDD yielded generally high rates of non-adherence and non-persistence.

Limitations

As this study was initiated in early 2014, agents receiving more recent approval for treatment of asthma patients were not considered. This includes tiotropium, which (among other LAMA agents) led to an exclusion of many patients, since it was originally approved only for treatment of COPD. Nevertheless, Supplementary Figure 1 shows that a minority of patients were excluded as a result of LAMA prescriptions. Due to the longitudinal limitations of our dataset, the observational period was limited to 12 months. However, since 87% of observed patients had already discontinued their observed therapy after 12 months, longer observational periods are unlikely to change our main findings.

We defined non-persistence as a treatment gap of >90 days and non-adherence as $MPR/PDC \leq 80\%$. While these thresholds are widely used in studies addressing persistence/adherence on the part of COPD/asthma patients [9,10], they have not been validated clinically [20]. We dealt with this weakness by conducting a sensitivity analysis which used different treatment gap assumptions to define non-persistence (>180 days) and included different dosing standards (DDD versus chart-review based PDD).

As in all claims data-based adherence/persistence analyses, we assume that observed data regarding filled prescriptions can serve as a proxy for measuring the method and amount of medication consumed by the patient. However, a filled prescription does not guarantee that a patient in fact took the medication. Thus, the actual non-adherence and non-persistence might have been underestimated in our study.

Finally, we had no knowledge about real-world dosing and whether physicians in all cases recommended continuous, daily use of prescribed long-acting agents. Theoretically, lack of alignment with clinical guidelines on dosing among physicians should have no influence on adherence if patients take their medication as prescribed by their treating physician. However, for the purpose of calculating the MPR, we consider dose sizes proposed by the WHO (DDD). In this study, if doctors prescribed a lower dose than the DDD amount, we will have assumed a higher level of non-adherence. To address this limitation, we also conducted a medical chart review to observe/assess the real-world prescribing behavior of physicians in Germany. Using the chart review we derived alternate PDD values for each agent included in the study.

Very low adherence and persistence rates for ICS therapy might also suggest that at least some patients use ICS only as needed. Under the established methodology, there is a potential for the misclassification of intermittent/seasonal asthma patients as non-persistent or non-adherent; this is a key limitation of the study since the need for continuous, long-acting treatment was assumed of all patients included in the observed patient cohorts. Even if some uncertainty results from this, it is still clear from high non-adherence and non-persistence figures that many asthma patients do not take their medicine on a regular or permanent basis.

Conclusions

In German asthma patients, persistence and adherence with respect to long-acting drug therapy is poor and does not correspond with recommendations provided by the current treatment guideline. We found that about 87% of patients fail to continue treatment after 12 months. In addition, about 85–89% of patients implement their treatment poorly. Our findings suggest a substantial potential for improvement in the real-world treatment of patients with long-acting asthma agents by (1) conducting more extensive research on the differential drivers of non-persistence and non-adherence, and (2) investing in effective interventions aimed at addressing drivers of non-adherence and non-persistence.

Authors' contributions

All authors have completed the author consent form and made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. Specifically, the main tasks the authors were engaged in were:

FH, SM: Study concept, Statistical analysis, Interpretation of results, Writing all parts of the paper, review and revision

TW: Study concept, project lead, participated in writing all parts of the paper

HT, VU, RW: Study concept, Interpretation of results, critical review of the manuscript

UM: Data collection/validation, interpretation of results, critical review of the manuscript

Declaration of interests and Acknowledgements

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Abbreviations

COPD: Chronic obstructive pulmonary disease; DDD: Defined daily dosage; ICS: Inhaled corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene receptor antagonist; MPR: Medication possession ratio;; PDC: Proportion of Days Covered; PDD: Prescribed daily dosage; WHO: World Health Organization; WIdO: German AOK Research Institute

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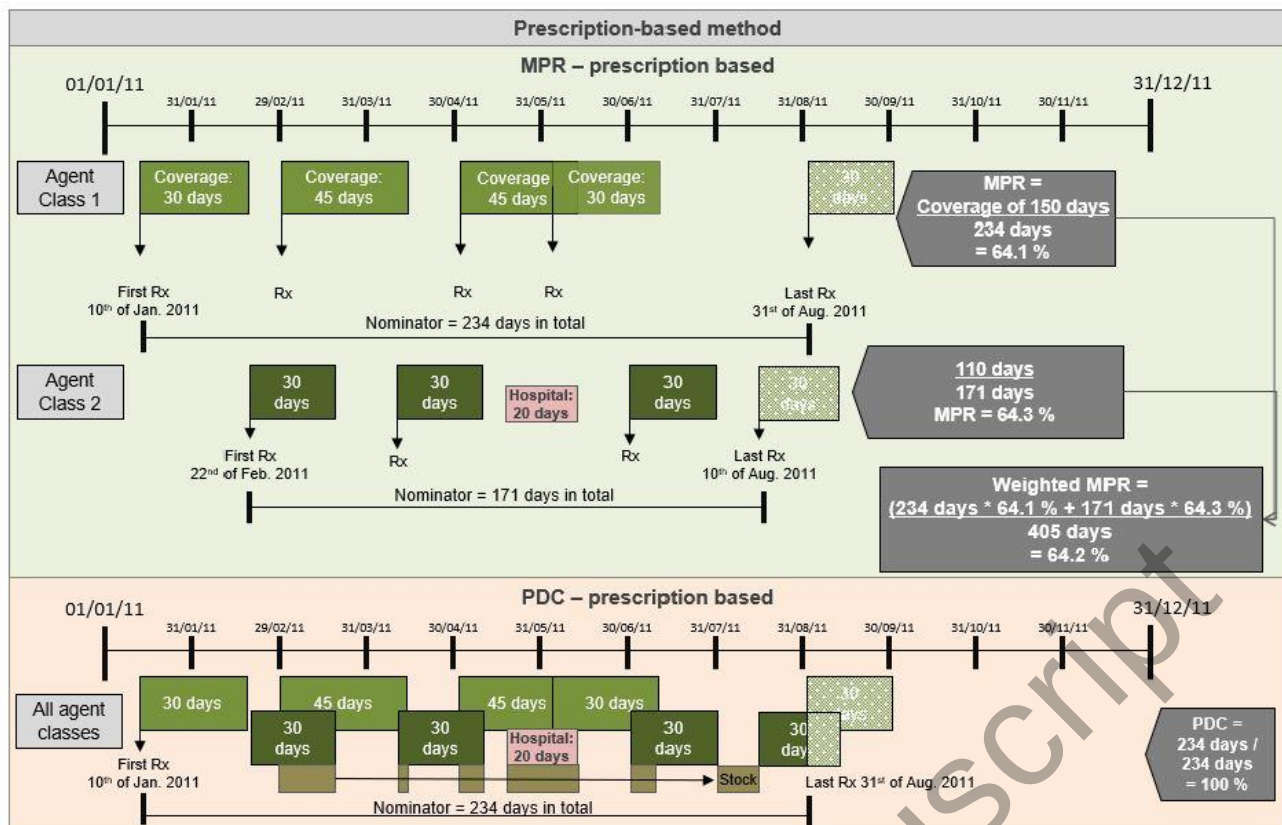


Figure 1: Methodology of non-adherence calculation.

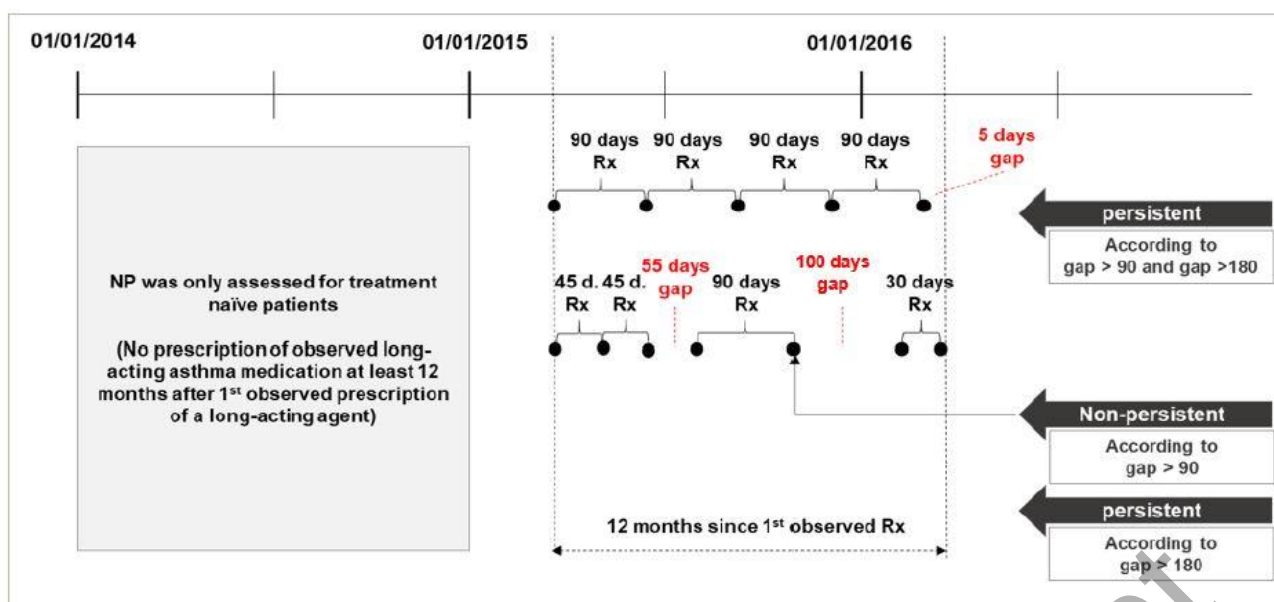


Figure 2 Methodology of non-persistence calculation.

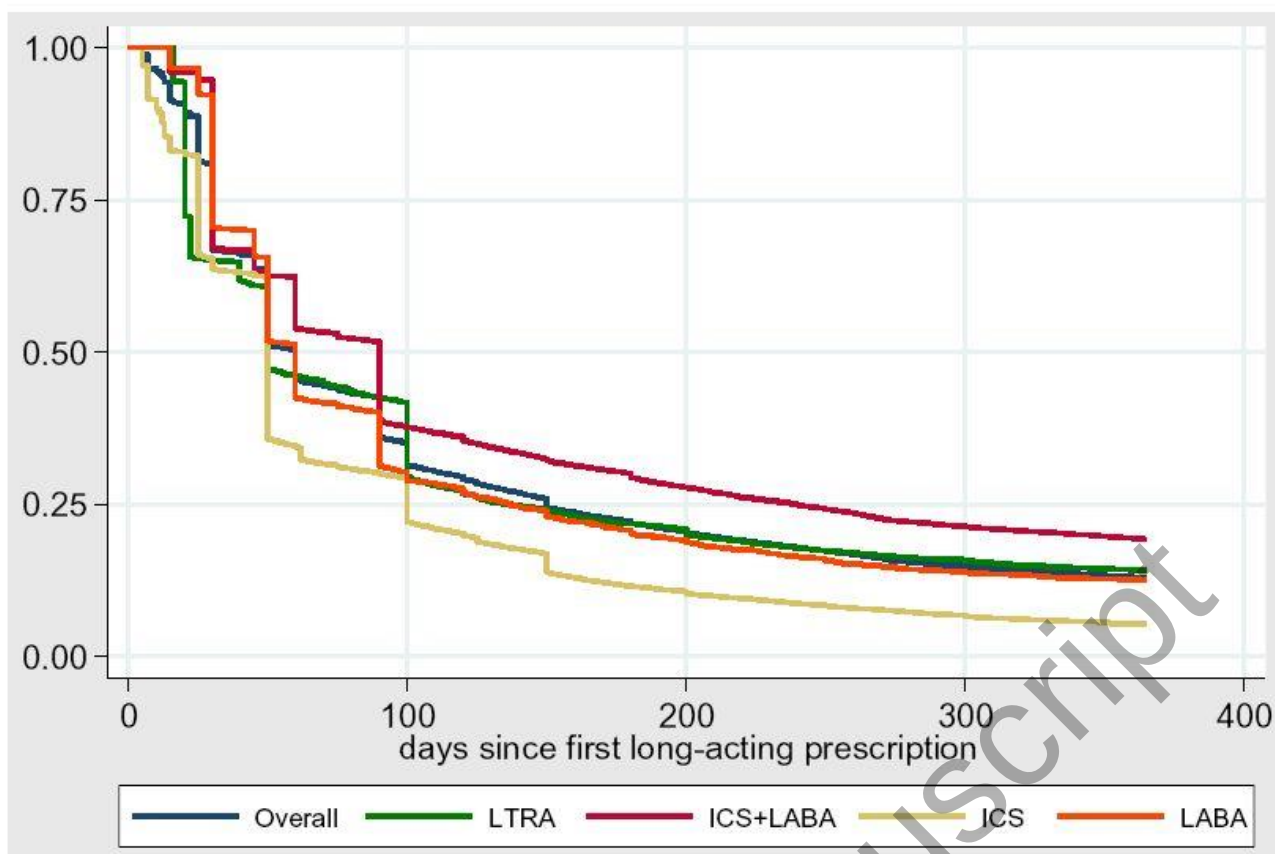


Figure 3 Persistence to long-acting asthma prescription - percentage of patients persistent after therapy initiation (gap >90 days; coverage: DDD).

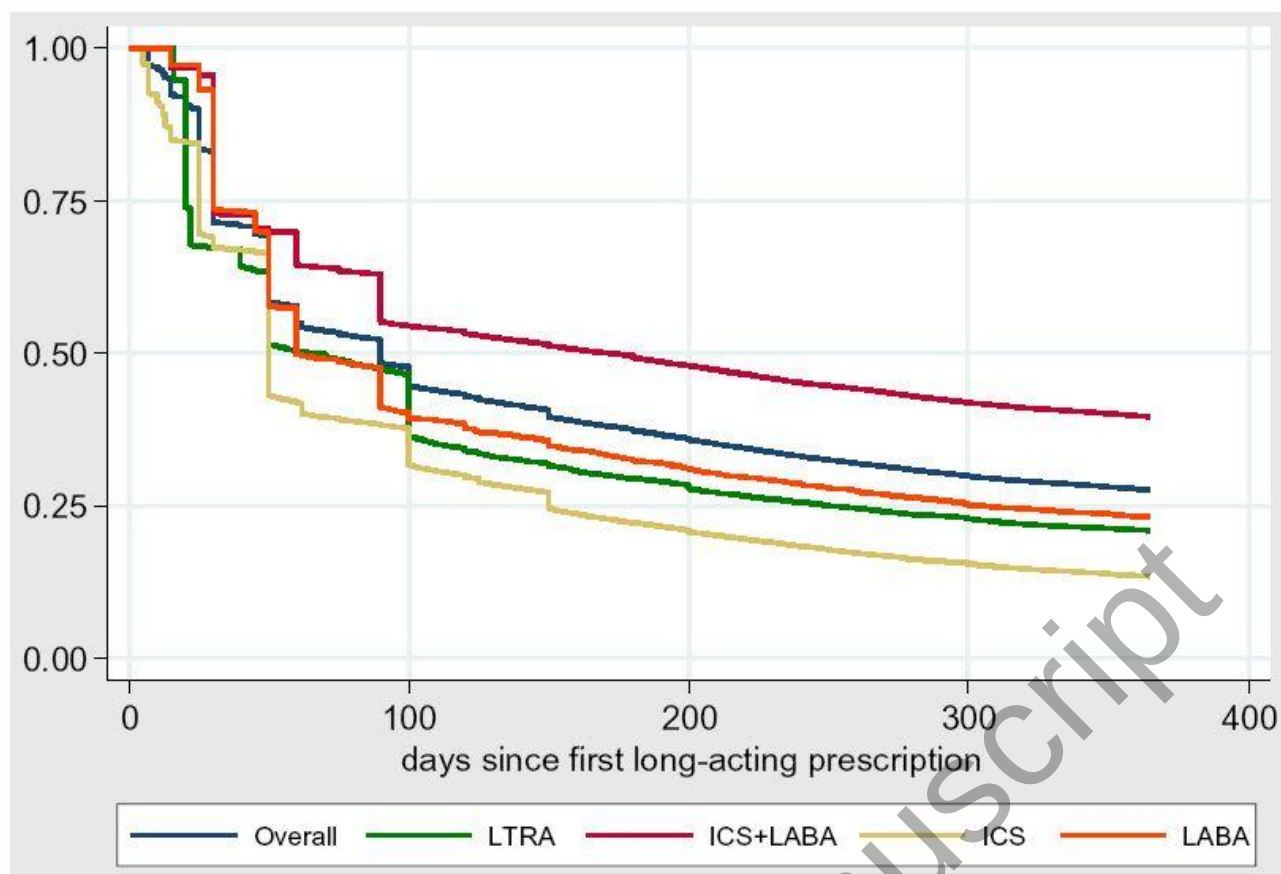


Figure 4 Persistence to long-acting asthma prescription - percentage of patients persistent after therapy initiation (gap >180 days; coverage: DDD).

Table 1 Characteristics of observed asthma patient samples.

Characteristics	All included asthma patients	All asthma patients with ≥ 1 prescription of a long-acting asthma therapy	All asthma patients with ≥ 2 prescription of the same agent class of long-acting medication in a 12 month period (cohort 1)	Treatment-naïve asthma patients who started an initial long-acting therapy (cohort 2)
N	207,930	71,569	52,508	50,660
Age in years at time of observation; Mean (SD)	36.8 (23.0)	39.1 (23.3)	40.1 (23.6)	39.7 (22.2)
Female gender; N (%)	117,204 (57.7)	41,721 (58.3)	30,651 (58.4)	29,783 (58.8)

Table 2 Extent of non-adherence in patient cohort 1.

		PDC	Average weighted MPR	ICS (MPR)	LABA (MPR)	ICS+LABA (MPR)	LTRA (MPR)
	N	54,064	52,508	25,044	3,220	27,835	7,263
Base case scenario: DDD	MPR/PDC (%)						
	Mean	40.4	38.5	31.8	48.6	42.9	56.2
	Median	33.7	33.0	24.4	45.3	38.4	58.8
	% of non-adherent patients						
	MPR/PDC $\leq$ 80%	85.9	89.4	91.8	80.9	86.7	71.6
Sensitivity: chart review based PDD	MPR/PDC (%)						
	Mean	54.5	53.1	48.3	64.2	57.7	59.4
	Median	52.5	51.1	42.5	68.4	57.3	63.5
	% of non-adherent patients						
	MPR/PDC $\leq$ 80%	65.2	74.6	75.9	60.8	71.0	65.2

Table 3 Extent of non-persistence in patient cohort 2 (treatment naive patients).

		Overall non-persistence	ICS	LABA	ICS+ LABA	LTRA
	N	50,660	24,238	2,163	29,208	5,895
Base case scenario: DDD						
Gap >90 days	% of non-persistent patients	86.7	94.5	86.7	80.6	85.6
	Drug survival time in days, mean (SD)	114.6 (118.1)	81.7 (91.9)	110.6 (112.7)	138.0 (129.8)	112.8 (120.8)
Gap >180 days	% of non-persistent patients	72.3	86.4	76.3	60.4	79.0
	Drug survival time in days, mean (SD)	159.6 (143.7)	112.2 (121.1)	145.5 (135.8)	197.4 (150.3)	135.1 (135.5)
Sensitivity: chart-review based PDD						
Gap >90 days	% of non-persistent patients	78.5	90.1	84.8	71.0	88.2
	Drug survival time in days, mean (SD)	157.3 (129.3)	123.5 (109.0)	138.2 (113.9)	181.0 (135.7)	109.2 (114.5)
Gap >180 days	% of non-persistent patients	66.7	82.5	76.6	56.2	83.2
	Drug survival time in days, mean (SD)	189.2 (140.9)	146.3 (124.5)	161.4 (127.7)	219.0 (142.9)	126.1 (127.4)