

Original article

Persistence with asthma treatment is low in Germany especially for controller medication – a population based study of 483 051 patients

Background: The objective of the present analysis was to evaluate treatment patterns and persistence with treatment of an unselected patient population with a diagnosis of asthma.

Methods: The database of the Bavarian statutory health insurance physician's association (Kassenärztliche Vereinigung) covering 83% of the population was analyzed for an index period from April 2005 to March 2006. Defined daily doses (DDD) were used to quantify treatment persistence. Results were compared with recent guidelines.

Results: The prevalence of physician diagnosed asthma in Bavaria was 4.8% in females and 4.5% in males; only 61.4% of these patients (of a total of $n = 483\,051$) received any anti-asthmatic pharmacotherapy; 68.3% received medical care from their general practitioner, and 8.3% from a pulmonologist alone. Most patients (65.1%) received no more than 90 DDDs of controller medication in the index period of 365 days, only about 1% received medication for the complete index period. Long- (40.1%) and short-acting β_2 -agonists (65.6%) were used more frequently than inhaled corticosteroids (ICS). 52.8% of asthma patients were treated in accordance with guidelines.

Conclusions: Persistence of asthma patients with medical treatment is low, especially for controller medication. The discrepancy between current knowledge, guidelines and clinical practice is substantial and may question the value of current guidelines for the treatment of patients with asthma in ambulatory care. In addition, the results of this study cast doubt on the impact of contemporary treatment on the decline of asthma mortality seen in recent years in Germany.

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Key words: asthma; defined daily doses; inhaled corticosteroids; long acting beta agonists; persistence.

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Accepted for publication 25 June 2009

Asthma ranks among the most common chronic diseases in the Western world (1). According to the database of the Robert Koch Institute, the German federal institution responsible for disease control and prevention, prevalence of bronchial asthma in Germany is approximately 5% in adults and 10% in children (2).

Guidelines on the treatment of asthma recommend a stepwise use of pharmacotherapy with four or (more recently) five steps, which are options to increase efficacy for different levels of severity and/or asthma control (3–6). Adequate medical therapy has been

recommended to prevent exacerbations, to improve and maintain quality of life and possibly to reduce the long-term effects of asthma. However, medication non-persistence might contribute to treatment failure with asthma exacerbations and possibly irreversible airway damage.

There are several published studies on the actual use of pharmacotherapy in clinical practice (7–11). A study on the management of asthma in seven European countries [AIRE (7)] reported a frequent use of β_2 -agonists (63%) and a lesser use of inhaled corticosteroids (ICS; 23%). Despite reporting severe persistent symptoms, about 50% of patients considered their asthma to be completely or well controlled. These data were essentially confirmed by a pharmacy database study in Canada (8) that demonstrated that, despite the development and dissemination of asthma management guidelines, there was no trend towards decreasing

Abbreviations: COPS, Chronic Obstructive Pulmonary Disease; CR, CRomoglycate; CS, CorticoSteroids; DDD, Defined Daily Doses; FD, Fixed Dose; ICS, Inhaled CorticoSteroids; ICD, International Classification of Diseases; LABA, Long-Acting β_2 -Agonist; LTRA, LeucoTriene Receptor Antagonists; SABA, Short-Acting β_2 -Agonists.

β_2 -agonist use over a 3-year follow up with an unexpected trend towards decreasing ICS use. The latest and largest study to document the failure to improve asthma control outcomes in primary practice has been the Personal Practice Assessment Program in more than 350 Canadian primary-care settings where physicians surveyed the asthma control status of more than 10 000 patients (10). Of the surveyed patients, 59% were considered uncontrolled. These uncontrolled patients were six times more likely to have an unscheduled health-care visit, were almost four times more likely to seek care in an emergency department, and were twice as likely to be admitted to hospital for out-of-control disease, compared with their controlled counterparts. Taken together, despite the widespread adoption of guidelines by academic specialists, translating this consensus knowledge into improved practice patterns and outcomes has been largely unsuccessful (12, 13).

Data for the situation in Germany are available from the 1998 German National Health Interview and Examination Survey (11), which documents an essentially similar pattern of treatment. According to this study, especially young patients with asthma were insufficiently treated with anti-inflammatory drugs. Although the data are slightly outdated more recent data for Germany are not available.

It was therefore the aim of this study to describe the treatment of patients with asthma, to analyze the treatment persistence, and to compare the findings to recent asthma treatment guidelines. To achieve this, the database of the Bavarian statutory health insurance physician's association (Kassenärztliche Vereinigung Bayern) provides a unique instrument in that it provides complete diagnoses and performed medical services for the majority (about 83%) of the citizens living in the second largest German state Bavaria.

Methods

The Bavarian statutory health insurance physician's association gathers, based on accounting information of Bavarian physicians, data on diagnoses and performed medical services of all patients within the statutory health insurance. Anonymized data for 12 months ranging from April 1st 2005 to March 31st 2006 were used for the present analyses, corresponding to four accounting quarters.

From within this database, patients were included with the diagnosis 'bronchial asthma' according to the international classification of diseases (ICD) 10 – Code (J.45) given that the diagnosis was marked to have been verified in the physicians' quarterly settlement. 'Predominantly allergic asthma' (J.45.0), 'non-allergic asthma' (J.45.1), 'mixed asthma' (J.45.8), and 'asthma, unspecified' (J.45.9) were not separated because the discrimination was regarded to be not reliable and reproducible on a patient basis. To allow for valid conclusions a group of patients with a consistent diagnosis of asthma was built, which included patients, which were assigned a diagnosis of asthma at least twice within an observation period of

2.5 years (including three quarters before and three quarters following the index period).

Data to evaluate pharmacotherapy were obtained from the corresponding pharmacy records. These included the generic drug, the frequency of prescriptions, and the prescribed package size. Using the defined daily doses (DDD), medication possession rates were calculated to quantify persistence. The WHO defined DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Asthma severity was graded using the prescribed medication as an indicator based on the current guidelines (3–6): Short-acting β_2 -agonists (SABA) only, stage 1; ICS and SABA, stage 2; ICS and other anti-asthmatic drugs and SABA, stage 3; and oral corticosteroids (CS) and other anti-asthmatic drugs, stage 4. New onset asthma was assumed if patients had a diagnosis of asthma in the second quarter of 2005 (first quarter of the index period) but in none of the previous three quarters.

To adjust for lower doses recommended for children and adolescents and to reduce a confounding comorbidity of chronic obstructive pulmonary disease (COPD) in the elderly a subgroup was built with newly diagnosed asthma in patients between 20 and 39 years.

Descriptive statistics were used to describe the results. As anonymized data were used for the analysis, an ethic's committee consultation was not needed.

Results

A total of 6 01 222 patients had at least one mentioning of the diagnosis of asthma (Fig. 1) in their accounting records. As only patients with at least two recorded diagnoses of asthma within 2.5 years were considered, the number was reduced to 4 83 051 patients (4.6% of all statutory health insurance patients) – called consistent patients (55.1% of these were female). A total of 1 18 171 patients only obtained the diagnosis once (1.1% of all statutory health insurance patients). In patients <20 years of age, the prevalence of asthma was particularly high in male (5.8%), but lower in female patients (4.0%). In patients between 60 and 80 years, the peak prevalence observed in males was 5.7% and in female patients 6.6%.

Patient care

During the index period 68.3% of the 4 83 051 consistent patients were cared for by primary care physicians (general practitioners, internists and pediatricians), and 8.3% of the patients by pulmonologists/respiratory medicine specialists; 9.5% of the patients consulted a primary care physician and in addition a pulmonologist. For 14.0% of patients, the primary physician was ticked as 'other specialist' (dermatologists, otolaryngologists, and gynecologists). Some 1.1% of the patients consulted a primary care physician and in addition a medical specialist within a period of 3 month. With an increase in asthma severity more patients were treated by pulmonologists alone or in cooperation with their general practitioner (38.2% in stage 4 asthma vs 20.1% in stage 1).

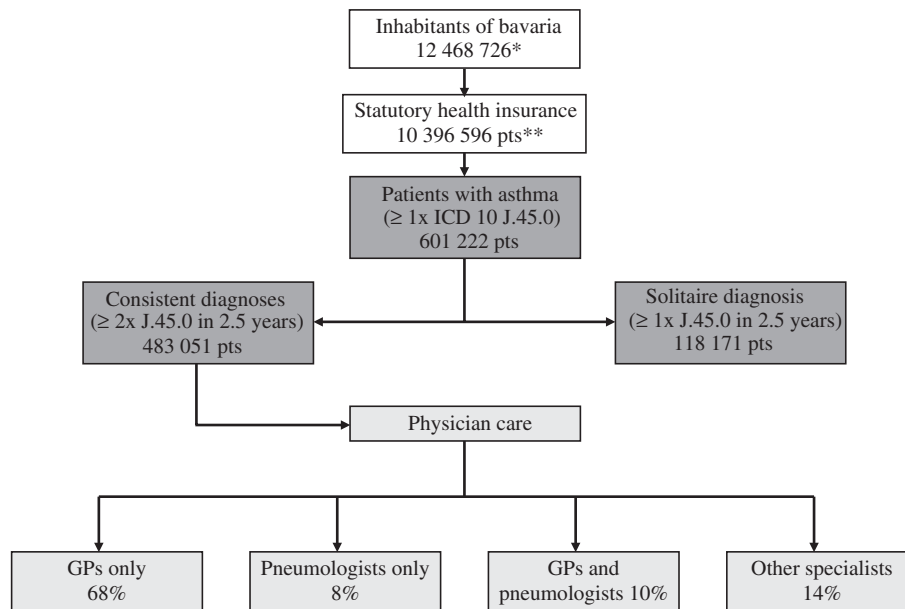


Figure 1. Patient disposition, * as to GENESIS tables (<http://www.statistikportal.de>; 31.12.2005); ** Statistics of the statutory health insurance (July 1st).

In patients with stage 1 asthma on the other hand, 69.3% were treated by their general practitioner alone (49.3% in stage 4 asthma). These analyses were based on a subsample of 1 56 834 patients for which medication use patterns allowed for a grading of severity.

Patients who received oral corticosteroids in addition with other anti-asthmatic drugs as regular treatment (stage 4 asthma) contacted their physician more frequently than patients who received prescriptions of SABA only (stage 1 asthma). As many as 45.9% of patients with stage 4 asthma visited their physician every quarter of the index period, while this was the case for only 23.5% of patients with stage 1 asthma. Patients who could not be assigned an asthma stage ($n = 326\,217$) showed a similar visit frequency when compared with patients with stage 1 asthma.

Pharmacotherapy of asthma

A total of 1 86 217 (38.6%) of 4 83 051 consistent patients received no pharmacotherapy for the treatment of asthma (any stage) within the index period of 12 months (37.0% male, 39.8% female). Of the 2 96 834 consistent patients with pharmacotherapy (see Fig. 2), the largest proportion received short-acting β_2 -agonists (SABA) only [1 33 207 (44.8%)] or in combination with a cromone [61 637 (20.8%)]. Further frequent prescriptions were long-acting β_2 -agonists (LABAs) alone [13 822 (4.7%)] or in a fixed combination with ICS [105 019 (35.4%)].

Pharmacotherapy of patients with ICS and/or Long-acting β_2 -agonist. A total of 74 420 patients (25.1% of 2 96 834

patients with pharmacotherapy) received ICS (median age 44 years, 54.3% female) for a median duration of 50 days. Based on DDDs, 65.1% ($n = 48\,471$) received ≤ 90 DDDs within the index period of 1 year (compatible with medication for one quarter). Most patients received ≤ 30 DDDs (absolute 33.3%) or > 30 & ≤ 60 DDDs (absolute 26.2%); 0.6% of patients ($n = 445$) received between 331 and 360 DDDs compatible with a 12-month supply (Fig. 3). Defined daily doses used for the calculation can be found in Table 1.

A total of 13 822 patients received any prescription of LABAs (median age 61 years, 54.9% female) for a median duration of 90 days. For reference see Tables 2 and 3. As many as 55.6% of these patients ($n = 7680$) received ≤ 90 DDDs only; 23.3% had medication for only 1 month, 20.0% for 2 months and 3.7% ($n = 506$) received DDDs for 12 months (Fig. 3).

Patients who used both ICS and LABAs (free combination) usually received similar DDD quantities with 21.0% ($n = 1483$) receiving more LABAs than ICS. Some 1.8% ($n = 126$) even received three times more DDDs of LABA than ICS. Of patients receiving fixed dose combinations of LABA and ICS, 53.5% ($n = 56\,185$) received medication for 90 days only, 15.8% received medication for a maximum of 30 days ($n = 16\,593$), 23.5% ($n = 24\,679$) for 31–60 days and 2.1% of (2205) patients received medication sufficient for 1 year (Fig. 3). The median supply lasted 90 days.

Pharmacotherapy of patients with short-acting β_2 -agonists. A total of 1 33 206 patients (27.6%) received SABA as a quick reliever for a median duration of 50 days, 72.3% ($n = 96\,674$) had DDDs for 3 months, 45.0%

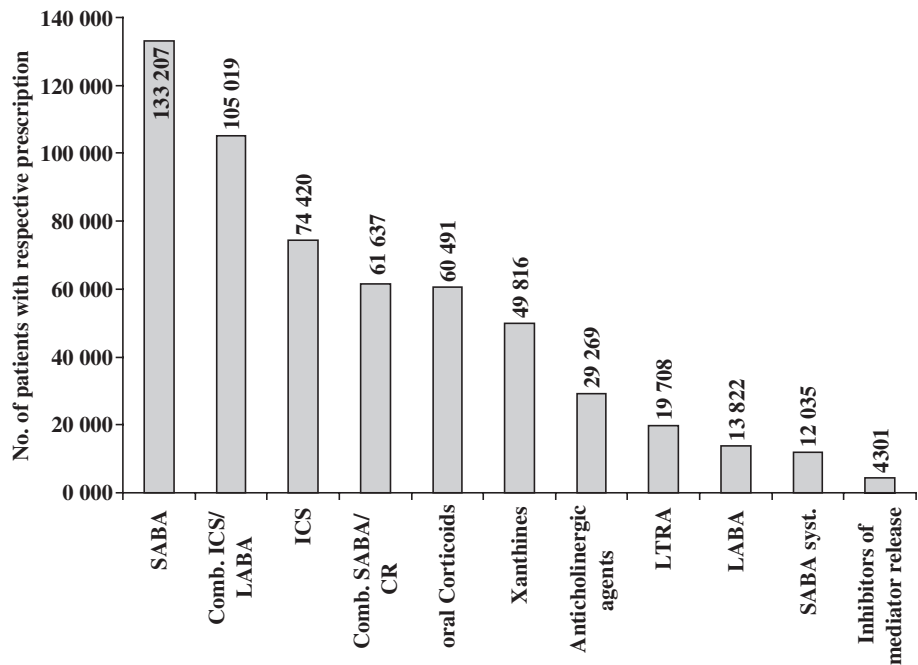


Figure 2. Number of asthma patients with corresponding prescription. SABA, short-acting β_2 -agonists; Comb. SABA + CR, SABA + Cromoglycate; SABA syst, systemic SABA; ICS, inhaled corticosteroids; LABA, long acting β_2 -agonists; Comb. ICS/LABA, ICS and LABA combined; LTRA, leukotriene receptor antagonists.

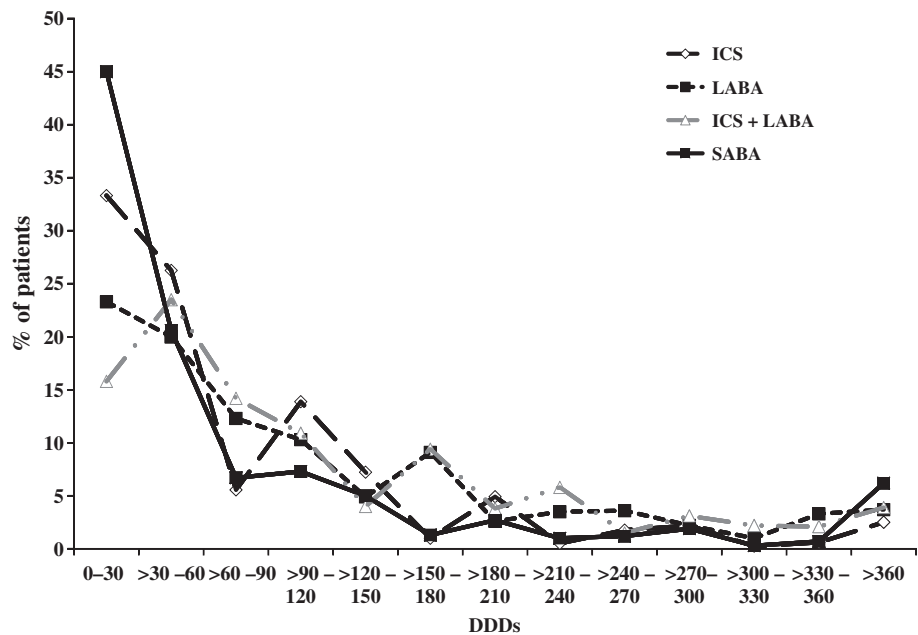


Figure 3. Proportion of patients receiving the indicated number of DDDs over the course of 1 year. ICS, inhaled corticosteroids; LABA, long acting β_2 -agonists; SABA, short-acting β_2 -agonists.

($n = 59\,986$) were supplied with medication for 30 days and 20.6% ($n = 27\,499$) for 31–60 days and 0.7% of patients ($n = 8272$) had enough medication for 1 year (330–360 DDDs). Of note, 8272 patients (6.2%) received more than 360 DDDs of SABA (Fig. 3).

Patients with newly diagnosed asthma, age 20–39 years

The subgroup comprised 3601 patients. According to the medication prescribed, 1176 patients were classified as having stage 1, 653 stage 2, 1574 stage 3 and 198 stage 4

Table 1. DDD used to compute treatment duration

Generic name	Trade name	DDD	
		Inhalation powder	Inhalation solution
Betamethason	Celestamine, Diprosone	0.8 mg	1.5 mg
Budesonid	Budecort, Budefast, Pulmicort	0.8 mg	1.5 mg
Fluticasone	Atemur, Flutide	0.6 mg	1.5 mg
Mometason	Asmanex	0.4 mg	
Flunisolid	Inhacort	1 mg	1.5 mg
Ciclesonid	Alvesco	0.08 mg*	
Formoterol	Foradil DA, Oxis DA	24 µg	24 µg
Salmeterol	Aeromax DA, Severent DA	0.1 mg	0.1 mg
Salmeterol + Fluticasone	Atmadisc, Viani, Seretide	2 puffs	
Budesonid + Formoterol	Symbicort	2 × 1–2 puffs	
Salbutamol	Sultanol, Apsomol, Loftan, Volmac	0.8 mg	10 mg

*No official DDD available.

Table 2. Overview about DDD use in asthma patients in Bavaria (proportion of patients with a maximum of 90 DDDs within the index period of 12 months)

Patientgroup	ICS % (n, N)	LABA % (n, N)	ICS/SABA (FD combo) % (n, N)	SABA % (n, N)
Consistent patients with pharmacotherapy 20–39 year old, new diagnosis	65.1% (48471/74420)	55.6% (7680/13822)	53.5% (56185/105019)	72.3% (96374/133206)
Stage 1	—	—	—	69.6% (819/1176)
Stage 2	67.1% (438/653)	—	—	70.5% (239/339)
Stage 3	42.6% (40/94)	58.3% (35/60)	61.4% (884/1439)	64.1% (347/536)
Stage 4	*	*	50.8% (95/187)	46.8% (51/109)

*Low patient numbers.

FD combo, fixed dose combination.

Table 3. Overview about DDD use in asthma patients in Bavaria (proportion of patients with 330–360 DDDs within the index period of 12 months)

Patientgroup	ICS % (n, N)	LABA % (n, N)	ICS/SABA (FD combo) % (n, N)	SABA % (n, N)
Consistent patients with pharmacotherapy 20–39 year old, new diagnosis	0.6% (445/74420)	3.3% (458/13822)	2.1% (2205/105019)	0.7% (992/133206)
Stage 1	—	—	—	–0.9% (11/1176)
Stage 2	>180 DDD 7.2% (47/653)*	—	—	>180 DDD 10.9% (37/339)*
Stage 3	>180 DDD 25.5% (24/94)*	>180 DDD 41.7% (25/60)*	2.7% (25/1439)	1.1% (6/536)
Stage 4	*	*	2.1% (4/187)	3.7% (4/109)

—, Not to be prescribed within this stage according to guideline; *, low patient numbers.

asthma. Most patients received medication for a maximum of 90 days, which was similar to the total group of patients (Tables 2 and 3).

Patients who used both ICS and LABA (in a free combination) usually received similar DDD quantities. This was analyzed in patients with stage 3 asthma [quantity of stage 4 patients was not sufficient to be analyzed ($n = 187$)]. The scatterplot in Fig. 4 illustrates that most patients received <200 DDDs of ICS and LABA. The proportion of patients with more ICS-DDDs was, however, higher than the proportion of patients with more LABA-DDDs. Of the 1626 patients receiving fixed

dose combinations of LABA and ICS, 61.4% ($n = 884$) received this medication for not more than 90 days only if they had stage 3 asthma (median 60 DDDs), and 50.8% ($n = 95$) if they had stage 4 asthma (median 90 DDDs); 1.8% of the 1626 patients collected prescriptions sufficient for the coverage of 1 year.

A total of 2172 patients received SABA (60.3%). While most patients received SABA for only 3 months (Table 2), which would be compatible with a as-needed use, about 1% received DDD compatible with a regular intake over 1 year (Table 3), and 6% received even more than 360 DDDs.

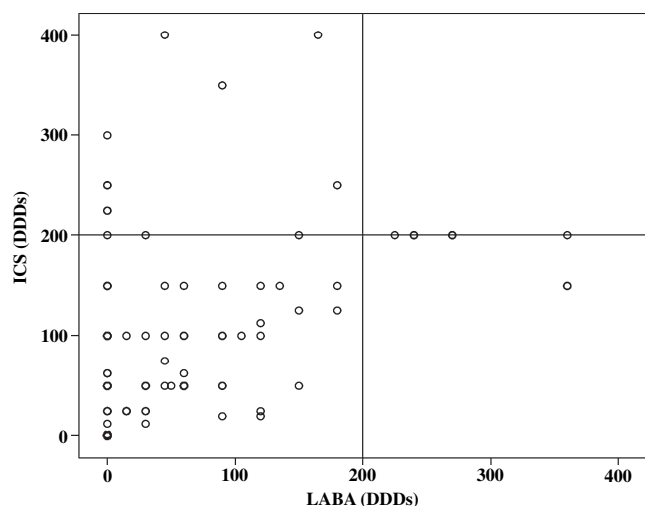


Figure 4. Scatterplot of 20 to 39-year-old patients with prescriptions within 1 year with stage 2 asthma – ICS vs LABA DDDs. ICS, inhaled corticosteroids; LABA, long acting β_2 -agonists.

Discussion

There is a variety of drugs and their combinations for which randomized, controlled trials have shown efficacy in the prevention of asthma exacerbations and possibly the long-term consequences of asthma. However, persistence with treatment is the key prerequisite for efficacious drugs to become effective in clinical practice. Our analysis of a large population based databank of 4 83 051 unselected asthma patients resulted in four key findings: (1) 61.4% of patients with a diagnosis of asthma received prescriptions for any pharmacotherapy; (2) most patients (68.3%) received medical care only from a general practitioner; (3) most patients received no more than 90 DDDs of controller medication in the index period of 365 days (only about 1% received medication for the complete index period; (4) there is a trend for an unbalanced preference of long- and in particular of short-acting β_2 -agonists compared with ICS.

Current guidelines (3–5) generally recommend the use of intermittent corticosteroids starting with stage 2 asthma, and their combination with long acting β_2 -agonists beginning with stage 3 asthma. Short-acting β_2 -agonists are recommended as a quick reliever only as they have been linked to an increased asthma-related morbidity and mortality (14–17) and an increase in the use of short-acting β_2 -agonists has been identified as a sign of deteriorating asthma control (6). This study revealed two remarkable violations against these recommendations. First, the proportion of patients actually receiving regular treatment with ICS and/or LABA as a controller medication is low given that most patients were prescribed a maximum of 90 DDDs within the index period of 12 months. Second, while fixed dose combina-

tions are frequently used, there is a disproportionate use of LABA in free combinations with ICS in many patients.

The under-utilization of ICS among patients with advanced stages of asthma is compatible with data from the 1999 AIRE study (7), where poor persistence with ICS was considered one of the reasons responsible for severe persisting symptoms in about 50% of patients. For German adolescents, this observation was confirmed in a study by Langen et al. (11). Rabe et al. (7) (AIRE study) discussed an immediate need to improve communication and awareness among patients and physicians regarding the reasons of the inappropriate underuse of anti-inflammatory medications, and the imperative need for an adequate use of such agents, to improve compliance and prevent the severe consequences of poor asthma control.

Similar to the findings in our study two further studies pointed out the need for fixed dose combination treatment to increase persistence and adherence with treatment (18, 19). In an administrative claims data base, O'Connor et al. (19) were able to show lower rates of asthma-related symptoms and exacerbations as measured by SABA refills and hospitalizations when patients received fluticasone propionate and salmeterol as a single inhaler compared with patients with concurrent use or fluticasone alone. Marceau et al. (18) compared persistence, adherence, and effectiveness between patients receiving ICS and LABA either as a fixed combination or as concurrent therapy. They were able to show that the rate of moderate to severe asthma exacerbations was reduced among combination users.

On the other hand, this study documented a more frequent use of β_2 -agonists as compared with ICS, which is again compatible with data from earlier studies (8). Long-Acting β_2 -Agonists but in particular SABAs were used more frequently, although the median number of DDDs provided within the index period was still low. A large placebo-controlled trial investigating the safety of the LABA salmeterol showed a small but significant increase in asthma-related deaths in patients receiving salmeterol compared with those with placebo (20–22). Consequently, the Food and Drug Administration regards long acting β_2 -agonists to be only indicated if asthma is not controlled with medium doses of inhaled corticosteroids and only in combination with ICS.

Persistence is the prerequisite for the beneficial action in particular of controller medication like ICS and possibly LABAs. Most patients in our analysis, however, received a prescription for a maximum of only 90 days. Although some of these patients might suffer from seasonal allergic asthma and might therefore, indeed require treatment for a limited time during the year only, such patients cannot account for these finding alone. The number of patients with a prescription of DDD sufficient for a full coverage over 12 months was low, not exceeding 1% in certain constellations that is in sharp contrast to current guidelines. Bender et al. (9) obtained similar results in the United States in that patients obtained their

controller medication on average on only 22.2% of days over a 1-year period.

Of note are the implications of these findings on morbidity and mortality of patients with asthma. Since about 1985, asthma mortality in Germany is on the decline (Federal Health Monitoring). A common explanation is the availability and appropriate administration of modern, evidence based asthma treatment strategies. The widespread poor persistence seen in this study, however, raises doubt about the relative impact of contemporary medication on this trend. Our analysis cannot exclude that the relatively low doses of medication prescribed were taken discontinuously by patients raising the possibility that lower than established doses may contribute to a general improvement in asthma morbidity even if the achieved treatment effect is below that advocated by guidelines and randomized controlled trials. This hypothesis would need to be substantiated by future trials. A 6-month trial in a patient with mild persistent asthma has shown that on demand therapy with ICS/short-acting β_2 -agonist combinations was as successful as regular ICS therapy (23).

Three limitations of this study deserve mentioning: First we were not able to reliably separate asthma patients into those with a 'predominantly allergic asthma' (J.45.0), 'non-allergic asthma' (J.45.1), 'mixed asthma' (J.45.8), and 'asthma, unspecified' (J.45.9) of the ICD 10 – Code (J.45) because these were considered unreliable on a patient basis. Thus, the seasonal variation in drug use, especially in patients with allergic asthma may compromise the results, which may have been alleviated, however, by the 12-month index period covering times with both intensive use and no use at all. Second, the severity of asthma was not coded in the accounting information and had to be assessed using the asthma medication as a proxy measure. It has to be accepted, however, that treatment prescribed by physicians may not necessarily be in line with current guidelines and therefore our estimation of severity is subject to an undefined imprecision. In addition, further possible use of asthma drugs in other indications like COPD or acute bronchitis cannot be completely ruled out (24). Third, as our data were derived from a physicians'

claims data base, patients with asthma who did not see a physician were not included in our database, which may result in an underestimation of the true asthma prevalence and in an overestimation of treatment rates.

Conclusions

The discrepancy between current guidelines on asthma therapy, medical attendance and patient adherence is substantial and indicates a need for careful re-evaluation of treatment strategies. Our finding confirms and extends previous studies that, by different methodology, have suggested that poor asthma control might in part be related to ineffective adherence to published guidelines. Efforts to educate patients and providers about the importance of daily controller medication appear to require reinforcement. In addition, further studies are required to address the discrepancy between an apparently improved overall asthma control in recent years in the general population despite these observed shortcomings in prescribing regular anti-asthmatic therapy. Based on our findings, we conclude that asthma control and consequently morbidity from asthma could be reduced by more effective adherence to published guidelines. However, further research is needed to identify if patient and/or physicians' attitudes towards anti-asthmatic therapy are responsible for these findings.

Acknowledgments

We would like to acknowledge the contribution and valuable help of Anne Pfeiffer, Sandra Pauli, and Rebekka Redel of the Bavarian statutory health insurance physician' association with the management of the data. The study was conducted without any support from pharmaceutical companies.

J. H., J. U., M. T., and J. C. V. designed and conducted the study and did the statistical analyses. P. B. evaluated the data and prepared the manuscript draft. All authors revised the draft for important intellectual content and approved the final version to be submitted.

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