ORIGINAL ARTICLE
ASTHMA

Prevalence of oral corticosteroid use in the German severe asthma population

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ABSTRACT

Aims: We investigated the prevalence of severe asthma, its comorbidities, and especially the use of oral corticosteroid (OCS) therapy in patients with severe asthma.

Methods: Pooled data from 3 961 429 patients insured (with statutory health insurance) during the year 2015 were analysed. Prevalence rates of severe asthma and its OCS-associated comorbidities in patients on high-dosage (HD) inhaled corticosteroid (ICS) in combination with a long-acting β agonist (LABA) therapy were compared with those of patients who were also treated with OCSs.

Results: The asthma prevalence was 7.3%, of which 8.7% (0.6% absolute) were treated with HD-ICS/LABAs. Of these, 33.6% received additional OCSs with calculated dosages between 0.9 and 9.1 mg·day^{-1}. More than 80% of patients on HD-ICS/LABAs had at least one comorbidity. Disorders of the heart (67.5%), metabolism/ nutrition (51.4%), psychiatric disorders (36.0%), skeletal muscle/connective tissue and bone disorders (20.3%), and eye disorders (20.0%) were predominant. The prevalence of these disorders increased for patients also receiving OCS therapy, depending on the length of treatment. Mean therapy costs ranged from €4266 per patient without OCS therapy to €11 253 per patient on long-term OCS treatment. The largest share of costs was attributable to inpatient care.

Conclusion: The analyses show that OCSs are frequently prescribed in patients receiving HD-ICS/LABAs because of severe asthma and are they are frequently associated with adverse effects commonly reported with steroid usage. These data support a necessary change in severe asthma treatment, which is reflected in current treatment guidelines.

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The prevalence of severe asthma in Germany is substantial. OCS therapy is frequent and associated with adverse effects. The data support a need for change in severe asthma treatment, which is already reflected in recent treatment guidelines. http://bit.ly/2z102iV

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Introduction

More than 330 million people suffer from bronchial asthma worldwide [1]. Adequate therapy enables many patients to achieve good asthma control. However, some patients with asthma remain inadequately controlled despite regular high-dosage (HD) administration of an inhaled corticosteroid (ICS) in combination with a second controller (usually a long-acting β_2 sympathomimetic (LABA)). These patients are classified with severe asthma according to the Global Initiative for Asthma (GINA) recommendation [2–4]. In contrast, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considers that the definition of severe asthma is recovered for patients with severe refractory asthma [3]. Patients with severe asthma often suffer from persistent symptoms like cough, shortness of breath and tightness in the chest, acute exacerbations and substantially impaired health-related quality of life. Few data exist about the exact prevalence of severe asthma. Estimations suggest that approximately 5–10% of all asthma patients are severe [5]; however, a more detailed analysis has reported a lower prevalence (3.6% of patients in the Netherlands) [6].

In daily routine care, many patients with severe, inadequately controlled asthma are dependent on oral corticosteroid (OCS) therapy. Because of their effectiveness for acute conditions, steroids continue to be frequently used not only for the management of acute exacerbations (OCS bursts at usually high dosages), but also as an anti-inflammatory maintenance therapy (OCS long-term therapy). At the same time, however, there is growing awareness that repeated use, especially in long-term therapy, is often accompanied by major adverse effects.

The most common OCS-induced comorbidities are osteoporosis, lipid metabolism disorders, psychiatric disorders, cardiovascular disorders (especially hypertension), diabetes mellitus, and cataracts [7–12]. It has also been postulated that short-term treatment with OCS (*e.g.* in the context of an OCS burst) can trigger long-term adverse effects and secondary injury [11, 12]. So far, however, there have been a lack of data analyses investigating this for the German healthcare landscape to determine both the burden of disease for these patients and the partly high direct and indirect costs associated with OCS therapy.

In this context, the objective of the current work was to compare adult patient groups with severe asthma and differing OCS treatment regimens, and to evaluate the cost and safety aspects of short- and long-term therapy with OCS by routine data from the statutory health insurance (SHI) in Germany.

Methods

Data source

The basis for this analysis was the InGef research database [13]. It contains data from approximately 75 health insurance providers (as of January 2017), with anonymised data on resource consumption at the individual patient level, and approximately 4 million patients representing 4.8% of the German population and 5.6% of the German SHI-insured. They match the German population structure in terms of age and sex (Federal Statistical Office; as on December 31, 2013). Of these, 80% were followed-up for 6 years.

The analysis period for the present work was the year 2015. Only those insures who were continuously monitored in 2015 were included. Data from people who died in 2015 were also included if these data covered the previous period accordingly and were complete, yielding a total sample size of 3 961 429.

Definitions of care

Based on the available routine data, the following definitions were used: HD-ICS/LABA patients were adult patients with an International Statistical Classification of Diseases and Related Health Problems (ICD)-10-coded diagnosis of bronchial asthma and a HD-ICS prescription (according to GINA [2]) in combination with a LABA. OCS patients were defined as those persons who received at least one OCS prescription per year.

Duration of the OCS therapy was used as the central differentiation parameter. The number of days of an OCS treatment was defined by the prescribed package size (assumption: one tablet per day). If a patient did not redeem a further OCS prescription within 7 days after consumption of the last OCS prescription, the therapy was considered terminated. On the basis of OCS therapy duration, the following six subgroups were formed: 1) "without OCS prescription"; 2) "short-term infrequent" (one OCS prescription in 2015 not exceeding 20 days); 3) "short-term frequent" (more than one OCS prescription in 2015 not exceeding 20 days each), also referred to in the text as recurrent OCS bursts; 4) "long-term >20 to ⩽90" (at least one OCS long-term treatment with a respective duration of more than 20 to 90 days); 5) "long-term >90 to ⩽180" (at least one OCS long-term treatment with a respective duration of more than 90 to 180 days); and 6) "long-term >180" (at least one OCS long-term treatment with a respective duration of more than 180 days).

Comorbidities and adverse effects were recorded on an outpatient basis (general practitioner (GP) or specialist diagnoses) or on an inpatient basis (discharge diagnoses) using the ICD-10 codes (three digits).

For all patients receiving OCSs, potential OCS-induced comorbidities based on the ICD-10 codes are described. Direct costs were defined as inpatient and outpatient costs, as well as costs for medication, remedies and aids. Indirect costs were defined as those that are paid by the SHI which include sickness benefit payments. In addition, days off work were recorded, and sick leave days were included, if they had an OCS adverse event-related ICD-10-GM diagnosis code.

Patient selection

In a first step, the observable population from 2015 was restricted to adults with asthma (ICD-10 codes J45.0, J45.1, J45.8, J45.9; J46). Next, a gradual selection by pharmacotherapy for asthma (using Anatomical Therapeutic Chemical (ATC) codes) took place [14]. This was initially done by restriction to patients with HD-ICSs plus LABAs. To this end, all patients were excluded who had not received a prescription of LABAs (ATC: R03AC12, R03AK06, R03AC13, R03AK07, R03AK08, R03AK09, R03AK10, R03AK11, R03CC12, R03AC14, R03CC13, R03CC63). Subsequently, the patients treated with at least one ICS interval with a mean dosage above the threshold for a HD-ICS according to the GINA criteria [2] were identified (ATC: R03BA01, R03BA02, R03BA08, R03BA05, R03BA07). In the last step, the medication selection was narrowed down to the patients with at least one OCS prescription in a year (ATC: H02AB02, H02AB04, H02AB06, H02AB07, H02AB08, H02AB14). Subsequently, the patients with at least one OCS prescription were grouped by the length of treatment duration (figure 1).

Statistical analysis

The data were evaluated descriptively [15, 16]. Since 89% of the OCS patients received prednisolone (ATC code H02AB06) as the active pharmaceutical ingredient (API), the quantitative consumption of other systemic corticosteroids was identified and analysed through prednisolone equivalents.

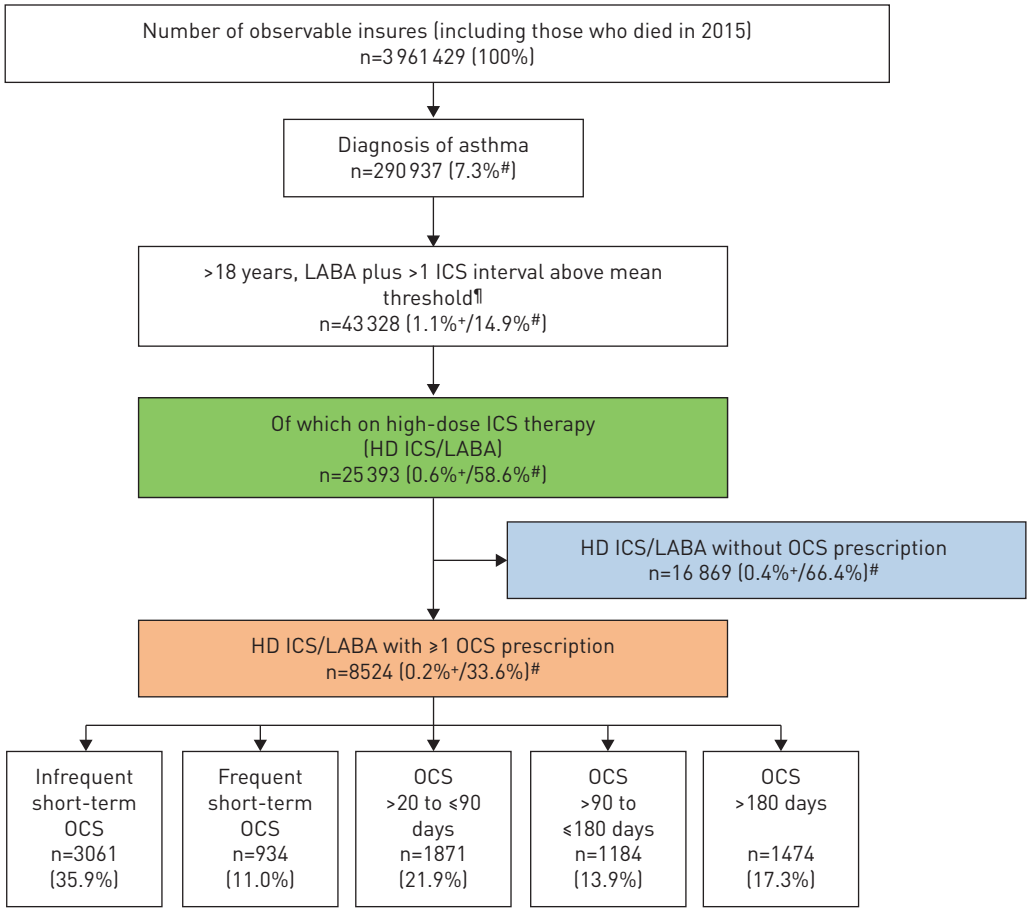

FIGURE 1 Selection steps of the oral corticosteroid (OCS) population (data year 2015). LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; HD: high-dose. #: relative to patients in the box just above; ¶: patients with at least one ICS interval with a mean dosage above the upper threshold according to GINA [2]; +: relative to total sample.

Results

Prevalence

For the present analysis, from the total cohort (n=3 961 429), 290 937 patients were diagnosed with asthma (7.3%), of whom 25 393 adult patients were identified as having HD-ICS/LABA therapy prescribed (figure 1). This corresponds to 8.7% of the patients with asthma having a diagnosis of severe asthma according to the GINA classification.

Of these patients (HD-ICS/LABA), 33.6% also received at least one OCS prescription (n=8524) which is 2.9% of the whole asthma population. Here, 3061 patients received a single short-term OCS prescription. For 5463 patients, which corresponds to 64.1% of asthma patients with HD-ICS/LABA treatment, recurrent OCS bursts (OCS short-term frequent) or maintenance therapy with OCS (corresponding to GINA level 5, defined here as therapy duration >20 days) was prescribed.

Dosage and quantity of OCS therapy

The total number of OCS prescriptions (89% prednisolone) in the sample was 19 669 (table 1). Of these, 15.6% (3062/19 669) were accounted for by a single OCS burst (mean API quantity 313 mg). All other patients needed more frequent OCS intake (three prescriptions; 1826 mg of the API). A total of 38% of all OCS prescriptions were in the group of patients requiring the most intensive long-term treatment (⩾180 days per treatment phase; 5.1 prescriptions; 3314 mg of the API). Average daily dosages increased from 0.9 mg to 9.1 mg according to increased intensity of the therapy group, as expected.

Comorbidities

For 81.9% (13 814/16 869) of the patients with severe asthma but without OCS prescription, and for 88.0% (7503/8524) of the patients with additional OCS therapy, at least one of the OCS-associated comorbidities examined was coded. The five most frequent comorbidities observed during regular OCS therapy were heart disorders (67.5%), metabolic and nutritional disorders (51.4%), psychiatric disorders (36.0%), skeletal muscle, connective tissue and bone disorders (20.3%) and eye disorders (20.0%). The frequency of accompanying diagnoses per patient increased with increasing therapy intensity (figure 2 and table 2). The number of all OCS-associated comorbidities relative to group size increased from 1.87 to 2.76 with increasing treatment intensity (mean of 2.24).

Direct health-related costs

Overall, the annual total cost for all patients on OCS therapy was €60 442 134 (n=8524), whereas the cost for the significantly larger group (n=16 869) of patients without OCS therapy was €72 million (table 3). The mean total annual cost per patient and year was €4266 for a patient without an OCS prescription. This increased continuously with the duration and intensity of therapy from €5096 per patient on infrequent short-term OCS treatment to €11 253 per patient on long-term treatment for >180 days in a treatment phase (figure 3).

The greatest share of the €7091 costs per patient was accounted for by inpatient care (€2953; 41.6%), followed by pharmacotherapy (€2301; 32.4%) and outpatient care (€1212; 24.2%). While average inpatient

TABLE 1 Prescription and cumulative oral corticosteroid (OCS) dose for short- and long-term treatments (in prednisolone equivalents, 2015)

	Patients	Female	Age years median (interquartile range)	Total prescriptions per year	Prescriptions per patient and year group mean	Cumulative OCS dose mg per patient per year	Cumulative OCS dose mg per patient per day
Infrequent short-term treatment	3061 (35.91%)	56.9%	59 (48–72)	3062	1.00	313	0.9 mg
Frequent short-term to long-term >180 days	5463 (64.09%)	60.5%	59 (49–71)	16 607	3.04	1826	5.0 mg
Frequent short-term	934 (10.96%)	63.0%	61 (51–72)	2261	2.42	771	2.1 mg
Long-term >20 to ⩽90 days	1871 (21.95%)	60.5%	62 (52–72)	3957	2.11	1203	3.3 mg
Long-term >90 to ⩽180 days	1184 (13.89%)	57.5%	65 (56–75)	2870	2.42	1790	4.9 mg
Long-term >180 days	1474 (17.29%)	57.3%	69 (59–76)	7519	5.10	3314	9.1 mg
OCS patients total	8524 (100%)	59.8%	61 (49–72)	19 669	2.31	1282	3.5 mg

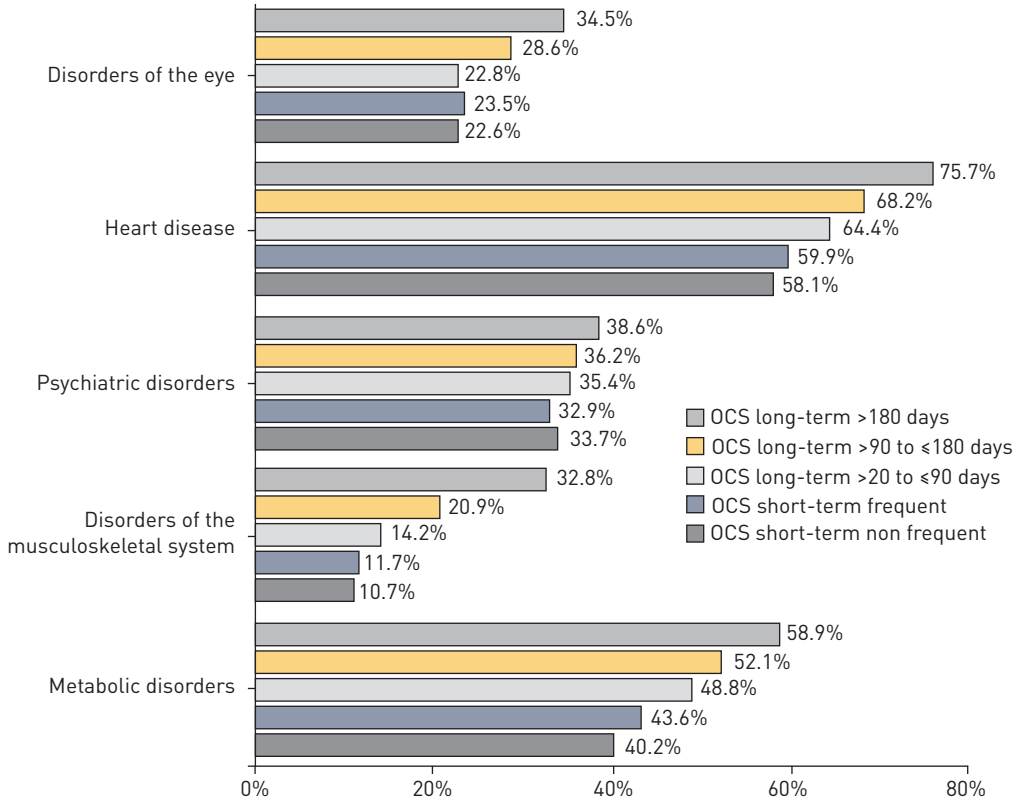

FIGURE 2 Top-5 oral corticosteroid (OCS)-induced comorbidities/adverse events.

costs, medication costs, and cost of remedies and aids per patient increased depending on the intensity and duration of OCS therapy, outpatient costs and sickness benefit payments remained stable (figure 3).

Indirect health-related costs

The percentage of patients on sick leave because of common OCS-associated comorbidities was 3.2% in both patient groups (without OCSs and with an OCS prescription; table 4). Patients on maintenance therapy >180 days per treatment phase were on sick leave for almost 1 week longer than patients with infrequent short-term treatment (43.0 *versus* 36.5 days). Overall, however, in association with the larger group size, the length of sick leave attributable to patients without OCS therapy was highest (18 245 days), accounting for 65.4% of the total group.

For all patients (regardless of actual sick leave), the insurance providers paid a total of €1 323 779, or €78 per patient per year, in sickness benefits for all patients without OCSs, and €865 275 (€102 per patient) for patients with OCSs. The group of patients with OCSs long-term >90 to ⩽180 received the greatest per capita sickness benefit payments, which amounted to €138 per patient. The actual costs for sickness benefits individually incurred by patients on sick leave were many times greater and increased with the duration and intensity of OCS therapy.

Discussion

The present study describes the prevalence of asthma in a representative sample from Germany in terms of age and sex, based on SHI routine data. In this sample of adult patients, the asthma prevalence was 7.3%, which is greater than the estimated 5% reported earlier for the overall German population [17]. Of these asthma patients, 8.7% (0.6% absolute) were treated with HD-ICS/LABAs, defined as steps 4/5 according to the GINA criteria [2], consistent with the reported global prevalence of severe asthma of approximately 5–10% of asthma patients [5, 6]. The frequency of patients on HD-ICS/LABAs who required additional OCSs was 2.9% and is comparable to data from the Netherlands that reported a frequency of 3.6% [5]. A possible explanation for the slightly lower prevalence in the present analysis may be a result of exclusive consideration of prescription data; since additional clinical data on current asthma control were not available within SHI, both prescription data and clinical data were considered in the analysis of the Dutch population. In 2015 82.9% of the asthma patients in Germany who had maintenance

TABLE 2 Oral corticosteroid (OCS)-associated comorbidities/adverse effects by OCS therapy (duration)

OCS-associated comorbidity/ adverse effect	No prescription (n=16 869)	Infrequent short-term treatment (n=3061)	Frequent short-term to long-term treatment >180 days					OCS patients total (n=8524)
			Total (n=5463)	Frequent short-term (n=934)	Long-term >20 to ⩽90 (n=1871)	Long-term >90 to ⩽180 (n=1184)	Long-term >180 (n=1474)	
Eye disorders	3521 (20.87%)	693 (22.64%)	1492 (27.31%)	219 (23.45%)	426 (22.77%)	338 (28.55%)	509 (34.53%)	2185 (25.63%)
Endocrine disorders	704 (4.17%)	121 (3.95%)	240 (4.39%)	34 (3.64%)	72 (3.85%)	48 (4.05%)	86 (5.83%)	361(4.24%)
Disorders of the skin and subcutaneous tissue	421 (2.50%)	88 (2.87%)	151 (2.76%)	28 (3.00%)	50 (2.67%)	37 (3.12%)	36 (2.44%)	239 (2.80%)
Blood and lymphatic disorders	183 (1.08%)	30 (0.98%)	125 (2.29%)	18 (1.93%)	36 (1.92%)	23 (1.94%)	48 (3.26%)	155 (1.82%)
Gastrointestinal disorders	315 (1.87%)	50 (1.63%)	158 (2.89%)	25 (2.68%)	48 (2.57%)	34 (2.87%)	51 (3.46%)	208 (2.44%)
Immune system disorders	2784 (16.50%)	596 (19.47%)	934 (17.10%)	173 (18.52%)	351 (18.76%)	193 (16.30%)	217 (14.72%)	1530 (17.95%)
Nervous system disorders	322 (1.91%)	46 (1.50%)	118 (2.16%)	8 (0.86%)	40 (2.14%)	31 (2.62%)	39 (2.65%)	164 (1.92%)
Cardiac disorders	9510 (56.38%)	1778 (58.09%)	3687 (67.49%)	559 (59.85%)	1205 (64.40%)	807 (68.16%)	1116 (75.71%)	5465 (64.11%)
Psychiatric disorders	4954 (29.37%)	1030 (33.65%)	1966 (35.99%)	307 (32.87%)	662 (35.38%)	428 (36.15%)	569 (38.60%)	2996 (35.15%)
Weakening of the immune defence with increased risk of infection	455 (2.70%)	105 (3.43%)	190 (3.48%)	25 (2.68%)	77 (4.12%)	40 (3.38%)	48 (3.26%)	295 (3.46%)
Musculoskeletal and connective tissue disorders	1600 (9.48%)	328 (1072%)	1106 (20.25%)	109 (11.67%)	266 (14.22%)	247 (20.86%)	484 (32.84%)	1434 (16.82%)
Metabolism and nutrition disorders	6850 (40.61%)	1229 (40.15%)	2805 (51.35%)	407 (43.58%)	913 (48.80%)	617 (52.11%)	868 (58.89%)	4034 (47.33%)
Patients with at least one OCS-associated comorbidity/adverse effect	13 814 (81.89%)	2574 (84.09%)	4929 (90.23%)	807 (86.40%)	1654 (88.40%)	1083 (91.47%)	1385 (93.96%)	7503 (88.02%)
Number of all OCS-associated comorbidities/adverse effects relative to group size	1.87	1.99	2.37	2.05	2.22	2.40	2.76	2.24

TABLE 3 Statutory health insurance (SHI) costs associated with oral corticosteroid (OCS) therapy for asthma in the sample (2015) rounded to full €

	(% of total costs) total	Cost per patient mean±SD	Extrapolation to SHI	Extrapolation to the German population
Inpatient costs				
No OCSs	24 275 598	1439±4503	433 420 485	497 577 478
OCS total	(41.6) 25 169 611	2953±8130	449 382 345	515 902 089
Infrequent short-term	5 584 650	1824±6208	99 709 247	114 468 691
Frequent short-term	1 917 646	2053±4676	34 237 959	39 306 027
Long-term >20 to ⩽90 days	5 171 143	2764±8572	92 326 439	105 993 045
Long-term >90 to ⩽180 days	4 764 609	4024±8234	85 068 115	97 660 308
Long-term >180 days	7 731 563	5245±11 465	138 040 585	158 474 019
Outpatient costs				
No OCSs	16 372 180	971±835	292 311 574	335 580 945
OCS total	(17.1) 10 335 019	1212±955	184 523 120	211 837 123
Infrequent short-term	3 486 655	1139±899	62 251 306	71 466 045
Frequent short-term	1 085 762	1162±874	19 385 367	22 254 882
Long-term >20 to ⩽90 days	2 271 890	1214±962	40 562 686	46 566 971
Long-term >90 to ⩽180 days	1 512 427	1277±1096	27 003 116	31 000 248
Long-term >180 days	1 978 286	1342±971	35 320 645	40 548 977
Medication costs				
No OCSs	24 788 284	1469±3549	442 574 076	508 086 027
OCS total	(32.4) 19 612 646	2301±6884	350 167 375	402 000 840
Infrequent short-term	5 126 605	1675±3550	91 531 236	105 080 132
Frequent short-term	1 554 272	1664±2576	27 750 222	31 857 943
Long-term >20 to ⩽90 days	4 016 750	2147±5261	71 715 702	82 331 407
Long-term >90 to ⩽80 days	3 414 204	2884±7136	60 957 754	69 981 016
Long-term >180 days	5 500 816	3732±12 821	98 212 460	112 750 343
Costs for remedies and aids				
No OCSs	5 211 548	309±1147	93 047 822	106 821 210
OCS total	(7.4) 4 459 583	523±2009	79 622 124	91 408 175
Infrequent short-term	1 081 684	353±957	19 312 558	22 171 296
Frequent short-term	363 416	389±1200	6 488 495	7 448 954
Long-term >20 to ⩽90 days	844 355	451±1816	15 075 249	17 306 760
Long-term >90 to ⩽180 days	931 294	787±3751	16 627 480	19 088 760
Long-term >180 days	1 238 834	840±2192	22 118 342	25 392 406
Sickness benefits				
No OCSs	1 323 779	78±803	23 634 960	27 133 521
OCS total	(1.4) 865 275	102±925	15 448 767	17 735 568
Infrequent short-term	319 927	105±1034	5 712 024	6 557 545
Frequent short-term	76 770	82±656	1 370 667	1 573 560
Long-term >20 to ⩽90 days	167 263	89±822	2 986 344	3 428 398
Long-term >90 to ⩽180 days	163 908	138±1091	2 926 434	3 359 619
Long-term >180 days	137 408	93±803	2 453 297	2 816 446
Total costs				
No OCSs	71 971 388	4266±6690	1 284 988 917	1 475 199 180
OCS total	(100) 60 442 134	7091±12 115	1 079 143 731	1 238 883 795
Infrequent short-term	15 599 520	5096±8206	278 516 370	319 743 708
Frequent short-term	4 997 866	5351±6670	89 232 710	102 441 367
Long-term >20 to ⩽90 days	12 471 401	6666±11 897	222 666 422	255 626 581
Long-term >90 to ⩽180 days	10 786 442	9110±12 785	192 582 900	221 089 950
Long-term >180 days	16 586 906	11 253±18 418	296 145 329	339 982 190

therapy with HD-ICS/LABAs and needed OCSs at least once, received an intensive therapy with OCSs (either frequent short-term or long-term).

The present analysis demonstrates that, in Germany, OCS therapy is an established and frequently applied treatment option for patients with severe, inadequately controlled asthma. While OCSs may be appropriate and a relatively well-tolerated treatment option for acute exacerbations (*i.e.* OCS bursts at usually high dosages), these data revealed the frequent use of comparatively high dosages during long-term treatment. Patients who received long-term OCS for more than 180 days in a year received an average of 9.1 mg of prednisolone equivalent per day and were substantially above the national and international guideline

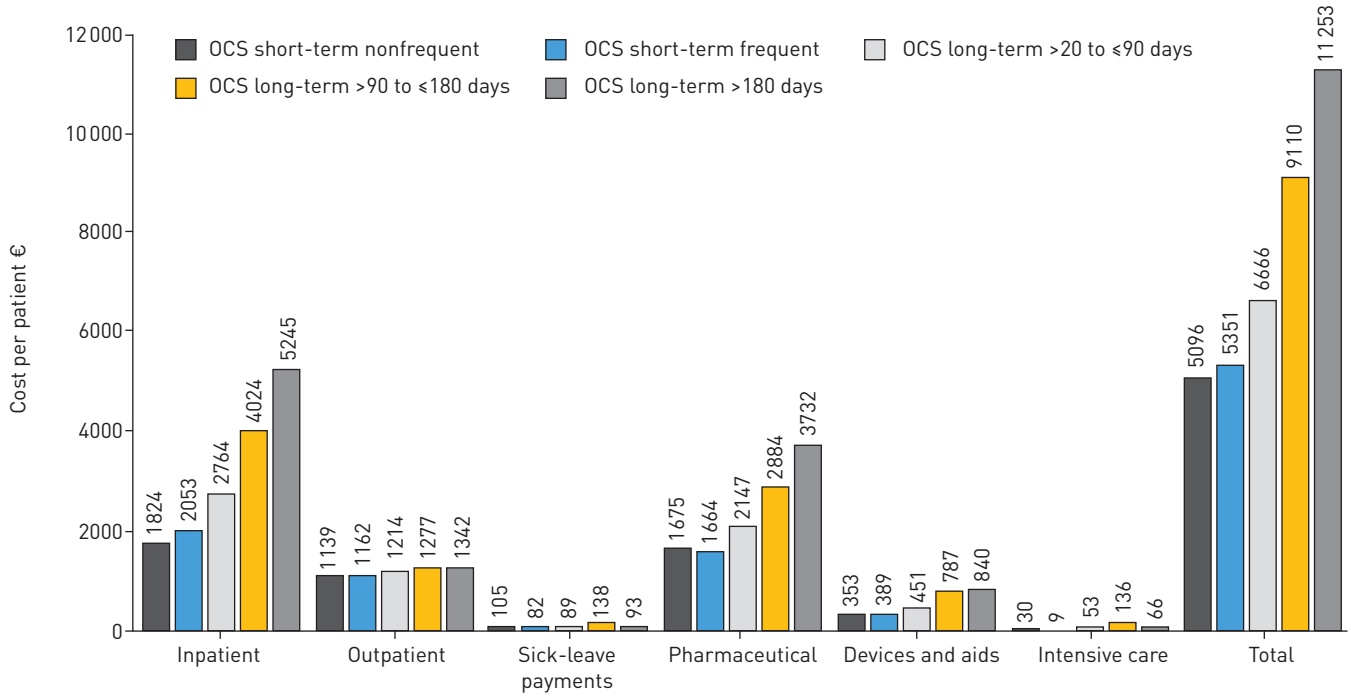

FIGURE 3 Statutory health insurance costs per patient associated with oral corticosteroid (OCS) therapy for asthma in the sample (2015) rounded to full €.

recommendations that recommend OCS maintenance therapy in step 5 of the therapy regimen only as secondary and intermittent treatment and at dosages of less than 7.5 mg of prednisolone equivalent per day [2, 18, 19]. In addition, OCSs at a rather high dosage (3.3 mg·day^{-1}) was also administered widely (*i.e.* for all patients with therapy duration >20 days), which is of concern, as frequent OCS-associated adverse effects have been reported with usage from a daily dosage >2.5 mg [20].

Comorbidities in patients with asthma are frequent, increase with the duration and intensity of OCS therapy, and mainly affect certain organ systems. Here, a distinction must be made between frequently accompanying but not causally linked comorbidities and direct/indirect, OCS-induced adverse effects [21]. Comparable frequencies were reported from the analysis of a healthcare database in the United Kingdom, which described at least one potential steroid-induced comorbidity in 93% and more than three in 53% of all patients with severe asthma [9]. The dosages used, amounting to 1960 mg per year, were essentially comparable with the data from our analysis (1826 mg), as was the profile of most frequently observed comorbidities, despite slightly different definitions. A further analysis of prescription data from the United States described an increase in comorbidities in asthmatic patients with intensive OCS therapy (at least

TABLE 4 Oral corticosteroid (OCS)-associated sick leave in asthma patients on high-dosage inhaled corticosteroids in combination with a long-acting β-agonist (LABA) and OCS therapy in the sample (2015)

	Total	Patients with at least one sick leave	Total days of sick leave in the subgroup	Sick leave days per patient	Mean number of days per sick leave[#]
No OCS	16869	537 (3.2%)	18245	1.1	34.0±10.9
All OCS patients	8524	270 (3.2%)	9641	1.1	35.7±11.5
Infrequent short-term	3061	122 (4.0%)	4458	1.5	36.5±13.4
Frequent short-term	934	34 (3.6%)	998	1.1	29.4±11.9
Long-term >20 to ⩽90 days	1871	54 (2.9%)	1476	0.8	27.3±7.8
Long-term >90 to ⩽180 days	1184	32 (2.7%)	1505	1.3	47.0±13.9
Long-term >180 days	1474	28 (1.9%)	1204	0.8	43.0±8.3
All HD-ICS/LABA patients	25393	870 (3.4%)	27886	1.1	34.6±11.1

HD: high-dosage; ICS: inhaled corticosteroids. [#]: in patients with at least one sick leave in 2015; sick leave was included if the patient was coded with an OCS adverse event-related International Classification of Diseases (10th Revision, German Modification) code as the diagnosis.

30 days with OCS intake per year) compared with asthma patients without OCS therapy, resulting in increased frequencies of osteoporosis, cataract/glaucoma, diabetes mellitus and hypertension. The frequencies of the comorbidities associated with OCS maintenance therapy described in the present analysis are comparable with the United States data clustered into categories of skeletal muscle, connective tissue and bone diseases, ocular disorders, metabolic and nutritional disorders, and cardiac conditions [10]. Dosage dependencies have been described by Amelink [7] both for psychiatric conditions and for diabetes. The increase in comorbidities we observed for patients receiving short-term OCS therapy also confirms data analysed from earlier studies reporting an increase in OCS-associated comorbidities with short-term OCS use for less than 30 days [12] and relatively low-dosage OCS maintenance therapy below the so-called Cushing threshold [9].

Asthma, and especially severe asthma, are a significant burden on payers. The cost analyses available for Germany, however, are predominantly outdated and do not relate to the current state of knowledge, modern treatment strategies, and cost and reimbursement structure [22, 23]. In addition, they rarely differentiate by asthma severity, and they take different perspectives (*e.g.* SHI, pension insurance), hampering comparability. For example, the direct total costs of patients with atopic asthma associated with seasonal allergic rhinitis are estimated by Schramm *et al.* [24] to be €569 per adult in mild asthma and up to €2048 for severe asthma. If the indirect costs are included, the amount increases to up to €9286 per year and patient. Kirsch *et al.* [23] determined total asthma costs per case and year of between €445 and €2543 by means of a systematic literature search.

We found that mean annual direct costs per patient and year increased from €5096, for patients with HD-ICS/LABAs and a one-time short-term OCS prescription, to €8208 for the group of patients with multiple OCS bursts of therapy or maintenance-therapy OCSs. Long-term treatment with OCSs for more than 180 days per year more than doubled the cost compared with the patient group with a one-time, short-term OCS prescription (€5096 *versus* €11 253). The latter amount roughly corresponds to the costs for severe asthma of €11 703 per patient and year determined in a meta-analysis for Europe, the United States and Canada, but is greater than the average costs calculated by Barry *et al.* [25] for England (€5137). According to the literature from Germany, medication costs account for the largest part of per patient costs, followed by hospitalisations [22, 24, 26]. In our current analysis, medication costs and hospitalisation were also the main cost drivers, reflecting a high OCS burden in association with the severity of the asthmatic disorder and comorbidities.

As a matter of principle, only billable data were registered as routine SHI data. These are collected at various interfaces in the healthcare system (*e.g.* physicians, pharmacists, hospitals), and inconsistencies and errors may occur, for example regarding confirmation of the asthma diagnosis [27]. This also relates to the potential other reasons for OCS use than asthma, including musculoskeletal and connective tissue disorders. Furthermore, eosinophilic granulomatosis with polyangiitis was not ruled out but, according to our analysis, only affected less than 0.5% of the population under investigation. Moreover, the total macroeconomic costs cannot be reflected conclusively, as only costs for a maximum of 6 weeks per year off work are covered by the SHI, while longer sickness absence, rehabilitation and early and partial retirement were covered by the pension fund. This may have led to distortions and loss of accuracy in further calculations (such as of the indirect costs) but more likely resulted in an underestimation of cost, rather than an overestimation. Distortions can also occur during the selection of billing codes (*e.g.* ICD-10 three-digit codes for comorbidities/adverse effects). For example, the percentage of OCS-induced conditions such as cataracts or osteopenia cannot be precisely estimated, since the groups of "eye disorders" or "skeletal muscle, connective tissue or bone disorders" can also include other diagnoses.

In conclusion, we have provided novel prevalence information that demonstrates that, despite maintenance therapy with HD-ICS/LABAs, severe asthma is inadequately controlled and requires the use of OCS maintenance therapy. It indicates that OCS therapy is applied at relatively high dosages in everyday care and is associated with many adverse effects, commonly reported with steroid usage. These data thus support a necessary change in the therapy of severe asthma, which is already reflected in national and international guidelines with the inclusion of biologics for respective patients.

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