



Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK

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This study gives a real-world snapshot of oral corticosteroid (OCS) use in western Europe, by highlighting an opportunity to shift towards corticosteroid-sparing therapies or safer alternatives that mitigate the risk of OCS-associated adverse effects <http://bit.ly/3cB8kk8>

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ABSTRACT Oral corticosteroids (OCS) are used to manage asthma exacerbations and severe, uncontrolled asthma, but OCS use is associated with adverse effects. We aimed to describe the patterns of OCS use in the real-world management of patients with asthma in western Europe.

We used electronic medical records from databases in France, Germany, Italy and the United Kingdom from July 2011 through February 2018. Patients aged ≥ 12 years with an asthma diagnosis, at least one non-OCS asthma medication within ± 6 months of diagnosis, and available data ≥ 6 months prior to and ≥ 90 days after cohort entry were included. High OCS use was defined as OCS ≥ 450 mg prescribed in a 90-day window during follow-up. Baseline characteristics and OCS use during follow-up were described overall and by OCS use status.

Of 702 685 patients with asthma, 14–44% were OCS users and 6–9% were high OCS users at some point during follow-up. Annual prevalence of high OCS use across all countries was $\sim 3\%$. High OCS users had a mean of between one and three annual OCS prescriptions, with an average daily OCS dosage of 1.3–2.2 mg. For patients who continued to meet the high-use definition, daily OCS exposure was generally stable at 5.5–7.5 mg for ≥ 2 years, increasing the risk of adverse effects.

Our study demonstrates that OCS use is relatively common across the four studied European countries. Data from this study may provide decisive clinical insights to inform primary care physicians and specialists involved in the management of severe, uncontrolled asthma.

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at <https://astrazenecagroup-dt.pharmacm.com/DT/Home>

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Introduction

Asthma is a chronic respiratory disease affecting an estimated 339 million people worldwide [1]. Prevalence is high across western and northern European countries [2], with studies over the past two decades reporting estimated asthma prevalence of 11–18% in the United Kingdom (UK), 10% in France, 6.3–10% in Germany and 6–11% in Italy [3–8].

National and international treatment guidelines recommend a stepwise approach to asthma therapy, aimed at optimising symptom control and reducing risk of exacerbations [9, 10]. Despite these guideline recommendations, patients with asthma remain at risk of severe exacerbations because of lack of adherence to maintenance therapy, overuse of reliever therapy, poor inhaler technique, comorbidities or difficult-to-treat asthma. Asthma exacerbations are commonly treated with short bursts of oral corticosteroids (OCS), with OCS treatment overall associated with increased risk of adverse effects, ranging from acute complications such as infections to chronic complications such as metabolic and cardiovascular events [11–14]. In addition, recent cohort studies have demonstrated a dose–response relationship between OCS and adverse effects [14, 15], with the risk of some systemic adverse effects becoming statistically significant at cumulative exposures of 0.5–<1 g, the equivalent of four lifetime OCS courses [15].

Until recently, the Global Initiative for Asthma (GINA) recommended OCS as add-on therapy for patients whose asthma remained uncontrolled despite receiving the highest possible inhaled corticosteroid (ICS) dosage. However, based on increasing evidence of OCS-related adverse effects and the availability of OCS-sparing biologic therapies, these recommendations have been updated to reflect that OCS add-on therapy should be considered carefully [9].

Despite increasing evidence and awareness of OCS-related adverse effects in general, data on OCS use patterns in European countries are limited, although country-specific evidence is essential to facilitate successful implementation of updated treatment recommendations in clinical practice. The current study aimed to describe OCS use patterns as well as demographics and clinical characteristics of patients with asthma prescribed OCS in France, Germany, Italy and the UK.

Materials and methods

Data source

This was a multicountry retrospective cohort study that used data from the following IQVIA electronic medical record databases from July 1, 2011 to February 28, 2018: IQVIA Medical Research Data (IMRD) incorporating The Health Improvement Network (THIN, a Cegedim database) in the UK [16, 17], Disease Analyzer in Germany [18], and Longitudinal Patient Data (LPD) in France [19] and Italy [20]. All data sources were carefully selected to contain nationally representative primary care data on patient demographics, diagnoses and medications, including prescription date and dosage. THIN includes data from >3.1 million active patients, representing nearly 5% of the UK population. Data are generally representative of the UK for age and sex comparisons, and quality outcome framework for chronic disease prevalence [16, 17]. The German Disease Analyzer is based on patient records continuously collected from 2500 computerised practices (~3% of all primary care physicians), providing information for >11 million patients throughout Germany [18]. In addition, information on hospital admissions was recorded in IMRD (UK), and pulmonologist care data were available for Germany. Hospital admission information was included to capture the wider healthcare resource implications of severe asthma. For Germany, pulmonologist care and general physician data were analysed separately, because the patients from these two panels were not mutually exclusive. The French and Italian LPDs collect medical information from proprietary practice management software used by physicians during patient office visits to record daily patient interactions, which, therefore, reflect routine clinical practice in the country. The panel of contributing physicians is maintained as a representative sample of the primary care physician population based on age, sex and geographical distribution, all of which are known to influence prescribing [19, 20].

Study population

Patients with active asthma (asthma diagnosis during the study period and at least one non-OCS asthma medication within ± 6 months of diagnosis) aged ≥ 12 years were included if data were available during ≥ 6 months prior to index date (baseline period) and ≥ 90 days after the index date. The index date (*i.e.* cohort entry date) was the day after the latest of 1) asthma diagnosis during the study period; 2) availability of ≥ 6 months of data within the study period; or 3) non-OCS asthma medication within the study period (and recorded within ± 6 months of a qualifying asthma diagnosis) (figure 1). Patients were followed until the first of the following events: end of the study period, loss to follow-up, or death.

Patients were excluded from all analyses if they had other respiratory conditions (COPD, lung cancer, idiopathic pulmonary fibrosis, pulmonary artery hypertension or cystic fibrosis), or conditions probably

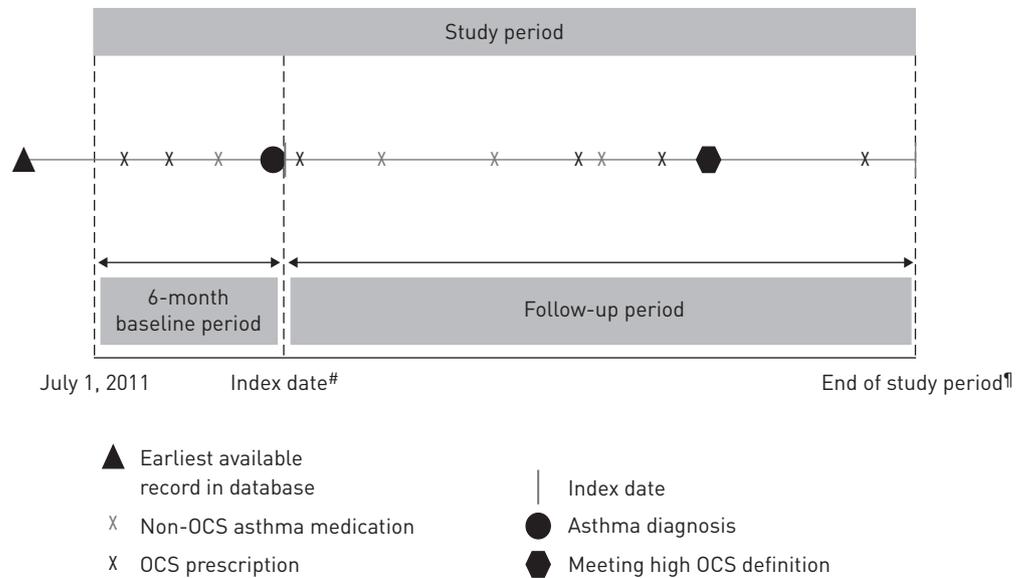


FIGURE 1 Illustration of the study period. OCS: oral corticosteroids. #: the day after the latest of an asthma diagnosis, a non-OCS asthma medication or availability of 6 months of data; ¶: UK IQVIA Medical Research Data: January 17, 2018; Germany Disease Analyzer and France Longitudinal Patient Data (LPD): February 28, 2018; Italy LPD: December 31, 2017.

requiring OCS (inflammatory bowel disease, rheumatoid arthritis or systemic lupus erythematosus) at any time in their medical histories.

Patient demographics and clinical variables

Patient age, sex, body mass index (BMI; adults only) and smoking history were described at study index date. In addition, asthma medications (per Gemscript in UK and Anatomical Therapeutic Chemical classification in other countries) during the baseline period and comorbid conditions recorded at any time in patients’ medical histories (per International Classification of Diseases (ICD)-9 (Italy), ICD-10 (Germany, France), and Read codes (UK)) were described. Asthma treatment step during the baseline period was obtained through an algorithm based on the GINA 2018 recommendations [1]. Asthma severity was categorised as mild (GINA steps 1–2), moderate (GINA step 3) and severe (GINA steps 4–5), or nonsevere (GINA steps 1–3) and severe (GINA steps 4–5). Over the baseline period, an exacerbation was defined as a single OCS prescription with total dosage ≤300 mg or duration ≤10 days. However, in the UK, OCS prescriptions with total dosage ≤300 mg prescribed during an annual asthma review were not considered in this definition, as we assumed these prescriptions were to be used on an as-needed basis. In addition, prescriptions meeting the exacerbation definition recorded within 14 days of each other were considered part of the same exacerbation event.

OCS exposure

The annual number of OCS prescriptions and average daily dosage were described through all available data during the follow-up period (post-index date). Patients were classified as high OCS users, low OCS users and non-OCS users based on their prednisone-equivalent dosages. High OCS use was defined as a cumulative dosage ≥450 mg within 90 days, corresponding to an average daily OCS dosage ≥5 mg (supplementary figure S1). A dose–response relationship between average daily or cumulative OCS dosages and OCS-related complications has been reported, suggesting that these measures can be used to track the burden of high OCS use [13, 15, 21–23]. Patients who were prescribed OCS but did not meet the high OCS criteria were classified as low OCS users. Non-OCS users were those who had no OCS prescriptions during the entire follow-up period.

Statistical analyses

Data were analysed descriptively with a complete-case approach, whereby patients with missing data for relevant variables were excluded. Analyses were stratified by OCS use (high, low, no use), asthma severity (non-severe (GINA steps 1–3), severe (GINA steps 4–5)) and baseline exacerbations (presence, absence). Annual prevalence of high OCS use was calculated as the percentage of patients at the beginning of each calendar year who met the high OCS use definition during each calendar year. Because patients had to have data available for ≥6 months before index date, annual prevalence of high OCS use was calculated

only for 2012–2017 to allow for a full year of follow-up data for most patients. Average daily dosage for patients who continued to meet the high OCS use definition was calculated for each 90-day period for up to 2 years after the patient first met the definition. All analyses were performed *via* SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

Study population

Across the four countries studied, a total of 702 685 patients met the study inclusion and exclusion criteria (figure 2). Median duration of follow-up was 33–55 months for all countries. Table 1 describes baseline characteristics of the study population per country. Mean age at index date across the countries was 42–48 years, 57–63% of patients were female and mean BMI was 26.8–28.2 kg·m⁻². The majority of patients (71–97%) did not have an exacerbation during the 6-month baseline period. Up to 27% of patients were prescribed short-acting β₂-agonists only, while 58–80% of patients were prescribed at least an ICS inhaler during baseline. ~40–50% of study populations across countries were categorised as having mild asthma (GINA steps 1–2), while 17–43% were categorised as having severe asthma (GINA steps 4–5). Comorbidity profiles of included patients are presented in table 1.

OCS exposure

Across the four countries studied, 14–44% of patients had an OCS prescription and 6–9% were classified as high OCS users at some point during follow-up (figure 3). Annual prevalence of high OCS use remained stable, at ~3% across all countries during 2012–2017 (figure 4). Prescription patterns and frequency of OCS use stratified by treatment intensity are presented in table 2. The average number of annual OCS prescriptions during follow-up was one to three for high OCS users and 0.5–0.6 for low users. The percentages of high and low OCS users receiving at least one OCS prescription per year were 33–72% and 11–18%, respectively. The corresponding ranges for four or more OCS prescriptions per year were 4–21% and 0.3–0.6% for high and low OCS users, respectively. On average, during the entire follow-up period, including the period when patients were not high OCS users, patients with high OCS use were exposed to an average daily OCS dosage from 1.3 mg (Italy) to 2.2 mg (UK). In contrast, patients with low OCS use had an average daily dosage from 0.2 to 0.3 mg.

During the 90-day period in which patients first met the high OCS use definition, average daily OCS dosage ranged from 7.2 to 10.3 mg across the four study countries. Following a decrease to ~2.5 mg·day⁻¹

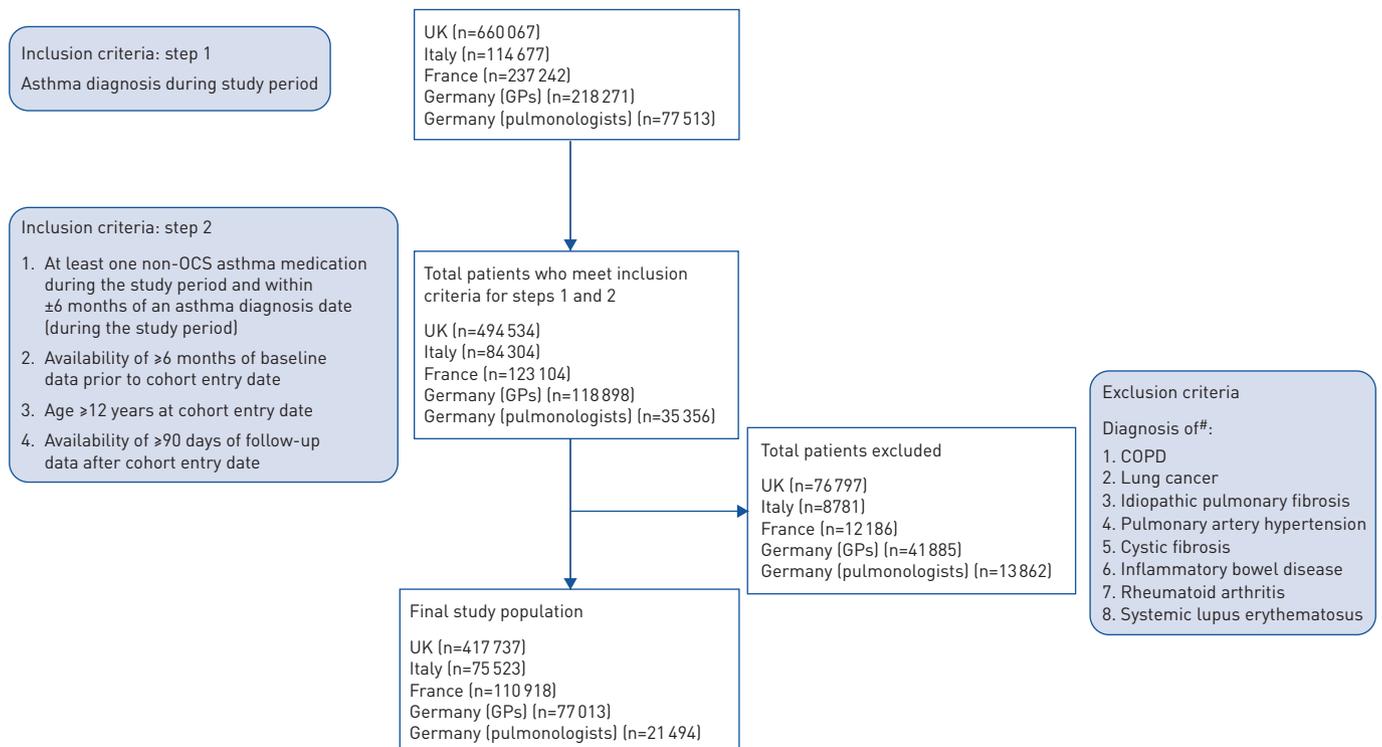


FIGURE 2 Patient flowchart. UK: United Kingdom; GPs: general physicians; OCS: oral corticosteroids. #: at any point in patient’s medical record.

TABLE 1 Demographics and baseline clinical characteristics of all included patients with asthma

	Country				
	UK	Italy	France	Germany (GPs)	Germany (pulmonologists)
Patients n	417737	75523	110918	77013	21494
Age years	42.4±19.1	46.2±19.6	42.7±19.6	43.5±18.5	47.5±17.7
Female	57.2	57.2	58.7	57.8	63.1
BMI[#]					
Patients n	376439	69730	98129	71823	20352
Mean±sd	28.1±6.4	26.8±5.5	27.3±6.3	28.2±6.2	28.2±5.7
<18.5 kg·m ⁻²	1.8	3.1	3.6	1.8	1.0
≥18.5-<25 kg·m ⁻²	33.1	38.0	37.3	31.9	31.7
≥25-<30 kg·m ⁻²	33.1	34.3	30.2	33.6	34.4
≥30 kg·m ⁻²	31.9	24.6	28.8	32.7	32.9
Number of exacerbations during baseline period					
0	88.5	82.1	70.5	95.8	96.6
1	9.1	14.6	25.0	3.8	3.2
≥2	2.4	3.3	4.5	0.5	0.2
Asthma medication use during baseline period					
SABA only (inhaled)	23.0	11.1	20.0	26.7	7.3
Any ICS medication	71.6	79.6	58.0	60.2	72.7
ICS/LABA or ICS+LABA	30.8	47.1	43.8	41.8	51.0
ICS/LABA/LAMA or ICS/LABA+LAMA	0.5	1.1	0.9	0.3	0.9
Any LTRA	4.2	9.6	10.4	2.1	5.5
Any theophylline	0.5	1.2	0.4	1.6	3.4
Other anti-allergic agents	15.9	27.3	37.7	7.7	3.4
Asthma severity during baseline period					
Mild (GINA steps 1–2)	42.4	41.4	44.0	50.9	38.0
Moderate (GINA step 3)	33.1	15.5	20.8	32.0	31.6
Severe (GINA steps 4–5)	24.5	43.1	35.1	17.1	30.4
Comorbidities					
Cardio-cerebrovascular disease	5.4	8.3	5.0	9.0	2.5
Cerebrovascular accident: stroke	2.9	6.1	2.8	4.5	0.9
Heart failure	1.7	2.0	1.5	4.4	1.2
Myocardial infarction	1.6	1.2	1.1	1.8	0.6
Renal impairment	7.2	3.7	3.1	3.4	0.1
Type 2 diabetes mellitus	11.4	5.5	7.5	9.3	2.1
Glaucoma	2.0	3.9	1.7	1.4	0.5
Osteoporosis	3.4	12.1	4.6	4.3	1.5
Peptic ulcer	1.8	2.8	2.5	2.0	0.1
Pneumonia	4.2	4.5	8.0	7.4	3.2

Data are presented as mean±sd or %, unless otherwise stated. UK: United Kingdom; GPs: general physicians; BMI: body mass index; SABA: short-acting β₂-agonists; ICS: inhaled corticosteroids; LABA: long-acting β₂-agonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene receptor antagonists; GINA: Global Initiative for Asthma. [#]: calculated for adult patients only.

between 91 and 180 days, the average daily OCS dosage remained stable at 5.5–7.5 mg for patients who continued to meet the high-use definition in subsequent intervals through to 631–720 days (figure 5, supplementary table S1).

Across the four study countries, 3–7% of patients with mild asthma at baseline became high OCS users during follow-up. Patients with severe asthma were more likely to become high OCS users than patients with mild or moderate disease (supplementary table S2). Prescription patterns and frequency of OCS use stratified by asthma severity and exacerbation history are presented in supplementary table S3. Patients with severe asthma at baseline had more OCS prescriptions and received greater average daily OCS dosages than patients with non-severe asthma. A similar trend was observed for patients with a history of exacerbations during the baseline period *versus* those without a history of exacerbations.

Characteristics of patients with high OCS use

Compared with low and non-OCS users, high OCS users were consistently more likely to be older, female, to have had more exacerbations and have greater asthma severity across the countries studied (supplementary table S4). In addition, high OCS users were more likely to have been prescribed ICS only,

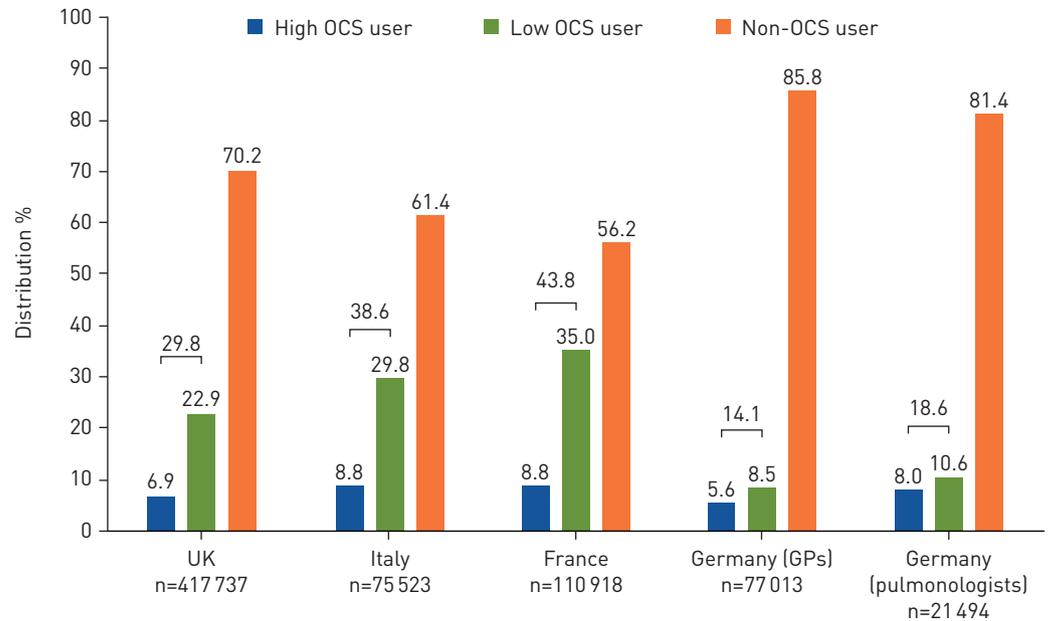


FIGURE 3 Distribution of oral corticosteroid (OCS) users during the study period. High OCS users are defined as having a cumulative dosage ≥ 450 mg within 90 days (average daily OCS dosage ≥ 5 mg); low OCS users were prescribed OCS, but did not meet high OCS criteria; non-OCS users had no OCS prescription during the entire follow-up period. GPs: general physicians.

dual or triple therapy, leukotriene receptor antagonists, any theophylline, and other anti-allergic agents during the baseline period compared with low or non-OCS users.

Discussion

In this study of >700 000 patients with active asthma, we aimed to describe the current state of OCS prescriptions for the treatment of asthma in France, Germany, Italy and the UK. In line with publications from database studies [23–25], we found that OCS prescribing was common (up to 44% of patients with asthma) across all countries studied. This finding corresponds with 21–50% of patients with asthma reporting steroid use in a large survey conducted for patients with asthma in Europe and Canada [26].

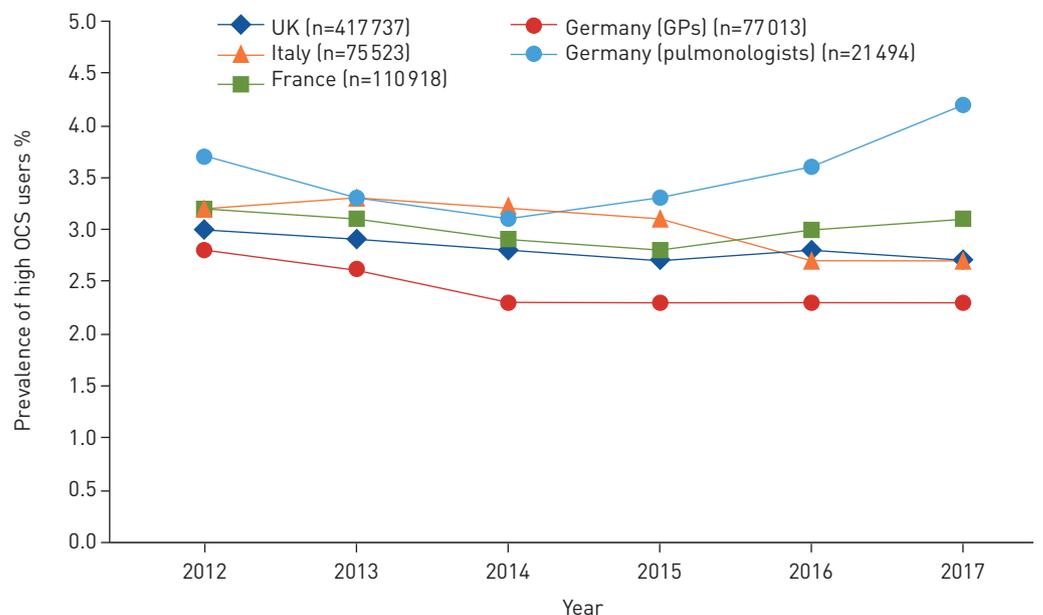


FIGURE 4 Percentage of patients with asthma identified as high oral corticosteroids (OCS) users by calendar year. UK: United Kingdom; GPs: general physicians.

TABLE 2 Prescriptions and daily oral corticosteroid (OCS) dosage

	UK		Italy		France		Germany (GPs)		Germany (pulmonologists)	
	High OCS	Low OCS	High OCS	Low OCS	High OCS	Low OCS	High OCS	Low OCS	High OCS	Low OCS
Patients n	28 774	95 748	6 679	22 503	9 751	38 834	4 330	6 571	1 712	2 279
Number of OCS prescriptions per year of follow-up	3.0±3.4	0.6±0.7	1.7±2.1	0.5±0.6	1.5±1.3	0.6±0.6	1.2±1.5	0.5±0.6	1.0±1.3	0.5±0.6
Number of OCS prescriptions per year of follow-up										
≥1	72.2	15.5	51.1	12.9	57.5	17.9	35.5	14.4	33.1	10.8
≥2	43.6	3.6	24.2	3.2	22.7	4.3	18.1	4.1	14.5	3
≥3	28.6	1.3	14.5	1.4	10.1	1.4	10.7	1.4	7.4	1.4
≥4	21.1	0.6	9.8	0.6	5.0	0.4	6.1	0.4	3.8	0.3
Median gap days between prescriptions[#]	25.1±7.6		26.9±6.8		27.8±5.5		77.7±24.3		85.5±20.5	
Average daily OCS dosage mg										
Mean±SD	2.2±3.2	0.3±0.3	1.3±1.8	0.2±0.2	1.5±2.7	0.3±0.5	2.2±3.3	0.3±0.3	1.8±2.6	0.3±0.4
Median	1.1	0.2	0.7	0.1	0.9	0.2	1.0	0.2	0.9	0.2
Average daily OCS dosage[¶]										
<2.5 mg	76.4	99.7	86.8	99.9	87.7	99.4	75.7	99.5	79.1	99.2
2.5–5 mg	12.6	0.3	8.5	0.1	8.3	0.5	13.2	0.5	12.9	0.8
5–7.5 mg	0	0	3.0	0	1.9	0	5.2	0	4.1	0
≥7.5 mg	0	0	1.7	0	2.1	0	5.9	0	3.9	0

Data are presented as mean±SD or %, unless otherwise stated. UK: United Kingdom; GPs: general physicians. [#]: during the first-year post-high OCS use date; [¶]: in the UK, the percentages of patients receiving average daily OCS dosages of 5.0–5.7 mg and ≥7.5 mg are suppressed because of small-count rules to prevent disclosure of an individual's information.

The variation in frequency of OCS prescriptions may have resulted from differences in prescribing practices across countries [27, 28], types of data used (e.g. administrative claims, electronic medical records, pharmacy prescriptions) and the definition of high OCS users (e.g. based on daily dosage, duration of prescription and number of refill prescriptions, as well as prescription cut-offs). Despite

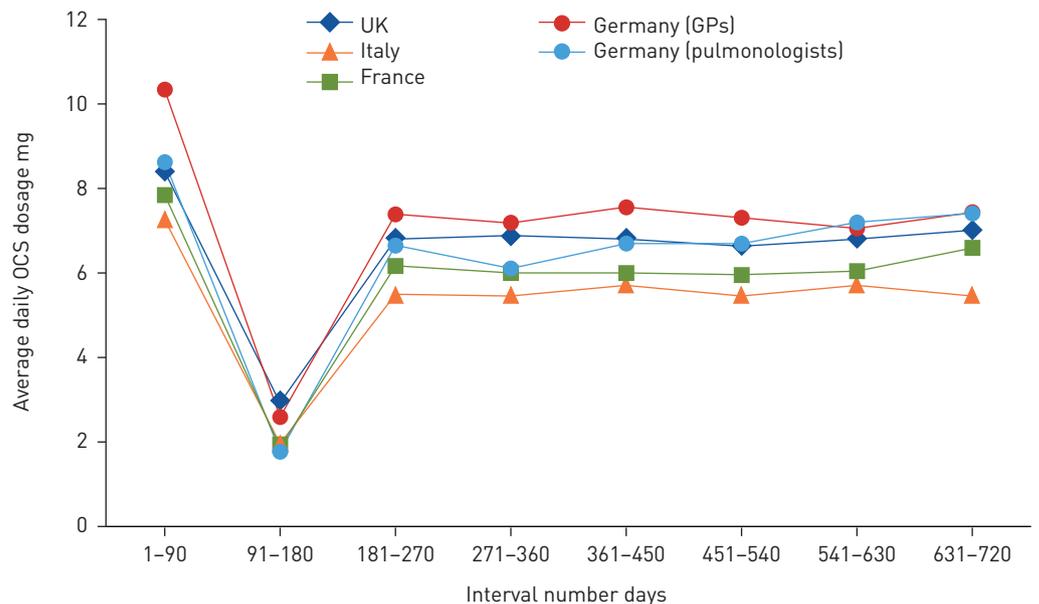


FIGURE 5 Average daily oral corticosteroid (OCS) dosage over time for patients identified as high OCS users. UK: United Kingdom; GPs: general physicians. Number of days is relative to high-user date (day 1). Patients are eligible for inclusion if they are identified as high OCS users at the beginning of or during the specific 90-day interval.

variations in frequency of overall OCS prescription, the percentage of patients classified as high OCS users (≥ 450 mg in 90 days) at any time during the study follow-up remained stable at 6–9%, and annual prevalence was stable at $\sim 3\%$ across the included European countries. The annual prevalence of high OCS use observed in our study is less than the 8.2% prevalence of chronic OCS use reported in a similar study in the United States that defined chronic OCS use as ≥ 2.5 mg-day⁻¹ over 1 year [23]. It is noteworthy that for this study, we selected a high OCS use definition (≥ 450 mg in 90 days) corresponding to an average daily OCS dosage ≥ 5 mg, which is known to be associated with an increased risk of OCS-related complications [13, 15, 21–23].

Annual prevalence of high OCS use has remained stable since 2012, indicating little change in OCS prescribing patterns despite the recent introduction of OCS-sparing therapies. Additionally, it is possible that prescribing patterns shifted from maintenance OCS to more short-term therapy or *vice versa*, which may have resulted in stable prevalence of high OCS use according to our study definition. Although a robust distinction between maintenance and short-term therapy was beyond the scope of this study, it is possible that other methods could have made this distinction.

Although few patients in the UK were prescribed an average daily OCS dosage > 5 mg, a greater percentage of UK patients received three or more OCS prescriptions per year compared with other countries. Seemingly, UK patients were prescribed lower dosages across more prescriptions compared with the other countries in this study. In contrast, Germany had the least number of prescriptions but similar average daily dosages compared with the other countries, suggesting fewer prescriptions with larger dosages per prescription than other countries. This probably reflects differences in the healthcare systems and reimbursement practices between the studied countries. A longitudinal UK study found that incidence of adverse outcomes of systemic corticosteroid use increased with cumulative OCS exposure, starting at a cumulative annual dosage as low as 0.5 g [15]. In our study, overall OCS exposure for both high and low OCS users was relatively consistent across all countries. The average daily dosage of ~ 1.5 –2 mg for high OCS users is equivalent to a cumulative annual OCS dosage of 0.55–0.73 g, suggesting that high OCS users with asthma may be at high risk of OCS-related adverse effects. In all countries, patients who continued to meet the definition of high OCS use had a daily exposure of 5.5–7.5 mg, equivalent to cumulative annual dosages of 2–2.7 g. It is unfortunate that a group of patients continued to be exposed to a stable and significant degree of OCS for a prolonged period (up to 2 years) (figure 5), placing them at particularly high risk of adverse effects during this period and possibly beyond. The lesser daily OCS dosage during the second 90-day interval (*i.e.* days 91–180) was the result of including all patients who met the high-use criterion in the previous (*i.e.* the first 90-day interval) or current interval in the denominator, while a percentage of the former decreased OCS use during the second 90-day interval.

In this study, OCS users, particularly high OCS users, were, in general, consistently older and more often female across countries compared with non-OCS users. In addition, high OCS users often had more severe asthma (GINA steps 4–5) and more baseline exacerbations compared with low OCS users. This was to be expected considering the recommendations for prescribing maintenance OCS to patients with severe, uncontrolled asthma, which would more likely result in patients meeting the high-use definition compared with patients with milder asthma for which OCS would most likely be prescribed for occasional exacerbations [23, 29]. Although this study did not address the association between OCS use and OCS-related comorbidities, the percentage of high OCS users with comorbidities was greater than the percentage of low OCS users with comorbidities, confirming the knowledge that OCS use is associated with significant comorbidities for patients [11–15].

The main strengths of the current study are the inclusion of a large number of patients with asthma from multiple data sources across different European countries and the use of standard definitions and algorithms for OCS exposure, disease severity and clinical outcomes. The selected data sources are representative samples of the national populations of each country examined, and the data collected should reflect routine clinical practices in each country. Despite differences in asthma treatment practices [27, 28, 30], reimbursement guidelines, treatment or referral incentives, national healthcare practices [31] and health delivery systems [32], we found consistent patterns of OCS prescriptions across the included countries, which adds confidence to our findings. As with many similar studies, having a recorded prescription does not mean the patient took the medication. Therefore, we could have overestimated OCS exposure. In addition, OCS exposure could have been overestimated because OCS prescriptions were not recorded with the medical condition being treated. To mitigate this risk, we excluded patients with several diseases that are commonly treated with OCS. Nor could we account for stockpiling of medication, which could have led to underestimation of exacerbations. Furthermore, with the lack of a consensus definition for high OCS use in the scientific community, it is difficult to compare our findings with those from studies with other definitions. Alternative approaches to defining high OCS use include using the number of OCS prescriptions within a specific period or OCS use duration. The primary care databases did not

contain information on biologic therapies, which limited the possibility of describing OCS use in the context of OCS-sparing therapies.

In summary, we found that OCS prescriptions for asthma management are common in France, Germany, Italy and the UK. This study highlights that a proportion of patients with asthma are exposed to high daily OCS dosages over a long period of time, and a smaller number of patients with mild disease are high OCS users. Taken together, these findings suggest suboptimal asthma management in all study countries. Further research is needed to understand the reasons for continued OCS prescribing, despite the evolving knowledge in this field and the availability of alternative OCS-sparing therapies. Considering the 2019 GINA guidelines, these findings provide a European benchmark for future reduction of OCS prescriptions in asthma management.

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Conflict of interest: T.N. Tran is an employee of AstraZeneca. E. King was external consultant with IQVIA at the time these analyses were conducted. R. Sarkar was an employee of IQVIA at the time these analyses were conducted. C. Nan is an employee of AstraZeneca and shareholder in GlaxoSmithKline. A. Rubino was an Evidera employee at the time these analyses were conducted, and is now an AstraZeneca employee. C. O'Leary is an employee of IQVIA. R. Muzwidzwa is an employee of IQVIA. L. Belton is contractor for AstraZeneca Cambridge; Imperial College received consulting fees from AstraZeneca. J.K. Quint is an employee of Imperial College London; IQVIA received payment from AstraZeneca for the conduct of this study.

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