Asthma drug ratios and exacerbations: claims data from universal health coverage systems

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ABSTRACT In claims data, controller-to-total asthma drug ratios may reflect adequacy of disease management. We verified whether asthma patients with high ratios ($\geqslant$50%) experienced fewer asthma-related outcomes. Two ratios were studied: that of the inhaled corticosteroids to total asthma drug (ICS/R03) and that of the inhaled corticosteroids plus leukotriene antagonist receptors-to-total asthma drug (ICS+LTRA/R03).

Patients aged 13–40 years, with $\geqslant$3 respiratory drugs dispensed prescriptions in 2005 were selected from the French national claims data. After excluding null ratios, two groups were defined according to ratio values in 2007: low-ratio group (0%$<$ratio$<$50%) and high-ratio group (ratio $\geqslant$50%). For both ratios, asthma-related outcomes and medical-resource utilisation were compared between groups.

Of 2162 patients (mean age 27 years and 52% female), patients with non-null ratios were 81% and 85% for ICS/R03 and ICS+LTRA/R03 ratios, respectively. Patients with high ratios were less likely to receive oral corticosteroids than those in the low-ratio group (relative risk 0.79, 95% CI 0.72–0.88, and 0.80, 95% CI 0.72–0.88, for ICS/R03 and ICS+LTRA/R03, respectively). High ratio groups also presented fewer asthma-related hospitalisations. Significant negative correlations were also observed for both ratios, when studied quantitatively, according to patients' dispensed level of oral corticosteroids in 2007.

In claims data, both ICS/R03 and ICS+LTRA/R03 $\geqslant$50% were related to fewer asthma-related outcomes. Ratios should be explored to identify asthma patients at risk of exacerbations. Low ratios can be considered as risk factors of exacerbation whatever the underlying cause.

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Introduction

Regular use of controller medications remains a key issue in asthma disease management. Observational studies have shown that inconsistent use of controller medications has a direct impact on medical resource utilisation [1, 2]. One promising approach to identifying patients with inconsistent controller use is through claims data, which include exhaustive information on reimbursed medical resource utilisation in the insured population. Using these data to identify patients at risk of insufficient control of chronic diseases, such as asthma, may help improve disease management [3].

Authors have investigated ratios measuring the proportion of dispensed controllers in total asthma therapy as a marker of the quality of care [4, 5]. Studies using these ratios have consistently shown higher levels of asthma-related hospital admissions and emergency room visits for patients with lower ratios [6]. The impact of ratios on oral corticosteroids (OCSs) has been less extensively explored.

Furthermore, unlike controller-to-total asthma drug ratio, the inhaled corticosteroid (ICS)-to-total asthma drug ratio (ICS/R03, where R03 codes for asthma therapy according to the Anatomical Therapeutic and Chemical (ATC) classification system) has been poorly studied. It is also unclear whether considering only ICSs or both ICS and leukotriene receptor antagonist (LTRA) agents in the numerator ratio yield concordant results.

Lastly, previous studies have relied on data from health management organisations, on specific populations and typically salaried persons with specific processes of care, and there is a need to replicate such studies in other healthcare systems with universal coverage, including patients with a high level of deprivation.

We investigated whether low ICS/R03 ratios, which suggest less consistent ICS exposure for a given disease severity, were related to more frequent asthma-related exacerbations and greater overall medical resource utilisation. Parallel investigations were conducted for ICS+LTRA/R03 ratio to verify whether both ratios yielded concordant findings. For each ratio, we also looked for differences in patient characteristics and controller therapy between the high and low ratio groups.

Methods

Study design and timelines

A historical cohort (2005–2008) was obtained from the Permanent Sample of Health Insurance Beneficiaries (EGB), a 1/97th random sample of the French National Claims Data Beneficiaries with individual linkage between ambulatory and hospital care. We selected patients aged 13–40 years on January 1, 2005, with continuous follow-up between 2005 and 2008, and $\geqslant$3 asthma drugs (R03 code) dispensed in three different quarters during 2005. The year 2006 was used to assess patients' asthma severity. Severity was approached by the total number of asthma drug classes (including OCSs) dispensed in 2006. We conducted analyses in 2007 and 2008 (fig. 1). This observational study was conducted on anonymised claims data, and the National Informatics and Liberty Committee has delivered an overall authorisation to use EGB data for research purposes.

Data collected

Patient characteristics were age, sex, long-term disease status and free-access-to-care status. Long-term disease status allows severe patients to receive therapy without advancing payment in pharmacies. Free-access-to-care status enables patients with socioeconomic difficulties to receive free medical care. Reimbursed therapy included asthma medications, OCSs and antibiotics. Medical contacts (family physicians and respiratory physicians) were counted in the database. We identified hospitalisations with asthma as primary or secondary diagnosis. The primary diagnosis corresponds to the disease that incurred the majority of the resources used during a given hospital stay.

ICS/R03 and ICS+LTRA/R03 ratios

The ratio of the number of ICS units (whether in fixed combination with long-acting β-agonists (LABAs) or not) to the overall units of asthma drugs (R03 ATC classification) dispensed in 2007 was computed. Asthma drug therapy included ICSs, LABAs, LABA–ICS fixed combinations, short-acting β-agonists (SABAs), LTRAs, anticholinergics, anticholinergics–SABA fixed combinations, xanthines and cromones (R03 according to ATC classification). Based on this ICS/R03 ratio in 2007, three groups were defined: 0% (no ICS), 0%$<$ ratio$<$50% (low ratio) and ratio $\geqslant$50% (high ratio). The choice of the 50% threshold was based on previous studies using controller-to-total respiratory drug ratios [4]. The ratio of ICS plus LTRA to total asthma drug (ICS+LTRA/R03), including both LTRA and ICS units in the numerator, was also computed and studied.

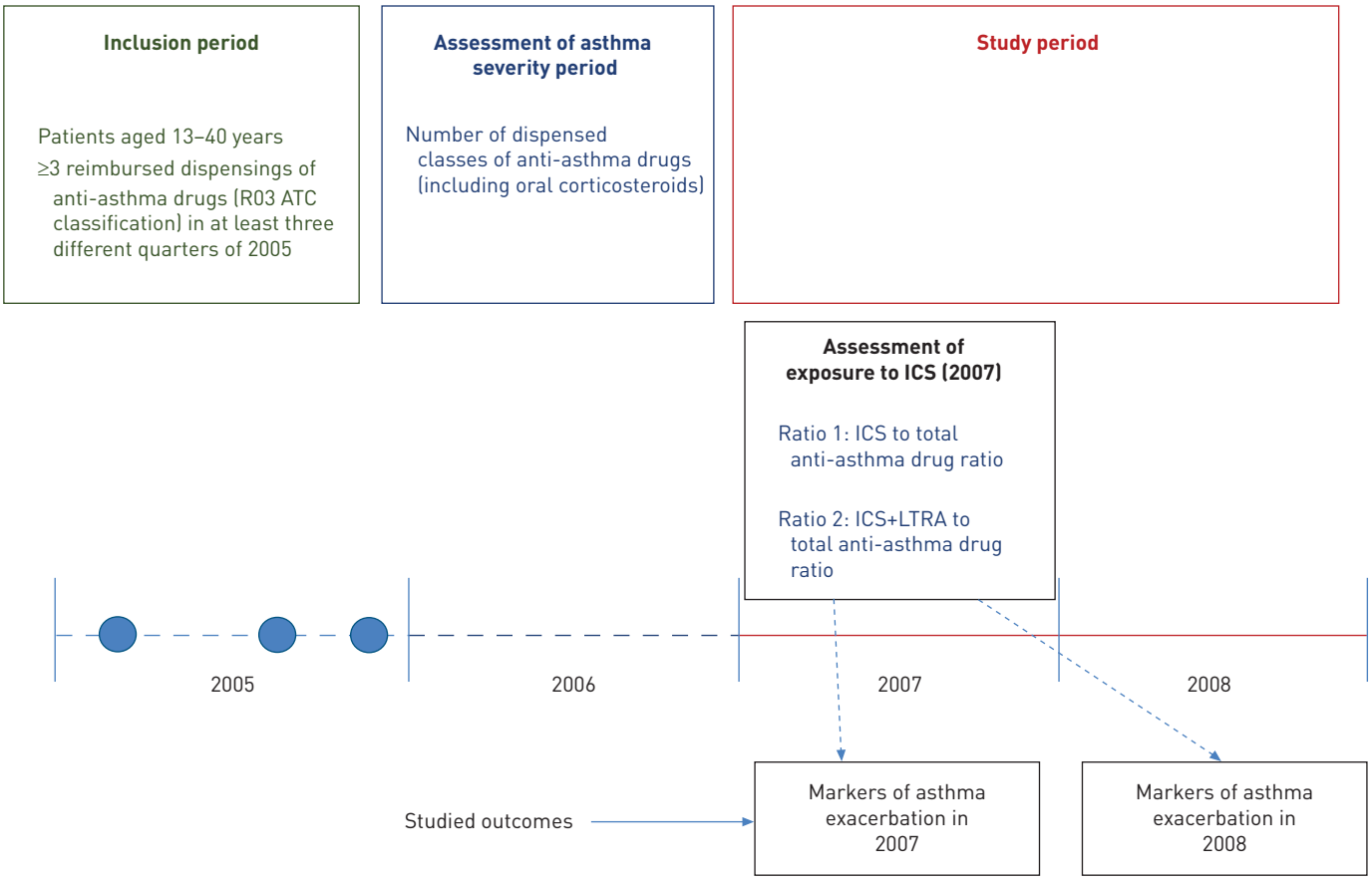

FIGURE 1 Study design. ICS: inhaled corticosteroid; R03 ATC: R03 coding for asthma therapy according to the Anatomical Therapeutic and Chemical classification system; LTRA: leukotriene receptor antagonist.

Outcome criteria

Outcomes were proxies for asthma exacerbations in 2007 and 2008 [7]. The main outcomes were dispensing of the drug classes commonly used to treat asthma exacerbations, *i.e.* OCSs (percentage of patients with at least one drug dispensed and mean number of prescriptions dispensed). The annual number of visits to a family physician was also investigated.

Other criteria were hospitalisations for asthma as primary diagnosis and hospitalisations for asthma as primary or secondary diagnosis. Percentages of patients with at least one hospitalisation, the number of stays per patient and the hospitalisation-related costs were studied in 2007 and 2008. Levels of SABAs dispensed were not used as an outcome, as they were included in the denominator of ICS/R03 ratios.

Analyses

Analyses were conducted in parallel for ICS/R03 and ICS+LTRA/R03 ratios. For both ratios, all analyses were restricted to low- and high-ratio groups (no null-ratio values).

First, baseline characteristics and controller therapy dispensed in 2007 were compared between groups. The outcomes were compared between groups in 2007 and in 2008 using standard Chi-squared test (Fisher's exact test when appropriate), ANOVA or Wilcoxon–Kruskal–Wallis test.

Then, multivariate Poisson models were run to compute the risks of receiving OCSs in 2007 (at least one dispensed prescription) for both ratios. It was verified whether patients in the high-ratio group presented lower risks of receiving OCSs in 2007 compared with those in the low-ratio group. Models were adjusted for age, sex, long-term disease status, free-access-to-care status, dispensing of at least one LABA–ICS fixed combination in 2007, and ratio group in 2007 (high *versus* low). Complementary models were also computed with an additional adjustment for the baseline severity variable. The aim was to verify the extent to which differences in outcomes between groups were due to factors other than baseline severity. In the absence of clinical and spirometric data, adjustment for baseline severity was approached by the number of

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dispensed respiratory drug classes in 2006, including OCSs (0–1, 2–3 and >3) [8]. Similar analyses were also conducted for receiving OCSs in 2008.

Owing to their low frequency, asthma-related hospitalisations were not studied in multivariate analyses. All analyses were performed on SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Additional analyses with quantitative ratios

Additional analyses with quantitative ratios were performed for ICS/R03 and ICS+LTRA/R03 ratios. In 2007, both ratios were studied according to the number of dispensed units of OCS in 2007, and then in 2008. Univariate and multivariate Poisson regressions were conducted. Multivariate analyses were adjusted for the same cofactors as those in the main analyses.

Results

Descriptive results

Both ratios were computed for 2162 patients (mean age 27 years and 52% female) who met the inclusion criteria, with at least one asthma drug dispensed in 2007. The proportions of patients in the no-ICS (null ratio), and low- and high-ICS ratio groups were 19%, 36% and 45%, respectively. Respective percentages for ICS+LTRA/R03 ratios were 15%, 25% and 59%. After excluding null ratios, analyses were conducted in 1758 and 1827 patients for ICS/R03 and ICS+LTRA/R03 ratios, respectively.

Patient characteristics and dispensed controller therapy according to the ICS/R03 and ICS+LTRA/R03 ratios

For both ratios, patients in the low-ratio groups more frequently had free-access-to-care and long-term-disease status (table 1). Conversely, there were no significant differences by either sex or age. Compared with the low-ratio groups, patients in the high-ratio groups received significantly more ICS units, particularly as LABA–ICS fixed combinations; received fewer LABAs (not combined); and had fewer primary care consultations in 2007, while they tended to visit more respiratory physicians, although this was not significant (table 1). Patients in the ICS/R03 high-ratio group received fewer LTRAs than those in the ICS/R03 low-ratio group. This was reversed for the ICS+LTRA/R03 ratio.

Asthma-related outcomes according to ICS/R03 and ICS+LTRA/R03 ratios

Compared with the low-ratio groups, patients in the high-ratio groups had fewer dispensed prescriptions of OCSs in 2007 and in 2008 (table 2). They also experienced fewer asthma-related hospitalisations.

Multivariate analyses

Patients with a high ratio had a significantly lower risk of receiving OCSs in 2007 compared with those in the low-ratio group. For both ratios, the association persisted in the complementary models, even after adjustment for baseline severity. Similar trends, although less marked, were also observed for receiving OCSs in 2008 (table 3).

Additional analyses with quantitative ratios

Significant decreases in mean ratios were observed with the number of dispensed units of OCSs in 2007 for both ICS/R03 and ICS+LTRA/R03 ratios. Similar downward trends, although less marked, also appeared with the OCSs dispensed in 2008. Results of regression models of ratios with OCS dispensing in 2007 remained significant in multivariate analyses (table 4).

Discussion

In our sample of 2162 patients, ICS/R03 and ICS+LTRA/R03 ratios were non-null ratios in 81% and 85%, respectively. In those with non-null ratios, the ICS/R03 high-ratio group accounted for 55% of patients. It accounted for 70% of the ICS+LTRA/R03 ratio. Overall, patients in the low-ratio groups experienced more use of OCSs and more asthma-related hospitalisations than those in the high-ratio group (table 2).

For both ratios, the risk of receiving OCSs in 2007 was significantly lower in the high-ratio group compared with the low-ratio group, even after adjustment for asthma severity (table 3). The complementary models indicate that the potential difference in asthma severity between groups can explain only in part the lower risks of outcomes in the high ratio group. Likewise, patients with a low ratio experienced more asthma-related hospitalisations.

Additional analyses showed a limited downward variation of quantitative ratios with patients' level of dispensed OCSs, although results were statistically significant in univariate analyses (table 4).

TABLE 1 Patients' characteristics according to ICS/R03 drug ratio in 2007

	ICS/R03			ICS+LTRA/R03		
	Low-ratio group[#]	High-ratio group[¶]	p-value	Low-ratio group[+]	High-ratio group[§]	p-value
Subjects n	792	966		548	1279	
Mean age[f] years	27.2	28.1	0.04	27.7	27.4	0.59
Males %	45.4	47.7	0.34	44.0	48.2	0.10
Long-term disease status[##] %	12.6	7.4	0.0003	11.7	8.7	0.04
Free-access-to-care status[¶¶] %	18.3	13.8	0.009	18.8	14.4	0.02
Medical resource utilisation in 2007						
⩾1 visit to a respiratory physician[++] %	2.9	4.4	0.09	2.6	4.2	0.08
Mean visits to family physician	7.0	5.7	0.0002	7.3	5.7	<0.0001
Controllers						
ICS (other than LABA–ICS fixed combination)						
⩾1 unit %	48.4	30.0	<0.0001	53.1	30.0	<0.0001
Mean number of dispensed units	2.02	0.98		2.12	1.09	<0.0001
LABA–ICS fixed combination						
⩾1 unit %	65.5	81.7	<0.0001	58.2	77.3	<0.0001
Mean number of dispensed units	3.04	4.79	<0.0001	2.40	4.46	<0.0001
Mean number of ICS units (any type)	5.06	5.77	<0.0001	4.52	5.55	<0.0001
LABA (not in LABA–ICS fixed combination)						
⩾1 unit %	28.7	6.6	<0.0001	33.3	8.9	<0.0001
Mean number of dispensed units	1.91	0.23	<0.0001	2.30	0.40	<0.0001
LTRA						
⩾1 unit %	45.3	11.6	<0.0001	21.0	33.2	<0.0001
Mean number of dispensed units	2.77	0.39	<0.0001	0.90	1.95	<0.0001

ICS: inhaled corticosteroid; R03: Anatomical Therapeutic and Chemical classification system code for asthma therapy; LTRA: leukotriene receptor antagonists. [#]: 0%<ICS/R03<50%; [¶]: ICS/R03 ⩾50%; [+]: 0%<ICS+LTRA/R03<50%; [§]: ICS+LTRA/R03⩾50%; [f]: age in 2005; [##]: patients are dispensed their asthma therapy without advancing the money at the pharmacy; [¶¶]: patients with socioeconomic difficulties receive free care; [++]: respiratory physicians with a private consulting room (dispensing resulting from prescriptions from hospital respiratory physicians cannot be identified in the data).

Overall, our main findings are in line with previous studies that reported fewer asthma-related hospitalisations and emergency room visits when the controller-to-total asthma drug ratio was ⩾50% [4, 5]. A lower risk of belonging to the high ratio group was found in controller-treated patients with at least two refills of OCSs (OR=0.89, 95% CI 0.82–0.98) [9]. However, SCHATZ *et al.* [10] identified a significantly lower risk of receiving OCSs only at a 90% threshold. The exclusion of null -ratios and potential differences in prescribing habits between countries may account for these differences.

Indeed, better asthma control and quality of life have been found by SCHATZ *et al.* [11] in patients with a controller-to-total asthma drug ratio of ⩾50%. In addition to lower exacerbation-related medical resource utilisation during the same calendar year, a high ICS/R03 ratio seems to predict outcomes in the following year, reinforcing a potential role for this marker. However, caution is needed given the more limited differences observed between groups with outcomes measured in 2008 (table 2).

Other differences between high- and low-ratio users are noteworthy. The number of medical visits was higher in patients with low ratios, possibly due to more frequent unscheduled visits. As expected, dispensed levels of ICS were higher in the high-ratio groups, although these differences between low- and high-ratio groups were not large (table 1). In addition, patients with high ratios tended to receive more LABA–ICS fixed combinations (table 1). This finding has also been observed by BRODER *et al.* [9]. Patients under LABA–ICS fixed combinations are less likely to require SABAs and do not use LABAs, which would decrease the ratio denominator. More regular dispensing of LABA–ICS fixed combinations compared with ICS alone has also been observed in claims data [12–14]. However, multivariate models clearly indicated that patients in the high-ratio groups were less likely to receive OCSs, irrespective of concomitant use of LABA–ICS fixed combinations.

The greater frequency of patients visiting specialists in the high-ratio group is in line with previous studies [9]. A better quality of care provided by respiratory physicians could account for a higher ICS dispensation.

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TABLE 2 Asthma-related outcomes according to ICS/R03 and ICS+LTRA/R03 ratios in 2007

	ICS/R03			ICS+LTRA/R03		
	Low-ratio group[#]	High-ratio group[¶]	p-value	Low-ratio group[+]	High-ratio group[§]	p-value
Subjects n	792	966		548	1279	
Oral corticosteroids						
In 2007						
At least one unit dispensed %	53.3	42.2	<0.0001	54.7	43.6	<0.0001
Mean dispensed units[f]	1.2	0.9	0.009	1.3	0.9	0.0004
In 2008						
At least one unit dispensed %	46.2	39.6	0.006	45.4	41.0	0.08
Mean dispensed units[f]	1.2	0.8	0.0006	1.3	0.8	0.0002
Asthma-related hospitalisations (primary diagnosis)						
In 2007						
Hospitalised %	1.9	0.2	0.003	2.2	0.5	0.001
Mean number of stays[f]	0.030	0.003	0.001	0.029	0.009	0.02
In 2008						
Hospitalised %	1.4	0.2	0.004	1.8	0.2	0.0006
Mean number of stays[f]	0.024	0.002	0.0071	0.033	0.002	0.0003
Asthma-related hospitalisations (primary or secondary diagnosis)						
In 2007						
Hospitalised %	5.9	2.8	0.001	6.2	3.4	0.006
Mean number of stays[f]	0.090	0.036	0.0003	0.080	0.048	0.02
In 2008						
Hospitalised %	4.9	2.2	0.002	5.1	2.6	0.006
Mean number of stays[f]	0.070	0.027	0.001	0.076	0.032	0.001

ICS: inhaled corticosteroid; R03: Anatomical Therapeutic and Chemical classification system code for asthma therapy; LTRA: leukotriene receptor antagonists. [#]: 0%<ICS/R03<50%; [¶]: ICS/R03 ⩾50%; [+]: 0%<ICS+LTRA/R03<50%; [§]: ICS+LTRA/R03⩾50%; [f]: computed in both users and non-users.

Nonetheless, caution is required, given the low number of private-sector respiratory physicians in our data and nonsignificant results.

Patients with free-access-to-care status were more common in low-ratio groups, suggesting that social difficulties may be an obstacle to reaching high ratios. Patients with long-term disease status were also more common among low-ratio users, suggesting potentially more severe asthma in this group with high levels of medical resource utilisation. These points require confirmation in new studies.

The ICS/R03 and ICS+LTRA/R03 ratio groups differed as to distribution, using the 50% cut-off value. In particular, patients using both ICS and LTRA were more likely to belong to the ICS/R03 low-ratio group, which was not the case for the ICS+LTRA/R03 ratio. Expectedly, the ICS+LTRA/R03 high-ratio group tended to receive more LTRA than the low-ratio group, while it was the other way round for the ICS/R03 ratio (table 1). Further investigations are needed to better understand the differences between both ratios. Our ICS+LTRA/R03 ratio was close to the defintion of SCHATZ *et al.* [4], although not identical. For instance, cromones and xanthines were not included in the numerator, while the denominator comprised all LABAs, whether or not as LABA–ICS fixed combinations. However, cromones and xanthines are used only marginally. Although there were still LABA users (not combined) at the time of the study (table 1), their proportion has noticeably dropped in France in recent years (personal communication; E. Van Ganse, Unité de Pharmacoépidémiologie, CHU-Lyon, Faculté d'Odontologie, Université Claude Bernard, Lyon, France). Nevertheless, despite these differences in definitions, concordant conclusions were obtained with previous studies, indicating a robustness of these markers of quality of care.

Besides simplicity of computation, an advantage of using the ratios is the consistency of the benefits observed in the high-ratio groups (⩾50%) [6], even when the numerator is limited to ICS therapy. The presence of all asthma therapy in the denominator partly accounts for asthma severity, ensuring robustness to an indication bias.

TABLE 3 Risks of receiving one or more dispensed prescription of OCSs in case of a high ratio value (⩾50%) for ICS/R03 (models 1 and 2) and for ICS+LTRA/R03 (models 3 and 4) multivariate models

	ICS/R03		ICS+LTRA/R03	
	Model 1	Model 2	Model 3	Model 4
Subjects n	1758	1758	1827	1827
Initial multivariate model[#]				
Low ratio (0%<ratio<50%)	1.00	1.00	1.00	1.00
High ratio (ratio ⩾50%)	0.79 (0.72–0.88)	0.84 (0.76–0.94)	0.80 (0.72–0.88)	0.89 (0.80–1.00)
Complementary model with additional adjustment for baseline severity[¶]				
Low ratio (0%<ratio<50%)	1.00	1.00	1.00	1.00
High ratio (ratio⩾50%)	0.89 (0.80–0.98)	0.92 (0.82–1.04)	0.85 (0.77–0.94)	0.94 (0.84–1.06)

Data are presented as relative risk (95% CI). Models 1 and 3: risk of receiving ⩾1 dispensed prescription of oral corticosteroids (OCSs) in 2007; models 2 and 4: risk of receiving ⩾1 dispensed prescription of OCSs in 2008. ICS: inhaled corticosteroid; R03: Anatomical Therapeutic and Chemical classification system code for asthma therapy; LTRA: leukotriene receptor antagonist. [#]: relative risk is adjusted for age (15–29, 30–35 and 35–40 years), sex, long-term disease status, free-access-to-care status, ⩾1 visit to a respiratory specialist in 2007 and ⩾1 dispensed presription of long-acting β-agonist–ICS fixed combination; [¶]: relative risk is adjusted for the same factors as [#], with an additional adjustment for baseline severity as assessed by the number of dispensed respiratory drug classes in 2006, including OCSs (0–1, 2–3 and >3 dispensed prescriptions).

Ratios could be used not only in administrative claims databases to identify asthma patients at risk of exacerbations, but could be of interest for identifying such patients in daily medical practice, *e.g.* from computerised medical records.

Some limitations must be acknowledged. Hospitalisations with asthma were uncommon, precluding models with these outcomes. It is noteworthy that our specific asthma-related hospitalisation rate was consistent with those previously reported by the National Health Service in the UK [15]. Although OCSs are

TABLE 4 Mean ratio values according to OCS dispensing levels in 2007 and in 2008

	OCS units dispensed n				Univariate Poisson regression[#]	Multivariate Poisson regression[#,¶]
	0	1	2	⩾3		
OCS units dispensed in 2007						
ICS/R03 ratio						
Number	928	428	202	199		
Mean %	56.1	53.1	49.9	46.5	β= -0.0055, z= -4.88, p<0.0001	β= -0.0026, z= -2.15, p=0.03
ICS+LTRA/R03 ratio						
Number	970	443	209	204		
Mean %	64.8	61.5	59.7	56.3	β= -0.0048, z= -4.45, p<0.0001	β= -0.0032, z= -2.86, p=0.0042
OCS units dispensed in 2008						
ICS/R03 ratio						
Number	1009	388	187	173		
Mean %	54.9	53.3	51.8	49.0	β= -0.0033, z= -2.69, p=0.007	β= -0.0012, z= -0.89, p=0.37
ICS+LTRA/R03 ratio						
Number	1053	403	195	175		
Mean %	63.3	63.0	61.0	57.7	β= -0.0027, z= -2.32, p=0.02	β= -0.0016, z= -1.34, p=0.18

OCS: oral corticosteroid; ICS: inhaled corticosteroid; R03: Anatomical Therapeutic and Chemical classification system code for asthma therapy; LTRA: leukotriene receptor antagonist. [#]: z stands for statistical test-value. [¶]: adjusted for age (15–29, 30–35 and 35–40 years), sex, long-term disease status, free-access-to-care status, ⩾1 visit to a respiratory specialist in 2007, ⩾1 dispensing of LABA–ICS fixed combination and baseline severity as approached by the number of dispensed respiratory drug classes in 2006, including OCSs (0–1, 2–3 and >3 dispensings).

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recommended in epidemiological studies as outcomes of severe asthma exacerbation [7], they may not be specific for asthma. Additionally, OCSs may be prescribed preventively to patients prior to episodes of exacerbation. However, despite these limitations, significant differences were noted for OCS dispensing levels between ratio groups (tables 3 and 4).

Our ratios did not take into account the number of doses per inhaler or the potency of ICS drugs. SCHATZ *et al.* [10] computed a more elaborate ratio including these variables. However, the basic ratio turned out to be more discriminating for asthma-related outcomes [10]. Severe patients, at higher risk of exacerbations tended to receive more potent ICSs and would more easily qualify as having a higher weighted ratio. Hence, more frequent outcomes would be expected in the high-ratio group when using weighted ratios, which could decrease the difference between low- and high-ratio groups. Additionally, basic ratios are easier to use in practice. Caution is also needed, given the absence of clinical data in claims data.

Also, our sample may not be representative of the overall population of asthma patients as it consists of a subgroup of selected patients with regular follow-up, accounting for 1.3% of patients aged 13–40 years in the EGB data. Less frequently treated asthma patients, potentially at high risk of adverse outcomes, were not included.

Finally, to define a high ratio, we used the same cut-off ($\geqslant$50%) as SCHATZ *et al.* [10], as this threshold has yielded consistent conclusions for various outcomes and facilitates comparisons with previous studies. A simple and unique threshold value, such as 50%, is desirable.

Our findings have several implications. Unlike private insurance data, a noticeable advantage of the French claims data lies in their representativeness of the French population, and our data confirm the interest of ratios in non-US healthcare systems. Our findings also support a role for both ICS/R03 and ICS+LTRA/R03 ratios computed from claims data to detect patients potentially at risk of exacerbations. Ratios, independent of the underlying levels of severity/control of the disease and mechanisms, could be used in public health and patient management as a tool to identify patients at higher risk of exacerbation.

Due to the paucity of patient characteristics and clinical data in claims databases, it is difficult to further explain differences between low- and high-ratio groups for medical and personal characteristics and, notably, from a socioeconomic point of view.

Our ability to identify a higher level of OCS dispensing in the case of low ratio using the 50% threshold does not mean that this value is the most discriminative value for this outcome. The next step of methodological investigations should be the determination of the optimal threshold for OCS dispensing, for both ratios. Another area of research of interest would be the identification of the determinants of such low ratios in a prospective design.

More generally, studying the impact of the ratios with complementary levels of drug exposure (prescriptions, dispensings and actual patient use) could shed light on the reasons for inconsistent use of ICS in asthma management. A low ICS/R03 ratio may be due to irregular dispensings of ICS, *e.g.* as a result of patients' incomplete adherence to prescribed therapy or irregular prescription of ICSs by physicians [16, 17].

In conclusion, patients with ICS/R03 ratio or ICS+LTRA/R03 ratio $\geqslant$50% experienced fewer markers of exacerbations, most notably compared with low ICS users, suggesting improved asthma control. Ratios may not only help to identify asthma patients at risk of severe exacerbations from claims data, but they may be of help in clinical practice as a tool to assess the management of asthma.

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