

Level of Asthma Controller Therapy Before Admission to the Hospital



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What is already known about this topic? Choice of controller therapy and adherence to treatment affect the risk of future asthma severe exacerbations leading to hospitalization.

What does this article add to our knowledge? Before an asthma-related hospitalization, more than 60% of patients received little controller therapy and 4% were exposed to unbalanced use of long-acting beta agonists relative to inhaled corticosteroids.

How does this study impact current management guidelines? A significant part of asthma-related hospitalizations could be prevented with improved management.

BACKGROUND: In asthma, choice of controller therapy and adherence to treatment can affect the risk of future severe exacerbations leading to hospitalization.

OBJECTIVE: Our objective was to characterize treatment dispensation profiles before hospital admission for asthma.

METHODS: Using a 1/97th random sample of the national French claims data, patients with asthma aged 6 to 40 years were identified between 2006 and 2014. Patients with subsequent asthma-related hospitalization were selected. On the basis of controller therapy dispensed in the 12 months before admission, treatment profiles were categorized into clusters, using Ward's minimum-variance hierarchical clustering method.

RESULTS: Of 17,846 patients with asthma, we identified 275 patients (1.5%) with an asthma-related hospitalization. Three distinct clusters were identified. The first cluster (63.6%) included patients with few dispensations of any controller medication (<1 unit). The second cluster

(32.4%) consisted of patients with frequent dispensations of long-acting beta agonists (LABAs)/inhaled corticosteroids (ICS) in fixed-dose combinations. The third cluster (4%) comprised patients receiving free combinations of ICS and LABAs, with more dispensations of LABAs than of ICS. **CONCLUSIONS:** In France, before an asthma-related hospitalization, more than 60% of patients received little controller therapy and 4% were exposed to higher dispensation of LABAs than of ICS. These results indicate that a large fraction of asthma-related hospitalizations can potentially be prevented with better pharmacotherapy. © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2016;4:877-83)

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This observational study was conducted on anonymized claims data (General Sample of Beneficiaries), and the National Informatics and Liberty Committee has delivered an overall authorization to use General Sample of Beneficiaries data for research purposes. This study was performed after approval by the Institute of Health Data (Institut des Données de Santé, approval 94, September 9, 2014). Participants' consent was not obtained, but the presented data are anonymized and risk of identification is low.

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Abbreviations used

COPD-chronic obstructive pulmonary disease
EGB-General Sample of Beneficiaries
FDC-fixed-dose combination
GPs-general practitioners
ICD-10-International Classification of Diseases, 10th Revision
ICS-inhaled corticosteroids
LABAs-long-acting beta agonists
LTD-long-term disease
LTRAs-leukotriene receptor antagonists
OCs-oral corticosteroids
SABAs-short-acting beta agonists
SNIIR-AM-Système National d'Information Inter-Régimes de l'Assurance Maladie

Asthma remains a pivotal public health issue mainly due to inappropriate use of controllers,¹ leading to poor asthma control,^{2,3} deteriorated quality of life,⁴ and high costs for individuals and society due to medical resource utilization⁵ and loss of productivity.⁶

Preventable factors have been identified in most asthma exacerbations and deaths.⁷ In addition, despite disseminated guidelines for asthma management^{8,9} and intensive research on asthma management in primary care,¹⁰ the age-standardized prevalence rate of uncontrolled asthma, as well as asthma-related morbidity and mortality, remains high throughout Europe in all age categories.¹¹ One reason might be the inappropriate prescribing and use of asthma medication. Asthma-related hospitalizations reflect severe exacerbation,¹² due in part to inappropriate use of asthma controllers,^{13,14} and they account for a noticeable part of medical resource utilization.^{5,15}

The link between the use of inhaled corticosteroids (ICS) and the occurrence of asthma-related hospitalization has been clearly established.¹⁶⁻¹⁸ *A contrario*, the part of hospital admissions for asthma that is due to inappropriate or nonuse of ICS, is little documented. Investigating health care utilization patterns before asthma-related hospitalizations is essential for improving the quality of asthma care services and preventing new occurrences of severe exacerbation. To provide effective care, services may need tailoring to different controller use profiles.

The General Sample of Beneficiaries (EGB; 1/97th random sample of national primary and secondary care claims data) offers a snapshot of disease management in real-life conditions, for example, from recorded drug dispensations and outcomes such as hospital admissions due to severe exacerbations.¹⁹⁻²¹ The aim of the present study was to use these data to investigate the patterns of use of asthma medication, so as to distinguish one or more therapeutic profiles of patients who end up being admitted to hospitals.

METHODS

This was a population-based study of a cohort of patients identified from the EGB database, a 1/97th representative random sample of the Système national d'information inter-régimes de l'Assurance maladie (SNIIR-AM),¹⁹⁻²¹ a French nationwide population-based record of individual and anonymized data on all reimbursements for health care utilization, including therapy and outpatient medical and nursing care. No direct information on the medical indication is linked with each reimbursement, but the SNIIR-AM includes information on long-term disease (LTD) status

coded in International Classification of Diseases, 10th Revision (ICD-10) codes. LTD status allows patients to receive treatment for severe and costly conditions without out-of-pocket payment. SNIIR-AM also contains information on free-access-to-care status, which enables patients of lower socioeconomic status to receive free medical care. Information from the SNIIR-AM database and medical information from the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information) about all patients admitted to hospital in France, including discharge diagnoses coded in ICD-10 codes, medical procedures, and French diagnosis-related groups, are cross-referenced.

This observational study was conducted on anonymized data, and the National Informatics and Liberty Committee has delivered an overall authorization to use EGB data for research purposes. This study was performed after approval by the French Institute for Health Data (Institut des Données de Santé, approval no. 94, September 9, 2014).

Study population

Subjects were eligible for inclusion in the cohort if, between 2006 and 2014, they filled at least 3 dispensations for asthma-related medications (all R03 Anatomical Therapeutic Chemical codes except R03DX05, R03AC18, R03BB04, R03BB01, R03AK03, and R03AK04) and if the patients were aged between 6 and 40 years at the third dispensation. These drugs were excluded because they were used for more severe asthma (omalizumab) managed by secondary care physicians, or not used for asthma in France at the time of the study (indacaterol, tiotropium, ipratropium), or not available in France (reproterol or salbutamol and cromoglicate) within any period of 12 successive months. Patients who suffered from chronic obstructive pulmonary disease were excluded on the basis of LTD status and/or hospitalizations (ICD-10 codes J41, J42, J44, and J961), or on the dispensation of tiotropium bromide (R03BB04 Anatomical Therapeutic Chemical code). Likewise, patients with cystic fibrosis were excluded (E84 ICD-10 code). So were patients receiving omalizumab (R03DX05 Anatomical Therapeutic Chemical code) because their asthma is mostly managed in secondary care by respiratory physicians. For each patient, we defined the entry date as the date of the third dispensation of respiratory medications that resulted in case identification. Within the cohort, we selected patients who experienced asthma-related hospitalization, defined as a hospital discharge with asthma (J45 and J46 ICD-10 codes) as primary or related reason for hospitalization. The date of the first asthma-related hospitalization was defined as the index date. In line with similar studies,^{16,22} we requested at least a 12-month baseline period between the entry date and the index date, during which patients with asthma-related hospitalization were excluded to ensure that there were sufficient longitudinal data to assess drugs received before the index date. If a patient had more than 1 asthma-related hospitalization, only the first one since the entry date was used for the analyses.

ANALYSIS

All analyses were performed in SAS V.9.3 (SAS Institute, Carry, NC). Subjects were categorized by an unsupervised classification algorithm that classified patients on the basis of controller therapy recorded, that is, ICS in a single canister, long-acting beta agonists (LABAs) in a single canister, or fixed-dose combinations (FDCs) of LABAs and ICS. Drug use was assessed in the 12 months before the index date, even if patients had more than 12 months between entry and index dates.

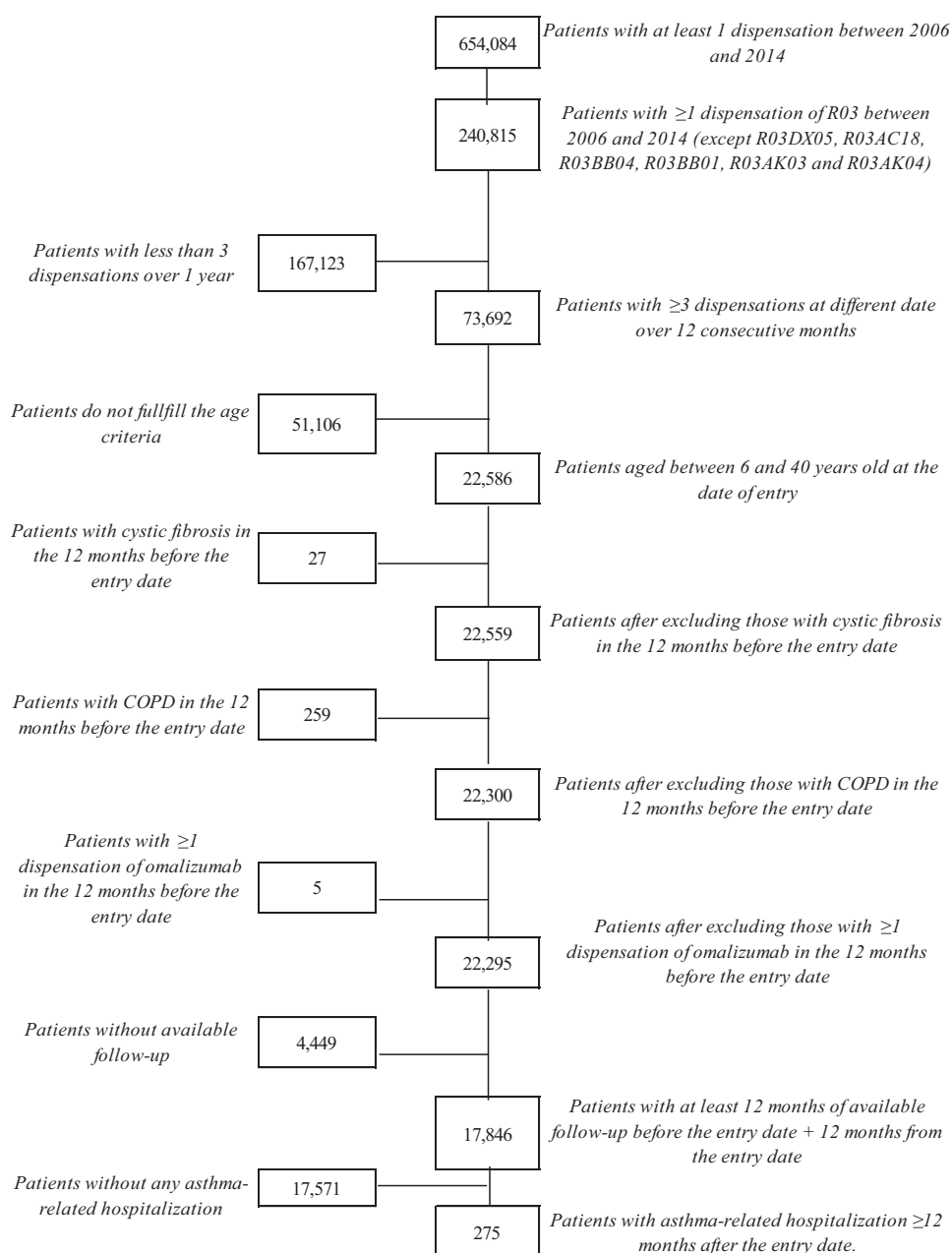


FIGURE 1. Flow chart. Between 2006 and 2014, we identified 73,692 patients with 3 or more dispensations for asthma-related medications during any 12-month period. Among selected patients, 30.6% were aged 6 to 40 years at the third dispensation. We excluded 259 patients with COPD, 27 patients with CF, and 5 patients taking omalizumab. We finally selected 275 patients (1.5%) with asthma-related hospitalization of 12 months or more after the *entry date*. CF, Cystic fibrosis; COPD, chronic obstructive pulmonary disease.

Ward's minimum-variance hierarchical clustering was performed using an agglomerative (bottom-up) approach, and Ward's linkage using 3 numerical variables (number of units of LABAs alone, ICS alone, and FDCs of LABAs + ICS) to categorize patients on drug received in the 12 months before the index date. With this algorithm, every possible cluster combination is considered at each step of agglomerative hierarchical clustering, and samples are merged into larger clusters to minimize the within-cluster sum of squares and to maximize the

between-cluster sum of squares. To compare the clusters, ANOVA, Kruskal-Wallis, and chi-square tests were used. Ward's method is a widely used algorithm that minimizes the variance within clusters.^{23,24} In Ward's minimum-variance method, the distance between 2 clusters is the ANOVA sum of squares between the 2 clusters added up over all the variables. At each generation, the within-cluster sum of squares is minimized over all partitions obtainable by merging 2 clusters from the previous generation. The sums of squares are easier to interpret when they

TABLE I. Subjects' characteristics and treatment dispensed before asthma-related hospitalization (n = 275)

Characteristics or medications	Patients with asthma-related hospitalization (n = 275)	
	n (%)	Mean $\pm$ SD
Age (y)	—	19.0 $\pm$ 11.7
Sex: Female	130 (47.3)	—
LTD status for asthma*	34 (12.4)	—
Free-access-to-care status	63 (22.9)	—
Variables ascertained in the 12-mo period before the index date		
Dispensations of FDCs of ICS + LABAs	155 (56.4)	5.1 $\pm$ 4.3
Dispensations of ICS alone	104 (37.8)	2.9 $\pm$ 2.5
Dispensations of LABAs alone	30 (10.9)	4.3 $\pm$ 3.4
Visits to GP	240 (87.3)	7.0 $\pm$ 6.3
Visits to lung specialist or pediatrician	46 (16.7)	2.3 $\pm$ 2.7
Outpatient visits (all specialists)	148 (53.8)	3.5 $\pm$ 4.1
Variables ascertained in the 3-mo period before the index date		
Dispensations of SABAs	178 (64.7)	2.5 $\pm$ 1.9
Dispensations of LTRAs	70 (25.5)	1.8 $\pm$ 0.9
Dispensations of OCs	121 (44.0)	1.8 $\pm$ 1.3

*Allows patients to receive treatment for severe and costly conditions without out-of-pocket payment.

are divided by the total sum of squares to give proportions of variance (squared semipartial correlations). SAS procedures CLUSTER and TREE were used for the cluster analysis and illustration.

The following variables were explored as illustrative variables: age at entry date, number of visits to general practitioners (GPs), lung specialists, pediatricians, and other specialists in the 12 months before the index date, and the number of dispensations of short-acting beta agonists (SABAs), leukotriene receptor antagonists (LTRAs), and oral corticosteroids (OCs) during the 3-month period before the index date. For dispensations of these drug classes, the time window was shortened to 3 months because of the short duration of action of these therapies. The quantitative variables were described as mean and SD and the categorical variables as frequencies and percentages. All analyses were conducted with an alpha level of 5%.

RESULTS

Between 2006 and 2014, we identified 73,692 patients with 3 or more dispensations for asthma-related medications during any 12-month period, corresponding to 11.3% of the French population recorded in the EGB between 2006 and 2014. Among selected patients, 22,586 (30.6%) were aged 6 to 40 years at the third dispensation. We excluded 259 patients (1.1%) with chronic obstructive pulmonary disease, 27 patients (0.1%) with cystic fibrosis, and 5 patients (0.02%) with dispensation of omalizumab. Among 17,846 remaining patients with at least 12 months of follow-up data available before and after the entry date, we finally selected 275 patients (1.5%) with asthma-related hospitalization of 12 months or more after the entry date (Figure 1).

Description of patients with asthma-related hospitalization

The mean age at cohort entry was 19.0 $\pm$ 11.7 years, and 47.3% of the subjects were women. A minority of subjects benefited from LTD status for asthma (12.4%) and patients with free-access-to-care status represented 22.9% of the cohort. Patients'

characteristics are provided in Table I. About 87% of patients had at least 1 contact with a GP, while 16% had at least 1 contact with a lung specialist or a pediatrician during the study period. During the 12 months before the index date, FDCs were dispensed to 56.4% of patients; 37.8% of patients received ICS in a single canister and 10.9% received LABAs in a single canister. During the 3 months preceding the index date, SABAs and OCs were dispensed to 64.7% and 44.0% of patients, respectively.

Treatment profiles before asthma-related hospitalization

Three different treatment profiles (clusters) appeared from the classification of the 275 patients hospitalized for asthma. One hundred seventy-five patients (63.6%) were identified in cluster 1, 89 patients (32.4%) in cluster 2, and 11 patients (4.0%) in cluster 3. The clusters characteristics are summarized in Table II. No difference was observed between the 3 clusters in terms of age ($P = .32$), sex ($P = .36$), or free-access-to-care status ($P = .40$). Conversely, patients from cluster 1 were less likely to benefit from LTD status (5.7%) than patients from clusters 2 (23.6%) and 3 (27.3%) ($P < .0001$).

In the 12 months preceding hospitalization, patients from cluster 1 had low levels of dispensation of controller medication, that is, ICS in a single canister (mean of 1.2 units dispensed), LABAs in a single canister (mean of 0.2 units dispensed), or FDCs (mean of 0.6 units dispensed). Cluster 2 patients primarily received FDCs (mean of 7.5 units dispensed) ($P < .0001$), whereas cluster 3 patients received free combinations of ICS (mean of 5.4 units dispensed) and LABAs (mean of 8.2 units dispensed) ($P < .0001$), with on average 50% more refills for LABAs than for ICS. Cluster profiles are graphically displayed in Figure 2.

Patients from cluster 1 had fewer visits to the GP (mean = 5.3 visits) in the 12 months preceding hospitalization than those from cluster 2 (mean of 7.7 visits) or cluster 3 (mean of 6.2 visits). No differences were observed regarding visits to lung specialists or to pediatricians ($P = .60$). Last, patients from cluster 1 had fewer dispensations of SABAs ($P = .01$) and LTRAs ($P < .0001$) than patients from clusters 2 and 3 during the

TABLE II. Characteristics of the clusters (n = 275)

Characteristic, n (%)	Cluster 1 (n = 175)	Cluster 2 (n = 89)	Cluster 3 (n = 11)	P value
Age (y)	18.3 (11.5)	19.9 (12.0)	22.2 (12.1)	.32
Sex: Female	85 (48.6)	38 (42.7)	7 (63.6)	.36
LTD status for asthma	10 (5.7)	21 (23.6)	3 (27.3)	<.0001
Free-access-to-care status	44 (25.1)	16 (18.0)	3 (27.3)	.40
Variables ascertained in the 12-mo period before the index date, mean $\pm$ SD				
Dispensations of FDCs of ICS + LABAs	0.6 $\pm$ 1.0	7.5 $\pm$ 4.1	1.0 $\pm$ 1.9	<.0001
Dispensations of ICS alone	1.2 $\pm$ 2.0	0.3 $\pm$ 0.8	5.4 $\pm$ 4.2	<.0001
Dispensations of LABAs alone	0.2 $\pm$ 0.8	0.0 $\pm$ 0.3	8.2 $\pm$ 1.7	<.0001
Visits to GP	5.3 $\pm$ 4.9	7.7 $\pm$ 8.5	6.2 $\pm$ 3.4	.02
Visits to lung specialist or pediatrician	0.3 $\pm$ 0.7	0.6 $\pm$ 2.2	0.2 $\pm$ 0.6	.60
Outpatient visits (all specialists)	1.8 $\pm$ 3.7	2.0 $\pm$ 3.2	1.9 $\pm$ 2.7	.35
Variables ascertained in the 3-mo period before the index date				
Dispensations of SABAs	1.3 $\pm$ 1.7	2.1 $\pm$ 2.2	2.1 $\pm$ 1.8	.01
Dispensations of LTRAs	0.3 $\pm$ 0.6	0.8 $\pm$ 1.1	1.0 $\pm$ 1.6	<.0001
Dispensations of OCs	0.7 $\pm$ 1.0	1.2 $\pm$ 1.7	0.3 $\pm$ 0.5	.05

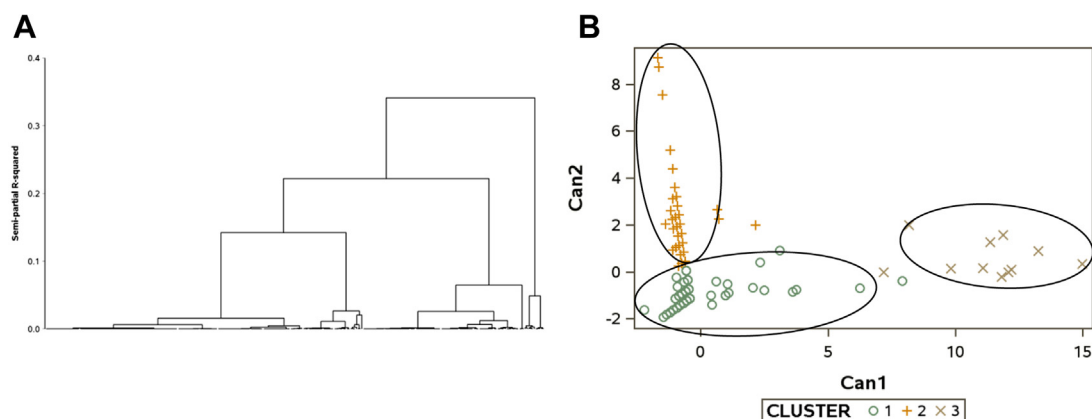


FIGURE 2. Clusters of patients before asthma-related hospitalization (n = 275). **A**, Dendrogram: The vertical axis represents the distance or dissimilarity between clusters. The horizontal axis represents the patients. Each joining (fusion) of 2 clusters is represented on the graph by the splitting of a vertical line into 2 vertical lines. The vertical position of the split, shown by the short horizontal bar, gives the distance (dissimilarity) between the 2 clusters. **B**, Cluster plot: The vertical axis and the horizontal axis represent the canonical variables 1 and 2. Hierarchical clustering is based on the core idea of objects being more related to nearby objects than to objects farther away. These algorithms connect “objects” to form “clusters” on the basis of their distance. A cluster can be described largely by the maximum distance needed to connect parts of the cluster.

3 months preceding hospitalizations. Cluster 3 received less OCs than did clusters 1 and 2 ($P = .05$).

DISCUSSION

In this study, using primary and secondary care data, we identified 3 distinct asthma treatment clusters before hospital admission for asthma, using an unsupervised learning algorithm based on controllers dispensed during the 12 months preceding hospitalization. The first cluster (63.6%) had very low dispensation of controller therapy, with around 1 refill of ICS, LABAs, or FDCs in 12 months. This cluster also had little dispensation of other treatments (SABAs, LTRAs, and OCs). The second cluster (32.4%) included patients with high use of FDCs (mean of 7.5 units in the 12 months preceding hospitalization) and SABAs, OCs, and LTRAs. These patients frequently visited GPs (7.7 visits

in 12 months). The last group (4.0%) included patients with non-FDCs of ICS and LABAs, with higher use of LABAs (8.2 refills) than of ICS (5.4 refills). This cluster was also characterized by common free-access-to-care status and LTD status for asthma.

Patients from cluster 1 were constantly untreated, be it with controller therapy during the full 12-month period preceding hospitalization, or with SABAs, LTRAs, or OCs during the 3 months before hospitalization. Underuse of controller therapy, especially ICS, has been highlighted by many studies¹⁶ as a major issue in asthma management. A recent meta-analysis, focused on the risk of asthma exacerbation after stopping low-dose ICS, concluded that patients with well-controlled asthma who stop regular use of low-dose ICS have an increased risk of exacerbation compared with those who continue ICS.²⁵ The high percentage of free-access-to-care status (25%, while the median coverage is around 8.6% in the overall population²⁶ and 11.8%

in patients with asthma⁴) strongly suggests low socioeconomic status, possibly linked with lower health literacy, which could contribute to the inappropriate management of asthma.²⁷⁻²⁹ In contrast, the low frequency of LTD status suggests that asthma was not recognized as being of high severity. In theory, acute asthma attacks could be included in this cluster because few SABAs and OCs were dispensed before hospitalization. We accepted SABAs to be used as sole respiratory drugs for inclusion (so not forcing the dispensing of at least 1 controller drug among the 3 respiratory treatments leading to inclusion) because asthma severity may be underestimated by prescribers who do not initiate controller therapy while it is needed, or by patients who do not acquire prescribed controller therapy. However, hospitalization is less preventable in this group, as the absence of controller therapy suggests intermittent asthma, at lower risk for adverse outcomes than persistent asthma. Information on symptoms and airflow limitation would have allowed characterization of persistent asthma and asthma severity, but these variables are not recorded in the database. Altogether, these data suggest a population of more deprived patients, not appropriately managed for their asthma, possibly poor perceivers of bronchoconstriction, and possibly with rapidly deteriorating asthma.

Patients from cluster 2 had regular controller therapy (FDCs), besides OCs and SABAs, and relatively more frequent medical contacts. Furthermore, the high frequency of free-access-to-care status (18%) and the high percentage of LTD status (27%) suggest more severe and not well-controlled asthma, possibly with poor quality of use of inhalers.^{30,31}

Finally, cluster 3 had high percentage of free-access-to-care status (27%), common LTD status for asthma (27%), and few contacts with specialists, again suggesting a more deprived population, with poor quality of care, and possibly low health literacy. Despite the absence of evidence of serious risk led by the use of LABAs associated with ICS in randomized controlled trials, likely due to infrequent occurrence of adverse events, the issue of safety of LABAs remains a matter of debate.³² Evidence is also limited in the observational context. A recent systematic review assessing the risk of LABAs associated with ICS, compared with ICS alone, did not indicate any increased risk for emergency department visits or hospital admissions.³³ However, no reliable conclusions could be reached for children, or for potential differences between LABAs associated with ICS, in FDCs, and in 2 separate canisters, due to a lack of data.³²

Some limitations must be acknowledged. Although the SNIIR-AM exhaustively records all reimbursed health care utilization in the covered population, patients with asthma needed to be identified from age, comorbidities, and asthma medication dispensations because of the absence of diagnostic codes.^{22,34,35} Precautions were, however, taken to include patients likely to suffer from persistent asthma, with the requirement of at least 3 dispensations of R03 over 12 months in a recent period. In addition, young children (aged <6 years), adults older than 40 years (to avoid including those with chronic obstructive pulmonary disease), and patients with cystic fibrosis were excluded. Consequently, our study was performed with a cohort that was highly likely to include patients with persistent asthma. Actually, the prevalence of asthma in our study was comparable to the prevalence observed in other studies,³⁶ supporting the validity of our identification algorithm. Additional limitations were the absence of information in the SNIR-AM on lung function or the therapy that was actually prescribed by health care providers.

In this study, treatment clusters were identified only in hospitalized patients, but different phenotypes based on medication utilization could possibly be identified in all patients (hospitalized or not). Indeed, it would have been desirable to compare findings in the hospitalized cohort to findings in a control group of patients who were not hospitalized. It was, however, not possible to identify a valid control group in this study because asthma discharge diagnoses were specifically used to identify cases with maximal validity, which would not be true for nonhospitalized controls, for whom equivalent diagnostic data would be mostly missing. Another potential marker of asthma, acute dispensings of OCs, would not be as reliable as a hospital discharge diagnosis because OCs may be used for several indications beyond asthma. This study should also be replicated using larger sample sizes, targeting populations at high risk, such as patients who experienced near-fatal asthma exacerbation or death. Furthermore, in our study, dispensation of controller therapy was evaluated in the 12 months before the hospitalization. However, in severe acute asthma, exacerbation could happen quickly, and precise information on drug use during the shorter time span before exacerbation could be more informative. Furthermore, clinical variables might be added to the hierarchical clustering method to better characterize profiles of patients. Also, data are not capturing "use," but dispensing as a surrogate for use. A linkage between data from field studies and data from Social Security claims could provide clinical variables and information on adherence or quality of inhalers use, for instance.

The results of this study are important because they revealed distinct patterns of use of therapy before hospitalization due to asthma, in longitudinal data sets with information on socioeconomic status. In our study, asthma therapy was clearly inappropriate in two-third of patients (clusters 1 and 3), conferring considerable risk of exacerbation. Because of the selection criteria applied, these results can be generalized to patients with persistent asthma. There are many plausible ways to improve the identified care gap in asthma. Clinicians could improve the quality of prescribing,³⁷ and patients should be informed on appropriate use of therapy¹⁴ and technical use of inhalers.³⁰ Clinicians should be informed on the actual controller use of their patients, for example, via feedback from claims data or from consulting practice prescribing records. Personal action plans should be written, describing how patients may recognize deterioration in their asthma and what steps they should take to reestablish control.⁹ Other clinical health care providers (eg, nurses) could also review the use of therapy and provide training and support to patients.³⁸ Policymakers should develop actions targeting both clinicians (eg, via asthma audits) and patients (eg, by providing ways for patients to have direct contacts with advisors, eg, using information technology, or through pharmacies).

In conclusion, we observed that most French patients with asthma were not exposed to controllers before an asthma-related hospitalization, while 4% were exposed to higher dispensation of LABAs than of ICS. Investigating these patterns in detail may lead to concrete measures to prevent exacerbations. Educational interventions and close monitoring at the population level are deemed necessary to reduce the asthma-associated exacerbation.

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