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Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and beta-adrenergic agonists (ICS/LABA): real-life study.

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ABBREVIATIONS

Abbreviation	Description
ATC	Anatomical Therapeutic Chemical Classification System
BDP/FORM	Beclomethasone/formoterol
BUD/FORM	Budesonide/formoterol
FEV_1	Maximum expiratory volume in the first second
FF/VI	Fluticasone furoate/vilanterol
FP/FORM	Fluticasone propionate/formoterol
FP/SAL	Fluticasone propionate/salmeterol
ICS	Inhaled corticosteroid
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist

FUNDING
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CONFLICT OF INTEREST
A. Sicras is an independent consultant funded by Mundipharma with respect to this manuscript. TF is an employee of Mundipharma. The other authors state they have no conflict of interest in relation to this study.

AUTHOR CONTRIBUTIONS
A. Sicras and T. Fernández conceived and designed the manuscript; data collection and the statistical analysis were made by A. Sicras; and the interpretation of the data, writing, review and approval of the manuscript submitted, by all authors.

ETHICS APPROVAL
His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

DATA AVAILABILITY
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

PATIENT CONSENT FOR PUBLICATION.
Not required.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Reducing the risk of exacerbations is an important goal of asthma treatment. It is estimated that 36% of patients with asthma have exacerbations of varying intensity.
- Patients undergoing treatment with FP/FORM and FF/VI were associated with greater treatment adherence (persistence, MPR) and lower rates of exacerbations.
- This study has the limitations of retrospective observational studies.

PATIENT AND PUBLIC INVOLVEMENT
No patient involved.

STROBE Statement—Checklist of items that should be included in reports of *observational studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalizability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and long-acting beta2-adrenergic agonists (ICS/LABA): a real-life study.

ABSTRACT

Objective. To determine treatment persistence and exacerbations in patients initiating inhaler treatment with fixed-dose combinations of inhaled corticosteroids/long-acting beta2-adrenergic agonists (ICS/LABA) for the treatment of asthma.

Design. Observational study conducted by review of medical records.

Setting. Longitudinal cohort. The follow-up period was one year.

Participants The study included patients aged ≥18 years who started treatment with ICS/LABA and met the inclusion/exclusion criteria.

Main outcomes and measures. The study groups were fluticasone propionate/salmeterol (FP/SAL), beclomethasone/formoterol (BDP/FORM), budesonide/formoterol (BUD/FORM), fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate/formoterol (FP/FORM). The main measurements were persistence, medication possession ratio (MPR), and exacerbations. Statistical significance was established as $p<0.05$.

Results. In total, 3,203 patients were extracted from a database: by groups, 31.1% FP/SAL, 28.6% BDP/FORM, 25.0% BUD/FORM, 8.2% FF/VI, and 7.0% FP/FORM. The mean age was 52.2 years, 60.8% were female, and 44.9% had persistent-moderate asthma. Treatment persistence was 61.7% (95% CI: 60.0-63.4%) and by study groups it was: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6%, (p=0.046). MPR by study group was FP/SAL: 74.3, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%. By treatment group, exacerbations were FP/SAL 21.9%, BDP/FORM 22.2%, BUD/FORM 22.8%, FF/VI 17.9% and FP/FORM 16% (p=0036).

Conclusions. Patients undergoing treatment with FP/FORM and FF/VI were associated with greater treatment adherence (persistence, MPR) and lower rates of exacerbations. The differences may be due to the pharmacological properties of the drugs or other, unmeasured factors.

Keywords: asthma, persistence, exacerbations, ICS/LABA.

INTRODUCTION

Asthma is a chronic inflammatory airway disease that courses with bronchial hyper-response and variable airflow blockage[1]. In Spain, the prevalence is around 5%, although there are variations between geographical areas[2]. Most patients achieve adequate control with inhaled corticosteroids (ICS) and long-lasting beta-adrenergic agonists (LABA), although some patients require additional therapy with other medications, including oral corticosteroids (OC)[1-2].

Reducing the risk of exacerbations is an important goal of asthma treatment[3]. It is estimated that 36% of patients with asthma have exacerbations of varying intensity[2,6]. Factors influencing an increased risk of exacerbations include previous exacerbations, poor asthma control, limitations on activity, lower forced expiratory volume in the first second (FEV_1), exposure to allergens, difficulty handling inhalation devices and treatment adherence[7]. Studies show anti-asthmatic adherence rates of <65%[1-2,7]. The most common cause of treatment discontinuation are side effects, improvements in symptoms and problems in reducing the effect of the drug over time, which lead to discontinuation being advised or spontaneous abandonment[7-10].

In Spain, there are few studies evaluating the relationship between the adherence rate and the risk of exacerbations[11]. Persistence (or discontinuation) of treatment is a key factor in disease progression and the risk of complications. In addition, there is a growing need to conduct studies representative of the real-life clinical conditions in which medicines are used, so the study may be of interest. The objective of the study was to evaluate treatment persistence and exacerbations in patients initiating inhaler treatment with combinations of ICS/LABA for the treatment of asthma in routine clinical practice.

PATIENTS AND METHODS

An observational, multicenter, longitudinal, retrospective study was carried out by review of medical records (computerized databases, with dissociated data). The study population was obtained from the computerized records of health care providers from various primary care centers (PCC) in Catalonia (unified in the dissociated database of the Fundacion RedISS (Health services research network; *www.rediss.es*). The data came from the OMIAPWIN computerized medical record and other complementary databases. The population assigned to the centers was mostly urban, of medium-low socioeconomic level.

Patients who sought care and initiated treatment with a fixed dose ICS/LABA combination between 01/01/2015 and 30/06/2016 (recruitment period, index date) were included in the study. The inclusion criteria were: (a) ≥ 18 years, (b) patients diagnosed with asthma ≥12 months before the index date, c) inclusion in the prescription program (with recorded dose, time interval and duration of each treatment administered; ≥ 2 prescriptions during the follow-up period), and (d) ensured

regular monitoring (≥ 2 clinical records in the computer system). Exclusion criteria were: (a) patients transferred to other centers, displaced or out-of-area, (b) permanently institutionalized patients, (c) a history of COPD, pulmonary emphysema, bronchiectasis, cystic fibrosis or bronchial neoplasm, and d) mixed asthma-COPD phenotype (asthma-COPD overlap)[1].

Five study groups were differentiated according to the initial fixed-dose combination of ICS/LABA: Budesonide /formoterol (BUD/FORM, R03AK07), Beclomethasone /formoterol (BDP/FORM, R03AK08), Fluticasone furoate/vilanterol (FF/VI, R03AK10), Fluticasone propionate/formoterol (FP/FORM, R03AK11) and Fluticasone propionate/salmeterol (FP/SAL, R03AK06). The follow-up period, from the date of inclusion of the patient was one year. Records of asthma patients were obtained using the International Classification of Primary Care in the European Community (ICPC-2; R93)[12], and/or the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9-MC; 493.x for asthma and/or flare-ups). The diagnosis of asthma was always made at the physician's discretion, according to spirometry values. Exacerbations were defined as an event in the natural course of the disease characterized by acute episodes identified by a progressive increase in breathing difficulties, feeling short of breath, wheezing, chest oppression or a combination of these symptoms, caused by intense airflow obstruction[1]. Outpatients or those attending the emergency department (mild-moderate asthma exacerbation) and hospitalized patients (severe asthma exacerbation) were identified. The record of each exacerbation was obtained to assess the rates before and after the index date, and the time from diagnosis (in years). In addition, the following variables were collected: body mass index (BMI, $kg/m^{2)}$, lung function (forced expiratory volume in the first second, FEV_1), asthma severity (intermittent, mild persistent, moderate persistent and severe persistent according to the GEMA criteria[1] at the start of the study before the index date. All-cause deaths were recorded.

Sociodemographic and comorbidity variables collected were age (continuous and by range), sex, and the personal history described in table 1. As a summary variable of general comorbidity: a) the Charlson[13] comorbidity index was used as an approximation to severity, b) the number of chronic comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted Clinical Groups (ACG), which is a patient classification system using iso-consumption of resources[14]. The ACG application provides resource utilization bands (RUB), allowing each patient to be grouped into one of five mutually exclusive categories based on their overall morbidity.

The medicines (active substances) indicated for treatment were obtained according to the Anatomical Therapeutic Chemical Classification System (ATC)[15] classification: oral/systemic corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA, R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients

receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient was at the discretion of the physician, as in routine clinical practice. The information was obtained from drug dispensing records. The scheduled dose of ICS administered was classified at low, medium or high[1]. Treatment persistence was calculated from the index date to the discontinuation date in months. The discontinuation date was the date on which the patient switched to another ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of follow-up. The percentage of therapeutic compliance was calculated based on the medicine possession ratio (MPR)[16]. This was evaluated from the first to the last prescription and represented the number of days of medication dispensed according to the number of days on treatment from the index date.

Records were validated to ensure the quality of the results. A descriptive-univariate statistical analysis was carried out. Qualitative data were described using absolute and relative frequencies and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI) used to estimate parameters were based on the total number of subjects with no missing values. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A multiple linear regression model was used to obtain the variables associated with the number of exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the model were: sex, age, general comorbidity (RUB), FEV_1, disease duration and asthma severity. Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The analysis was made using SPSSWIN version 23. Statistical significance was established as $p<0.05$.

Ethics Approval: His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

Patient and public involvement: no patient involved.

RESULTS

Of an initial population of 8,725 subjects diagnosed with asthma (prevalence: 5.4%; 95% CI: 5.2-5.7%), 3,203 patients who met the inclusion/exclusion criteria and could be followed during the study period were analysed. Table 1 shows the baseline characteristics of participants according to the five ICS/LABA study groups. The mean age was 52.2 years, 60.8% were women, the mean RUB was 2.9 points, and the mean Charlson index was 0.7 points. Allergic rhinitis (62.3%), dyslipidemia (41%), gastroesophageal reflux (39.6%) and high blood pressure (28.4%) were the most frequent comorbidities: 44.9% of patients had persistent-moderate asthma, with a mean FEV_1 of 74.6%. According to the initial ICS/LABA prescribed, the study groups were as follows: 31.1%

(N=996) FP/SAL, 28.6% (N=917) BDP/FORM, 25% (N=802) BUD/FORM, 8.2% (N=263) FF/VI and 7.0% (N=225) FP/FORM. There was acceptable comparability in the baseline characteristics of the study groups.

Medication administered and treatment adherence (persistence and MPR) during the follow-up period according to the study groups are detailed in table 2: 95.7% of patients were receiving short-term beta-2 agonists (SABA) as rescue treatment, 27.7% were receiving oral corticosteroids (20% for regular/chronic use) and 18.2% leukotriene antagonists. There was acceptable homogeneity between the groups. Treatment persistence at 12 months was 61.7% (95% CI: 60-63.4%) and, by study group, was as follows: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6% (p=0.046). The MPR was FP/SAL: 74.3%, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%.

Exacerbations by study group are described in table 3. Overall, 21.5% of patients had some form of exacerbation, and the rates were slightly lower in groups treated with FP/FORM and FF/VI. The percentages of patients with exacerbations according to study group were FP/SAL: 21.9%, BDP/FORM: 22.2%, BUD/FORM: 22.8%, FF/VI: 17.9% and FP/FORM: 16% (p=0.036). The differences were most evident in patients with severe exacerbations (7.9%, 6.0%, 7.9%, 6.8% and 4.0%, respectively (p<0.001)). The reductions in exacerbations from baseline to 12 months were: FP/SAL: -6.8%, BDP/FORM: -5.9%, BUD/FORM: -6.1%, FF/VI: -8.6% and FP/FORM: -9.3%, respectively (p-0.037). In the multivariate model, the number of exacerbations during the follow-up was associated with previous exacerbations (β-0.798), FEV_1 (β-0.075) and persistence (β-0.011) (p<0.033). The model determination coefficient was 85.1%. Figure 1 details the percentage of exacerbations according to asthma severity and figure 2 shows the median treatment persistence during the follow-up period.

DISCUSSION

The results of the study show that patients initiating fixed-dose treatment with FP/FORM and FF/VI were associated with increased persistence and MPR, resulting in fewer exacerbations compared with other ICS/LABA. Only patients receiving FP/FORM were associated with a lower rate of severe asthma exacerbations. FP/FORM and FF/VI, which are newer combinations, were less often prescribed (7% and 8.2%, respectively).

ICS /LABA are the basis of persistent asthma treatment, although the literature reviewed shows a low rate of adherence to medication (<65% per year)[11,16-17]. A review of 19 studies shows treatment adherence ranged between 22% and 63% and that 24% of exacerbations and 60% of asthma-related hospitalizations were attributable to poor adherence[18]. Zhang[19] found a persistence of 33.6% in children with persistent asthma on monotherapy. Our results are similar or perhaps slightly

higher than those reported but are still low. There may be several possible explanations: a) the method of measuring persistence/MPR, b) the dose indicated at the beginning of the study, c) ours is a more recent study, d) the patients who sought care assiduously attended check-ups, and/or e) are subject to specific nursing follow-up. In addition, in the studies reviewed, therapeutic non-compliance was associated with young patients with mild asthma, while fixed combinations improve adherence, as confirmed by our results[18,20].

Our results show that 21.5% of patients had some form of exacerbation, and that the rate was slightly lower in patients treated with FP/FORM and FF/VI. The risk of exacerbations was associated with clinical severity (FEV_1), previous exacerbations, limitations on activity, allergic rhinitis, insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed treatment[20]. Schmidt[21], in a year-long prospective observational real-life study, found that treatment with FP/FORM was associated with clinical improvements in asthma (degree of control, severe exacerbation, quality of life and lung function). Usmani[22] studied patients with controlled asthma and found that a reduction in the dose of FP/FORM did not affect exacerbations and was well tolerated. A comparative review of the rate of severe asthma exacerbations observed in clinical trials of different fixed-dose combinations of ICS/LABA by Papi[20] found that the incidence of exacerbations with FP/FORM was lower than that for other combinations of ICS/LABA (especially those that result in hospitalization) and that the difference cannot be explained solely by the characteristics of the studies (design, population, etc.) and could be related to the pharmacological (molecular) characteristics of the combination. A clinical trial of FF/VI also found a lower rate of asthma exacerbations, although it was similar to FP/SAL[23]. Another recent real-life trial found that FF/VI showed better asthma control than habitual optimized treatment, but that there were no differences in the rate of asthma exacerbations[24.] With design limitations, our data is in line with the literature consulted[20,25]. However, the different definitions of asthma exacerbation make comparisons difficult; in our study the definition of exacerbation was at the clinician's discretion and was based on the use of health resources.

The study has some limitations. These affect the categorization of the disease and the possible classification bias of patients, including the possible inaccuracy of diagnostic coding with regard to the diagnosis of asthma and other comorbidities, the definition of exacerbation, the imbalance between the groups in terms of numbers, or the lack of variables that might influence the results (socioeconomic level of patients, environmental/work exposure, evolution of the prescribed pharmacological dose, verification of the inhalation technique, including bronchoconstrictor therapy and/or the differentiation of phenotypes) should also be considered as limitations. In addition, the external validity of the results with respect to the representativeness of the population and the small number of patients per study group should also be considered as limitations. When using an

efficient inhaler therapy[24-25], the factors that most influence compliance include the type of device, the technique used, and the health-education instructions received.

The future perspectives offered by this study are those of its replication in other health institutions and interventional strategies aimed at promoting patient self-care (structured and individualized educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with increased treatment adherence (persistence, MPR) and lower rates of exacerbations. These differences could be due to the pharmacological properties of the drugs or other unmeasured factors. However, further studies will be needed to strengthen the consistency of the results.

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Table 1. Baseline characteristics of the series studied by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25.0%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	p
Sociodemographic features						
Mean age, years	52.3 (19.3)	53.0 (18.5)	51.0 (16.8)	52.5 (17.7)	52.8 (17.1)	0.245
Sex (female)	60.0%	61.1%	61.6%	61.6%	60.4%	0.968
General comorbidity						
Mean diagnoses	6.8 (3.9)	6.4 (3.9)	6.2 (3.6)	6.3 (3.6)	6.8 (3.8)	0.075
Charlson index	0.8 (0.8)	0.7 (0.8)	0.7 (0.6)	0.7 (0.8)	0.8 (0.9)	0.097
Mean RUB	3.0 (0.7)	2.9 (0.7)	2.9 (0.8)	3.0 (0.8)	2.9 (0.7)	0.198
1 (very low comorbidity)	4.1%	3.6%	8.2%	6.1%	4.9%	
2 (low comorbidity)	10.3%	20.4%	12.5%	13.3%	12.0%	
3 (moderate comorbidity)	71.1%	65.5%	63.1%	56.7%	67.6%	
4 (high comorbidity)	14.0%	9.9%	15.8%	23.6%	14.7%	
5 (very high comorbidity)	0.5%	0.5%	0.4%	0.4%	0.9%	0.111
Associated comorbidity						
High blood pressure	29.9%	28.9%	29.1%	29.3%	29.3%	0.991
Diabetes mellitus	13.4%	12.8%	13.0%	13.3%	12.9%	0.996
Dyslipidemia	41.0%	41.3%	41.3%	40.7%	39.8%	0.811
Obesity	27.9%	28.6%	27.7%	26.2%	27.6%	0.963
Ischemic heart disease	4.3%	4.0%	4.0%	3.8%	4.0%	0.994
Cerebrovascular accident	7.3%	7.0%	7.0%	6.8%	6.7%	0.995
Cardiovascular event	11.8%	9.2%	9.1%	10.6%	10.2%	0.272
Depressive syndrome	19.5%	19.6%	20.2%	20.9%	20.4%	0.982
Malignancies	10.9%	10.5%	10.3%	11.8%	10.2%	0.964
Allergic rhinitis	61.7%	63.1%	61.8%	63.5%	62.2%	0.959
Nasal polyposis	15.5%	15.4%	15.3%	14.1%	16.4%	0.969
Gastroduodenal reflux	39.1%	40.9%	38.0%	41.1%	40.9%	0.739
Asthma severity						
Intermittent	13.0%	14.9%	12.0%	12.5%	12.0%	
Mild persistent	25.0%	21.5%	24.6%	25.1%	25.3%	
Moderate persistent	44.5%	45.1%	45.3%	43.3%	45.4%	
Severe/severe persistent	17.6%	18.4%	18.2%	19.0%	18.2%	0.844
Other variables						
BMI, kg/m^2	28.4 (5)	28.6 (5.0)	28.4 (5.0)	28.6 (5.5)	27.9 (4.9)	0.228
FEV_1 (% theoretical)	74.8%	74.3%	74.7%	74.6%	74.8%	0.954

Values expressed as percentage or mean (standard deviation), p: statistical significance. RUB: Resource utilization bands.
BMI: Body mass index, kg/m^2, FEV_1: Forced expiratory volume in the first second.
Groups: Fluticasone propionate/salmeterol (FP/SAL), Beclomethasone /formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).

Table 2. Medication administered and treatment persistence during the follow-up period

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7.0%)	p
Medication use						
Oral corticosteroids	24.6%	22.8%	26.7%	25.5%	24.9%	0.465
Oral corticosteroids for chronic use	22.0%	18.5%	20.2%	18.6%	18.7%	0.373
Systemic antibiotics	10.0%	9.2%	10.1%	10.3%	10.1%	0.959
Short-lasting beta-2 agonists	90.0%	93.0%	91.2%	89.5%	92.2%	0.221
Long-lasting anticholinergics	17.0%	15.2%	13.8%	16.0%	13.8%	0.414
Systemic beta-2 agonists (xanthines)	3.8%	3.5%	3.2%	5.7%	3.1%	0.431
Leukotriene receptor antagonists	17.7%	17.4%	19.5%	17.5%	19.6%	0.782
Biologicals: omalizumab	1.3%	1.4%	1.2%	1.5%	1.3%	0.997
Inhaled corticosteroid doses						
Low	10.5%	9.8%	10.1%	11.1%	10.7%	
Average	47.1%	46.5%	45.0%	46.2%	47.1%	
High	42.4%	43.7%	44.9%	42.7%	42.2%	0.547
Other variables						
Time from diagnosis, years	12.5 (4.5)	12.7 (4.4)	12.8 (4.2)	12.6 (3.9)	12.3 (3.9)	0.373
Treatment possession, months	8.9 (3.6)	8.9 (3.4)	9.0 (3.3)	9.6 (3.3)*	9.7 (3.1)*	0.046
Duration of treatment, months	9.9 (3.5)	9.7 (3.6)	10.0 (3.5)	10.2 (3.4)*	10.3 (3.2)*	0.036
Medication possession rate	74.3%	73.8%	74.6%	79.4%*	80.6%*	0.028
95% CI	71.6-77.0%	70.5-76.3%	71.6-77.6%	74.5-84.3%	75.4-85.8%	
Treatment persistence, months						
6 months	81.9%	81.2%	82.4%	86.0%*	87.6%*	0.014
12 months	60.7%	61.2%	60.3%	66.7%*	67.6%*	0.046
Death	3.0%	2.7%	3.1%	2.3%	2.7%	0.954

Values expressed as percentage or mean (SD: standard deviation), p: statistical significance. CI: Confidence intervals.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (observed > expected).

Table 3. Exacerbations by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	pd
Follow-up period (one year)						
Exacerbations, %	21.9%	22.2%	22.8%	17.9%*	16.0%*	0.036
Mean exacerbations	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)	0.3 (0.8)	0.3 (0.8)	0.087
Number of exacerbations/year						
0	78.1%	78.3%	77.2%	82.1%	84.0%	
1	15.0%	14.9%	13.8%	9.9%	7.1%	
2	2.9%	2.6%	5.5%	1.9%	5.3%	
3+	4.0%	4.1%	3.5%	6.1%	3.6%	<0.001
Patients with exacerbations						
Mild-Moderate	20.1%	21.7%	22.2%	17.5%*	16.0%*	<0.001
Severe (hospital admission)	7.9%	6.0%	7.9%	6.8%	4.0%*	<0.001
Previous year						
Exacerbations, %	28.7%	28.1%	28.9%	25.5%	25.3%	0.698
Mean exacerbations	0.5 (0.9)	0.5 (0.9)	0.5 (0.9)	0.5 (1.0)	0.4 (0.9)	0.973
Number of exacerbations/year						
0	71.3%	71.9%	71.1%	74.5%	74.7%	
1	17.1%	15.3%	15.1%	14.1%	15.6%	
2	5.9%	8.4%	9.1%	3.0%	2.7%	
3+	5.7%	4.5%	4.7%	8.4%	7.1%	<0.001
Patients with exacerbations						
Mild-Moderate	27.5%	27.4%	28.7%	24.1%	25.4%	0.111
Severe (hospital admission)	11.7%	10.8%	12.2%	10.6%	10.7%	0.217
Differences between the two periods						
Exacerbations, %	-6.8%	-5.9%	-6.1%	-8.6%*	-9.3%*	0.037
Mild-Moderate	-7.4%	-5.7%	-6.5%	-7.6%	-8.4%	0.282
Severe (hospital admission)	-3.8%	-4.8%	-4.4%	-5.8%*	-6.7%*	0.044

Values expressed as percentage or mean (SD: standard deviation), p: statistical significance.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (effects observed > expected).

Figure 1. Percentage of patients with exacerbations according to their severity

Values expressed as a percentage of patients with exacerbations during the follow-up year.
In grey, statistically significant results ($p<0.05$).
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM).

Figure 2. Median treatment persistence during the follow-up period

Kaplan-Meier Curve: Log Rank Procedure (Mantel-Cox): Chi-square-9,643; p-0.039.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).

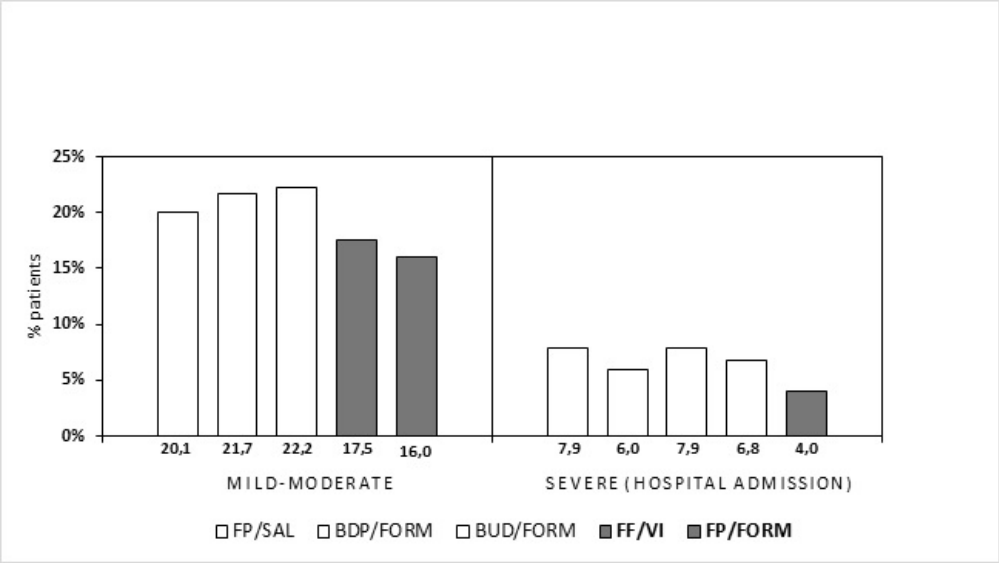

Figure 1. Percentage of patients with exacerbations according to their severity

171x97mm (96 x 96 DPI)

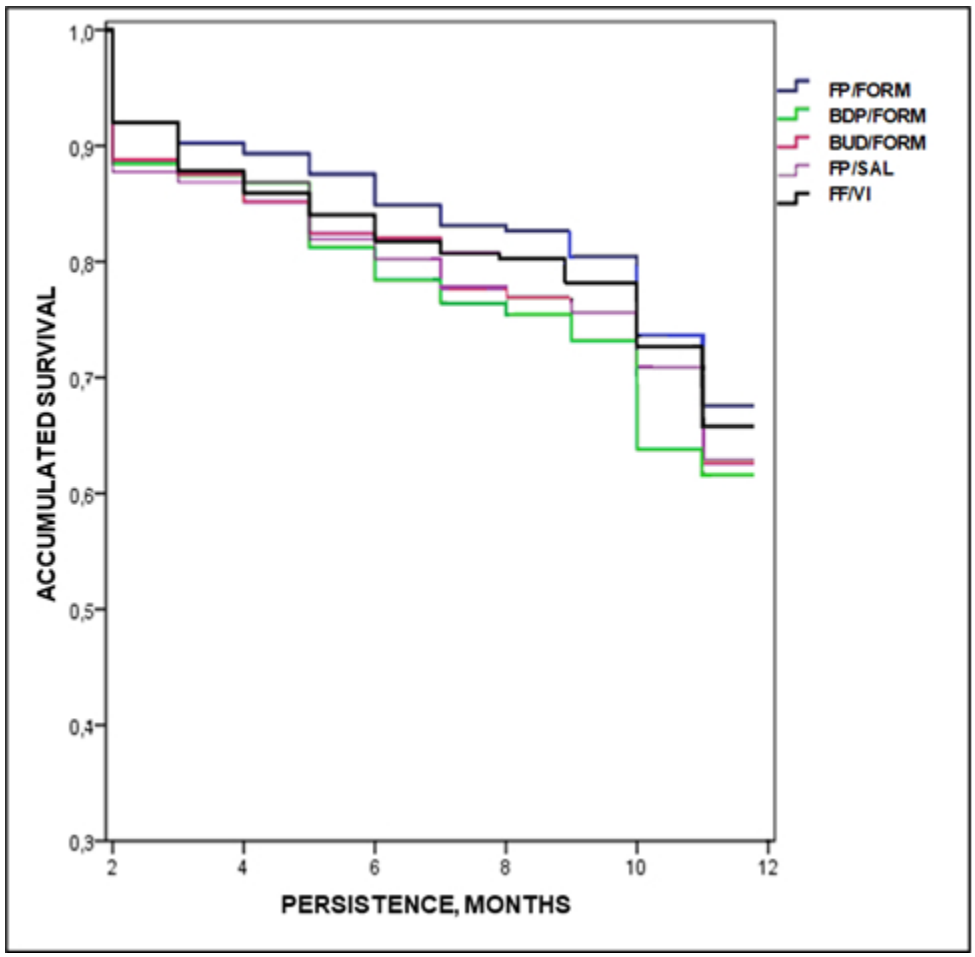

Figure 2. Median treatment persistence during the follow-up period

325x316mm (38 x 38 DPI)

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Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and beta-adrenergic agonists: retrospective cohort study

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Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and beta-adrenergic agonists: retrospective cohort study

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ABBREVIATIONS

Abbreviation	Description
ATC	Anatomical Therapeutic Chemical Classification System
BDP/FORM	Beclomethasone/formoterol
BUD/FORM	Budesonide/formoterol
FEV_1	Maximum expiratory volume in the first second
FF/VI	Fluticasone furoate/vilanterol
FP/FORM	Fluticasone propionate/formoterol
FP/SAL	Fluticasone propionate/salmeterol
ICS	Inhaled corticosteroid
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist

FUNDING
Associates of Vectura licensed a formoterol/fluticasone inhaler to Mundipharma Pharmaceuticals. Mundipharma has since developed, registered, marketed and distributed this product and sponsored this study. This study was designed and completed prior to acquisition of Vectura by Philip Morris International.

CONFLICT OF INTEREST
A. Sicras is an independent consultant funded by Mundipharma with respect to this manuscript. ST and TF are employees of Mundipharma. The other authors state they have no conflict of interest in relation to this study.

AUTHOR CONTRIBUTIONS
A. Sicras and T. Fernández conceived and designed the manuscript; data collection and the statistical analysis were made by A. Sicras; and the interpretation of the data, writing, review and approval of the manuscript submitted, by all authors.

ETHICS APPROVAL
His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

DATA AVAILABILITY
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

PATIENT CONSENT FOR PUBLICATION.
Not required.

STROBE Statement—Checklist of items that should be included in reports of *observational studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalizability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and long-acting beta2-adrenergic agonists: retrospective cohort study

ABSTRACT

Objective. To determine treatment persistence and exacerbations in patients initiating inhaler treatment with fixed-dose combinations of inhaled corticosteroids/long-acting beta2-adrenergic agonists (ICS/LABA) for the treatment of asthma.

Design. Retrospective observational study conducted by review of electronic medical records (database: Fundacion RedISS).

Setting. Retrospective cohort study. The follow-up period was one year.

Participants The study included patients aged ≥18 years who started treatment with ICS/LABA and met the inclusion/exclusion criteria.

Main outcomes and measures. The study groups were fluticasone propionate/salmeterol (FP/SAL), beclomethasone/formoterol (BDP/FORM), budesonide/formoterol (BUD/FORM), fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate/formoterol (FP/FORM). The main measurements were persistence, medication possession ratio (MPR), and exacerbations. Statistical significance was established as $p<0.05$.

Results. In total, 3,203 patients were recruited for the study. By groups, 31.1% FP/SAL, 28.6% BDP/FORM, 25.0% BUD/FORM, 8.2% FF/VI, and 7.0% FP/FORM. The mean age was 52.2 years, 60.8% were female, and 44.9% had persistent-moderate asthma. Treatment persistence was 61.7% (95% CI: 60.0-63.4%) and by study groups it was: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6%, (p=0.046). MPR by study group was FP/SAL: 74.3, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%. By treatment group, exacerbations were FP/SAL: 21.9% (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), p=0.036.

Conclusions. Patients undergoing treatment with FP/FORM and FF/VI vs. FP/SAL, BDP/FORM, BUD/FORM, were associated with greater treatment adherence (persistence, MPR) and lower rates of exacerbations. However, further studies will be needed to strengthen the consistency of the results.

Keywords: asthma, persistence, exacerbations, ICS/LABA.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Reducing the risk of exacerbations is an important goal in the treatment of asthma. However, in our country there are few studies that evaluate this by analyzing the effect of double inhalation therapy at the level of active ingredient (molecule).
- The results of the study were obtained in a situation of routine clinical practice, far from the idyllic conditions of randomized clinical trials.
- This study has the limitations of retrospective observational studies; for example, the possible underreporting of information, the difficulty in measuring the confounding variables and the impossibility of establishing a causal relationship between the variables.

INTRODUCTION

Asthma is a chronic inflammatory airway disease that courses with bronchial hyper-response and variable airflow blockage[1]. In Spain, the prevalence is around 5%, although there are variations between geographical areas[2]. Most patients achieve adequate control with inhaled corticosteroids (ICS) and long-lasting beta-adrenergic agonists (LABA), although some patients require additional therapy with other medications, including oral corticosteroids (OC)[1-2].

Reducing the risk of exacerbations is an important goal of asthma treatment[3]. It is estimated that 30-52% of patients with asthma have exacerbations of varying intensity[2,6]. Factors influencing an increased risk of exacerbations include previous exacerbations, poor asthma control, limitations on activity, lower forced expiratory volume in the first second (FEV_1), exposure to allergens, difficulty handling inhalation devices and treatment adherence[7]. Studies show anti-asthmatic adherence rates of <65%[1-2,7]. The most common cause of treatment discontinuation are side effects, improvements in symptoms and problems in reducing the effect of the drug over time, which lead to discontinuation being advised or spontaneous abandonment[7-10].

In Spain, there are few studies evaluating the relationship between the adherence rate and the risk of exacerbations[11]. Persistence (or discontinuation) of treatment is a key factor in disease progression and the risk of complications. In addition, there is a growing need to conduct studies representative of the real-life clinical conditions in which medicines are used, so the study may be of interest. The objective of the study was to evaluate treatment persistence and exacerbations in patients initiating inhaler treatment with combinations of ICS/LABA for the treatment of asthma in routine clinical practice.

PATIENTS AND METHODS

Patient and public involvement: no patient involved.

We performed a retrospective observational analysis of electronic medical records (EMR) obtained from the administrative database of the RediSS Foundation (Health services research network; www.rediss.es), a source of secondary data. The primary data came from various primary care centers in Catalonia (Spain), which are computerized with the OMIAPWIN (EMR). Before export to RediSS Foundation, data are rigorously anonymized and it is not possible to identify the territory, health care provider, treating physician, or patient or access any other information that would permit individual identification. This procedure ensures adherence to current law governing the protection of personal data. The population assigned to the centers was mostly urban, of medium-low socioeconomic level.

Patients who sought care and initiated treatment with a fixed dose ICS/LABA combination between 01/01/2015 and 30/06/2016 (recruitment period, index date) were included in the study. The inclusion criteria were: (a) ≥ 18 years, (b) patients diagnosed with asthma ≥12 months before the index date, c) inclusion in the prescription program (with recorded dose, time interval and duration of each treatment administered; ≥ 2 prescriptions during the follow-up period), and (d) ensured regular monitoring (≥ 2 clinical records in the computer system). Exclusion criteria were: (a) patients transferred to other centers, displaced or out-of-area, (b) permanently institutionalized patients, (c) a history of COPD, pulmonary emphysema, bronchiectasis, cystic fibrosis or bronchial neoplasm, and d) mixed asthma-COPD phenotype (asthma-COPD overlap)[1].

Five study groups were differentiated according to the initial fixed-dose combination of ICS/LABA: Budesonide /formoterol (BUD/FORM, R03AK07), Beclomethasone /formoterol (BDP/FORM, R03AK08), Fluticasone furoate/vilanterol (FF/VI, R03AK10), Fluticasone propionate/formoterol (FP/FORM, R03AK11) and Fluticasone propionate/salmeterol (FP/SAL, R03AK06). The follow-up period, from the date of inclusion of the patient was one year. Records of asthma patients were obtained using the International Classification of Primary Care in the European Community (ICPC-2; R93)[12], and/or the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9-MC; 493.x for asthma and/or flare-ups). The diagnosis of asthma was always made at the physician's discretion, according to spirometry values. Exacerbations were defined as an event in the natural course of the disease characterized by acute episodes identified by a progressive increase in breathing difficulties, feeling short of breath, wheezing, chest oppression or a combination of these symptoms, caused by intense airflow obstruction[1]. Outpatients or those attending the emergency department (mild-moderate asthma exacerbation) and hospitalized patients (severe asthma exacerbation) were identified. The record of each exacerbation was obtained to assess the rates before and after the index date, and the time from diagnosis (in years).

In addition, the following variables were collected: body mass index (BMI, kg/m$^{2)}$, lung function (forced expiratory volume in the first second, FEV_1), asthma severity (intermittent, mild persistent, moderate persistent and severe persistent according to the GEMA criteria[1] at the start of the study before the index date. All-cause deaths were recorded.

Sociodemographic and comorbidity variables collected were age (continuous and by range), sex, and the personal history described in table 1. As a summary variable of general comorbidity: a) the Charlson[13] comorbidity index was used as an approximation to severity, b) the number of chronic comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted Clinical Groups (ACG), which is a patient classification system using iso-consumption of resources[14]. The ACG application provides resource utilization bands (RUB), allowing each patient to be grouped into one of five mutually exclusive categories based on their overall morbidity.

The medicines (active substances) indicated for treatment were obtained according to the Anatomical Therapeutic Chemical Classification System (ATC)[15] classification: oral/systemic corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA, R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient was at the discretion of the physician, as in routine clinical practice. The information was obtained from drug dispensing records. The scheduled dose of ICS administered was classified at low, medium or high[1]. Treatment persistence was calculated from the index date to the discontinuation date in months. The discontinuation date was the date on which the patient switched to another ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of follow-up. The percentage of therapeutic compliance was calculated based on the medicine possession ratio (MPR)[16]. This was evaluated from the first to the last prescription and represented the number of days of medication dispensed according to the number of days on treatment from the index date.

Records were validated to ensure the quality of the results. A descriptive-univariate statistical analysis was carried out. Qualitative data were described using absolute and relative frequencies and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI) used to estimate parameters were based on the total number of subjects with no missing values. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A multiple linear regression model was used to obtain the variables associated with the number of

exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the model were: sex, age, general comorbidity (RUB), FEV_1, disease duration and asthma severity. Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The analysis was made using SPSSWIN version 23. Statistical significance was established as $p<0.05$.

Ethics Approval: His protocol was reviewed and approved at Foundation RediSS (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

RESULTS

Of an initial population of 8,725 subjects diagnosed with asthma (prevalence: 5.4%; 95% CI: 5.2-5.7%), 3,203 patients who met the inclusion/exclusion criteria and could be followed during the study period were analysed. Table 1 shows the baseline characteristics of participants according to the five ICS/LABA study groups. The mean age was 52.2 years, 60.8% were women, the mean RUB was 2.9 points, and the mean Charlson index was 0.7 points. Allergic rhinitis (62.3%), dyslipidemia (41%), gastroesophageal reflux (39.6%) and high blood pressure (28.4%) were the most frequent comorbidities: 44.9% of patients had persistent-moderate asthma, with a mean FEV_1 of 74.6%. According to the initial ICS/LABA prescribed, the study groups were as follows: 31.1% (N=996) FP/SAL, 28.6% (N=917) BDP/FORM, 25% (N=802) BUD/FORM, 8.2% (N=263) FF/VI and 7.0% (N=225) FP/FORM. There was acceptable comparability in the baseline characteristics of the study groups.

Medication administered and treatment adherence (persistence and MPR) during the follow-up period according to the study groups are detailed in table 2: 95.7% of patients were receiving short-term beta-2 agonists (SABA) as rescue treatment, 27.7% were receiving oral corticosteroids (20% for regular/chronic use) and 18.2% leukotriene antagonists. There was acceptable homogeneity between the groups. Treatment persistence at 12 months was 61.7% (95% CI: 60-63.4%) and, by study group, was as follows: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6% (p=0.046). The MPR was FP/SAL: 74.3%, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%.

Exacerbations by study group are described in table 3. Overall, 21.5% of patients had some form of exacerbation, and the rates were slightly lower in groups treated with FP/FORM and FF/VI. The percentages of patients with exacerbations according to study group were FP/SAL: 21.9% (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), p=0.036. The differences were most evident in patients with severe exacerbations (7.9%, 6.0%, 7.9%, 6.8% and 4.0%, respectively (p<0.001)). The reductions in exacerbations from baseline to 12 months were: FP/SAL: -6.8%, BDP/FORM: -5.9%, BUD/FORM: -6.1%, FF/VI: -8.6% and FP/FORM: -9.3%, respectively (p-0.037). In the multivariate model, the number of exacerbations during the follow-up was associated with previous exacerbations (β-0.798), FEV_1 (β-0.075) and persistence (β-0.011) (p<0.033). The model determination coefficient was 85.1%. Figure 1 details the percentage of exacerbations according to asthma severity and figure 2 shows the median treatment persistence during the follow-up period.

DISCUSSION

The results of the study show that patients initiating fixed-dose treatment with FP/FORM and FF/VI were associated with increased persistence and MPR, resulting in fewer exacerbations compared with other ICS/LABA. Only patients receiving FP/FORM were associated with a lower rate of severe asthma exacerbations. FP/FORM and FF/VI, which are newer combinations, were less often prescribed (7% and 8.2%, respectively).

ICS /LABA are the basis of persistent asthma treatment, although the literature reviewed shows a low rate of adherence to medication (<65% per year)[11,16-17]. A review of 19 studies shows treatment adherence ranged between 22% and 63% and that 24% of exacerbations and 60% of asthma-related hospitalizations were attributable to poor adherence[18]. Zhang[19] found a persistence of 33.6% in children with persistent asthma on monotherapy. Our results are similar or perhaps slightly higher than those reported but are still low. There may be several possible explanations: a) the method of measuring persistence/MPR, b) the dose indicated at the beginning of the study, c) ours is a more recent study, d) the patients who sought care assiduously attended check-ups, and/or e) are subject to specific nursing follow-up. In addition, in the studies reviewed, therapeutic non-compliance was associated with young patients with mild asthma, while fixed combinations improve adherence, as confirmed by our results[18,20].

Our results show that 21.5% of patients had some form of exacerbation, and that the rate was slightly lower in patients treated with FP/FORM and FF/VI. The risk of exacerbations was associated with clinical severity (FEV_1), previous exacerbations, limitations on activity, allergic rhinitis, insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed treatment[20]. Schmidt[21], in a year-long prospective observational, found that treatment with FP/FORM was associated with clinical improvements in asthma (degree of control, severe exacerbation, quality of life and lung function). Usmani[22] studied patients with controlled asthma and found that a reduction in the dose of FP/FORM did not affect exacerbations and was well tolerated. A comparative review of the rate of severe asthma exacerbations observed in clinical trials of different fixed-dose combinations of ICS/LABA by Papi[20] found that the incidence of exacerbations with FP/FORM was lower than that for other combinations of ICS/LABA (especially those that result in hospitalization) and that the difference cannot be explained solely by the characteristics of the studies (design, population, etc.) and could be related to the pharmacological (molecular) characteristics of the combination. A clinical trial of FF/VI also found a lower rate of asthma exacerbations, although it was similar to FP/SAL[23]. Another recent trial found that FF/VI showed better asthma control than habitual optimized treatment, but that there were no differences in the rate of asthma exacerbations[24.] With design limitations, our data is in line with the literature consulted[20,25]. However, the different definitions of asthma exacerbation make comparisons difficult;

in our study the definition of exacerbation was at the clinician's discretion and was based on the use of health resources.

The study has some limitations. Principally those typical of retrospective studies (underreporting / absence of information). In this sense, the categorization of the disease (asthma) and the possible classification bias of patients, including the possible inaccuracy of diagnostic coding about the diagnosis of asthma and other comorbidities, are some examples, attributable to the information system. To reduce this bias, a validation of the variables was carried out before analysis. The definition of exacerbation was analyzed based on the use of resources (administered drugs, hospital admissions) in the absence of a specific coding system. However, it is a consensus criterion in retrospective studies and should affect all the cohorts analyzed in a similar way. In addition, other unmeasured factors could have influenced the results, for example, the socioeconomic level of patients, environmental/work exposure, evolution of the prescribed pharmacological dose, verification of the inhalation technique, including bronchoconstrictor therapy and/or the differentiation of phenotypes. In addition, based on the demand for medical care, non-disease factors may have influenced the results, such as access to health resources, comorbidity or patient specifics, which could cause worsening episodes not to be reported by the patient and therefore remain untreated. It is possible that through a prospective study, some of these factors can be minimized. The capturing patient behavior through treatment persistence cannot be directly assessed through structured data available in electronic databases. Time to discontinuation is assumed to be a proxy to estimate patient persistence. In addition, the external validity of the results with respect to the representativeness of the population and the small number of patients per study group should also be considered as limitations. When using an efficient inhaler therapy[24-25], the factors that most influence compliance include the type of device, the technique used, and the health-education instructions received. However, these limitations should affect all the analyzed cohorts in a similar way and should not affect the external validity of the results.

The future perspectives offered by this study are those of its replication in other health institutions and interventional strategies aimed at promoting patient self-care (structured and individualized educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with increased treatment adherence (persistence, MPR) and lower rates of exacerbations. However, further studies will be needed to strengthen the consistency of the results.

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Table 1. Baseline characteristics of the series studied by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25.0%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	p
Sociodemographic features						
Mean age, years	52.3 (19.3)	53.0 (18.5)	51.0 (16.8)	52.5 (17.7)	52.8 (17.1)	0.245
Sex (female)	60.0%	61.1%	61.6%	61.6%	60.4%	0.968
General comorbidity						
Mean diagnoses	6.8 (3.9)	6.4 (3.9)	6.2 (3.6)	6.3 (3.6)	6.8 (3.8)	0.075
Charlson index	0.8 (0.8)	0.7 (0.8)	0.7 (0.6)	0.7 (0.8)	0.8 (0.9)	0.097
Mean RUB	3.0 (0.7)	2.9 (0.7)	2.9 (0.8)	3.0 (0.8)	2.9 (0.7)	0.198
1 (very low comorbidity)	4.1%	3.6%	8.2%	6.1%	4.9%	
2 (low comorbidity)	10.3%	20.4%	12.5%	13.3%	12.0%	
3 (moderate comorbidity)	71.1%	65.5%	63.1%	56.7%	67.6%	
4 (high comorbidity)	14.0%	9.9%	15.8%	23.6%	14.7%	
5 (very high comorbidity)	0.5%	0.5%	0.4%	0.4%	0.9%	0.111
Associated comorbidity						
High blood pressure	29.9%	28.9%	29.1%	29.3%	29.3%	0.991
Diabetes mellitus	13.4%	12.8%	13.0%	13.3%	12.9%	0.996
Dyslipidemia	41.0%	41.3%	41.3%	40.7%	39.8%	0.811
Obesity	27.9%	28.6%	27.7%	26.2%	27.6%	0.963
Ischemic heart disease	4.3%	4.0%	4.0%	3.8%	4.0%	0.994
Cerebrovascular accident	7.3%	7.0%	7.0%	6.8%	6.7%	0.995
Cardiovascular event	11.8%	9.2%	9.1%	10.6%	10.2%	0.272
Depressive syndrome	19.5%	19.6%	20.2%	20.9%	20.4%	0.982
Malignancies	10.9%	10.5%	10.3%	11.8%	10.2%	0.964
Allergic rhinitis	61.7%	63.1%	61.8%	63.5%	62.2%	0.959
Nasal polyposis	15.5%	15.4%	15.3%	14.1%	16.4%	0.969
Gastroduodenal reflux	39.1%	40.9%	38.0%	41.1%	40.9%	0.739
Asthma severity						
Intermittent	13.0%	14.9%	12.0%	12.5%	12.0%	
Mild persistent	25.0%	21.5%	24.6%	25.1%	25.3%	
Moderate persistent	44.5%	45.1%	45.3%	43.3%	45.4%	
Severe/severe persistent	17.6%	18.4%	18.2%	19.0%	18.2%	0.844
Other variables						
BMI, kg/m^2	28.4 (5)	28.6 (5.0)	28.4 (5.0)	28.6 (5.5)	27.9 (4.9)	0.228
FEV_1 (% theoretical)	74.8%	74.3%	74.7%	74.6%	74.8%	0.954

Values expressed as percentage or mean (standard deviation), p: statistical significance. RUB: Resource utilization bands.
BMI: Body mass index, kg/m^2, FEV_1: Forced expiratory volume in the first second.
Groups: Fluticasone propionate/salmeterol (FP/SAL), Beclomethasone /formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).

Table 2. Medication administered and treatment persistence during the follow-up period

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7.0%)	p
Medication use						
Oral corticosteroids	24.6%	22.8%	26.7%	25.5%	24.9%	0.465
Oral corticosteroids for chronic use	22.0%	18.5%	20.2%	18.6%	18.7%	0.373
Systemic antibiotics	10.0%	9.2%	10.1%	10.3%	10.1%	0.959
Short-lasting beta-2 agonists	90.0%	93.0%	91.2%	89.5%	92.2%	0.221
Long-lasting anticholinergics	17.0%	15.2%	13.8%	16.0%	13.8%	0.414
Systemic beta-2 agonists (xanthines)	3.8%	3.5%	3.2%	5.7%	3.1%	0.431
Leukotriene receptor antagonists	17.7%	17.4%	19.5%	17.5%	19.6%	0.782
Biologicals: omalizumab	1.3%	1.4%	1.2%	1.5%	1.3%	0.997
Inhaled corticosteroid doses						
Low	10.5%	9.8%	10.1%	11.1%	10.7%	
Average	47.1%	46.5%	45.0%	46.2%	47.1%	
High	42.4%	43.7%	44.9%	42.7%	42.2%	0.547
Other variables						
Time from diagnosis, years	12.5 (4.5)	12.7 (4.4)	12.8 (4.2)	12.6 (3.9)	12.3 (3.9)	0.373
Treatment possession, months	8.9 (3.6)	8.9 (3.4)	9.0 (3.3)	9.6 (3.3)*	9.7 (3.1)*	0.046
Duration of treatment, months	9.9 (3.5)	9.7 (3.6)	10.0 (3.5)	10.2 (3.4)*	10.3 (3.2)*	0.036
Medication possession rate	74.3%	73.8%	74.6%	79.4%*	80.6%*	0.028
95% CI	71.6-77.0%	70.5-76.3%	71.6-77.6%	74.5-84.3%	75.4-85.8%	
Treatment persistence, months						
6 months	81.9%	81.2%	82.4%	86.0%*	87.6%*	0.014
12 months	60.7%	61.2%	60.3%	66.7%*	67.6%*	0.046
Death	3.0%	2.7%	3.1%	2.3%	2.7%	0.954

Values expressed as percentage or mean (SD: standard deviation), p: statistical significance. CI: Confidence intervals.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (observed > expected).

Table 3. Exacerbations by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	pd
Follow-up period (one year)						
Exacerbations, %	21.9%	22.2%	22.8%	17.9%*	16.0%*	0.036
Mean exacerbations	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)	0.3 (0.8)	0.3 (0.8)	0.087
Number of exacerbations/year						
0	78.1%	78.3%	77.2%	82.1%	84.0%	
1	15.0%	14.9%	13.8%	9.9%	7.1%	
2	2.9%	2.6%	5.5%	1.9%	5.3%	
3+	4.0%	4.1%	3.5%	6.1%	3.6%	<0.001
Patients with exacerbations						
Mild-Moderate	20.1%	21.7%	22.2%	17.5%*	16.0%*	<0.001
Severe (hospital admission)	7.9%	6.0%	7.9%	6.8%	4.0%*	<0.001
Previous year (pre-index)						
Exacerbations, %	28.7%	28.1%	28.9%	25.5%	25.3%	0.698
Mean exacerbations	0.5 (0.9)	0.5 (0.9)	0.5 (0.9)	0.5 (1.0)	0.4 (0.9)	0.973
Number of exacerbations/year						
0	71.3%	71.9%	71.1%	74.5%	74.7%	
1	17.1%	15.3%	15.1%	14.1%	15.6%	
2	5.9%	8.4%	9.1%	3.0%	2.7%	
3+	5.7%	4.5%	4.7%	8.4%	7.1%	<0.001
Patients with exacerbations						
Mild-Moderate	27.5%	27.4%	28.7%	24.1%	25.4%	0.111
Severe (hospital admission)	11.7%	10.8%	12.2%	10.6%	10.7%	0.217
Differences between the two periods						
Exacerbations, %	-6.8%	-5.9%	-6.1%	-8.6%*	-9.3%*	0.037
Mild-Moderate	-7.4%	-5.7%	-6.5%	-7.6%	-8.4%	0.282
Severe (hospital admission)	-3.8%	-4.8%	-4.4%	-5.8%*	-6.7%*	0.044

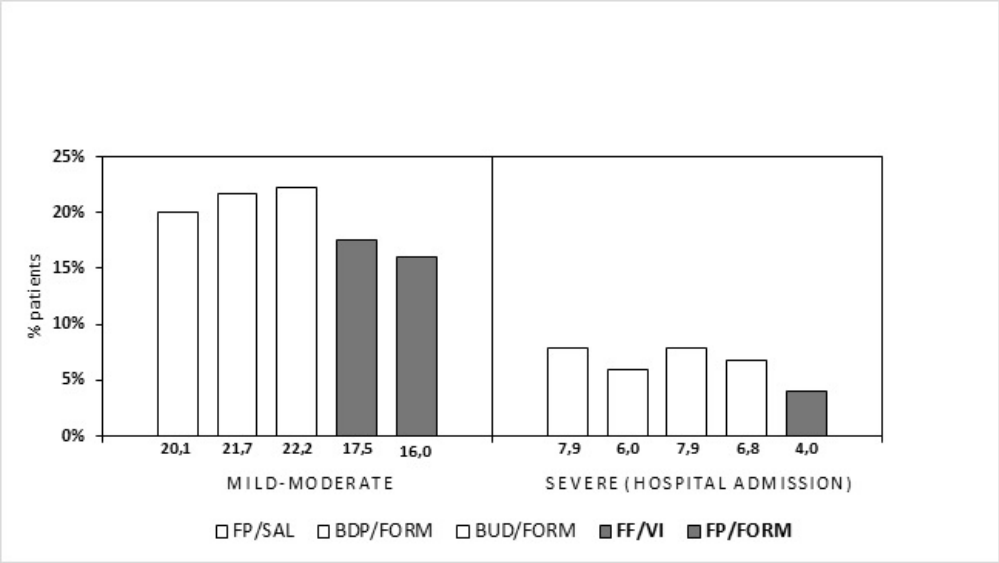
Values expressed as percentage or mean (SD: standard deviation), p: statistical significance.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (effects observed > expected).

Figure 1. Percentage of patients with exacerbations according to their severity

Values expressed as a percentage of patients with exacerbations during the follow-up year.
In grey, statistically significant results ($p<0.05$).
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM).

Figure 2. Median treatment persistence during the follow-up period

Kaplan-Meier Curve: Log Rank Procedure (Mantel-Cox): Chi-square-9,643; p-0.039.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).



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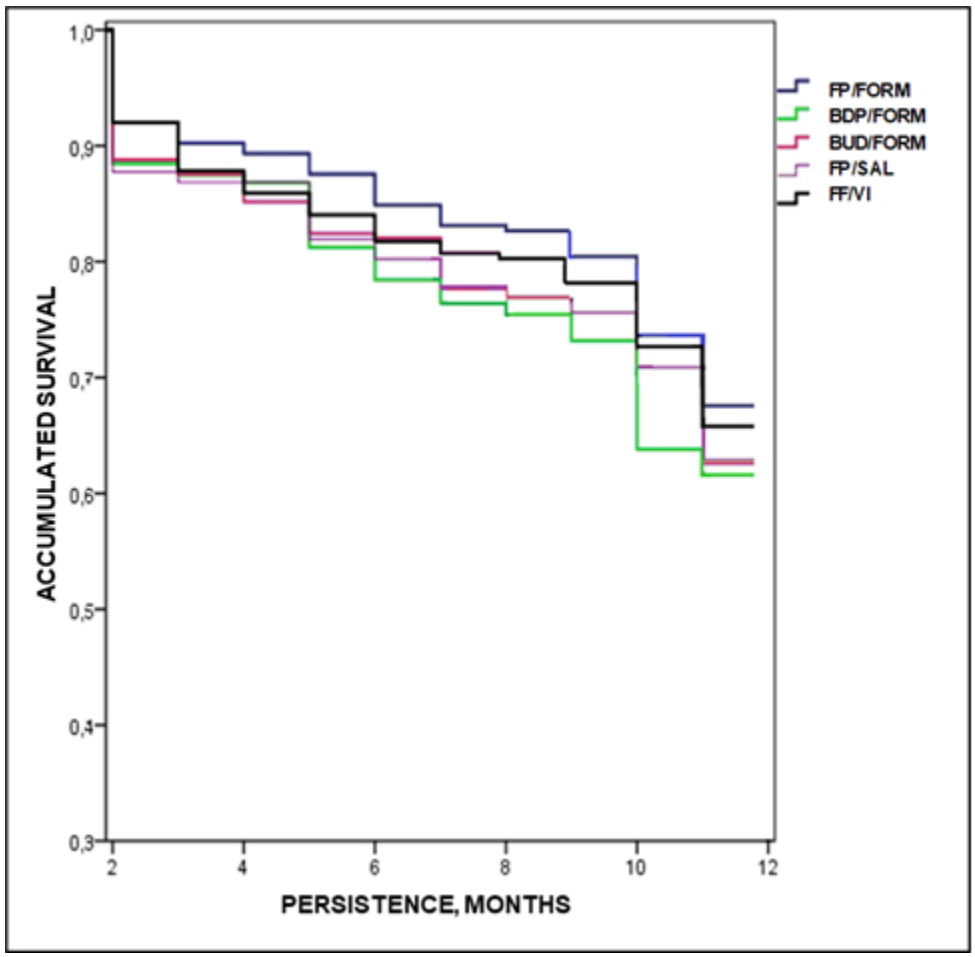

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Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and beta-adrenergic agonists: retrospective cohort study

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Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and beta-adrenergic agonists: retrospective cohort study

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ABBREVIATIONS

Abbreviation	Description
ATC	Anatomical Therapeutic Chemical Classification System
BDP/FORM	Beclomethasone/formoterol
BUD/FORM	Budesonide/formoterol
FEV_1	Maximum expiratory volume in the first second
FF/VI	Fluticasone furoate/vilanterol
FP/FORM	Fluticasone propionate/formoterol
FP/SAL	Fluticasone propionate/salmeterol
ICS	Inhaled corticosteroid
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist

FUNDING
Associates of Vectura licensed a formoterol/fluticasone inhaler to Mundipharma Pharmaceuticals. Mundipharma has since developed, registered, marketed and distributed this product and sponsored this study. This study was designed and completed prior to acquisition of Vectura by Philip Morris International.

CONFLICT OF INTEREST
A. Sicras is an independent consultant funded by Mundipharma with respect to this manuscript. ST and TF are employees of Mundipharma. The other authors state they have no conflict of interest in relation to this study.

AUTHOR CONTRIBUTIONS
AS and TF participated in the planning, coordination, conception and design of the study. AS and TF were responsible for data acquisition. AS performed the statistical analysis. AS, BG, ST, TF and JLV reviewed the results report. AS, BG, ST, TF and JLV participated in the critical interpretation of the data obtained, the writing of the manuscript (review) and the final approval of the version to be published. Additionally, AS, BG, ST, TF and JLV were responsible for ensuring the adequacy of all aspects of the study.

ETHICS APPROVAL
His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

DATA AVAILABILITY
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

PATIENT CONSENT FOR PUBLICATION.
Not required.

STROBE Statement—Checklist of items that should be included in reports of *observational studies.*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalizability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled corticosteroids and long-acting beta2-adrenergic agonists: retrospective cohort study

ABSTRACT

Objective. To determine treatment persistence and exacerbations in patients initiating inhaler treatment with fixed-dose combinations of inhaled corticosteroids/long-acting beta2-adrenergic agonists (ICS/LABA) for the treatment of asthma.

Design. Retrospective observational study conducted by review of electronic medical records (database: Fundacion RedISS).

Setting. Retrospective cohort study. The follow-up period was one year.

Participants The study included patients aged ≥18 years who started treatment with ICS/LABA and met the inclusion/exclusion criteria.

Main outcomes and measures. The study groups were fluticasone propionate/salmeterol (FP/SAL), beclomethasone/formoterol (BDP/FORM), budesonide/formoterol (BUD/FORM), fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate/formoterol (FP/FORM). The main measurements were persistence, medication possession ratio (MPR), and exacerbations. Statistical significance was established as $p<0.05$.

Results. In total, 3,203 patients were recruited for the study. By groups, 31.1% FP/SAL, 28.6% BDP/FORM, 25.0% BUD/FORM, 8.2% FF/VI, and 7.0% FP/FORM. The mean age was 52.2 years, 60.8% were female, and 44.9% had persistent-moderate asthma. Treatment persistence was 61.7% (95% CI: 60.0-63.4%) and by study groups it was: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6%, (p=0.046). MPR by study group was FP/SAL: 74.3, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%. By treatment group, exacerbations were FP/SAL: 21.9% (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), p=0.036.

Conclusions. Patients undergoing treatment with FP/FORM and FF/VI vs. FP/SAL, BDP/FORM, BUD/FORM, were associated with greater treatment adherence (persistence, MPR) and lower rates of exacerbations. However, further studies will be needed to strengthen the consistency of the results.

Keywords: asthma, persistence, exacerbations, ICS/LABA.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Reducing the risk of exacerbations is an important goal in the treatment of asthma. However, in our country there are few studies that evaluate this by analyzing the effect of double inhalation therapy at the level of active ingredient (molecule).
- The results of the study were obtained in a situation of routine clinical practice, far from the idyllic conditions of randomized clinical trials. This circumstance can be interpreted as a strength of the study, since the data are potentially more generalizable, showing greater external validity of the observed results.
- This study has the limitations of retrospective observational studies; for example, the possible underreporting of information, the difficulty in measuring the confounding variables and the impossibility of establishing a causal relationship between the variables.

INTRODUCTION

Asthma is a chronic inflammatory airway disease that courses with bronchial hyper-response and variable airflow blockage[1]. In Spain, the prevalence is around 5%, although there are variations between geographical areas[2]. Most patients achieve adequate control with inhaled corticosteroids (ICS) and long-lasting beta-adrenergic agonists (LABA), although some patients require additional therapy with other medications, including oral corticosteroids (OC)[1-2].

Reducing the risk of exacerbations is an important goal of asthma treatment[3-5]. It is estimated that 30-52% of patients with asthma have exacerbations of varying intensity[2,6]. Factors influencing an increased risk of exacerbations include previous exacerbations, poor asthma control, limitations on activity, lower forced expiratory volume in the first second (FEV_1), exposure to allergens, difficulty handling inhalation devices and treatment adherence[7]. Studies show anti-asthmatic adherence rates of <65%[1-2,7]. The most common cause of treatment discontinuation are side effects, improvements in symptoms and problems in reducing the effect of the drug over time, which lead to discontinuation being advised or spontaneous abandonment[7-10].

In Spain, there are few studies evaluating the relationship between the adherence rate and the risk of exacerbations[11]. Persistence (or discontinuation) of treatment is a key factor in disease progression and the risk of complications. In addition, there is a growing need to conduct studies representative of the real-life clinical conditions in which medicines are used, so the study may be of interest. The objective of the study was to evaluate treatment persistence and exacerbations in patients initiating inhaler treatment with combinations of ICS/LABA for the treatment of asthma in routine clinical practice.

PATIENTS AND METHODS

We performed a retrospective observational analysis of electronic medical records (EMR) obtained from the administrative database of the RediSS Foundation (Health services research network; www.rediss.es), a source of secondary data. The primary data came from various primary care centers in Catalonia (Spain), which are computerized with the OMIAPWIN (EMR). Before export to RediSS Foundation, data are rigorously anonymized and it is not possible to identify the territory, health care provider, treating physician, or patient or access any other information that would permit individual identification. This procedure ensures adherence to current law governing the protection of personal data. The population assigned to the centers was mostly urban, of medium-low socioeconomic level.

Patients who sought care and initiated treatment with a fixed dose ICS/LABA combination between 01/01/2015 and 30/06/2016 (recruitment period, index date) were included in the study. The inclusion criteria were: (a) ≥ 18 years, (b) patients diagnosed with asthma ≥12 months before the index date, c) inclusion in the prescription program (with recorded dose, time interval and duration of each treatment administered; ≥ 2 prescriptions during the follow-up period), and (d) ensured regular monitoring (≥ 2 clinical records in the computer system). Exclusion criteria were: (a) patients transferred to other centers, displaced or out-of-area, (b) permanently institutionalized patients, (c) a history of COPD, pulmonary emphysema, bronchiectasis, cystic fibrosis or bronchial neoplasm, and d) mixed asthma-COPD phenotype (asthma-COPD overlap)[1].

Five study groups were differentiated according to the initial fixed-dose combination of ICS/LABA: Budesonide /formoterol (BUD/FORM, R03AK07), Beclomethasone /formoterol (BDP/FORM, R03AK08), Fluticasone furoate/vilanterol (FF/VI, R03AK10), Fluticasone propionate/formoterol (FP/FORM, R03AK11) and Fluticasone propionate/salmeterol (FP/SAL, R03AK06). The follow-up period, from the date of inclusion of the patient was one year. Records of asthma patients were obtained using the International Classification of Primary Care in the European Community (ICPC-2; R93)[12], and/or the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9-MC; 493.x for asthma and/or flare-ups). The diagnosis of asthma was always made at the physician's discretion, according to spirometry values. Exacerbations were defined as an event in the natural course of the disease characterized by acute episodes identified by a progressive increase in breathing difficulties, feeling short of breath, wheezing, chest oppression or a combination of these symptoms, caused by intense airflow obstruction[1]. Outpatients or those attending the emergency department (mild-moderate asthma exacerbation) and hospitalized patients (severe asthma exacerbation) were identified. The record of each exacerbation was obtained to assess the rates before and after the index date, and the time from diagnosis (in years). In addition, the following variables were collected: body mass index (BMI, kg/m$^{2)}$, lung function (forced expiratory volume in the first second, FEV_1), asthma severity (intermittent, mild persistent,

moderate persistent and severe persistent according to the GEMA criteria[1] at the start of the study before the index date. All-cause deaths were recorded.

Sociodemographic and comorbidity variables collected were age (continuous and by range), sex, and the personal history described in table 1. As a summary variable of general comorbidity: a) the Charlson[13] comorbidity index was used as an approximation to severity, b) the number of chronic comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted Clinical Groups (ACG), which is a patient classification system using iso-consumption of resources[14]. The ACG application provides resource utilization bands (RUB), allowing each patient to be grouped into one of five mutually exclusive categories based on their overall morbidity.

The medicines (active substances) indicated for treatment were obtained according to the Anatomical Therapeutic Chemical Classification System (ATC)[15] classification: oral/systemic corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA, R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient was at the discretion of the physician, as in routine clinical practice. The information was obtained from drug dispensing records. The scheduled dose of ICS administered was classified at low, medium or high[1]. Treatment persistence was calculated from the index date to the discontinuation date in months. The discontinuation date was the date on which the patient switched to another ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of follow-up. The percentage of therapeutic compliance was calculated based on the medicine possession ratio (MPR)[16]. This was evaluated from the first to the last prescription and represented the number of days of medication dispensed according to the number of days on treatment from the index date.

Records were validated to ensure the quality of the results. A descriptive-univariate statistical analysis was carried out. Qualitative data were described using absolute and relative frequencies and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI) used to estimate parameters were based on the total number of subjects with no missing values. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A multiple linear regression model was used to obtain the variables associated with the number of exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the model were: sex, age, general comorbidity (RUB), FEV_1, disease duration and asthma severity.

Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The analysis was made using SPSSWIN version 23. Statistical significance was established as $p<0.05$.

Ethics Approval: His protocol was reviewed and approved at Foundation RediSS (Ethical Research Committee; International University of Catalonia; code: ANT-PER-2017-01).

Patient and public involvement

Patients/the public were not involved in developing this research question, designing the study, or providing input to study conduct.

RESULTS

Of an initial population of 8,725 subjects diagnosed with asthma (prevalence: 5.4%; 95% CI: 5.2-5.7%), 3,203 patients who met the inclusion/exclusion criteria and could be followed during the study period were analysed. Table 1 shows the baseline characteristics of participants according to the five ICS/LABA study groups. The mean age was 52.2 years, 60.8% were women, the mean RUB was 2.9 points, and the mean Charlson index was 0.7 points. Allergic rhinitis (62.3%), dyslipidemia (41%), gastroesophageal reflux (39.6%) and high blood pressure (28.4%) were the most frequent comorbidities: 44.9% of patients had persistent-moderate asthma, with a mean FEV_1 of 74.6%. According to the initial ICS/LABA prescribed, the study groups were as follows: 31.1% (N=996) FP/SAL, 28.6% (N=917) BDP/FORM, 25% (N=802) BUD/FORM, 8.2% (N=263) FF/VI and 7.0% (N=225) FP/FORM. There was acceptable comparability in the baseline characteristics of the study groups.

Medication administered and treatment adherence (persistence and MPR) during the follow-up period according to the study groups are detailed in table 2: 95.7% of patients were receiving short-term beta-2 agonists (SABA) as rescue treatment, 27.7% were receiving oral corticosteroids (20% for regular/chronic use) and 18.2% leukotriene antagonists. There was acceptable homogeneity between the groups. Treatment persistence at 12 months was 61.7% (95% CI: 60-63.4%) and, by study group, was as follows: FP/SAL: 60.7%, BDP/FORM: 61.2%, BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6% (p=0.046). The MPR was FP/SAL: 74.3%, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6% (p=0.028). The mortality rate was 2.9%.

Exacerbations by study group are described in table 3. Overall, 21.5% of patients had some form of exacerbation, and the rates were slightly lower in groups treated with FP/FORM and FF/VI. The percentages of patients with exacerbations according to study group were FP/SAL: 21.9% (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), p=0.036. The differences were most evident in patients with severe exacerbations (7.9%, 6.0%, 7.9%, 6.8% and 4.0%, respectively (p<0.001)). The reductions in exacerbations from baseline to 12 months were: FP/SAL: -6.8%, BDP/FORM: -5.9%, BUD/FORM: -6.1%, FF/VI: -8.6% and FP/FORM: -9.3%, respectively (p-0.037). In the multivariate model, the number of exacerbations during the follow-up was associated with previous exacerbations (β-0.798), FEV_1 (β-0.075) and persistence (β-0.011) (p<0.033). The model determination coefficient was 85.1%. Figure 1 details the percentage of exacerbations according to asthma severity and figure 2 shows the median treatment persistence during the follow-up period.

DISCUSSION

The results of the study show that patients initiating fixed-dose treatment with FP/FORM and FF/VI were associated with increased persistence and MPR, resulting in fewer exacerbations compared with other ICS/LABA. Only patients receiving FP/FORM were associated with a lower rate of severe asthma exacerbations. FP/FORM and FF/VI, which are newer combinations, were less often prescribed (7% and 8.2%, respectively).

ICS /LABA are the basis of persistent asthma treatment, although the literature reviewed shows a low rate of adherence to medication (<65% per year)[11,16-17]. A review of 19 studies shows treatment adherence ranged between 22% and 63% and that 24% of exacerbations and 60% of asthma-related hospitalizations were attributable to poor adherence[18]. Zhang[19] found a persistence of 33.6% in children with persistent asthma on monotherapy. Our results are similar or perhaps slightly higher than those reported but are still low. There may be several possible explanations: a) the method of measuring persistence/MPR, b) the dose indicated at the beginning of the study, c) ours is a more recent study, d) the patients who sought care assiduously attended check-ups, and/or e) are subject to specific nursing follow-up. In addition, in the studies reviewed, therapeutic non-compliance was associated with young patients with mild asthma, while fixed combinations improve adherence, as confirmed by our results[18,20].

Our results show that 21.5% of patients had some form of exacerbation, and that the rate was slightly lower in patients treated with FP/FORM and FF/VI. The risk of exacerbations was associated with clinical severity (FEV_1), previous exacerbations, limitations on activity, allergic rhinitis, insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed treatment[20]. Schmidt[21], in a year-long prospective observational, found that treatment with FP/FORM was associated with clinical improvements in asthma (degree of control, severe exacerbation, quality of life and lung function). Usmani[22] studied patients with controlled asthma and found that a reduction in the dose of FP/FORM did not affect exacerbations and was well tolerated. A comparative review of the rate of severe asthma exacerbations observed in clinical trials of different fixed-dose combinations of ICS/LABA by Papi[20] found that the incidence of exacerbations with FP/FORM was lower than that for other combinations of ICS/LABA (especially those that result in hospitalization) and that the difference cannot be explained solely by the characteristics of the studies (design, population, etc.) and could be related to the pharmacological (molecular) characteristics of the combination. A clinical trial of FF/VI also found a lower rate of asthma exacerbations, although it was similar to FP/SAL[23]. Another recent trial found that FF/VI showed better asthma control than habitual optimized treatment, but that there were no differences in the rate of asthma exacerbations[24.] With design limitations, our data is in line with the literature consulted[20,25]. However, the different definitions of asthma exacerbation make comparisons difficult;

in our study the definition of exacerbation was at the clinician's discretion and was based on the use of health resources[26-27].

The study has some limitations. Principally those typical of retrospective studies (underreporting / absence of information). In this sense, the categorization of the disease (asthma) and the possible classification bias of patients, including the possible inaccuracy of diagnostic coding about the diagnosis of asthma and other comorbidities, are some examples, attributable to the information system. To reduce this bias, a validation of the variables was carried out before analysis. The definition of exacerbation was analyzed based on the use of resources (administered drugs, hospital admissions) in the absence of a specific coding system. However, it is a consensus criterion in retrospective studies and should affect all the cohorts analyzed in a similar way. In addition, other unmeasured factors could have influenced the results, for example, the socioeconomic level of patients, environmental/work exposure, evolution of the prescribed pharmacological dose, verification of the inhalation technique, including bronchoconstrictor therapy and/or the differentiation of phenotypes. In addition, based on the demand for medical care, non-disease factors may have influenced the results, such as access to health resources, comorbidity or patient specifics, which could cause worsening episodes not to be reported by the patient and therefore remain untreated. It is possible that through a prospective study, some of these factors can be minimized. The capturing patient behavior through treatment persistence cannot be directly assessed through structured data available in electronic databases. Time to discontinuation is assumed to be a proxy to estimate patient persistence. In addition, the external validity of the results with respect to the representativeness of the population and the small number of patients per study group should also be considered as limitations. When using an efficient inhaler therapy[24-25], the factors that most influence compliance include the type of device, the technique used, and the health-education instructions received. However, these limitations should affect all the analyzed cohorts in a similar way and should not affect the external validity of the results.

The future perspectives offered by this study are those of its replication in other health institutions and interventional strategies aimed at promoting patient self-care (structured and individualized educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with increased treatment adherence (persistence, MPR) and lower rates of exacerbations. However, further studies will be needed to strengthen the consistency of the results.

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Table 1. Baseline characteristics of the series studied by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25.0%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	p
Sociodemographic features						
Mean age, years	52.3 (19.3)	53.0 (18.5)	51.0 (16.8)	52.5 (17.7)	52.8 (17.1)	0.245
Sex (female)	60.0%	61.1%	61.6%	61.6%	60.4%	0.968
General comorbidity						
Mean diagnoses	6.8 (3.9)	6.4 (3.9)	6.2 (3.6)	6.3 (3.6)	6.8 (3.8)	0.075
Charlson index	0.8 (0.8)	0.7 (0.8)	0.7 (0.6)	0.7 (0.8)	0.8 (0.9)	0.097
Mean RUB	3.0 (0.7)	2.9 (0.7)	2.9 (0.8)	3.0 (0.8)	2.9 (0.7)	0.198
1 (very low comorbidity)	4.1%	3.6%	8.2%	6.1%	4.9%	
2 (low comorbidity)	10.3%	20.4%	12.5%	13.3%	12.0%	
3 (moderate comorbidity)	71.1%	65.5%	63.1%	56.7%	67.6%	
4 (high comorbidity)	14.0%	9.9%	15.8%	23.6%	14.7%	
5 (very high comorbidity)	0.5%	0.5%	0.4%	0.4%	0.9%	0.111
Associated comorbidity						
High blood pressure	29.9%	28.9%	29.1%	29.3%	29.3%	0.991
Diabetes mellitus	13.4%	12.8%	13.0%	13.3%	12.9%	0.996
Dyslipidemia	41.0%	41.3%	41.3%	40.7%	39.8%	0.811
Obesity	27.9%	28.6%	27.7%	26.2%	27.6%	0.963
Ischemic heart disease	4.3%	4.0%	4.0%	3.8%	4.0%	0.994
Cerebrovascular accident	7.3%	7.0%	7.0%	6.8%	6.7%	0.995
Cardiovascular event	11.8%	9.2%	9.1%	10.6%	10.2%	0.272
Depressive syndrome	19.5%	19.6%	20.2%	20.9%	20.4%	0.982
Malignancies	10.9%	10.5%	10.3%	11.8%	10.2%	0.964
Allergic rhinitis	61.7%	63.1%	61.8%	63.5%	62.2%	0.959
Nasal polyposis	15.5%	15.4%	15.3%	14.1%	16.4%	0.969
Gastroduodenal reflux	39.1%	40.9%	38.0%	41.1%	40.9%	0.739
Asthma severity						
Intermittent	13.0%	14.9%	12.0%	12.5%	12.0%	
Mild persistent	25.0%	21.5%	24.6%	25.1%	25.3%	
Moderate persistent	44.5%	45.1%	45.3%	43.3%	45.4%	
Severe/severe persistent	17.6%	18.4%	18.2%	19.0%	18.2%	0.844
Other variables						
BMI, kg/m^2	28.4 (5)	28.6 (5.0)	28.4 (5.0)	28.6 (5.5)	27.9 (4.9)	0.228
FEV_1 (% theoretical)	74.8%	74.3%	74.7%	74.6%	74.8%	0.954

Values expressed as percentage or mean (standard deviation), p: statistical significance. RUB: Resource utilization bands.
BMI: Body mass index, kg/m^2, FEV_1: Forced expiratory volume in the first second.
Groups: Fluticasone propionate/salmeterol (FP/SAL), Beclomethasone /formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).

Table 2. Medication administered and treatment persistence during the follow-up period

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7.0%)	p
Medication use						
Oral corticosteroids	24.6%	22.8%	26.7%	25.5%	24.9%	0.465
Oral corticosteroids for chronic use	22.0%	18.5%	20.2%	18.6%	18.7%	0.373
Systemic antibiotics	10.0%	9.2%	10.1%	10.3%	10.1%	0.959
Short-lasting beta-2 agonists	90.0%	93.0%	91.2%	89.5%	92.2%	0.221
Long-lasting anticholinergics	17.0%	15.2%	13.8%	16.0%	13.8%	0.414
Systemic beta-2 agonists (xanthines)	3.8%	3.5%	3.2%	5.7%	3.1%	0.431
Leukotriene receptor antagonists	17.7%	17.4%	19.5%	17.5%	19.6%	0.782
Biologicals: omalizumab	1.3%	1.4%	1.2%	1.5%	1.3%	0.997
Inhaled corticosteroid doses						
Low	10.5%	9.8%	10.1%	11.1%	10.7%	
Average	47.1%	46.5%	45.0%	46.2%	47.1%	
High	42.4%	43.7%	44.9%	42.7%	42.2%	0.547
Other variables						
Time from diagnosis, years	12.5 (4.5)	12.7 (4.4)	12.8 (4.2)	12.6 (3.9)	12.3 (3.9)	0.373
Treatment possession, months	8.9 (3.6)	8.9 (3.4)	9.0 (3.3)	9.6 (3.3)*	9.7 (3.1)*	0.046
Duration of treatment, months	9.9 (3.5)	9.7 (3.6)	10.0 (3.5)	10.2 (3.4)*	10.3 (3.2)*	0.036
Medication possession rate	74.3%	73.8%	74.6%	79.4%*	80.6%*	0.028
95% CI	71.6-77.0%	70.5-76.3%	71.6-77.6%	74.5-84.3%	75.4-85.8%	
Treatment persistence, months						
6 months	81.9%	81.2%	82.4%	86.0%*	87.6%*	0.014
12 months	60.7%	61.2%	60.3%	66.7%*	67.6%*	0.046
Death	3.0%	2.7%	3.1%	2.3%	2.7%	0.954

Values expressed as percentage or mean (SD: standard deviation), p: statistical significance. CI: Confidence intervals.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (observed > expected).

Table 3. Exacerbations by study groups

Study groups Number of patients, %	FP/SAL N=996 (31.1%)	BDP/FORM N=917 (28.6%)	BUD/FORM N=802 (25%)	FF/VI N=263 (8.2%)	FP/FORM N=225 (7%)	pd
Follow-up period (one year)						
Exacerbations, %	21.9%	22.2%	22.8%	17.9%*	16.0%*	0.036
Mean exacerbations	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)	0.3 (0.8)	0.3 (0.8)	0.087
Number of exacerbations/year						
0	78.1%	78.3%	77.2%	82.1%	84.0%	
1	15.0%	14.9%	13.8%	9.9%	7.1%	
2	2.9%	2.6%	5.5%	1.9%	5.3%	
3+	4.0%	4.1%	3.5%	6.1%	3.6%	<0.001
Patients with exacerbations						
Mild-Moderate	20.1%	21.7%	22.2%	17.5%*	16.0%*	<0.001
Severe (hospital admission)	7.9%	6.0%	7.9%	6.8%	4.0%*	<0.001
Previous year (pre-index)						
Exacerbations, %	28.7%	28.1%	28.9%	25.5%	25.3%	0.698
Mean exacerbations	0.5 (0.9)	0.5 (0.9)	0.5 (0.9)	0.5 (1.0)	0.4 (0.9)	0.973
Number of exacerbations/year						
0	71.3%	71.9%	71.1%	74.5%	74.7%	
1	17.1%	15.3%	15.1%	14.1%	15.6%	
2	5.9%	8.4%	9.1%	3.0%	2.7%	
3+	5.7%	4.5%	4.7%	8.4%	7.1%	<0.001
Patients with exacerbations						
Mild-Moderate	27.5%	27.4%	28.7%	24.1%	25.4%	0.111
Severe (hospital admission)	11.7%	10.8%	12.2%	10.6%	10.7%	0.217
Differences between the two periods						
Exacerbations, %	-6.8%	-5.9%	-6.1%	-8.6%*	-9.3%*	0.037
Mild-Moderate	-7.4%	-5.7%	-6.5%	-7.6%	-8.4%	0.282
Severe (hospital admission)	-3.8%	-4.8%	-4.4%	-5.8%*	-6.7%*	0.044

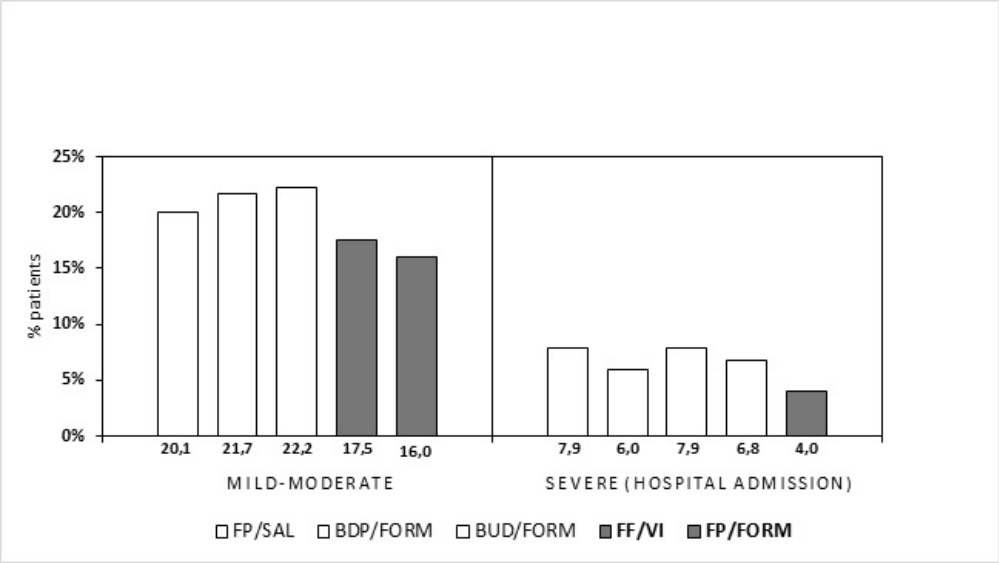
Values expressed as percentage or mean (SD: standard deviation), p: statistical significance.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM). *: Statistically significant results (effects observed > expected).

Figure 1. Percentage of patients with exacerbations according to their severity

Values expressed as a percentage of patients with exacerbations during the follow-up year.
In grey, statistically significant results ($p<0.05$).
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate/formoterol (FP/FORM).

Figure 2. Median treatment persistence during the follow-up period

Kaplan-Meier Curve: Log Rank Procedure (Mantel-Cox): Chi-square-9,643; p-0.039.
Groups: Fluticasone propionate /salmeterol (FP/SAL), Beclomethasone/formoterol (BDP/FORM), Budesonide/formoterol (BUD/FORM), Fluticasone furoate/vilanterol (FF/VI) and Fluticasone propionate /formoterol (FP/FORM).



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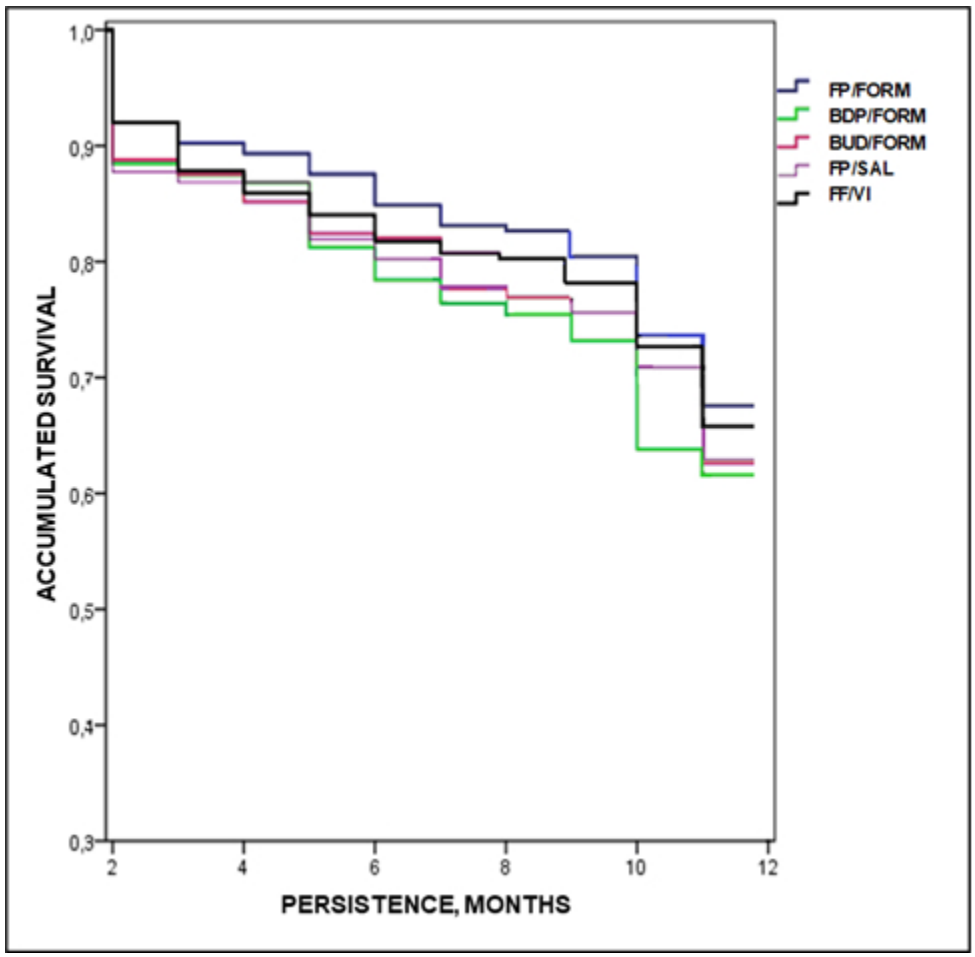

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