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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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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

The study was sponsored by Mundipharma Pharmaceuticals.

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

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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% ($p=0.036$).

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 blockage¹. In Spain, the prevalence is around 5%, although there are variations between geographical areas². 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 treatment³. 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 (FEV₁), exposure to allergens, difficulty handling inhalation devices and treatment adherence⁷. 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 abandonment⁷⁻¹⁰.

In Spain, there are few studies evaluating the relationship between the adherence rate and the risk of exacerbations¹¹. 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

1 regular monitoring (≥ 2 clinical records in the computer system). Exclusion criteria were: (a) patients
2 transferred to other centers, displaced or out-of-area, (b) permanently institutionalized patients, (c)
3 a history of COPD, pulmonary emphysema, bronchiectasis, cystic fibrosis or bronchial neoplasm,
4 and d) mixed asthma-COPD phenotype (asthma-COPD overlap)¹.
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10 Five study groups were differentiated according to the initial fixed-dose combination of ICS/LABA:
11 Budesonide /formoterol (BUD/FORM, R03AK07), Beclomethasone /formoterol (BDP/FORM,
12 R03AK08), Fluticasone furoate/vilanterol (FF/VI, R03AK10), Fluticasone propionate/formoterol
13 (FP/FORM, R03AK11) and Fluticasone propionate/salmeterol (FP/SAL, R03AK06). The follow-up
14 period, from the date of inclusion of the patient was one year. Records of asthma patients were
15 obtained using the International Classification of Primary Care in the European Community (ICPC-
16 2; R93)¹², and/or the International Classification of Diseases (ninth edition) Clinical Modification
17 (ICD-9-MC; 493.x for asthma and/or flare-ups). The diagnosis of asthma was always made at the
18 physician's discretion, according to spirometry values. Exacerbations were defined as an event in
19 the natural course of the disease characterized by acute episodes identified by a progressive
20 increase in breathing difficulties, feeling short of breath, wheezing, chest oppression or a
21 combination of these symptoms, caused by intense airflow obstruction¹. Outpatients or those
22 attending the emergency department (mild-moderate asthma exacerbation) and hospitalized
23 patients (severe asthma exacerbation) were identified. The record of each exacerbation was
24 obtained to assess the rates before and after the index date, and the time from diagnosis (in years).
25 In addition, the following variables were collected: body mass index (BMI, kg/m²), lung function
26 (forced expiratory volume in the first second, FEV₁), asthma severity (intermittent, mild persistent,
27 moderate persistent and severe persistent according to the GEMA criteria¹ at the start of the study
28 before the index date. All-cause deaths were recorded.
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41 Sociodemographic and comorbidity variables collected were age (continuous and by range), sex,
42 and the personal history described in table 1. As a summary variable of general comorbidity: a) the
43 Charlson¹³ comorbidity index was used as an approximation to severity, b) the number of chronic
44 comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted
45 Clinical Groups (ACG), which is a patient classification system using iso-consumption of
46 resources¹⁴. The ACG application provides resource utilization bands (RUB), allowing each patient
47 to be grouped into one of five mutually exclusive categories based on their overall morbidity.
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53 The medicines (active substances) indicated for treatment were obtained according to the
54 Anatomical Therapeutic Chemical Classification System (ATC)¹⁵ classification: oral/systemic
55 corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2
56 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA,
57 R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients
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1 receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those
2 receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient
3 was at the discretion of the physician, as in routine clinical practice. The information was obtained
4 from drug dispensing records. The scheduled dose of ICS administered was classified at low,
5 medium or high¹. Treatment persistence was calculated from the index date to the discontinuation
6 date in months. The discontinuation date was the date on which the patient switched to another
7 ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2
8 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of
9 follow-up. The percentage of therapeutic compliance was calculated based on the medicine
10 possession ratio (MPR)¹⁶. This was evaluated from the first to the last prescription and represented
11 the number of days of medication dispensed according to the number of days on treatment from
12 the index date.

22 Records were validated to ensure the quality of the results. A descriptive-univariate statistical
23 analysis was carried out. Qualitative data were described using absolute and relative frequencies
24 and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI)
25 used to estimate parameters were based on the total number of subjects with no missing values.
26 The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate
27 analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A
28 multiple linear regression model was used to obtain the variables associated with the number of
29 exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the
30 model were: sex, age, general comorbidity (RUB), FEV₁, disease duration and asthma severity.
31 Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The
32 analysis was made using SPSSWIN version 23. Statistical significance was established as $p < 0.05$.

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

44 *Patient and public involvement: no patient involved.*

47 RESULTS

48 Of an initial population of 8,725 subjects diagnosed with asthma (prevalence: 5.4%; 95% CI: 5.2-
49 5.7%), 3,203 patients who met the inclusion/exclusion criteria and could be followed during the
50 study period were analysed. Table 1 shows the baseline characteristics of participants according to
51 the five ICS/LABA study groups. The mean age was 52.2 years, 60.8% were women, the mean
52 RUB was 2.9 points, and the mean Charlson index was 0.7 points. Allergic rhinitis (62.3%),
53 dyslipidemia (41%), gastroesophageal reflux (39.6%) and high blood pressure (28.4%) were the
54 most frequent comorbidities: 44.9% of patients had persistent-moderate asthma, with a mean FEV₁
55 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 ($\beta=0.798$), FEV₁ ($\beta=0.075$) and persistence ($\beta=0.011$) ($p<0.033$). 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 adherence¹⁸. Zhang¹⁹ found a persistence of 33.6% in children with persistent asthma on monotherapy. Our results are similar or perhaps slightly

1 higher than those reported but are still low. There may be several possible explanations: a) the
2 method of measuring persistence/MPR, b) the dose indicated at the beginning of the study, c) ours
3 is a more recent study, d) the patients who sought care assiduously attended check-ups, and/or e)
4 are subject to specific nursing follow-up. In addition, in the studies reviewed, therapeutic non-
5 compliance was associated with young patients with mild asthma, while fixed combinations improve
6 adherence, as confirmed by our results^{18,20}.
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12 Our results show that 21.5% of patients had some form of exacerbation, and that the rate was
13 slightly lower in patients treated with FP/FORM and FF/VI. The risk of exacerbations was associated
14 with clinical severity (FEV₁), previous exacerbations, limitations on activity, allergic rhinitis,
15 insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed
16 treatment²⁰. Schmidt²¹, in a year-long prospective observational real-life study, found that treatment
17 with FP/FORM was associated with clinical improvements in asthma (degree of control, severe
18 exacerbation, quality of life and lung function). Usmani²² studied patients with controlled asthma
19 and found that a reduction in the dose of FP/FORM did not affect exacerbations and was well
20 tolerated. A comparative review of the rate of severe asthma exacerbations observed in clinical
21 trials of different fixed-dose combinations of ICS/LABA by Papi²⁰ found that the incidence of
22 exacerbations with FP/FORM was lower than that for other combinations of ICS/LABA (especially
23 those that result in hospitalization) and that the difference cannot be explained solely by the
24 characteristics of the studies (design, population, etc.) and could be related to the pharmacological
25 (molecular) characteristics of the combination. A clinical trial of FF/VI also found a lower rate of
26 asthma exacerbations, although it was similar to FP/SAL²³. Another recent real-life trial found that
27 FF/VI showed better asthma control than habitual optimized treatment, but that there were no
28 differences in the rate of asthma exacerbations²⁴. With design limitations, our data is in line with the
29 literature consulted^{20,25}. However, the different definitions of asthma exacerbation make
30 comparisons difficult; in our study the definition of exacerbation was at the clinician's discretion and
31 was based on the use of health resources.
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46 The study has some limitations. These affect the categorization of the disease and the possible
47 classification bias of patients, including the possible inaccuracy of diagnostic coding with regard to
48 the diagnosis of asthma and other comorbidities, the definition of exacerbation, the imbalance
49 between the groups in terms of numbers, or the lack of variables that might influence the results
50 (socioeconomic level of patients, environmental/work exposure, evolution of the prescribed
51 pharmacological dose, verification of the inhalation technique, including bronchoconstrictor therapy
52 and/or the differentiation of phenotypes) should also be considered as limitations. In addition, the
53 external validity of the results with respect to the representativeness of the population and the small
54 number of patients per study group should also be considered as limitations. When using an
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1 efficient inhaler therapy²⁴⁻²⁵, the factors that most influence compliance include the type of device,
2 the technique used, and the health-education instructions received.
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6 The future perspectives offered by this study are those of its replication in other health institutions
7 and interventional strategies aimed at promoting patient self-care (structured and individualized
8 educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with
9 increased treatment adherence (persistence, MPR) and lower rates of exacerbations. These
10 differences could be due to the pharmacological properties of the drugs or other unmeasured
11 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25.0%)	N=263 (8.2%)	N=225 (7%)	
<i>Sociodemographic features</i>						
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
<i>General comorbidity</i>						
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
<i>Associated comorbidity</i>						
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
<i>Asthma severity</i>						
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
<i>Other variables</i>						
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/m², FEV₁: 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7.0%)	
<i>Medication use</i>						
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
<i>Inhaled corticosteroid doses</i>						
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
<i>Other variables</i>						
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%	
<i>Treatment persistence, months</i>						
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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	pd
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7%)	
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).

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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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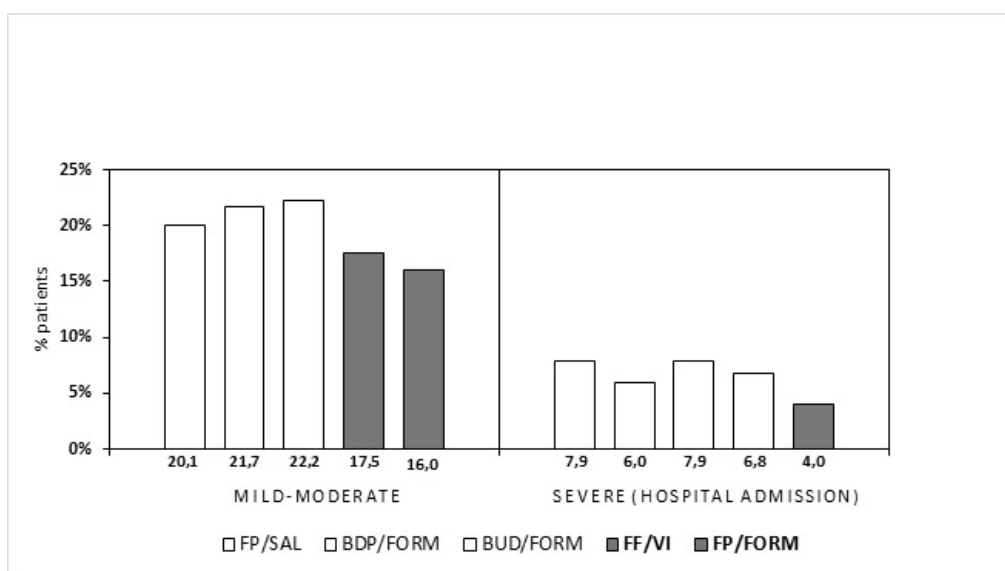


Figure 1. Percentage of patients with exacerbations according to their severity

171x97mm (96 x 96 DPI)

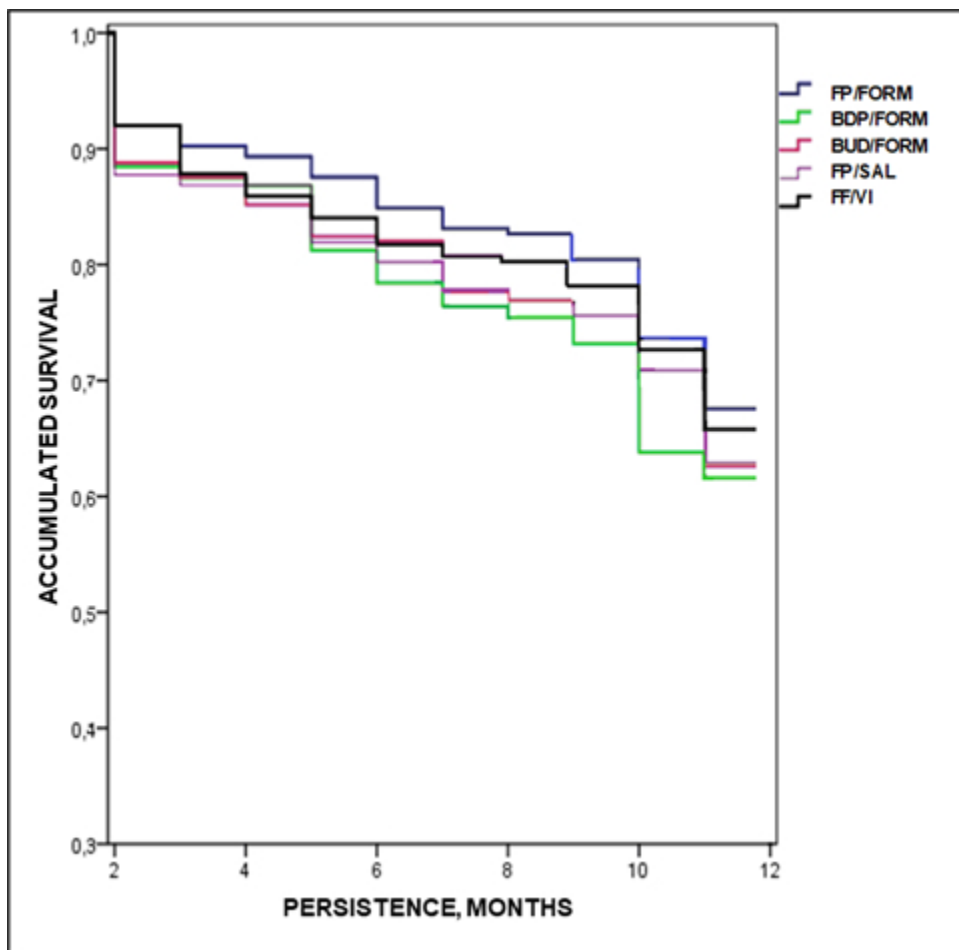


Figure 2. Median treatment persistence during the follow-up period

325x316mm (38 x 38 DPI)

BMJ Open

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

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2 36
3 37 **FUNDING**

4 38 Associates of Vectura licensed a formoterol/fluticasone inhaler to Mundipharma Pharmaceuticals.
5 39 Mundipharma has since developed, registered, marketed and distributed this product and
6 40 sponsored this study. This study was designed and completed prior to acquisition of Vectura by
7 41 Philip Morris International.
8 42

9 43 **CONFLICT OF INTEREST**

10 44 A. Sicras is an independent consultant funded by Mundipharma with respect to this manuscript. ST
11 45 and TF are employees of Mundipharma. The other authors state they have no conflict of interest in
12 46 relation to this study.
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14 48
15 49 **AUTHOR CONTRIBUTIONS**

16 50 A. Sicras and T. Fernández conceived and designed the manuscript; data collection and the
17 51 statistical analysis were made by A. Sicras; and the interpretation of the data, writing, review and
18 52 approval of the manuscript submitted, by all authors.
19 53

20 54
21 55 **ETHICS APPROVAL**

22 56 His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee;
23 57 International University of Catalonia; code: ANT-PER-2017-01).
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25 59 **DATA AVAILABILITY**

26 60 The datasets generated during and/or analyzed during the current study are available from the
27 61 corresponding author upon reasonable request.
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29 63 **PATIENT CONSENT FOR PUBLICATION.**

30 64 Not required.
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68 **STROBE Statement—Checklist of items that should be included in reports of *observational studies*.**

69

	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

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2 73 **Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled**
3 74 **corticosteroids and long-acting beta2-adrenergic agonists: retrospective cohort study**
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7 77 **ABSTRACT**
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10 79 **Objective.** To determine treatment persistence and exacerbations in patients initiating inhaler
11 80 treatment with fixed-dose combinations of inhaled corticosteroids/long-acting beta2-adrenergic
12 81 agonists (ICS/LABA) for the treatment of asthma.

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14 82 **Design.** Retrospective observational study conducted by review of electronic medical records
15 83 (database: Fundacion RedISS).

16
17 84 **Setting.** Retrospective cohort study. The follow-up period was one year.

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19 85 **Participants** The study included patients aged ≥ 18 years who started treatment with ICS/LABA
20 86 and met the inclusion/exclusion criteria.

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22 87 **Main outcomes and measures.** The study groups were fluticasone propionate/salmeterol
23 88 (FP/SAL), beclomethasone/formoterol (BDP/FORM), budesonide/formoterol (BUD/FORM),
24 89 fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate/formoterol (FP/FORM). The main
25 90 measurements were persistence, medication possession ratio (MPR), and exacerbations.
26 91 Statistical significance was established as $p < 0.05$.

27
28 92 **Results.** In total, 3,203 patients were recruited for the study. By groups, 31.1% FP/SAL, 28.6%
29 93 BDP/FORM, 25.0% BUD/FORM, 8.2% FF/VI, and 7.0% FP/FORM. The mean age was 52.2 years,
30 94 60.8% were female, and 44.9% had persistent-moderate asthma. Treatment persistence was
31 95 61.7% (95% CI: 60.0-63.4%) and by study groups it was: FP/SAL: 60.7%, BDP/FORM: 61.2%,
32 96 BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6%, ($p=0.046$). MPR by study group was
33 97 FP/SAL: 74.3, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6%
34 98 ($p=0.028$). The mortality rate was 2.9%. By treatment group, exacerbations were FP/SAL: 21.9%
35 99 (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-
36 100 25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), $p=0.036$.

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38 101
39 102 **Conclusions.** Patients undergoing treatment with FP/FORM and FF/VI vs. FP/SAL, BDP/FORM,
40 103 BUD/FORM, were associated with greater treatment adherence (persistence, MPR) and lower rates
41 104 of exacerbations. However, further studies will be needed to strengthen the consistency of the
42 105 results.

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44 106
45 107 **Keywords:** asthma, persistence, exacerbations, ICS/LABA.
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3 111 **ARTICLE SUMMARY**
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6 114 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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- 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.
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126 INTRODUCTION

127 Asthma is a chronic inflammatory airway disease that courses with bronchial hyper-response and
128 variable airflow blockage¹. In Spain, the prevalence is around 5%, although there are variations
129 between geographical areas². Most patients achieve adequate control with inhaled corticosteroids
130 (ICS) and long-lasting beta-adrenergic agonists (LABA), although some patients require additional
131 therapy with other medications, including oral corticosteroids (OC)¹⁻².

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133 Reducing the risk of exacerbations is an important goal of asthma treatment³. It is estimated that
134 30-52% of patients with asthma have exacerbations of varying intensity^{2,6}. Factors influencing an
135 increased risk of exacerbations include previous exacerbations, poor asthma control, limitations on
136 activity, lower forced expiratory volume in the first second (FEV₁), exposure to allergens, difficulty
137 handling inhalation devices and treatment adherence⁷. Studies show anti-asthmatic adherence
138 rates of <65%^{1-2,7}. The most common cause of treatment discontinuation are side effects,
139 improvements in symptoms and problems in reducing the effect of the drug over time, which lead
140 to discontinuation being advised or spontaneous abandonment⁷⁻¹⁰.

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142 In Spain, there are few studies evaluating the relationship between the adherence rate and the risk
143 of exacerbations¹¹. Persistence (or discontinuation) of treatment is a key factor in disease
144 progression and the risk of complications. In addition, there is a growing need to conduct studies
145 representative of the real-life clinical conditions in which medicines are used, so the study may be
146 of interest. The objective of the study was to evaluate treatment persistence and exacerbations in
147 patients initiating inhaler treatment with combinations of ICS/LABA for the treatment of asthma in
148 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 obstruction¹. 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).

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2 188 In addition, the following variables were collected: body mass index (BMI, kg/m²), lung function
3 189 (forced expiratory volume in the first second, FEV₁), asthma severity (intermittent, mild persistent,
4 190 moderate persistent and severe persistent according to the GEMA criteria¹ at the start of the study
5 191 before the index date. All-cause deaths were recorded.
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10 193 Sociodemographic and comorbidity variables collected were age (continuous and by range), sex,
11 194 and the personal history described in table 1. As a summary variable of general comorbidity: a) the
12 195 Charlson¹³ comorbidity index was used as an approximation to severity, b) the number of chronic
13 196 comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted
14 197 Clinical Groups (ACG), which is a patient classification system using iso-consumption of
15 198 resources¹⁴. The ACG application provides resource utilization bands (RUB), allowing each patient
16 199 to be grouped into one of five mutually exclusive categories based on their overall morbidity.
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22 201 The medicines (active substances) indicated for treatment were obtained according to the
23 202 Anatomical Therapeutic Chemical Classification System (ATC)¹⁵ classification: oral/systemic
24 203 corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2
25 204 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA,
26 205 R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients
27 206 receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those
28 207 receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient
29 208 was at the discretion of the physician, as in routine clinical practice. The information was obtained
30 209 from drug dispensing records. The scheduled dose of ICS administered was classified at low,
31 210 medium or high¹. Treatment persistence was calculated from the index date to the discontinuation
32 211 date in months. The discontinuation date was the date on which the patient switched to another
33 212 ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2
34 213 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of
35 214 follow-up. The percentage of therapeutic compliance was calculated based on the medicine
36 215 possession ratio (MPR)¹⁶. This was evaluated from the first to the last prescription and represented
37 216 the number of days of medication dispensed according to the number of days on treatment from
38 217 the index date.
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51 219 Records were validated to ensure the quality of the results. A descriptive-univariate statistical
52 220 analysis was carried out. Qualitative data were described using absolute and relative frequencies
53 221 and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI)
54 222 used to estimate parameters were based on the total number of subjects with no missing values.
55 223 The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate
56 224 analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A
57 225 multiple linear regression model was used to obtain the variables associated with the number of
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2 226 exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the
3 227 model were: sex, age, general comorbidity (RUB), FEV₁, disease duration and asthma severity.
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5 228 Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The
6 229 analysis was made using SPSSWIN version 23. Statistical significance was established as p<0.05.

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8 230
9 231 *Ethics Approval: His protocol was reviewed and approved at Foundation RediSS (Ethical Research*
10 232 *Committee; International University of Catalonia; code: ANT-PER-2017-01).*

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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 FEV₁ 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), FEV₁ (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 adherence¹⁸. Zhang¹⁹ 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 (FEV₁), previous exacerbations, limitations on activity, allergic rhinitis, insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed treatment²⁰. Schmidt²¹, 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). Usmani²² 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 Papi²⁰ 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/SAL²³. 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 exacerbations²⁴. With design limitations, our data is in line with the literature consulted^{20,25}. However, the different definitions of asthma exacerbation make comparisons difficult;

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2 308 in our study the definition of exacerbation was at the clinician's discretion and was based on the
3 309 use of health resources.
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6 311 The study has some limitations. Principally those typical of retrospective studies (underreporting /
7 312 absence of information). In this sense, the categorization of the disease (asthma) and the possible
8 313 classification bias of patients, including the possible inaccuracy of diagnostic coding about the
9 314 diagnosis of asthma and other comorbidities, are some examples, attributable to the information
10 315 system. To reduce this bias, a validation of the variables was carried out before analysis. The
11 316 definition of exacerbation was analyzed based on the use of resources (administered drugs,
12 317 hospital admissions) in the absence of a specific coding system. However, it is a consensus criterion
13 318 in retrospective studies and should affect all the cohorts analyzed in a similar way. In addition, other
14 319 unmeasured factors could have influenced the results, for example, the socioeconomic level of
15 320 patients, environmental/work exposure, evolution of the prescribed pharmacological dose,
16 321 verification of the inhalation technique, including bronchoconstrictor therapy and/or the
17 322 differentiation of phenotypes. In addition, based on the demand for medical care, non-disease
18 323 factors may have influenced the results, such as access to health resources, comorbidity or patient
19 324 specifics, which could cause worsening episodes not to be reported by the patient and therefore
20 325 remain untreated. It is possible that through a prospective study, some of these factors can be
21 326 minimized. The capturing patient behavior through treatment persistence cannot be directly
22 327 assessed through structured data available in electronic databases. Time to discontinuation is
23 328 assumed to be a proxy to estimate patient persistence. In addition, the external validity of the results
24 329 with respect to the representativeness of the population and the small number of patients per study
25 330 group should also be considered as limitations. When using an efficient inhaler therapy²⁴⁻²⁵, the
26 331 factors that most influence compliance include the type of device, the technique used, and the
27 332 health-education instructions received. However, these limitations should affect all the analyzed
28 333 cohorts in a similar way and should not affect the external validity of the results.
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44 335 The future perspectives offered by this study are those of its replication in other health institutions
45 336 and interventional strategies aimed at promoting patient self-care (structured and individualized
46 337 educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with
47 338 increased treatment adherence (persistence, MPR) and lower rates of exacerbations. However,
48 339 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25.0%)	N=263 (8.2%)	N=225 (7%)	
<i>Sociodemographic features</i>						
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
<i>General comorbidity</i>						
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
<i>Associated comorbidity</i>						
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
<i>Asthma severity</i>						
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
<i>Other variables</i>						
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/m², FEV₁: 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7.0%)	
<i>Medication use</i>						
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
<i>Inhaled corticosteroid doses</i>						
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
<i>Other variables</i>						
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%	
<i>Treatment persistence, months</i>						
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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	pd
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7%)	
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).

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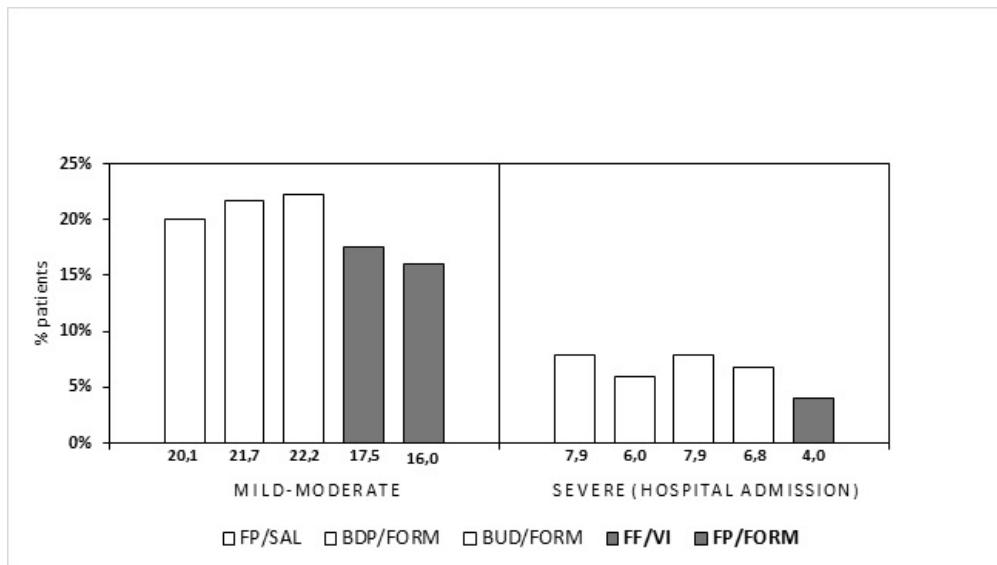
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Figure 2. Median treatment persistence during the follow-up period

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).

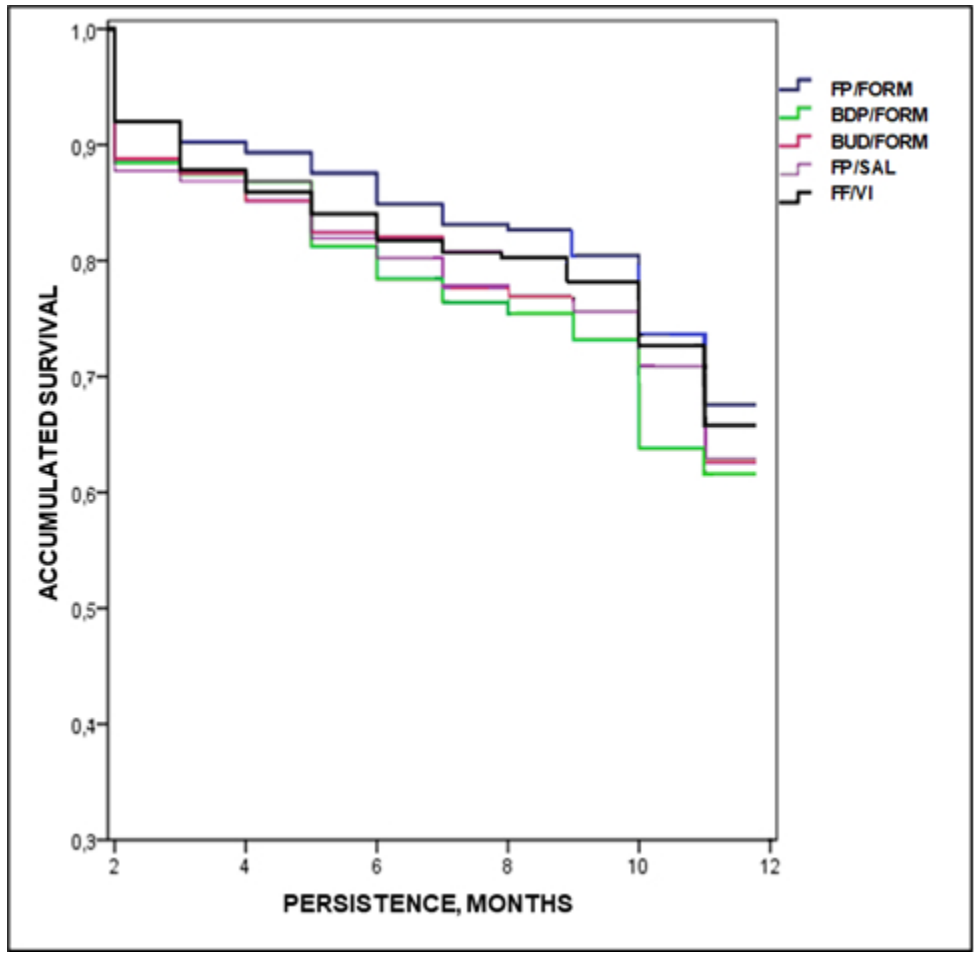
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BMJ Open

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

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2 36
3 37 **FUNDING**

4 38 Associates of Vectura licensed a formoterol/fluticasone inhaler to Mundipharma Pharmaceuticals.
5 39 Mundipharma has since developed, registered, marketed and distributed this product and
6 40 sponsored this study. This study was designed and completed prior to acquisition of Vectura by
7 41 Philip Morris International.
8 42

9 43 **CONFLICT OF INTEREST**

10 44 A. Sicras is an independent consultant funded by Mundipharma with respect to this manuscript. ST
11 45 and TF are employees of Mundipharma. The other authors state they have no conflict of interest in
12 46 relation to this study.
13 47

14 48
15 49 **AUTHOR CONTRIBUTIONS**

16 50 AS and TF participated in the planning, coordination, conception and design of the study. AS and
17 51 TF were responsible for data acquisition. AS performed the statistical analysis. AS, BG, ST, TF and
18 52 JLV reviewed the results report. AS, BG, ST, TF and JLV participated in the critical interpretation of
19 53 the data obtained, the writing of the manuscript (review) and the final approval of the version to be
20 54 published. Additionally, AS, BG, ST, TF and JLV were responsible for ensuring the adequacy of all
21 55 aspects of the study.
22 56

23 57 **ETHICS APPROVAL**

24 58 His protocol was reviewed and approved at Foundation Redis (Ethical Research Committee;
25 59 International University of Catalonia; code: ANT-PER-2017-01).
26 60

27 61 **DATA AVAILABILITY**

28 62 The datasets generated during and/or analyzed during the current study are available from the
29 63 corresponding author upon reasonable request.
30 64

31 65 **PATIENT CONSENT FOR PUBLICATION.**

32 66 Not required.
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2 72 **STROBE Statement—Checklist of items that should be included in reports of *observational studies*.**
3 73

	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

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2 77 **Treatment persistence and exacerbations in asthmatic patients initiating treatment with inhaled**
3 78 **corticosteroids and long-acting beta2-adrenergic agonists: retrospective cohort study**
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6
7 81 **ABSTRACT**
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9
10 83 **Objective.** To determine treatment persistence and exacerbations in patients initiating inhaler
11 84 treatment with fixed-dose combinations of inhaled corticosteroids/long-acting beta2-adrenergic
12 85 agonists (ICS/LABA) for the treatment of asthma.

13
14 86 **Design.** Retrospective observational study conducted by review of electronic medical records
15 87 (database: Fundacion RedISS).

16
17 88 **Setting.** Retrospective cohort study. The follow-up period was one year.

18
19 89 **Participants** The study included patients aged ≥ 18 years who started treatment with ICS/LABA
20 90 and met the inclusion/exclusion criteria.

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22 91 **Main outcomes and measures.** The study groups were fluticasone propionate/salmeterol
23 92 (FP/SAL), beclomethasone/formoterol (BDP/FORM), budesonide/formoterol (BUD/FORM),
24 93 fluticasone furoate/vilanterol (FF/VI) and fluticasone propionate/formoterol (FP/FORM). The main
25 94 measurements were persistence, medication possession ratio (MPR), and exacerbations.
26 95 Statistical significance was established as $p < 0.05$.

27
28 96 **Results.** In total, 3,203 patients were recruited for the study. By groups, 31.1% FP/SAL, 28.6%
29 97 BDP/FORM, 25.0% BUD/FORM, 8.2% FF/VI, and 7.0% FP/FORM. The mean age was 52.2 years,
30 98 60.8% were female, and 44.9% had persistent-moderate asthma. Treatment persistence was
31 99 61.7% (95% CI: 60.0-63.4%) and by study groups it was: FP/SAL: 60.7%, BDP/FORM: 61.2%,
32 100 BUD/FORM: 60.3%, FF/VI: 66.7% and FP/FORM: 67.6%, ($p=0.046$). MPR by study group was
33 101 FP/SAL: 74.3, BDP/FORM: 73.8%, BUD/FORM: 74.6%, FF/VI: 79.4% and FP/FORM: 80.6%
34 102 ($p=0.028$). The mortality rate was 2.9%. By treatment group, exacerbations were FP/SAL: 21.9%
35 103 (95% CI: 19.3-24.5), BDP/FORM: 22.2% (95% CI: 19.5-24.9), BUD/FORM: 22.8% (95% CI: 19.9-
36 104 25.7), FF/VI: 17.9% (95% CI: 14.9-20.7) and FP/FORM: 16.0% (95% CI: 12.2-19.3), $p=0.036$.

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38 105
39 106 **Conclusions.** Patients undergoing treatment with FP/FORM and FF/VI vs. FP/SAL, BDP/FORM,
40 107 BUD/FORM, were associated with greater treatment adherence (persistence, MPR) and lower rates
41 108 of exacerbations. However, further studies will be needed to strengthen the consistency of the
42 109 results.

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44 110
45 111 **Keywords:** asthma, persistence, exacerbations, ICS/LABA.
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3 115 **ARTICLE SUMMARY**
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6 118 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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- 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.

132 INTRODUCTION

133 Asthma is a chronic inflammatory airway disease that courses with bronchial hyper-response and
134 variable airflow blockage¹. In Spain, the prevalence is around 5%, although there are variations
135 between geographical areas². Most patients achieve adequate control with inhaled corticosteroids
136 (ICS) and long-lasting beta-adrenergic agonists (LABA), although some patients require additional
137 therapy with other medications, including oral corticosteroids (OC)¹⁻².

138
139 Reducing the risk of exacerbations is an important goal of asthma treatment³⁻⁵. It is estimated that
140 30-52% of patients with asthma have exacerbations of varying intensity^{2,6}. Factors influencing an
141 increased risk of exacerbations include previous exacerbations, poor asthma control, limitations on
142 activity, lower forced expiratory volume in the first second (FEV₁), exposure to allergens, difficulty
143 handling inhalation devices and treatment adherence⁷. Studies show anti-asthmatic adherence
144 rates of <65%^{1-2,7}. The most common cause of treatment discontinuation are side effects,
145 improvements in symptoms and problems in reducing the effect of the drug over time, which lead
146 to discontinuation being advised or spontaneous abandonment⁷⁻¹⁰.

147
148 In Spain, there are few studies evaluating the relationship between the adherence rate and the risk
149 of exacerbations¹¹. Persistence (or discontinuation) of treatment is a key factor in disease
150 progression and the risk of complications. In addition, there is a growing need to conduct studies
151 representative of the real-life clinical conditions in which medicines are used, so the study may be
152 of interest. The objective of the study was to evaluate treatment persistence and exacerbations in
153 patients initiating inhaler treatment with combinations of ICS/LABA for the treatment of asthma in
154 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 obstruction¹. 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/m²), lung function (forced expiratory volume in the first second, FEV₁), asthma severity (intermittent, mild persistent,

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2 194 moderate persistent and severe persistent according to the GEMA criteria¹ at the start of the study
3 195 before the index date. All-cause deaths were recorded.
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6 197 Sociodemographic and comorbidity variables collected were age (continuous and by range), sex,
7 198 and the personal history described in table 1. As a summary variable of general comorbidity: a) the
8 199 Charlson¹³ comorbidity index was used as an approximation to severity, b) the number of chronic
9 200 comorbidities was obtained, and c) the individual case-mix index was obtained from the Adjusted
10 201 Clinical Groups (ACG), which is a patient classification system using iso-consumption of
11 202 resources¹⁴. The ACG application provides resource utilization bands (RUB), allowing each patient
12 203 to be grouped into one of five mutually exclusive categories based on their overall morbidity.
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19 205 The medicines (active substances) indicated for treatment were obtained according to the
20 206 Anatomical Therapeutic Chemical Classification System (ATC)¹⁵ classification: oral/systemic
21 207 corticosteroids (CO, H02AB), short-lasting beta-2 agonists (SABA, R03AC), systemic beta-2
22 208 agonists (xanthines, R03*), leukotriene receptor antagonists (R03DC), anticholinergics (LAMA,
23 209 R03BB04: tiotropium bromide) and omalizumab (biologicals, R03DX05). In addition, patients
24 210 receiving chronic doses of long-lasting oral/systemic corticosteroids were differentiated from those
25 211 receiving them only for stabilization of an exacerbation. The choice of drug for a specific patient
26 212 was at the discretion of the physician, as in routine clinical practice. The information was obtained
27 213 from drug dispensing records. The scheduled dose of ICS administered was classified at low,
28 214 medium or high¹. Treatment persistence was calculated from the index date to the discontinuation
29 215 date in months. The discontinuation date was the date on which the patient switched to another
30 216 ICS/LABA or interrupted treatment for ≥ 60 days without renewing the medication and/or had ≥ 2
31 217 prescriptions dispensed. The rate of treatment persistence was obtained at 6 and 12 months of
32 218 follow-up. The percentage of therapeutic compliance was calculated based on the medicine
33 219 possession ratio (MPR)¹⁶. This was evaluated from the first to the last prescription and represented
34 220 the number of days of medication dispensed according to the number of days on treatment from
35 221 the index date.
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47 223 Records were validated to ensure the quality of the results. A descriptive-univariate statistical
48 224 analysis was carried out. Qualitative data were described using absolute and relative frequencies
49 225 and quantitative data as means and standard deviation (SD). The 95% confidence intervals (CI)
50 226 used to estimate parameters were based on the total number of subjects with no missing values.
51 227 The normality of the distribution was assessed using the Kolmogorov-Smirnov test. In the bivariate
52 228 analysis, ANOVA, the Chi squared test and comparison of means were used for paired data. A
53 229 multiple linear regression model was used to obtain the variables associated with the number of
54 230 exacerbations (dependent variables; procedure: consecutive steps). The covariates included in the
55 231 model were: sex, age, general comorbidity (RUB), FEV₁, disease duration and asthma severity.
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2 232 Persistence was assessed using Kaplan-Meier curves (Log rank procedure; Mantel-Cox). The
3 233 analysis was made using SPSSWIN version 23. Statistical significance was established as $p < 0.05$.

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5 235 *Ethics Approval: His protocol was reviewed and approved at Foundation RediSS (Ethical Research*
6 236 *Committee; International University of Catalonia; code: ANT-PER-2017-01).*

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9 239 **Patient and public involvement**

10 240 Patients/the public were not involved in developing this research question, designing the study, or
11 241 providing input to study conduct.

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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 FEV₁ 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), FEV₁ (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 adherence¹⁸. Zhang¹⁹ 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 (FEV₁), previous exacerbations, limitations on activity, allergic rhinitis, insufficient preventive anti-inflammatory treatment and/or poor compliance with the prescribed treatment²⁰. Schmidt²¹, 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). Usmani²² 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 Papi²⁰ 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/SAL²³. 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 exacerbations²⁴. With design limitations, our data is in line with the literature consulted^{20,25}. However, the different definitions of asthma exacerbation make comparisons difficult;

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2 316 in our study the definition of exacerbation was at the clinician's discretion and was based on the
3 317 use of health resources²⁶⁻²⁷.

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6 319 The study has some limitations. Principally those typical of retrospective studies (underreporting /
7 320 absence of information). In this sense, the categorization of the disease (asthma) and the possible
8 321 classification bias of patients, including the possible inaccuracy of diagnostic coding about the
9 322 diagnosis of asthma and other comorbidities, are some examples, attributable to the information
10 323 system. To reduce this bias, a validation of the variables was carried out before analysis. The
11 324 definition of exacerbation was analyzed based on the use of resources (administered drugs,
12 325 hospital admissions) in the absence of a specific coding system. However, it is a consensus criterion
13 326 in retrospective studies and should affect all the cohorts analyzed in a similar way. In addition, other
14 327 unmeasured factors could have influenced the results, for example, the socioeconomic level of
15 328 patients, environmental/work exposure, evolution of the prescribed pharmacological dose,
16 329 verification of the inhalation technique, including bronchoconstrictor therapy and/or the
17 330 differentiation of phenotypes. In addition, based on the demand for medical care, non-disease
18 331 factors may have influenced the results, such as access to health resources, comorbidity or patient
19 332 specifics, which could cause worsening episodes not to be reported by the patient and therefore
20 333 remain untreated. It is possible that through a prospective study, some of these factors can be
21 334 minimized. The capturing patient behavior through treatment persistence cannot be directly
22 335 assessed through structured data available in electronic databases. Time to discontinuation is
23 336 assumed to be a proxy to estimate patient persistence. In addition, the external validity of the results
24 337 with respect to the representativeness of the population and the small number of patients per study
25 338 group should also be considered as limitations. When using an efficient inhaler therapy²⁴⁻²⁵, the
26 339 factors that most influence compliance include the type of device, the technique used, and the
27 340 health-education instructions received. However, these limitations should affect all the analyzed
28 341 cohorts in a similar way and should not affect the external validity of the results.
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44 343 The future perspectives offered by this study are those of its replication in other health institutions
45 344 and interventional strategies aimed at promoting patient self-care (structured and individualized
46 345 educational programs). In conclusion, patients receiving FP/FORM and FF/VI were associated with
47 346 increased treatment adherence (persistence, MPR) and lower rates of exacerbations. However,
48 347 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25.0%)	N=263 (8.2%)	N=225 (7%)	
<i>Sociodemographic features</i>						
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
<i>General comorbidity</i>						
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
<i>Associated comorbidity</i>						
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
<i>Asthma severity</i>						
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
<i>Other variables</i>						
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/m², FEV₁: 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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	p
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7.0%)	
<i>Medication use</i>						
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
<i>Inhaled corticosteroid doses</i>						
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
<i>Other variables</i>						
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%	
<i>Treatment persistence, months</i>						
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	FP/SAL	BDP/FORM	BUD/FORM	FF/VI	FP/FORM	pd
Number of patients, %	N=996 (31.1%)	N=917 (28.6%)	N=802 (25%)	N=263 (8.2%)	N=225 (7%)	
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).

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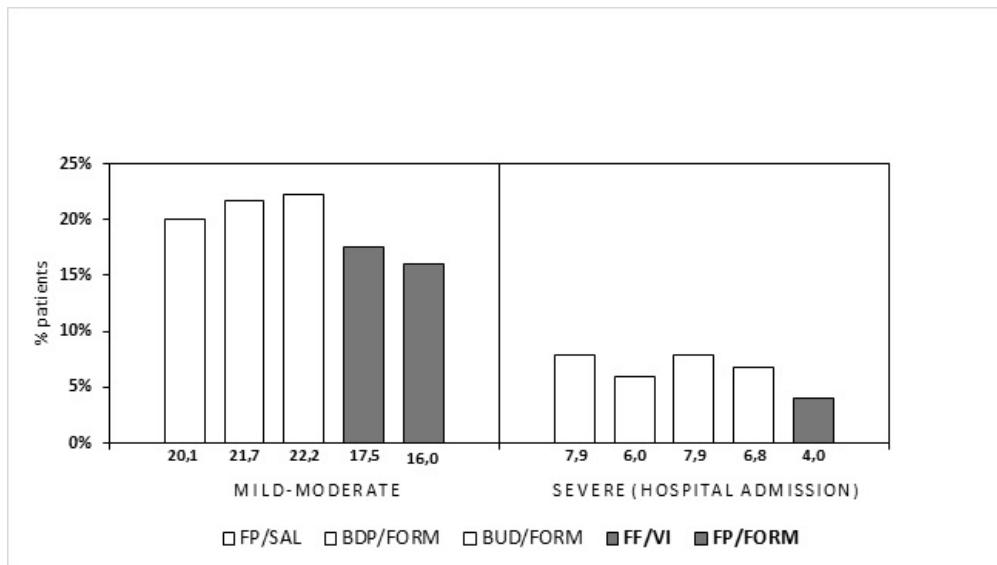
Figure 2. Median treatment persistence during the follow-up period

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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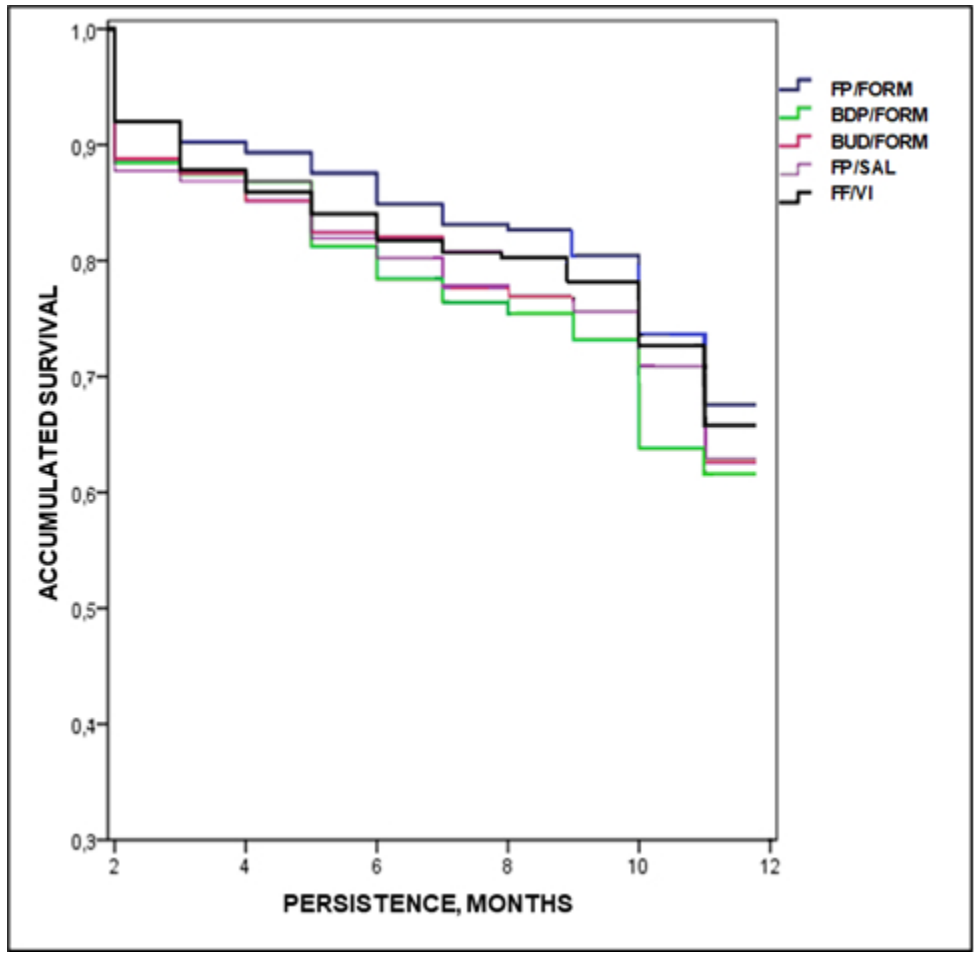
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