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ORIGINAL ARTICLE

Factors associated with inhaled corticosteroids prescription in primary care patients with COPD: A cross-sectional study in the Balearic Islands (Spain)

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KEY MESSAGES

- The proportion of COPD patients with ICS prescriptions in Balearic primary care is lower than proportions observed in other studies.
- Asthma comorbidity, exacerbations, severe bronchial-obstruction, smoking status and spirometry-registered data were associated with ICS prescription.
- High-dose ICS prescription was associated with severe obstruction, exacerbations and co-morbid asthma.

ABSTRACT

Background: There is a worldwide over-prescription of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD), off-label prescribing, and unnecessary prescription of high doses.

Objectives: Our aim was to assess the prescription rate of ICS and to identify sociodemographic and clinical factors associated with ICS prescription among patients with COPD, treated in Balearic primary healthcare.

Methods: This cross-sectional study included all patients with a clinical COPD diagnosis, who attended a primary care centre of the Balearic Islands (Spain) during 2012. Also, a sub-population with spirometry-confirmed COPD was defined. Data were obtained on patient demographics, smoking status, spirometry, ICS prescriptions, other respiratory medication, exacerbations and comorbidities. Associations with ICS and high-dose ICS prescription were assessed using multivariate regression analyses.

Results: In total, 15,440 patients were included (70% men, mean age 68.6 years), and 44.6% were prescribed ICS. The largest association with ICS prescription was asthma comorbidity (OR: 3.50; 95%CI: 3.12–3.92), followed by exacerbation history (OR: 2.23; 95%CI: 2.07–2.47). In addition, smoking status, spirometry, atopic dermatitis, allergic rhinitis and mean age were significantly ($P < 0.001$) associated with ICS treatment. In the spirometry-confirmed population, asthma (OR: 2.89; 95%CI: 2.29–3.64) and exacerbations were also the major factors (OR: 2.85; 95%CI: 2.45–3.32) followed by severe bronchial-obstruction (OR: 2.63; 95%CI: 2.24–3.08). High-dose ICS prescription was mainly associated with severe obstruction (OR: 2.27; 95%CI: 1.93–2.68).

Conclusion: The percentage of COPD patients prescribed ICS in Balearic primary care is relatively low. Asthma comorbidity, exacerbation history, severe bronchial-obstruction, smoking status and a spirometry-confirmed COPD diagnosis were significantly associated with ICS prescription.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease.[1] It puts a significant burden on morbidity, mortality and is associated with considerable direct and indirect public health costs.[2] COPD affects 10.2% of the Spanish population between 40 and 80 years; however, only 27% are

currently diagnosed.[3] Data from the Balearic Islands showed similar results, with a prevalence of 12.8% in this age group.[4]

Pharmacologic and non-pharmacologic treatments can help to improve COPD control and symptoms and slow down disease progression.[1] In contrast to asthma, where inhaled corticosteroids (ICS) are the

main pharmacological treatment, their efficacy and role in the treatment of COPD is less evident.[5] Furthermore, it is mainly in association with long-acting bronchodilators (LAB) in COPD patients with moderate to severe airflow limitation and frequent exacerbations where a reduction in exacerbations has been shown.[6,7] A recent Cochrane network meta-analysis compared different COPD treatments and concluded that the combination of ICS with long-acting beta-agonists (LABA) showed the largest benefits regarding trough forced expiratory volume in one second (FEV₁) and quality of life.[8] However, they add additional expenses and increased risk for pneumonia. Another recent meta-analysis, although showing benefit of fixed-dose combinations in reducing the number of exacerbations, was not conclusive regarding the trade-off between benefits and adverse events.[9] In addition to severe adverse events like pneumonias, local adverse events like candidiasis and upper respiratory tract infections have increased among ICS users.[9,10] Patients with COPD are in general older, use multiple medications and have multi-morbidity, so the over-prescription of ICS in mild to moderate patients without a clear indication could be harmful, increases costs and should, therefore, be avoided.[11]

Still, there is a worldwide over-prescription of ICS in patients with COPD, off-label prescribing, and unnecessary prescription of high doses. From 50% of COPD patients treated in primary care in 1999 to 61.5% in 2003, and more than 80% in 2008 the majority of them receiving fixed-dose combinations and high doses.[12–14] Regarding ICS prescription, current primary care practice is still sub-optimal, however, increasing the use of spirometry and better adherence to clinical guidelines offer potential to optimize treatment.[15] Notably, approximately 61% of the Spanish COPD patients are treated in primary care.[16]

Factors that have been previously associated with ICS prescription include the performance of spirometry to confirm diagnosis,[17] severity of airflow obstruction, quality of life and emergency department visits in the last year; however, recent Spanish studies are limited.[13] The objective of this study was to assess the prescription rates of ICS and to identify sociodemographic and clinical factors associated with ICS prescription among patients with COPD, treated in Balearic primary healthcare.

Methods

Study design

This cross-sectional study was performed using data from all primary care centres in the Balearic Islands, Spain.

Box 1. ICD-9 codes to define COPD population, comorbidities and COPD exacerbations.

Clinical COPD diagnosis

- Obstructive chronic bronchitis: 491.2, 491.20, 491.21
- Emphysema: 492 (all)
- Chronic airway obstruction/COPD: 496 (all)

Comorbidities

- Asthma: 493 (all)
- Allergic rhinitis: 477 (all), 478.8
- Atopic dermatitis: 691 (all)

COPD exacerbation

- Obstructive chronic bronchitis with (acute) exacerbation: 491.21

Ethics

To safeguard patients' anonymity, all identifying information in the database was anonymized. This study was approved by the Majorca Primary Care Research Committee (25 October 2012).

Study population

The study population covered all patients ≥ 35 years old, who have a clinical diagnosis of COPD with an ICD-9 code who were registered in the Balearic electronic clinical records information system for primary care ('e-SIAP') during 2012 (Box 1). Patients should have visited a primary care centre at least once in the previous two years (February 2010–February 2012). In addition, a sub-population with spirometry confirmed COPD (FEV₁/FVC < 0.7) registered in the e-SIAP system was defined.

Measurements

The main study outcome variable, prescription of ICS, was extracted from the electronic prescription system (RELE-system). The RELE-system registers every outpatient prescription coming both from primary or secondary care doctors. Inpatient medication is not included.

To identify the factors associated with the prescription of ICS, patients prescribed at least two ICS inhalers in the last three years, alone or in combination, were included in the ICS group. The group of patients prescribed with high ICS doses ($\geq 1.000 \mu\text{g}$ fluticasone or $\geq 800 \mu\text{g}$ budesonide daily) was assessed separately.

Table 1. Characteristics of the total patient population with a primary care diagnosis of COPD ($n = 15,440$, mean age = 68.5 years, standard deviation = 12.2).

Variables	<i>n</i> (%)
Sex	
Men	10,808 (70.0)
Women	4632 (30.0)
Smoking status	
Non-smoker	3802 (24.6)
Ex-smoker	5151 (33.4)
Smoker	4766 (30.9)
Unknown	1721 (11.1)
≥1 COPD exacerbation in the last two years	5868 (38.0)
Concurrent asthma diagnosis	2155 (14.0)
Concurrent allergic rhinitis	1117 (7.2)
Concurrent atopic dermatitis	527 (3.4)
Spirometry data registered	7173 (46.5)
Spirometry confirmed COPD	4367 (28.3)
Prescription of ICS	6887 (44.6)
Prescription of ICS + LABA	6469 (41.9)
Prescription of high-dose ICS	2624 (17.0)
Prescription of other respiratory medication	8205 (53.1)

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta agonists.

Other variables were demographics (sex and age), smoking status, spirometry, pulmonary function values and results of post-bronchodilator (PBD) tests in the last three years. Severe obstruction was defined as an FEV₁ lower than 50% of predicted, in line with current guidelines.[18] The PBD-test was considered positive when a change of minimal 12% and 200 ml in FEV₁ was observed. In addition, COPD exacerbations (at least one in the previous two years) were included, as well as co-morbidities (asthma, allergic rhinitis and atopic dermatitis) (Table 1).

Statistical analyses

Data were analysed using SPSS for Windows, version 15.0 (Chicago, SPSS Inc., USA). Chi-square tests were used for categorical variables and student *t*-tests for quantitative variables. Analyses were conducted in all clinically diagnosed COPD patients as well as in the spirometry confirmed sub-population. In addition, univariate (unadjusted) logistic regression was performed to assess the crude association of each variable with the prescription of ICS or high-dose ICS. Patients with spirometry values that were out of the pre-specified range (range to be included was FEV₁/FVC: 0.1–1.0; FEV₁% predicted: 10–140%) and patients with unknown smoking status or unknown PBD-test, were excluded from the corresponding univariate regression analyses. Finally, to estimate the independent effect of the different variables on ICS prescription, we performed multivariate (adjusted) logistic regression analyses in which all study variables were included. Backward logistic regression techniques were used

and at each step, the accuracy of the model was checked, along with the changes in the beta coefficients to assess confusion. For each association, 95% confidence intervals were calculated.

Results

From a population of 474,273 persons older than 35 years registered in the primary care health system of the Balearic Islands, 15,440 patients with a clinical COPD diagnosis (3.3%) were identified. Demographic and clinical population characteristics are presented in Table 1.

In the Balearic Islands, 44.6% of the COPD patients were treated with ICS. Of those, 93.9% were prescribed ICS in a fixed-dose combination with a long-acting beta agonist and 38.1% were prescribed high-dose ICS. Notably, 36.7% were not prescribed any pharmacological treatment for COPD. From those taking any medication, approximately 77% were prescribed ICS.

In Table 2, factors associated with the prescription of ICS in patients with COPD are presented. Ex-smokers have greater probability to have ICS prescribed than smokers and non-smokers. In addition, those who have a spirometry registered or allergic rhinitis or dermatitis had higher probability of ICS prescription. Comorbidity of asthma had the highest association with ICS prescription (OR: 3.50), followed by a history of exacerbations (OR: 2.23).

From the 7178 patients with registered spirometry data, 60.9% had a FEV₁/FVC-ratio <0.7, resulting in a sub-population with spirometry confirmed COPD of 4367 patients (28.3% of the total clinically diagnosed COPD population). Table 3 presents the sub-analysis in patients with confirmed COPD. In this subpopulation, the overall percentage of patients treated with ICS was higher (54.4%). Asthma showed the strongest association with ICS prescription (OR: 2.89), followed by exacerbation history (OR: 2.85). In this sub-group, we could define obstruction severity and patients with an FEV₁% predicted <50% had higher odds to be prescribed ICS (OR: 2.63). Although a positive PBD-test showed an association (OR: 3.16) with ICS prescription in the univariate analysis, the small number of patients with a test record did not allow assessing this variable in the adjusted regression model.

The associations for patients prescribed high-dose ICS in the total COPD population showed a mostly comparable pattern. However, exacerbation history showed the strongest association.

Table 2. Factors associated with prescription of ICS in total COPD population ($n = 15,440$).

Factor	ICS <i>n</i> (%)	No ICS <i>n</i> (%)	<i>P</i> -value	OR (95%CI) unadjusted	OR (95%CI) adjusted
Age					
Mean (SD)	71.0 (11.2)	66.7 (12.6)	<0.001	1.03 (1.02–1.03)	1.02 (1.02–1.03)
Sex					
Women	2105 (30.6)	2527 (29.5)	0.17	1	–
Men	4782 (44.2)	6026 (70.5)		0.95 (0.88–1.02)	
Smoking status					
Non-smoker	1965 (28.5)	1837 (21.5)	<0.001	1	1
Ex-smoker	2628 (38.2)	2523 (29.5)		0.97 (0.89–1.05)	1.22 (1.11–1.33)
Smoker	1651 (24.0)	3115 (36.4)		0.49 (0.45–0.54)	0.82 (0.74–0.91)
Unknown	643 (9.3)	1078 (12.6)		–	–
Spirometry registered					
No	3377 (49.0)	4890 (57.2)	<0.001	1	1
Yes	3510 (51.0)	3663 (42.8)		1.38 (1.30–1.47)	1.55 (1.44–1.67)
Exacerbations					
No	3464 (50.3)	6108 (71.4)	<0.001	1	1
Yes	3423 (49.7)	2445 (28.6)		2.46 (2.31–2.63)	2.23 (2.07–2.47)
Asthma					
No	5347 (77.6)	7938 (92.8)	<0.001	1	1
Yes	1540 (22.4)	615 (7.2)		3.71 (3.36–4.10)	3.50 (3.12–3.92)
Allergic rhinitis					
No	6313 (91.7)	8010 (93.4)	<0.001	1	1
Yes	574 (8.3)	543 (6.3)		1.34 (1.18–1.51)	1.15 (1.00–1.32)
Dermatitis					
No	6622 (96.2)	8291 (96.9)	0.008	1	–
Yes	265 (3.8)	262 (3.1)		1.26 (1.06–1.50)	

95%CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; ICS, Inhaled corticosteroids; OR, odds ratio; SD, standard deviation.

Table 3. Factors associated with the prescription of ICS in the spirometry confirmed COPD sub-population ($n = 4367$).

Factor	ICS <i>n</i> (%)	No ICS <i>n</i> (%)	<i>P</i> -value	OR (95%CI) unadjusted	OR (95%CI) adjusted
Age					
Mean (SD)	69.5 (10.8)	66.5 (11.2)	<0.001	1.03 (1.02–1.03)	1.01 (1.00–1.02)
Sex					
Women	596 (25.1)	476 (23.9)	0.37	1	1
Men	1781 (74.9)	1514 (76.1)		0.94 (0.81–1.07)	0.81 (0.68–0.96)
Smoking status					
Non-smoker	507 (21.3)	275 (13.8)	<0.001	1	1
Ex-smoker	1089 (45.8)	732 (36.8)		0.80 (0.67–0.96)	1.03 (0.83–1.27)
Smoker	698 (29.4)	920 (46.2)		0.41 (0.34–0.49)	0.65 (0.52–0.82)
Unknown	83 (3.5)	63 (3.2)		–	–
Exacerbations					
No	1196 (50.3)	1571 (78.9)	<0.001	1	1
Yes	1181 (49.7)	419 (21.1)		3.70 (3.23–4.23)	2.85 (2.45–3.32)
Asthma					
No	1899 (79.9)	1852 (93.1)	<0.001	1	1
Yes	478 (20.1)	138 (6.9)		3.37 (2.76–4.12)	2.89 (2.29–3.64)
Allergic rhinitis					
No	2195 (92.3)	1872 (94.1)	0.03	1	–
Yes	182 (7.7)	118 (5.9)		1.31 (1.00–1.67)	
Dermatitis					
No	2289 (96.3)	1932 (97.1)	0.15	1	–
Yes	88 (3.7)	58 (2.9)		1.28 (0.91–1.79)	
Severity					
FEV ₁ ≥ 50%pred	1267 (53.3)	1482 (74.5)	<0.001	1	1
FEV ₁ < 50%pred	905 (38.1)	335 (16.8)		3.16 (2.73–3.65)	2.63 (2.24–3.08)
Out of range	205 (8.6)	173 (8.7)		–	–
PBD					
Negative <12%	647 (27.2)	763 (38.3)	<0.001	1	–
Positive ≥12%	435 (18.3)	242 (12.2)		2.12 (1.75–2.56)	
Unknown	1295 (54.5)	985 (49.5)		–	

95%CI, 95% confidence interval; FEV₁, forced expiratory volume in one second; ICS, inhaled corticosteroids; OR, odds ratio; PBD, post bronchodilator test; SD, standard deviation.

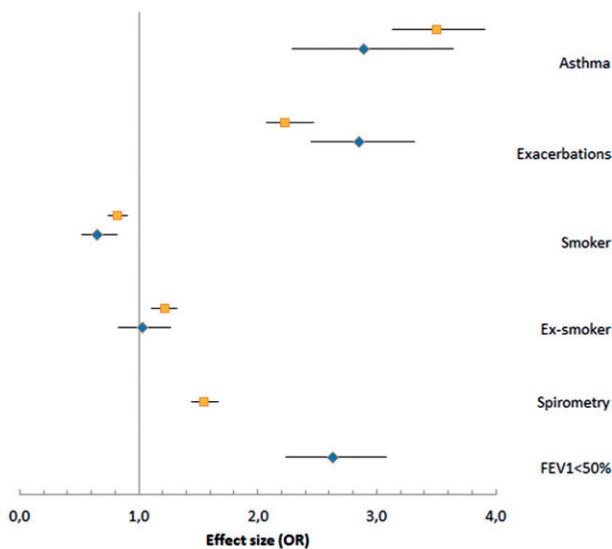


Figure 1. Main associations with ICS prescription in total COPD population (squares) and spirometry-confirmed COPD sub-population (diamonds). OR, Odds ratio; FEV1 < 50%, forced expiratory volume in one second smaller than 50% of predicted value.

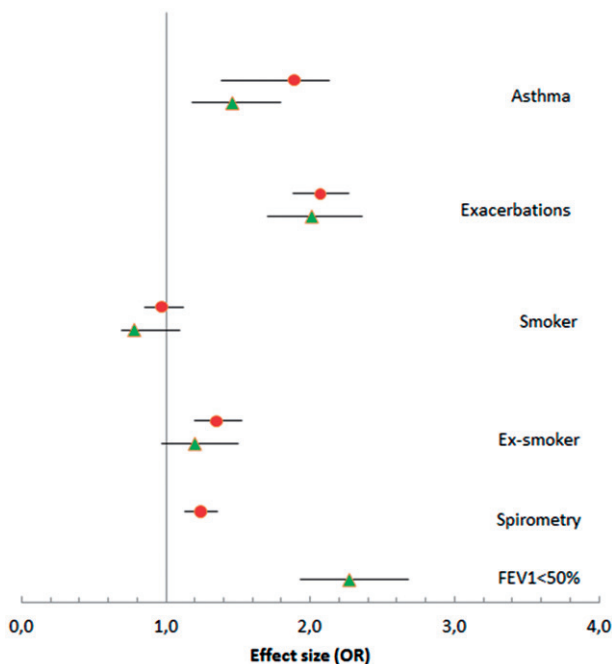


Figure 2. Main associations with high-dose ICS prescription in total COPD population (circles) and spirometry-confirmed COPD sub-population (triangles). OR, Odds ratio; FEV1 < 50%, forced expiratory volume in one second smaller than 50% of predicted value.

In the sub-analysis in patients with spirometry confirmed COPD, the strongest association with

prescription of high-dose ICS was a FEV₁% predicted < 50% (OR: 2.27).

In Figures 1 and 2, overviews of the main associations for the total COPD population and the spirometry confirmed COPD sub-population are presented separately by ICS prescription and high-dose ICS prescription.

Discussion

Main findings

This study showed that from all the patients visiting a primary care practice during the previous year with clinically diagnosed COPD, 44.6% were prescribed ICS. Asthma comorbidity, exacerbation history and severe bronchial obstruction were independently associated with a higher probability of ICS prescription. Current smoking was negatively associated with ICS prescription, while ex-smoking was positively associated. Notably, in the subpopulation with spirometry confirmed COPD (28.3%), these associations were mostly similar. High-dose ICS prescription was mainly associated with severe bronchial obstruction, exacerbation history and asthma comorbidity.

Comparison with other studies

In a recent study using a large UK primary care database, the authors concluded that COPD is not treated according to GOLD guidelines because most patients receive ICS irrespective of the severity of airflow limitation, asthma diagnosis, and exacerbation history. In this observational study, 53.7% of the COPD total population were receiving ICS.[19]

A recent similar analysis of Catalonian primary care real-life data shows that only 45.2% of patients were initially treated with ICS, which were frequently prescribed in asthma-COPD overlap syndrome (ACOS) (69.2%) and in the exacerbator phenotype patients (52.4%) while ICS use has decreased from 43.8% in 2007 to 35.8% in 2012 in non-exacerbator patients.[20] These results from Catalonia are comparable to our results, and they both could be a consequence of current prescription patterns among primary care physicians in Spain according to new Spanish phenotype based COPD guidelines.[1]

In our study, asthma comorbidity was one of the factors associated with prescription of ICS, which is in line with the recommendations of the Spanish guidelines (GesEPOC).[1] The prevalence of ACOS in this study (14%) was similar to earlier Spanish studies with prevalence rates of respectively 17% and 11%.[20–22] There

is scarce data about ICS prescription in primary care. We only found one study assessing the predictors of prescribing ICS/LABA in COPD patients treated in Norwegian primary care. In this study, asthma was also identified as the major predictor (OR: 3.1).[23]

A second major factor that was associated with ICS prescription was severity of the disease in terms of bronchial obstruction. The strength of this association was greater for prescription of high-dose ICS. Notably, only 27% of the patients with COPD and a FEV₁% predicted <50% were not treated with ICS. Also in the study by De Miguel et al. in a secondary care COPD population, a lower FEV₁ was associated with ICS treatment.[24]

In addition, exacerbations were significantly related to ICS prescription in our study. Almost 60% with at least one exacerbation in the previous two years were prescribed ICS. In the Norwegian primary care study, exacerbations were also identified as the second major predictor for ICS/LABA prescribing (OR: 2.0).[25]

In general, ICS prescribing is in line with current recommendations from GesEPOC¹ and GOLD: exacerbations, ACOS, and an FEV₁% <50% being main prescription drivers. However, about half of the patients with FEV₁% >50% were prescribed ICS.[1,18] When compared to other epidemiological studies, the rate of ICS prescription seems relatively low. In 2010, it was reported that about 70% of patients diagnosed with COPD were treated with ICS in the UK.[5]

Recent Spanish studies show that 71% of the patients with COPD received ICS of which the majority were high doses and 62.1% were treated with a fixed-dose combination of LABA/ICS.[14,25] In this study, having spirometry values recorded was associated with ICS prescription same as De Miguel et al., who showed that more patients were prescribed ICS if they had a spirometry registered (61.0% versus 53.7%).[13]

Surprisingly, only 17.3% of our patients were prescribed high-dose ICS. The Spanish and GOLD Guidelines are unclear regarding the dose of ICS to be used but GOLD states that the evidence for ICS/LABA use is only for 'moderate and high-dose ICS'.[18]

Strengths and limitations

The strength of this study is the use of a database covering the entire Balearic population, allowing a large observational study with representative real-world estimates of COPD prevalence and its characteristics. The proportion of COPD identified by family physicians in our population may be of interest as it reflects real-life practice and helps to

identify key points for the improvement of the quality of COPD care. Note that the COPD prevalence (3.3%) seems lower than seen in previous epidemiological studies (12.8%), however, this perfectly aligns with the reported under diagnosis of nearly 73%.[3]

A limitation of our study is that the database contained only COPD patients that were already diagnosed, implicating a slight underestimation as some patients with early, less severe COPD were missed.[26] Another limitation lies in the quality of registered data. A high percentage of patients (53.5%) did not have record of spirometry and only in 28.3% of the population was the diagnosis confirmed by an FEV₁/FVC ratio <0.7. Therefore, it is possible that in these patients the diagnosis was made based only on symptoms, the results of spirometry were not electronically recorded or the spirometry could be performed in hospital and not communicated to primary care. The analysis of the spirometry confirmed subpopulation shows similar results and tries to increase their validity. Other common limitations of database research are related to miscoding, under-registration, invalid data and incomplete data.[27] For example, patients' and doctors' preferences and other psychological factors cannot be explored with this kind of observational design. Therefore, the validity and accuracy of observational studies have been questioned.[28] However, the call for 'real life' evidence is increasing, especially with regard to the effectiveness of interventions in heterogeneous populations.[29]

Regarding the external validity of these results, note that local guidelines and the level of primary care practice may have influenced the appropriateness of ICS prescribing. Therefore, factors that were identified in our study may show a different pattern in other regions.

Consequences for practice

Results of this study stress the need for a targeted prescription of ICS according to criteria proposed in current guidelines. A main factor to determine which patients would benefit from ICS is related to a good initial assessment of the COPD phenotype, adequate registration of exacerbations, and lung function and health status in primary care. In addition to educational interventions, combinations of long-acting muscarinic antagonists and long-acting beta agonists may offer an alternative to ICS in severe and very severe patients that are not controlled with single bronchodilators.[30]

Further research

More research is needed to establish the appropriate place of inhaled corticosteroids in clinical COPD management and guidelines. In addition, viable strategies to de-implement ICS prescription in current users without a guideline indication should be explored.

Conclusion

The current prescription rate of inhaled corticosteroids in Balearic primary care COPD population is relatively low compared to those reported in previous Spanish studies. Asthma co-morbidity, exacerbation history, severe bronchial obstruction, smoking status and spirometry records in primary care were significantly associated with ICS prescription. Assessment of the factors that were related to ICS prescription in primary care reveals that the majority of ICS prescriptions were in line with guideline recommendations. Still, considerable room for improvement was signalled.

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All authors have contributed to the study and protocol design, FV, CC, GL, MRR and ME designed the coding search, MRR, ME, FV and JvB developed the data analysis. All authors have contributed to the development of the manuscript, general discussion and manuscript review. MRR and JvB carried out the English translation.

Declaration of interest

The authors declare that they have no conflicts of interest related to this paper. The authors alone are responsible for the content and writing of the paper.

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