

Inhaled corticosteroids, blood eosinophils, and FEV₁ decline in patients with COPD in a large UK primary health care setting

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Background: Inhaled corticosteroid (ICS)-containing medications slow rate of decline of FEV₁. Blood eosinophil (EOS) levels are associated with the degree of exacerbation reduction with ICS.

Purpose: We investigated whether FEV₁ decline differs between patients with and without ICS, stratified by blood EOS level.

Patients and methods: The UK Clinical Practice Research Datalink (primary care records) and Hospital Episode Statistics (hospital records) were used to identify COPD patients aged 35 years or older, who were current or ex-smokers with ≥ 2 FEV₁ measurements ≥ 6 months apart. Prevalent ICS use and the nearest EOS count to start of follow-up were identified. Patients were classified at baseline as higher stratum EOS (≥ 150 cell/ μ L) on ICS; higher stratum EOS not on ICS; lower stratum EOS (< 150 cells/ μ L) on ICS; and lower stratum EOS not on ICS. In addition, an incident ICS cohort was used to investigate the rate of FEV₁ change by EOS and incident ICS use. Mixed-effects linear regression was used to compare rates of FEV₁ change in mL/year.

Results: A total of 26,675 COPD patients met our inclusion criteria (median age 69, 46% female). The median duration of follow up was 4.2 years. The rate of FEV₁ change in prevalent ICS users was slower than non-ICS users (-12.6 mL/year vs -21.1 mL/year; $P = 0.001$). The rate of FEV₁ change was not significantly different when stratified by EOS level. The rate of FEV₁ change in incident ICS users increased ($+4.2$ mL/year) vs -21.2 mL/year loss in non-ICS users; $P < 0.001$. In patients with high EOS, incident ICS patients showed an increase in FEV₁ ($+12$ mL/year) compared to non-ICS users whose FEV₁ decreased (-20.8 mL/year); $P < 0.001$. No statistical difference was seen in low EOS patients. Incident ICS use is associated with an improvement in FEV₁ change, however, over time this association is lost.

Conclusion: Regardless of blood EOS level, prevalent ICS use is associated with slower rates of FEV₁ decline in COPD.

Keywords: COPD, lung function, eosinophil, inhaled corticosteroids

Introduction

In 2016, COPD ranked the ninth leading cause of death worldwide and it is projected to increase to the third leading cause of death and the seventh leading cause of disability-adjusted life years (DALYs) lost worldwide by 2030.^{1,2} One of the hallmarks of COPD is decline in lung function, which is thought to be more rapid compared to the decline in the general population.³

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Initial treatment of COPD usually comprises long-acting bronchodilators, ie, long-acting beta₂-agonists (LABA) and long-acting muscarinic antagonists (LAMA), which increase and maintain lung function, improve health-related quality of life, and reduce the risk of exacerbations of COPD (AECOPD).⁴ Inhaled corticosteroids (ICS) are additionally recommended by NICE in combination with LABA or LAMA/LABA for people with frequent AECOPD or who remain breathless. Studies to date have shown that ICS reduce the rate of moderate and severe AECOPD, reduce the rate of hospitalization, and decrease the rate of decline of forced expiratory volume in 1 s (FEV₁) over time.^{5,6} However, studies also suggest that ICS increase the risk of pneumonia and increase the risk of upper respiratory tract infections, suggesting that more careful phenotyping of patients most likely to benefit from ICS is required.^{7,8}

Blood eosinophils have been considered a potential biomarker in COPD in relation to ICS. Studies have shown that ICS are more effective in COPD patients with higher blood eosinophil counts rather than lower in terms of reducing AECOPD risk.^{9–11} A few studies have explored the relationship between ICS and blood eosinophil count in terms of FEV₁ decline, but the majority have consisted of randomized control trials with strict inclusion criteria, and short-term follow-up of roughly less than 3 years limiting their external validity to the wider COPD population.^{9,10,12}

Using Clinical Practice Research Datalink (CPRD), a primary care research database, we investigated whether the rate of FEV₁ decline in COPD patients differed between patients on ICS and patients not on ICS, stratified by blood eosinophil level.

Methods

Study population

The data

We used general practice (GP) electronic health records from the Clinical Practice Research Datalink (CPRD) linked Hospital Episode Statistics (HES) data (see supplementary material for further information).

The population

The study population included patients with a validated diagnosis of COPD whose records were deemed to be of research standard from January 1, 2004. Briefly, the validated definition required specific COPD codes.¹³ COPD patients were included if they were aged 35 years or older, were current or ex-smokers at baseline, had at least one blood eosinophil count at baseline, and had at least two FEV₁ measurements at least six months apart over the study period. Patients with a history of asthma were included in the main analysis, but later excluded in a sensitivity analysis due to the potential for misclassification between asthma and COPD.¹⁴

Study design

Patients were followed up from their first FEV₁ measurements after January 2004, date of COPD diagnosis, date of registration with an eligible practice, and the date at which patients turned 35. Patients were followed until February 2016, date of death, last collection date, date of transfer out of an eligible GP practice, or date of prescribed ICS-containing medication (if they were not on an ICS-containing medication at baseline) whichever was earlier (Figure 1).

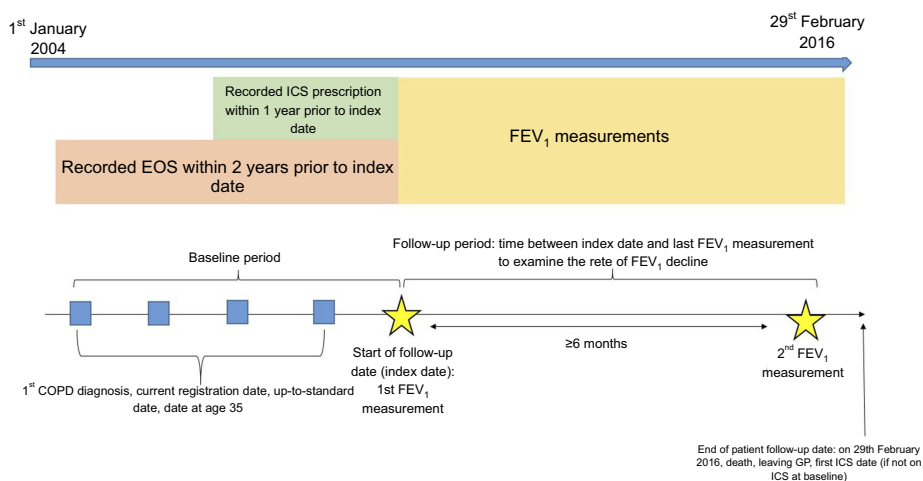


Figure 1 Study design.

Abbreviations: GP, general practice; EOS, eosinophil; ICS, inhaled corticosteroids.

Variables

Exposures

Prevalent ICS. ICS use was defined as the presence of at least one ICS-containing medication in the year prior to the patient's index date, determined through recorded ICS-containing prescriptions in the patient's data. Patients were categorized into those using an ICS-containing medication and those not using an ICS-containing medication at baseline.

Incident ICS. Incident ICS use was defined as the presence of at least one ICS-containing medication in the first year after patients' index date and no prevalent ICS use in the year prior to their index date.

Blood eosinophil count. Absolute blood eosinophil counts two years prior to the patient's index date were identified and counts that were within four weeks of an AECOPD or prescribed oral corticosteroid were not included in order to identify stable eosinophil measurements. The last absolute blood eosinophil count prior to the patient's index date was used to group patients into high and low blood eosinophil counts using a cut off of 150 cells/ μ L.¹⁵ A recent study on blood eosinophil counts in COPD patients using CPRD found that eosinophil counts are relatively stable over a period of two years.¹⁵

Outcome

The outcome of interest was rate of change of FEV₁. At least two FEV₁ measurements (measured in milliliters) recorded at least 6 months apart were used in order to analyze the rate of change of FEV₁. Since 2004 as part of the Quality and Outcomes framework, FEV₁ should be measured every 15 months in COPD patients at their GP and quality of spirometry in primary care is of good quality.^{16,17}

Covariates

Covariates included smoking status, gender, age at index date, BMI, Medical Research Council (MRC) dyspnea score, history of gastro-oesophageal reflux disease (GORD), anxiety, depression myocardial infarction (MI), stroke, heart failure, lung cancer, bronchiectasis, heart failure, white blood cell count, neutrophil count, COPD severity, AECOPD frequency in the first year of follow-up, current or history of asthma (see online supplement for further details).

Statistical analysis

Main analysis (prevalent ICS use)

In order to investigate the relationship between blood eosinophil counts and ICS on rate of change in FEV₁

Table 1 Reference and comparison patient groups

Reference group	Comparison group
High blood eosinophils and ICS	High blood eosinophils and no ICS Low blood eosinophils and ICS
Low blood eosinophils and ICS	Low blood eosinophils and no ICS High blood eosinophils and ICS

Abbreviation: ICS, inhaled corticosteroids.

patients were grouped into the following based on baseline exposures: 1) high blood eosinophil counts and prevalent ICS use; 2) high blood eosinophil counts and not on ICS; 3) low blood eosinophil counts and prevalent ICS use; 4) low blood eosinophil counts and not on ICS.

Baseline characteristics were described and compared between the four groups of patients. Mixed-effects linear regression was used due to the repeated measures of FEV₁ within patients. The model used two reference categories to evaluate the relationship between ICS and blood eosinophil level (Table 1). All covariates were included in the adjusted models.

Incident ICS use

We additionally investigated the relationship between incident ICS-containing medication use, blood eosinophil level, and rate of change in FEV₁ using an incident ICS-containing medication cohort. This cohort differed as patients were not censored at 1st ICS-containing medication prescription date. Patients not on ICS-containing medication at baseline were included and grouped into incident ICS-containing medication users or non-ICS-containing medication users based on ICS-containing medication prescriptions in their first year of follow-up. Mixed-effects linear regression was used to investigate the relationship between blood eosinophil counts and incident ICS use on the rate of change in FEV₁. Reference and comparison groups were the same (Table 1). All covariates were included in the adjusted models.

Sensitivity and exploratory analyses

Sensitivity analyses included using blood eosinophil cut-offs of 300 and 500 cells/ μ L, continuous blood eosinophil count, excluding patients with a history of asthma, and restricting the sample to patients with at least 3 FEV₁ measurements. Exploratory analyses included stratification by airflow obstruction, AECOPD frequency smoking status, ICS-duration, and type of ICS (see online supplement for further detail).

Power calculation

Sample size calculations were based on the rate of FEV₁ change. Table 2 shows the number of patients needed to detect a 2–10 mL/year difference in the rates of change of FEV₁ in patients on an ICS and not on an ICS.

Results

Baseline characteristics

A total of 26,675 patients were included in this study. Figure 2 illustrates the distribution of patients in each eosinophil/ICS group. Table 3 describes the included population in terms of baseline characteristics, and Table 4 illustrates the proportion of baseline COPD medications used by patients in each ICS use group. The median length of follow-up in this study was 4.2 years (IQR:2.5–6.5), the median number of FEV₁ measurements during follow-up was 3 (IQR: 2–5), and

Table 2 Sample size needed to detect a difference in rates of change of FEV₁ between ICS and non-ICS groups of patients

Δ (mL/year)	Initial sample size		Sample size after Bonferonni correction	
	Total sample (N)	Patients on ICS	Total sample (N)	Patients on ICS
2	55,293	13,016	64,275	17,021
3	24,575	5,785	28,567	7,565
4	13,824	3,254	16,069	4,255
5	8,847	2,082	10,284	2,723
7	4,514	1,063	5,247	1,389
10	2,212	521	2,571	681

Abbreviation: ICS, inhaled corticosteroids.

the time between FEV₁ measurements did not differ between blood eosinophil and ICS group.

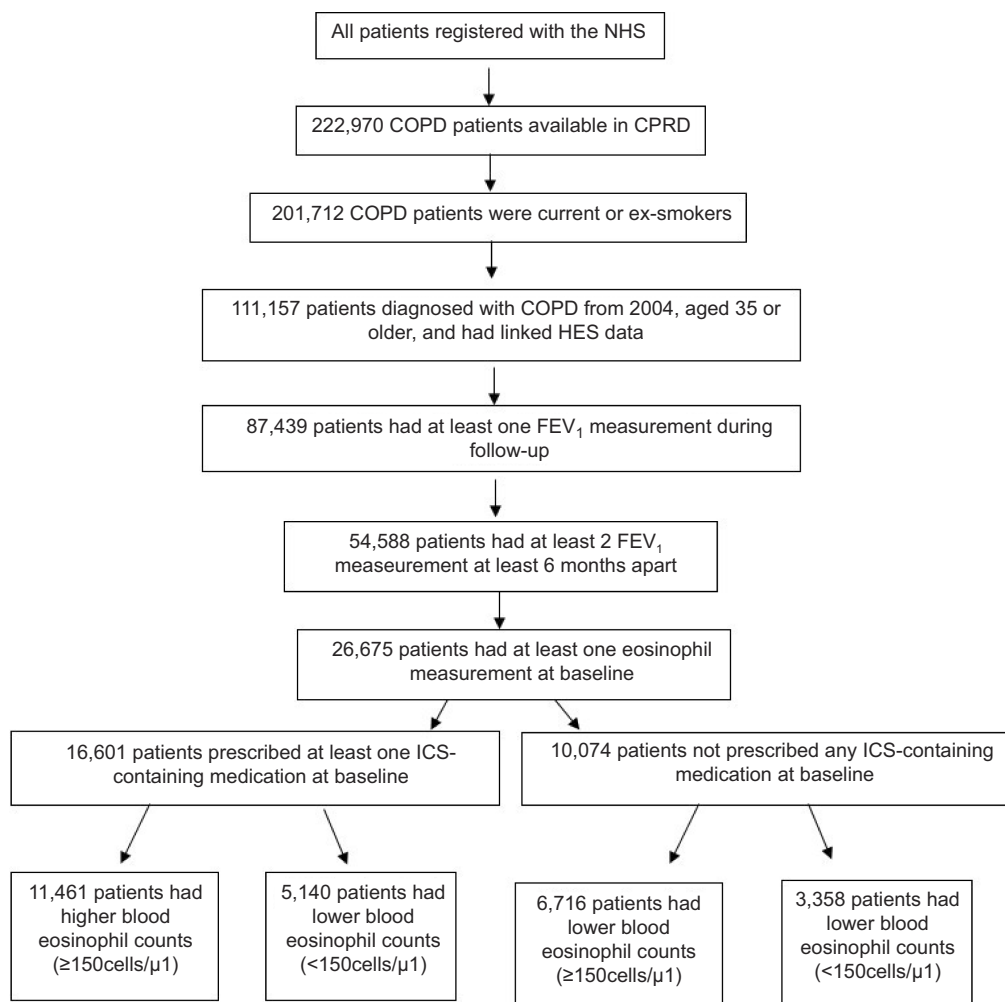


Figure 2 Flow diagram of included patients.

Abbreviation: ICS, inhaled corticosteroids.

Table 3 Baseline characteristics for all included patients (N=26,675). Values are n (%) or median (IQR)

Variables	All patients (N=26,675)	Blood eosinophil and ICS group			
		Higher blood eosinophils & ICS (N=11,461)	Higher blood eosinophils & no ICS (N=6,716)	Lower blood eosinophils & ICS (N=5,140)	Lower blood eosinophils & no ICS (N=3,358)
Female gender	12,379 (46.4)	5,206 (45.4)	2,574 (38.3)	2,920 (56.8)	1,679 (50.0)
Age (years)	69 (62–89)	69 (62–76)	69 (62–76)	70 (62–77)	69 (62–77)
Current smoking status	12,825 (48.1)	5,195 (45.3)	3,564 (53.1)	2,361 (45.9)	1,705 (50.8)
History of MI	2,415 (9.1)	1,105 (9.6)	687 (10.2)	380 (7.4)	243 (7.2)
History of stroke	401 (1.5)	165 (1.4)	104 (1.6)	76 (1.5)	56 (1.7)
History of heart failure	1,802 (6.8)	786 (6.9)	428 (6.4)	380 (7.4)	208 (6.2)
History of lung cancer	171 (0.6)	56 (0.5)	42 (0.6)	43 (0.8)	30 (0.9)
History of bronchiectasis	616 (2.3)	317 (2.8)	91 (1.4)	154 (3.0)	54 (1.6)
History of GORD	1,761 (6.6)	780 (6.8)	371 (5.5)	378 (7.4)	232 (6.9)
History of anxiety	2,133 (8.0)	919 (8.0)	453 (6.8)	466 (9.1)	295 (8.8)
History of depression	2,343 (8.8)	1,028 (9.0)	545 (8.1)	488 (9.5)	282 (8.4)
History of asthma	9,623 (36.1)	5,839 (51.0)	574 (8.6)	2,540 (49.4)	279 (8.3)
BMI (kg/m ²) (N=25,528)	26.8 (23.3–30.8)	27.3 (23.7–31.3)	26.9 (23.4–30.8)	26.5 (23.0–30.7)	25.7 (22.3–29.7)
White blood cell count (cells/ μ L)	7.6 (6.4–9.1)	7.9 (6.6–9.3)	7.8 (6.6–9.2)	7.2 (6.0–8.7)	7.1 (5.9–8.5)
Neutrophil count (cells/ μ L) (N=26,585)	4.5 (3.6–5.7)	4.7 (3.7–5.8)	4.5 (3.6–5.6)	4.5 (3.5–5.8)	4.3 (3.4–5.5)
Airflow obstruction (N=26,518)					
Mild (\geq 80% FEV ₁ predicted)	5,550 (20.9)	2,185 (19.2)	1,556 (23.3)	957 (18.8)	852 (25.5)
Moderate (50–80% FEV ₁ predicted)	13,834 (52.2)	5,640 (49.5)	3,879 (58.1)	2,469 (48.4)	1,846 (55.3)
Severe (30–50% FEV ₁ predicted)	5,988 (22.6)	2,935 (25.8)	1,092 (16.3)	1,407 (27.6)	554 (16.6)
Very severe (\leq 30% FEV ₁ predicted)	1,146 (4.3)	633 (5.6)	154 (2.3)	270 (5.3)	89 (2.7)
AECOPD frequency					
0	11,105 (41.6)	4,000 (34.9)	3,501 (52.1)	1,828 (35.6)	1,776 (52.9)
1	6,593 (24.7)	2,788 (24.3)	1,688 (25.1)	1,212 (23.6)	905 (27.0)
\geq 2	8,977 (33.7)	4,673 (40.8)	1,527 (22.7)	2,100 (40.9)	677 (20.2)
MRC dyspnoea score (N=18,090)					
1	3,749 (20.7)	1,313 (17.6)	1,287 (26.2)	531 (15.8)	618 (26.2)
2	7,457 (41.2)	2,911 (39.0)	2,177 (44.3)	1,315 (39.2)	1,054 (44.7)
3	4,435 (24.5)	2,030 (27.2)	986 (20.1)	945 (28.2)	474 (20.1)
4	2,066 (11.4)	998 (13.4)	396 (8.1)	493 (14.7)	179 (7.6)
5	383 (2.1)	215 (2.9)	66 (1.3)	68 (2.0)	34 (1.4)

Abbreviations: AECOPD, exacerbations of COPD; BMI, body mass index; ICS, inhaled corticosteroids; MI, myocardial infarction; GORD, gastro-oesophageal reflux disease.

Table 4 Medication prescribed in the year prior to start of follow-up by baseline ICS use. Values are n (%)

COPD medications	ICS combinations at baseline (n=16,601)		No ICS at baseline (n=10,074)
	ICS (n=6,515 (40%))	ICS/LABA (n=10,086 (60%))	
LABA	1,764 (27)	n/a	658 (7)
LAMA	1,061 (16)	4,110 (41)	1,728 (17)
LABA and LAMA	288 (4)	286 (3)	154 (2)

Abbreviations: ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; LABA, long active beta agonist.

Rate of change in FEV₁ with prevalent ICS use

The mean adjusted rate of change of FEV₁ in those on ICS-containing medication was -12.6 mL/year and -21.1 mL/year in patients not on an ICS-containing medication (P=0.001). Reference classes include women, ex-smokers, no comorbidities, mild airflow obstruction, no AECOPD in first year of follow-up, MRC score of 1, mean BMI (27.1 kg/m²), mean WBC (7,700 cells/μL), and mean neutrophil count (4,600 cells/μL).

Table 5 illustrates the rates of change in FEV₁ for each blood eosinophil/ICS group. Irrespective of blood eosinophil level, patients on an ICS-containing medication have

slower rates of change in FEV₁ compared to those not on an ICS-containing medication.

Rate of FEV₁ change with incident ICS use

A total of 12,469 patients who were not on an ICS-containing medication at baseline were included in this cohort of which 3,417 newly initiated ICS-containing medication (LABA/ICS 2,604 (76%); ICS 813 (24%)). It is important to note patients prescribed ICS only were on other maintenance therapies including LAMA, SABA, and SAMA. The median number of FEV₁ measurements during follow-up was 4 (IQR:3–6) and the time between FEV₁ measurements in ICS groups was significantly shorter than the time between FEV₁ measurements in non-ICS groups (P<0.001).

The mean adjusted rate of change in FEV₁ in patients on newly initiating ICS-containing medication was +4.2 mL/year and -21.2 mL/year in patients not on an ICS-containing medication (P<0.0001). Reference classes include women, ex-smokers, no comorbidities, mild airflow obstruction, no AECOPD in first year of follow-up, MRC score of 1, mean BMI (26.8 kg/m²), mean WBC (8,300 cells/μL), and mean neutrophil count (4,800 cells/μL).

A significant difference was seen between patients with higher blood eosinophils on ICS-containing medication and all other groups (Table 6). Whilst FEV₁ declined slower in patients with lower eosinophils on an ICS-containing medication, there was no significant difference

Table 5 Rates of change of FEV₁ by blood eosinophil/ICS group in prevalent ICS cohort

	Crude rate of FEV ₁ change ml/year (95% CI) (N=26,675)	P-value for significant differences between rates		Adjusted* rate of FEV ₁ change ml/year (95% CI) (N=17,557)	P-value for significant differences between rates	
High blood eosinophil level & ICS (crude n=11,461, adjusted n=7,255)	-16.8 (-18.9 to -14.8)	Ref		-13.7 (-16.8 to -10.5)	Ref	
High blood eosinophil level & no ICS (crude n=6,716, adjusted n=4,783)	-24.3 (-30.5 to -18.2)	<0.001		-20.8 (-29.8 to -11.9)	0.016	
Low blood eosinophil level & ICS (crude n=5,140, adjusted n=3,238)	-15.5 (-21.2 to -9.7)	0.479	Ref	-10.2 (-19.0 to -1.3)	0.229	Ref
Low blood eosinophil level & no ICS (crude n=3,358, adjusted n=2,281)	-28.4 (-35.8 to -21.0)	<0.001	<0.001	-21.7 (-32.7 to -10.8)	0.043	0.008

Notes: *Adjusted for: gender, age, smoking status, MI, stroke, HF, lung cancer, bronchiectasis, GORD, anxiety, depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and MRC dyspnea.

Abbreviations: BMI, body mass index; HF, heart failure; ICS, inhaled corticosteroids; AECOPD, exacerbations of COPD; MI, myocardial infarction; MRC, Medical Research Council; GORD, gastro-oesophageal reflux disease; WBC, white blood cell.

Table 6 Rates of change of FEV₁ by blood eosinophil/ICS group in incident ICS cohort

	Crude rate of FEV ₁ change ml/-year (95% CI) (N=12,469)	P-value for significant differences between rates		Adjusted* rate of FEV ₁ change ml/year (95% CI) (N=6,402)	P-value for significant differences between rates	
High blood eosinophil level & ICS (crude n=2,336, adjusted n=315)	-10.7 (-15.5 to -5.9)	Ref		12.2 (-25.0 to 27.0)	Ref	
High blood eosinophil level & no ICS (crude n=5,984, adjusted n=4,006)	-25.9 (-36.9 to -15.0)	<0.001		-20.8 (-51.1 to 9.5)	<0.001	
Low blood eosinophil level & ICS (crude n=1,081, adjusted n=148)	-15.5 (-29.0 to -1.9)	0.284	Ref	-15.7 (-56.7 to 25.2)	0.037	Ref
Low blood eosinophil level & no ICS (crude n=3,068, adjusted n=1,933)	-29.7 (-41.6 to -17.9)	<0.001	0.002	-21.3 (-52.5 to 9.8)	<0.001	0.632

Note: *Adjusted for: gender, age, smoking status, history of MI, history of stroke, history of HF, history of lung cancer, history of bronchiectasis, history of GORD, history of anxiety, history of depression, BMI, WBC count, neutrophil count, airflow obstruction, AECOPD frequency, and MRC dyspnea.

Abbreviations: BMI, body mass index; HF, heart failure; ICS, inhaled corticosteroids; AECOPD, exacerbations of COPD; MI, myocardial infarction; MRC, Medical Research Council; GORD, gastro-oesophageal reflux disease; WBC, white blood cell.

between patients with ICS and lower blood eosinophils and those with no ICS-containing medication.

Exploratory analyses results

The rate of change of FEV₁ between the four groups was not significantly different when stratified by airflow obstruction (Table S1). When stratified by AECOPD frequency, the rate of change of FEV₁ was slower in ICS-containing groups compared to non-ICS-containing medication groups; however, no significant difference was seen (Table S2). The rate of change of FEV₁ was significantly slower in ex-smokers with high blood eosinophils whether on ICS or not. Whilst a similar trend was seen in lower blood eosinophil groups, no significant difference was seen between smokers and ex-smokers (Table S3).

Those on ICS-containing medication continuously for 1–3 months prior to start of follow-up had a lower rate of change of FEV₁ (-5.5 mL/year) compared to those on ICS continuously for 4–6 months (-15.8 mL/year) and a significantly lower rate compared to 10–12 months (-17.6 mL/year) in the all-patient analysis. Similar differences were seen after stratification by lower blood eosinophils. A significant difference was seen between patients with higher blood eosinophils on

ICS-containing medication continuously for 1–3 months and 10–12 months (Table S4). In terms of drug type, no significant difference in the rate of change of FEV₁ was seen between patients on any ICS-containing medication (Table S5).

Sensitivity analyses results

When using blood eosinophil cut offs of 300 and 500 cells/ μ L, we found that in lower blood eosinophil patients, those on an ICS-containing medication had significantly lower rates of change of FEV₁ compared to those not on an ICS-containing medication; however, patient numbers were low in these sub-groups and there was inadequate statistical power for a reliable analysis (Table S6). In addition, continuous eosinophil level was not associated with change in FEV₁ (Table S7). There were 17,052 patients in the cohort that excluded a history of asthma. The decline in FEV₁ across groups varied from -12.3 mL/year to -21.6 mL/year. The pattern of differences between eosinophil/ICS groups was similar to that in the main analysis, but there was no significant difference was seen between groups (Table S8). When restricted to patients with at least 3 FEV₁ measurements, similar rates were observed (Table S9).

Discussion

Main findings

This is the first observational study to investigate the relationship between ICS-containing medication and blood eosinophils on the rate of change of FEV₁ over an extended period. We have included COPD patients of different degrees of airflow limitation, who may not have met inclusion criteria for some of the randomized clinical trials, in which FEV₁ decline has been previously investigated. We found a difference in the rate of decline of FEV₁ between patients on prevalent ICS-containing medication at baseline and those not, regardless of blood eosinophil level. In addition, we found an increase in FEV₁ in patients with higher blood eosinophils who initiated ICS-containing treatment. These results suggest that whilst receiving an ICS-containing medication slows down the rate of FEV₁ decline in COPD patients, new ICS-users with higher blood eosinophils may benefit more when first started on ICS than those with lower blood eosinophils. Overall, however, our results suggest ICS-containing medication use in COPD patients is associated with lower rate of FEV₁ decline irrespective of eosinophil level.

Previous literature

Few observational studies have investigated the relationship between the rate of change of FEV₁, ICS-containing medication, and blood eosinophils. In contrast to our main finding, a study in non-asthma COPD patients from the Korean COPD Subtype Study (KOCOSS) cohort found no difference in rate of decline in FEV₁ between those with higher or lower blood eosinophils (using 200 cells/ μ L and 600 cells/ μ L cut-off), whether on ICS/LABA, or not. Findings from KOCOSS showed that FEV₁ increased in patients with higher eosinophils, regardless of being on an ICS or not and in those with lower eosinophils (\leq 200 cells/ μ L) FEV₁ declined faster in ICS users.¹² Differences between cohorts may explain discrepancies between findings. Our study included a larger sample of ex- and current smoking COPD patients from primary care in the UK whereas the KOCOSS included a smaller sample of patients from hospitals in Korea.

Furthermore, in contrast to our main finding, a further study on blood eosinophils and FEV₁ over time found that higher blood eosinophils $>$ 400 cells/ μ L were associated with greater FEV₁ decline in a relatively small general population.¹⁸ No difference in the rate of FEV₁ decline in high or low blood eosinophil groups was seen in our

study; however, we included older patients and used a different definition of high and low eosinophil level.

Similar to our incident ICS-containing medication findings, a post-hoc analysis of the ISOLDE trial found that COPD patients with higher blood eosinophil levels greater than 2% of their total WBC count who were on an ICS had lower rates of FEV₁ decline compared to those on a placebo. No difference was seen between patients with lower blood eosinophil counts on an ICS or a placebo.¹⁰ However, a post-hoc analysis of two RCTs found that there was a numerically lower mean improvement in trough FEV₁ over one year in patients treated with ICS/LABA in with lower eosinophils, compared to those with higher eosinophils, but the confidence intervals between the two groups overlapped widely.⁹ Those studies, like the majority of RCTs, included a wash-out period before initiating patients on randomized medication and are therefore similar to our incident cohort design.

Limitations

Despite using a highly sensitive algorithm to identify patients with COPD, misdiagnosis of asthma as COPD and vice versa could not be excluded, notably in patients over the age of forty.^{14,18} Based on findings from previous work on misclassification of asthma and COPD, we included patients with a history of asthma but undertook a sensitivity analysis in which we excluded those with an asthma diagnosis more than 2 years prior to study start.¹⁹ After excluding patients with a history of asthma, no significant differences were seen between groups in the rate of decline in FEV₁. This is probably due to a smaller sample size and thus underpowered analysis rather than asthma driving the association between ICS-containing medication and rate of change of FEV₁, given we adjusted for history of asthma in all other analyses.

Only COPD patients whose GP practices contribute to CPRD were included in our cohort and patients may not be representative of the true UK population of people with COPD. In addition, included patients had to have at least one blood eosinophil measurement at baseline, which introduces selection bias. Blood tests for COPD patients may have been performed due to reasons other than COPD, such as infections. Whilst research suggests that blood eosinophils are stable over relatively short periods of time, the ECLIPSE study showed that 49% of COPD patients had fluctuating eosinophil counts that varied above and below the cut off over 3 years.^{15,20} The median

study duration was 4.2 years and blood eosinophils were identified 2 years prior to study start. Therefore, it is possible that patients' blood eosinophil measurements did not represent their eosinophil levels throughout the whole study. However, in order to try to obtain a patient's stable blood eosinophil measurement using the data available, we excluded blood eosinophil counts that were within four weeks of an AECOPD or prescribed oral corticosteroid.

Spirometry is measured in general practice and not standardized in terms of time of day, machine used, and quality of spirometry or pre or post bronchodilation. In addition, we found that the change in FEV₁ was highly variable among patients, as seen by wide 95% confidence intervals. This is consistent with previous research, including RCTs, showing that the rate of FEV₁ decline is heterogeneous.^{21,22} Variation in the rate of FEV₁ decline was seen when stratified by severity of COPD whereby patients with milder COPD had faster rates of decline compared to those with more severe COPD. This may be because COPD patients with milder disease have more lung function to lose compared to those with severe COPD with less lung function to start with. In addition, rates of FEV₁ change in severe to very severe COPD may be influenced by survival bias. Furthermore, shorter time periods between FEV₁ measurements in incident ICS users may explain some of the short-term increase in FEV₁ in patients with high eosinophils. It is important to note that these results may not reflect changes in FEV₁ over long periods of time.

Furthermore, whilst a strength of this study is that it is an observational study and the population is more generalisable to the wider population of COPD patients, it is important to note that the number and frequency of spirometry measurements available in the data may not have been adequate. The median number of spirometry measurements was 3, and the majority of intervals between measurements within patients were not consistent, despite the introduction of QOF.^{16,17}

In addition, missing data were present for the BMI, MRC, neutrophil count, and degree of airflow obstruction, so we performed complete case analysis for our adjusted models and our results may not be generalizable to the wider COPD population.

It is important to note that whilst we found mainly significant differences between the rates of FEV₁ in patients on ICS and patients not on ICS the actual differences ranged from 8 mL/year to 33 mL/year. The American Thoracic Society and the European Respiratory Society propose that minimal clinically important differences in FEV₁ between treatment groups

range from 100 mL to 140 mL.²³ Therefore, it could be argued that the differences seen in this study may not be clinically important. Despite this, our estimates are averaged per year and therefore over a longer period of time these differences may become more apparent. In addition, minimal clinically important differences suggested by the American Thoracic Society and the ERS are based off of pharmacological trials and clinically important differences in a more generalizable population of COPD patients may be less.

Lastly, this study is an observational study so we cannot infer causation. It is also important to note that residual confounding may still exist due to the observational nature such as ICS dosage and mortality during follow-up.

Conclusion

In conclusion, we found that in a large primary care cohort of COPD patients, decline in FEV₁ was slower in prevalent ICS-containing medication patients, regardless of blood eosinophil level. Incident ICS-containing medication in patients with higher blood eosinophil levels showed more benefit compared to patients with lower blood eosinophils however, over time this difference was lost. Further, long-term observational studies on the use of ICS-containing medications stratified by eosinophil levels are needed. Research into further possible biomarkers and patient characteristics may help define a subgroup of COPD patients who benefit from ICS-containing medications more than others in terms of FEV₁ decline.

Abbreviation list

ICS, Inhaled corticosteroids; EOS, eosinophils; FEV₁, Forced expiratory volume in 1 s; LAMA, Long-acting muscarinic antagonist; LABA, long active beta agonist; BMI, Body mass index; MI, Myocardial infarction; HF, Heart failure; GORD, Gastro-oesophageal reflux disease; WBC, White blood cell; AECOPD, Exacerbation of COPD; RCT, Randomized control trial.

Ethics approval

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 17_229R) and the approved protocol was made available to the journal and reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Acknowledgments

This manuscript was funded by GlaxoSmithKline; study number 208602. This study has been previously presented as an abstract at the European Respiratory Society Conference in Paris, September 2018. Steven J Kiddle and Jennifer K Quint are joint last authors for this study.

Author contributions

Hannah R Whittaker: data management, data analysis, data interpretation, writing, figures & tables. Hana Müllerova, Steven J Kiddle, Jennifer K Quint: data analysis, data interpretation, writing. Deborah Jarvis, Neil C Barnes, Paul W Jones, Chris H Compton: data interpretation, writing. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Miss Whittaker reports grants from GlaxoSmithKline, during the conduct of the study; Dr Müllerova was employed by and reported personal fees from GlaxoSmithKline, during the conduct of the study; Dr Jarvis reports grants from European Union and Cystic Fibrosis Trust, outside the submitted work; she also reports grants from GlaxoSmithKline, during the conduct of the study. Dr Barnes is employed, holds shares and reports personal fees from GlaxoSmithKline, outside the submitted work; he also received grants from GlaxoSmithKline, during the conduct of the study. Dr Jones is employed by and reports personal fees from GlaxoSmithKline, during the conduct of the study; Dr Compton is employed, holds shares and reports personal fees from GlaxoSmithKline, during the conduct of the study; Dr Kiddle reports grants from MRC, during the conduct of the study; grants from Roche Diagnostics, Engineering and Physical Sciences Research Council, Biotechnology and Biological Sciences Research Council, National Institute for Health Research, Alzheimer's Society, Eli Lilly, and Janssen, outside the submitted work; Dr Kiddle was supported by a MRC Career Development Award (MR/PO21573/1). Dr Quint reports grants from GlaxoSmithKline, during the conduct of the study; grants from The Health Foundation, MRC, Wellcome Trust, British Lung Foundation, Insmmed, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, Teva, and GlaxoSmithKline, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Collaborators GCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:10100. doi:10.1016/S0140-6736(17)31928-1
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017. GOLD executive summary report. *Am J Respir Crit Care Med*. 2017;195(5):557–582. doi:10.1164/rccm.201701-0218PP
3. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J*. 1977;1:1645–1648.
4. Rossi A, Khirani S, Cazzola M. Long-acting β_2 -agonists (LAB) in chronic obstructive pulmonary disease: efficacy and safety. *Int J COPD*. 2008;3(4):521–529.
5. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet*. 2016;387(10030):1817–1826. doi:10.1016/S0140-6736(16)30069-1
6. Vestbo J, Leather D, Diar Bakerly N, et al. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. *N Engl J Med*. 2016;375(13):1253–1260. doi:10.1056/NEJMoa1608033
7. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68(11):1029–1036. doi:10.1136/thoraxjnl-2012-202872
8. Yang M, Chen H, Zhang Y, et al. Long-term use of inhaled corticosteroids and risk of upper respiratory tract infection in chronic obstructive pulmonary disease: a meta-analysis. *Inhal Toxicol*. 2017;29(5):219–226. doi:10.1080/08958378.2017.1346006
9. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med*. 2015;3(6):435–442. doi:10.1016/S2213-2600(15)00106-X
10. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J*. 2016;47(5):1374–1382. doi:10.1183/13993003.01370-2015
11. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax*. 2016;71(2):118–125. doi:10.1136/thoraxjnl-2015-207021
12. Song JH, Lee CH, Kim JW, et al. Clinical implications of blood eosinophil count in patients with non-asthma-COPD overlap syndrome COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2455–2464. doi:10.2147/COPD.S129321
13. Quint JK, Mullerova H, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open*. 2014;4(7):e005540. doi:10.1136/bmjopen-2014-005540
14. Tinkelman DG, Price DB, Nurdyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. *J Asthma*. 2006;43(1):75–80. doi:10.1080/02770900500448738
15. Landis SH, Suruki R, Hilton E, Compton C, Galwey NW. Stability of blood eosinophil count in patients with COPD in the UK clinical practice research datalink. *Copd*. 2017;14(4):382–388. doi:10.1080/15412555.2017.1313827
16. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence Publication; 2018.

17. Rothnie KJ, Chandan JS, Goss HG, Mullerova H, Quint JK. Validity and interpretation of spirometric recordings to diagnose COPD in UK primary care. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1663–1668. doi:10.2147/COPD.S133891
18. Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. *Eur Respir J*. 2018. doi:10.1183/13993003.02536-2017
19. Nissen F, Morales D, Mullerova H, Smeeth L, Quint JK, Douglas I. Misdiagnosis of COPD in asthma patients in the UK electronic health records (Clinical practice research datalink). *A59. Epidemiol Airways Chron Lung Dis*. 2017;195:A2026–A2026.
20. Singh D, Kolsun U, Brighling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J*. 2014;44:1697–1700. doi:10.1183/09031936.00162414
21. Tashkin DP. Variations in FEV(1) decline over time in chronic obstructive pulmonary disease and its implications. *Curr Opin Pulm Med*. 2013;19(2):116–124. doi:10.1097/MCP.0b013e32835d8ea4
22. Babu KS, Kastelik JA, Morjaria JB. Inhaled corticosteroids in chronic obstructive pulmonary disease: a pro-con perspective. *Br J Clin Pharmacol*. 2014;78(2):282–300. doi:10.1111/bcp.12334
23. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med*. 2014;189(3):250–255. doi:10.1164/rccm.201310-1863PP. Available from: <http://hdl.handle.net/10044/1/68961>. Accessed April 10, 2019.

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